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THE OSLO STUDY OF UNTREATED SYPHILIS

AN EPIDEMIOLOGIC INVESTIGATION OF THE NATURAL COURSE OF THE SYPHILITIC INFECTION BASED UPON A RE-STUDY OF THE BOECK-BRUUSGAARD MATERIAL

by
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PREFACE

A re-analysis of the Boeck—Bruusgaard material on untreated syphilis had for a long time been on the list of potential research projects at the Department of Dermatology of the University Hospital (Rikshospitalet), Oslo, Norway (Chief: professor dr. med. Niels Danbolt), but due to various circumstances the plans did not materialize until 1948.

The present study, supported by the Research Grants Division of the United States Public Health Service, owes its origin to the continued interest in Bruusgaard's work by many persons, particularly professor Joseph Earle Moore, M.D. of Baltimore, and those associated with him as staff and students in Medicine I of the Johns Hopkins Hospital. In addition to several reviews of Bruusgaard's work by Colonel L. W. Harrison of England, the most critical appraisal was made by Wilson T. Sowder, M.D. working at Johns Hopkins.

The actual instigation of the present investigation came as a result of several related circumstances: a) A visit to the United States in 1946 by professor Danbolt, during which the possibilities were discussed with dr. Thorstein Guthe, M.D. (now Chief of the Venereal Disease and Treponematoses Division of the World Health Organization, then a post-graduate student at the Medicine I of the Johns Hopkins Hospital). b) Dr. Joseph Earle Moore's visit to Oslo in 1947 to look over the basic data. c) The interest taken in this project by dr. J. R. Heller, M.D. (then Chief of the Venereal Disease Division of the United States Public Health Service), and d) his and dr. Moore's influence in securing funds to finance the study.

I want to take this opportunity to express my gratitude to the Research Grants Division of the United States Public Health Service. Without its generous appropriations during the years 1948—49, 1949—50, 1950—51, and 1951—52, this investigation would not have been possible. Also I wish to offer my grateful tribute to all those who instigated the study.

The study was carried out under the joint supervision of the Surgeon General's Office of the Norwegian Public Health Service (Chief: dr. Karl Evang, M.D.) and the Dermatological Department of the University Hospital, Oslo, Norway (Chief: professor dr. med. Niels Danbolt, M.D.).

The investigation was done at the Dermatological Department of the University Hospital during the period 1949—1951, under the guidance of

professor Niels Danbolt, M.D. Professor Danbolt put at my disposal all the facilities of the department and offered me ideal working conditions. For this, and for his neverfailing interest in my work and expert advice as regards the many complex problems of clinical syphilology, I am greatly indebted to professor Danbolt.

The Surgeon General of the Norwegian Public Health Service had the administrative and financial responsibility for the project, the funds being appropriated directly to him from the United States Public Health Service. I want to acknowledge my deep obligation to Surgeon General dr. Karl Evang, M.D., for having sponsored this project from the beginning, and for advice and encouragement throughout the task.

A great part of the analysis was done while the author was a research associate in 1951—1952 at Columbia University, School of Public Health, Department of Epidemiology (Chief: dr. E. Gurney Clark, M.D., Dr. P. H.). For professor Clark's gracious and unfailingly helpful response to the demands made upon him and his department, for stimulating and friendly criticism, and for the many valuable discussions, I offer my heartiest thanks. I feel a special obligation to professor Clark for having introduced me to the modern concepts of epidemiology, concepts that form the very basis on which the present study rests.

My hearty thank-you also to John W. Fertig, Ph.D. (Professor of Biostatistics, Columbia School of Public Health), and his staff, for invaluable assistance in many ways.

Finally, to the staff of the Bureau of Applied Social Research, Department of Sociology, Columbia University (Director: Kingsley Davis, Ph.D.), go my grateful acknowledgement for generous cooperation in establishing the code and the punch cards.

The roll of others who helped me carry out this investigation is long. To these others I make grateful acknowledgement here: Dr. Georg Henriksen, M.D., of the Neurologic Department of the University Hospital, for performing most of the neurologic examinations on the patients. City Health Commissioners dr. Andreas Diesen, M.D., and dr. Trygve Iversen, M.D., for permitting me to use the Oslo City Health Department records. I am especially obliged to dr. H. Chr. Gjessing, M.D. (Chief of the Oslo City Health Department, V.D. Division), for having put at my disposal the records of the division for the entire period 1891—1951. Mrs. Karin Tegnèr Hansen, secretary to the City Health Commissioner of Oslo, for having provided the great majority of the death certificates. Dr. Arve Madsen, M.D. (Chief of the Municipal Hospital of Oslo, Dermatological Department), for permission to use the records of the department for the entire period 1891—1951. Secretary of the Oslo Population Register, Hans Danielsen, for his most valuable contribution to the solution of the difficult tracing problems this investigation posed us. Secretary of the Oslo Bureau of the Indigents, Steinar Rydland, whose meticulous work over the entire period of investigation (1949

—1951), in assembling data on the patients actually enabled us to trace a far greater number of the original patients than otherwise would have been possible. Dr. Philos. Julie E. Backer and her staff at the Central Bureau of Statistics, for having put at my disposal important data on marriages and deaths. Knut Hernæs of the Central Bureau of Statistics for valuable assistance as a punch card operator. Berthe Halvorsen, R.N., and nurse Elizabeth Knudzon, who acted as medical secretaries and public health nurses combined. I am specially indebted to Berthe Halvorsen on whom rested the responsibility of typing, filing and accounting, and who also was in charge of the transportation of the patients to and from the hospital, thus rendering valuable services throughout the investigation. Civil Engineer Egil B. Bolstad of the Geophysical Institute, University of Bergen, for expert technical services in photographing tables and graphs. To Mrs. Edna Sande of Bergen I extend my most grateful appreciation for her untiring efforts and unflagging interest in preparation of the manuscript.

I fully realise that many others not named herein have contributed to the realization of the project. Particular reference must be made to the staffs of the Dermatological Department and other departments at the University Hospital, and to the many colleagues in hospitals, asylums, clinics and private practice all over the country, who all gave unstinted cooperation in providing clinical data. To these persons, though unnamed, go my grateful acknowledgement.

To the University of Oslo goes my grateful appreciation for financial aid granted me through «Statssekretær Jacob Aall og hustrus legat» and «C. H. Homans legat og Legatet til Henrik Homans Minde».

Finally I am indebted to the University of Bergen for the fellowship given me during the period 1951—1953, which greatly facilitated my work.

Bergen in December 1954.

Trygve Gjestland.

Part I. Females.

Patient No.	First						Second						Third		
	Type and Amount of Treatment*	Duration of Infection, in years	Examinations**				Type and Amount of Treatment	Duration of Infection, in years	Examinations				Type and Amount of Treatment	Duration of Infection, in years	
			S. T. S.	C. S. F.	X-ray	Neuro.			S. T. S.	C. S. F.	X-ray	Neuro.			S. T. S.
1	0	31	0	0	0	0	Bi (22)	37	+	-	-	-			
2	Potassium Iodide.	14	0	0	0	0	As + Bi (1/5)	34	+	-	-	0			
3	Potassium Iodide.	6	0	0	0	0	As + Bi (15/18)	28	+	0	-	0			
4	0	20	-	0	0	0	As (13)	21	+-	0	0	0			
5	Potassium Iodide.	4	0	0	0	0	Hg. inunc. (No. unknown)	6	0	0	0	0			
6	0	11	0	0	0	0	As (6)	26	+	0	0	0			
7	0	4	0	0	0	0	As (5)	11	+	0	0	0			
8	Potassium Iodide.	11	+	0	0	0	As (6)	14	+	0	0	0			
9	Potassium Iodide.	8	0	0	0	0	Potassium Iodide.	10	0	0	0	0	Hg. inunc. (92)	11	0
10	0	7	0	0	0	0	Potassium Iodide.	11	0	0	0	0	Bi (No. unknown)	33	+
11	Hg.inunc. (30)	1	0	0	0	0	Hg. inunc. (30)	2	0	0	0	0	Hg. inunc. (30)	4	0
12	Potassium Iodide.	2	0	0	0	0	Potassium Iodide.	10	0	0	0	0	Hg. inunc. (No. unknown)	12	0
13	Potassium Iodide.	18	+	0	0	0	As (4)	19	+	0	0	0	As (5)	20	0
14	Potassium Iodide.	7	0	0	0	0	0	11	0	0	0	0	Potassium Iodide.	12	0
15	As (11)	6	+	0	0	0	As (10)	11	+	0	0	0	As (13)	11	+-
16	Potassium Iodide.	2	0	0	0	0	Potassium Iodide.	3	0	0	0	0	Potassium Iodide.	4	0

Part II. Males.

1	Potassium Iodide.	4/12	0	0	0	0	Hg. inunc. (30)	16/12	0	0	0	0	Potassium Iodide.	2	0
2	Potassium Iodide.	7	0	0	0	0	Potassium Iodide.	8	0	0	0	0	Hg. inunc. (22)	9	+

*0: Unknown, local, or none.
Numbers in parenthesis denote number of injections (As or Bi), or number of inunctions (Hg.).
**S. T. S.: Serologic test serum.
C. S. F.: Spinal fluid examination.
X-ray: X-ray of heart and aorta.
Neuro.: Complete neurologic examination.
+: Positive. —: Negative. 0: Not done or unknown.

Annex Table VIII.

» Tertiary Syphilis Treated Specifically, According to Type and Amount of Treatment, Duration of Infection and Examinations for Syp

Outbreaks																		
Third						Fourth						Fifth						
nd of ent	Duration of Infection, in years	Examinations				Type and Amount of Treatment	Duration of Infection, in years	Examinations				Type and Amount of Treatment	Duration of Infection, in years	Examinations				T Ar Tr
		S. T. S.	C. S. F.	X-ray	Neuro.			S. T. S.	C. S. F.	X-ray	Neuro.			S. T. S.	C. S. F.	X-ray	Neuro.	
c.)	11	0	0	0	0													
n)	33	+	0	-	0													
c.)	4	0	0	0	0	Potassium Iodide.	5	0	0	0	0							
c.	12	0	0	0	0	Potassium Iodide.	14	0	0	0	0							
n))	20	0	0	0	0	Potassium Iodide.	21	0	0	0	0	0	22	-	0	0	0	
n	12	0	0	0	0	Potassium Iodide.	24	0	0	0	0	As (2)	26	+	0	0	0	
)	11	+-	-	0	0	Potassium Iodide.	21	0	0	0	0	As + Bi (20/20)	28	+	-	-	0	
n	4	0	0	0	0	Potassium Iodide.	5	0	0	0	0	Potassium Iodide.	7	0	0	0	0	H

n	2	0	0	0	0	Potassium Iodide.	6	0	0	0	0							
c.)	9	+	0	0	0	As (1)	10	0	0	0	0	Potassium Iodide.	11	-	0	0	0	/

aminations for Syphilis, by Sex.

			Sixth						Seventh					
aminations			Type and Amount of Treatment	Duration of Infection, in years	Examinations				Type and Amount of Treatment	Duration of Infection, in years	Examinations			
F.	X-ray	Neuro.			S. T. S.	C. S. F.	X-ray	Neuro.			S. T. S.	C. S. F.	X-ray	Neuro.
	0	0												
	0	0												
	-	0	0	41	+	-	–	0						
	0	0	Hg. inunc. (4)	21	+	0	0	0	As (2)	22	+	0	0	0
	0	0	As (3)	13	-	0	0	0						

Chapter I

INTRODUCTION

The addition of penicillin to modern syphilis therapy and the dramatic effects following its use combined with other accepted syphilis control measures have changed little the comprehensive definition of syphilis introduced by Stokes et al. (1944 — p. 1) as follows: «Syphilis is an infectious disease due to *Spirochaeta pallida;* of great chronicity; systemic from the outset, capable of involving practically every structure of the body in its course; distinguished by florid manifestations on the one hand and years of completely asymptomatic latency on the other; able to simulate a large proportion of the entities comprising the field of medicine, surgery and the specialties; transmissible to offspring in man; transmissible to certain laboratory animals; and treatable to the point of presumptive — but not, thus far, demonstrable — cure by the use of derivatives of arsenic, mercury, bismuth, the iodides and nonspecific or fever therapy. To this range and to this essentially Machiavellian facility in disguise, deceit and malevolence we owe an interest in syphilis among medical and scientific men everywhere which is all but unique and which is the mainspring of much of the progress already made against it.»

Despite the significant progress made against syphilis another statement by Stokes et al. (1944 — p. 1) is as true today as then, «No one who has had even a limited experience in answering the questions on which students and physicians seek information in their practical contacts with the disease, can fail to realize that the great ailment of modern syphilological practice is a lack of comprehension of the why and wherefore rather than the «what to do».»

One of the main reasons for this «lack of comprehension of the why and wherefore» is that the prognosis of *untreated* syphilis is not accurately known. Long term studies of patients treated in all stages of syphilis attest to the beneficial effects of treatment in modifying the biologic course of syphilis infection, but what happens to those who go untreated is unknown from a quantitative and comparative standpoint. Kampmeier (1943 — p. 215) expressed his opinion on this point as follows: «It would be of great value if the prognosis in untreated syphilis were accurately known. As was indicated in Chap. 2, this is not known, and probably never will be known in these days of more or less universal treatment of the disease. Figures indicating the prevalence of latency among hospital or clinic patients are misleading since they represent a selected group. The selection is such that the percentage of latent cases will be smaller than it should be. A greater number of cases of clinical syphilis will be represented in such groups than would be found in surveys of the population at large.» Moore, (1944 — p. 38) after having considered the problem of spontaneous «cure» of syphilis, states: «. . . The only way to solve the problem of spontaneous «cure» would be to study and to determine the ultimate outcome, clinical and serologic, of a large group of untreated patients with early syphilis after a period of many years . . .»

The most important reason why the basic question of prognosis in syphilis can not be answered authoritatively is the lack of large groups of untreated patients, thoroughly diagnosed and observed over sufficient periods of time. However, thanks to Professor Caesar Boeck,[1] Chief of the syphilis clinic at the University Hospital of Oslo, Norway, at the turn of the century, there does exist a large group of patients untreated for primary and secondary syphilis, which, if properly studied, may provide the much needed data on this subject.

Between 1891 and 1910 Boeck hospitalized approximately 2,000 patients with primary and secondary syphilis until lesions healed without treatment, believing that the patient's own defense mechanisms alone could better combat the disease than the antisyphilitic treatment of his day. Boeck's successor, E. Bruusgaard, who had also been Boeck's deputy during part of the period 1891—1910, attempted a follow-up of the above mentioned approximately 2,000 patients during 1925—27 (Bruusgaard 1929 a).

By means of personal examination and a search of clinic, hospital, and autopsy records Bruusgaard was able to get information on 309 living patients examined 3—40 years after infection, and on 164 of the original patients who had died. According to Bruusgaard's account: «The patients we called in for re-examination, from among the total material for the years 1891—1910, therefore included only those whose infection lay 15 to 40 years back. As to the rest of the patients we have information only in regard to those who later returned to the hospital voluntarily because of some symptom connected with the previous ailment, or who were admitted to the Municipal Hospital of Oslo

[1] On January 1st 1889 Caesar Boeck, M.D., (1845—1917), was appointed Chief of the Department of Dermatology & Venereology, University Hospital (Rikshospitalet), Oslo, Norway, and lecturer in Dermatology and Venereology, University of Oslo, Medical School. On November 2nd 1896 he was made full professor. He withdrew on July 1st 1915 and was succeeded by E. Bruusgaard, M.D., (1869—1934), whose successor, N. Danbolt, M.D., professor of Dermatology and Venereology, (1900—), is the present Chief of the department, appointed in 1936.

for various other specific or non-specific diseases. The patients who appeared for re-examination were subjected to a careful heart examination which included roentgenograms in two planes. A general neurological examination was also carried out on each of them. The cerebrospinal-fluid, however, was only examined in a very few cases. A Wassermann of the blood was made in the great majority of cases. Information on the paralytics and tabetics was obtained from hospitals and institutions for the insane.» In regard to the dead he states: «In addition to these patients examined during life, there are 164 dead, where the cause of death is known; 40 of these again had been autopsied».

Thus, information on 473 patients, or 21.7 per cent of the original material, was available in 1927 at the time the investigation was closed. Bruusgaard says in conclusion: «Our investigation gave on the whole the following results: 309 patients were examined 3 to 40 years after infection. In addition there were 164 dead, making a total of 473. Among these 131, or 27.7 per cent, were symptom-free — seronegative; 70, or 14.8 per cent, symptom-free — seropositive; 67 (counting living and dead), or 14.1 per cent, had heart and vessel disease; 13, or 2.76 per cent, general paresis; 6, or 1.27 per cent tabes dorsalis.» It must be emphasized here that this is the *only* numerical summing up found in Bruusgaard's paper, the summary itself (as shown later) containing no figures.

The detailed findings of Bruusgaard as disclosed in his paper (Bruusgaard 1929 a) are given in annex tables I, II, III, IV, V and VI (only tables considered important for the understanding of the subsequent discussions are presented). Tables I—IV show the clinical status of the living patients at final observation, 30—40 years, 20—30 years, 10—20 years, and 3—10 years after infection. Tables V and VI give the causes of death and age of those not living. Comparable death rates and per cent distributions were not calculated.

A careful study of Bruusgaard's report and the tables presented in support of his thesis reveals the following points essential for present interpretations:

1. There are no detailed descriptions of age distribution, year of admittance, occupation, previous treatment, length of stay in hospital or admitting agency.
2. There is no outline of the procedure used in tracing, the method of collecting clinical data, or the process of identification of the patients. These questions are touched upon only slightly in some of the discussions.
3. Whether any of the patients received specific treatment in the interim between discharge from Boeck's clinic and re-examination, is not mentioned by Bruusgaard.
4. It is noteworthy that the analysis is not done on a sex-specific basis although the tables present the data according to sex.

The following captioned paragraphs relate to the original tables shown in Annex I and by quotation and paraphrase express Bruusgaard's interpretation of the different complications of the untreated infection.

«Benign» Tertiary Syphilis of the Skin, Bones, and Mucosal Membranes. He does not deal with this question at any length, but about annex tables III and IV he remarks among other things: «*In the first place one sees here as in the preceding group, the increasing dominance of tertiary skin and bone affections as we come closer to the time of infection*».[1]

Cardiovascular Syphilis. «The patients in whom disease of the heart and aorta is determined beyond doubt, have as a rule long shown symptoms of the disease. These have not, however, caused the patients enough inconvenience to persuade them to seek medical help. They have also been able to do their daily work, though not as easily as before. These serious complications may, therefore, extend over a long period of time. This is also true of the fully developed disease.» Bruusgaard does not discuss the quality of the diagnoses of cardiovascular syphilis in the living patients, but goes on to elaborate on this problem as regards the dead. «The dominating role of heart and vessel diseases will be seen from table VIa (annex table V). Counting 6 cases of aortitis diagnosed through autopsy, but where this disease was not the cause of death, the total number of heart and vessel diseases is 46; of these 20 are in the group examined between 20 and 30 years after infection, and 11 in the group examined between 30 and 40 years after infection, a remarkable length of time. It must be assumed that most of these diseases were specific in nature; the cases of aneurysm and aortitis were certainly so, and it is probable that most of the cases in the groups paralysis of the heart, organic disease of the heart, apoplexy of the brain and arteriosclerosis also were specific. But — not all, those cases in which autopsy did not reveal any specific disease are of course omitted. As all autopsies were performed by professor Harbitz and Dr. Heiberg Hansteen, who have devoted special attention to these diseases, it is hardly likely that any case has been overlooked. Even if a few non-syphilitic cases should have been included here, the number is unlikely to be too high. On the contrary, it may be assumed that if a larger number of the deceased had been autopsied, it would have been still higher.»

Neurosyphilis. «General paresis occurred in 13 cases (2.76 per cent) and tabes dorsalis in 6 (1.27 per cent). Special importance may be attached to these figures: They are the result of a careful examination of medical records of the two large insane asylums of south and east Norway (Gaustad and Dikemark), of the dermatology and neurology section of the Municipal Hospital of Oslo, and the corresponding departments of the Rikshospital in Oslo, covering the

[1] Italicized by Bruusgaard.

years 1903 through 1927. As the great majority of paralytics are treated in hospitals for the insane and as our patients come from Oslo and the eastern part of Norway, we may assume that we have located most of them. Even if a few cases have been treated in other asylums or have died in foreign countries the number of paralytics compared with the total number of patients is very small. In the total of 2181 patients there are only 13 cases of paresis (0.60 per cent) and 6 cases of tabes dorsalis (0.27 per cent). With reference to tabes the situation is somewhat different as many abortive cases of this disease are not diagnosed. These patients frequently being able to work, do not see the doctor. Only the typical cases with pronounced symptoms go to the hospital. The above number of tabetics is therefore too small.»

Duration of Infection. Bruusgaard's comments on the various groups relative to duration of infection are scanty, but this observation is found in relation to annex table I «Patients examined 30—40 years after infection»: «One takes note of the comparatively large number of men; this indicates that the men have been easier to trace.» He gives the following account of the group examined 10—15 years after infection (see annex table III), «Those infected from 10 to 15 years ago and on whom we have information, are either patients who have visited the hospital because of some suspicious symptom, or who have been admitted to the Municipal Hospital of Oslo for various ailments, specific or non-specific. Many symptom-free patients have therefore been missed and thus this category is too small, but I could find no reason for dividing this group into two parts.» And in this same connection about annex table IV he writes: «These are patients who, because of suspect symptoms either came to the out-patient department or were admitted to the hospital. Mothers with congenital syphilitic children made up no small part of them. Thus the number of symptom-free cases is too small.»

Quality of Diagnoses at Death. This is somewhat difficult to evaluate. Although the autopsied group is discussed (as mentioned above under cardiovascular syphilis), it was not disclosed whether the diagnoses on the rest of the dead were based on death certificates alone, or on certificates plus clinical records.

These data have been summarized by Moore (1944), as shown in tables 1 and 2 following. Any discrepancies noted in these and the annex tables I—VI are due to differing interpretations of Bruusgaard's data.

Without sweeping quantitative statements Bruusgaard draws the following conclusions in his summary, which is given here in full, as follows: «If the natural course of syphilis is followed for many years, as we have been able to do with a comparatively large part of our material (regarding the men we have information on about 25 per cent of the total) — the results may be summarized as follows, *with the reservations the nature of the material*

Table 1.

The Outcome in Untreated Early Syphilis (Modified from Bruusgaard)

Of 2,181 patients with primary or secondary syphilis admitted to the Oslo Clinic 1891—1910, who received either no treatment, or only a little mercury or potassium iodide by mouth, author followed (1925—1927) 473, of whom 309 were living, and 164 dead.

Part I: 309 living patients*

Status of patient at time of final examination	Interval between infection and final examination			
	30—40 years	20—30 years	10—20 years	3—10 years
Neurosyphilis	8†	10	11	4
Cardiovascular syphilis	9†	10	1	—
Skin, mucosal, or bone syphilis	2	8	21	27
Symptom-free, seropositive	11	18	9	29
Symptom-free, seronegative	35	54	24	19
Total cases	64	100	66	79

* All cases had thorough physical examinations, with especial emphasis on heart and nervous system. Spinal puncture rarely employed. Later developments may therefore reduce the groups of symptom-free seropositive and seronegative patients.

† One duplication.

Part II: 164 dead patients (necropsy in 40)

Cause of death		Duration of infection				
		3—10 years	10—20 years	20—30 years	30—40 years	Total
Syphilis certain 19	Cardiovascular syphilis	—	3	8	3	14
	Neurosyphilis	—	—	3	2	5
Syphilis questionable 38	Probably cardiovascular syphilis	1	10	10	6	27
	Probably neurosyphilis	—	1	4	2	7
	Other forms of syphilis probable or certain	1	—	3	—	4
Other causes 107	Cancer, tumor	2	7	10	10	29
	Tuberculosis	4	17	7	1	29
	Other diseases	5	20	18	6	49

Reproduced from Moore, J. E.: «The Modern Treatment of Syphilis», 2nd ed. Charles C. Thomas, Springfield, Ill., 1944.
(Moore's table 5, p. 39).

necessitates.[1] It is a disease which is accompanied by severe complications as early as in its secondary stage. Eye and ear affections are here the most frequent and prognostically the most significant; they are often symptoms of a meningeal disease.

Far more important, however, are the late syphilitic diseases. First among these are affections of the heart and the blood vessels, which play a predominant part as well in regard to frequency as to cause of death. In comparison parenchymatous syphilis of the central nervous system (tabes, paresis) lies far behind. Even if we must assume that these are minimum figures, the total number of patients, living as well as dead, is so large, that we are justified in considering these two diseases as having occurred strikingly seldom in this material.

The investigations made in hospitals and insane asylums which have come into consideration as regards these patients also emphasize this. The cause or causes for this may be an open question, actually one does not know.

Neither do tertiary eruptions of the skin, mucous membranes and bones give particularly high figures when infection lies somewhat back in time. It is certain that in a considerable percentage of cases, the body itself commands defensive forces in sufficient strength not only to keep the infection in check, but to completely overcome it. Caesar Boeck held this theory and he placed great emphasis on it in understanding the varying course of the disease and its prognosis, and this has more than historical interest. It holds true even to this day when we possess such powerful specific drugs for treatment. The great importance of the body in finally overcoming the disease is again being emphasized, and not without reason. (Finger, Kyrle, Nonne, Buschke and Wagner-Jauregg.)[2]

This theory is the corner-stone for the practice now of treating syphilis with non-specific remedies for the purpose of increasing the body's resistance and thereby strengthening the action of the specific drugs. We see the practical results of this in Wagner-Jauregg's malaria therapy for paresis. It is still too early to determine its value as a preventive treatment in cases where the central nervous system is threatened, but in this field too the results so far are very encouraging and promising.»

This, then, is the well-known and widely quoted Boeck-Bruusgaard material, which, as far as we know, constitutes the only such material of its kind in the world. It is not surprising therefore, that the results have formed the basis for prognostic statements concerning both untreated and treated syphilis for more than 20 years. Bruusgaard himself warned that acceptance of the data should be made «with the reservations the nature of the material necessitates». In spite

[1] Italicized by the present author.

[2] Authors referred to by Bruusgaard.

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Table 2.

Summary of Bruusgaard's Data as to Ultimate Outcome of Untreated Early Syphilis

Patients showing at re-examination or death	Per cent of total number (473 patients)
Neurosyphilis	9.5
Cardiovascular syphilis	12.8
Benign late syphilis	12.2
Latent syphilis (no clinical evidence, blood serologic test positive)	14.1
Spontaneous «cure» (no clinical evidence, blood serologic test negative)	27.9
Died of syphilis other than cardiovascular or central nervous system	0.8
Died of some other cause (cancer, tuberculosis, scattering)	22.6

Reproduced from Moore, J. E.: «The Modern Treatment of Syphilis», 2nd ed. Charles C. Thomas, Springfield, Ill., 1944.
(Moore's table 6, p. 40).

of this warning, quantitative estimates of the outcome of untreated syphilis based on these data have passed from textbook to textbook and from one scientific paper to the other, and have taken on a significance unwarranted by the nature of the data themselves. Despite their own admonitions as to interpretation, authors of papers on prognosis as well as authors of leading textbooks have sponsored these data as the most significant material we have on the prognosis of untreated syphilis. Some examples of their opinions follow:

1. From Moore, J. E., The Modern Treatment of Syphilis, (1944), p. 41: «Taking the data at their face value, they indicate that of every 100 patients acquiring syphilis, 23 will develop a late lesion which will incapacitate or kill; 12 will develop a more benign late manifestation; and 64 will probably pass through life unharmed, so far as they themselves are concerned . . .»
2. Stokes, J. H., Modern Clinical Syphilology, (1944), p. 180: «. . . One-third of untreated early syphilitics will develop a benign or dangerous late lesion, but two-thirds will pass through life unharmed».
3. Kampmeier, R. H., Essentials of Syphilology, (1943), p. 216: «In spite of these observations[1] it seems probable that Bruusgaard's findings will be the only ones ever available to give at least an approximate idea of what may be expected in untreated syphilis . . .».
4. Thomas, Evan W., Syphilis: Its Course and Management, (1949), p. 18: «The nearest approach to a scientific experiment based on the observation

[1] Refers to precautions in interpretation.

of a large group of individuals diagnosed as being syphilitic but deliberately left untreated is that reported by Bruusgaard . . . Nevertheless, the figures given by Bruusgaard confirm the impression given above — that from 60 to 70 per cent of untreated syphilitics never develop late manifestations of the disease.»

5. Willcox, R. R., A Textbook of Venereal Diseases, (1950), p. 108: «About a quarter of the cases burn themselves out and achieve apparent spontaneous cure; approximately an equal number show no signs, but the serological tests remain persistently positive and, though post-mortems may often reveal microscopical evidence of syphilis, these patients die from some other more respectable cause.»
6. Sequiera, J. E., The Modern Treatment of Syphilis; Its Communal and Individual Aspects, (1931), p. 212: «Bruusgaard's observations suggest that the outlook of a patient who has had no specific treatment may be actually better than that of one who has been through the orthodox course».
7. Morgan, H. J., The Prognosis of Syphilis, (1939), p. 311: «When acute syphilis is untreated about 25 per cent of the patients will eventually attain a state in which no clinical evidence of the disease is manifest («spontaneous cure»), about 25 per cent will die of other cause than syphilis, about 15 per cent will have serologic (blood serum) evidence of syphilis but will remain otherwise free of sign or symptom, about 12 per cent will experience syphilis of skin, mucous membrane or bone, approximately the same percentage will have cardiovascular syphilis and a slightly smaller percentage will have neurosyphilis. In summary, somewhat less than 25 per cent will eventually die or become incapacitated by syphilis, about 12 per cent will have relatively benign active syphilis and the remainder will experience no personal menace to health from the disease . . .»

Other uses of these data are numerous and include:

a) comparisons of treated and untreated syphilis,
b) Broch's (1947) estimates of the total early syphilis reservoir from which patients with late syphilis were originally drawn,
c) the comparison made in Rosahn's autopsy study (see page 33).

Some authors have gone a bit farther and have directed attention to the size of Bruusgaard's sample (21.7 per cent of the total) and have tried to demonstrate the extent of selection that has taken place. This is not an unreasonable approach in view of the fact that the «Unknown» group comprises 78.3 per cent of the original 2,181 patients observed by Boeck. The most persistent voice urging caution has been that of Harrison, (1931), (1940), (1941), who has stated emphatically that there were very serious limitations to Bruusgaard's findings.

Table 3.

Distribution of Original Cases by Sex and Investigated Cases by Sex and Duration of Infection

	Total		Male		Female	
	No.	%	No.	%	No.	%
Original cases (by Boeck)	2181	100.0	793	36.4	1388	63.6
Investigated cases (by Bruusgaard)	473	100.0	213	45.0	260	55.0
Cases found living	309	100.0	122	39.5	187	60.5
3 to 10 yr. after infection	79	100.0	14	17.7	65	82.3
10 to 20 yr. after infection	66	100.0	23	34.9	43	65.1
20 to 30 yr. after infection	100	100.0	46	46.0	54	54.0
30 to 40 yr. after infection	64	100.0	39	60.9	25	39.1
Cases found dead	164	100.0	91	55.5	73	44.5

Reproduced from Sowder, W. T.: An Interpretation of Bruusgaard's Paper on the Fate of Untreated Syphilitics, Am. J. Syph., Gonor. & Ven. Dis., 24: 684, 1940.
(Sowder's table II).

Sowder, (1940), has also called attention to possible selection, and summarized his views in this manner, «A study of Bruusgaard's article on the outcome of untreated syphilis indicates that more selection took place in the cases followed than is commonly supposed, and that the direction of this selection has been to exaggerate the seriousness of the disease rather than to minimize it». It is obvious that the very limited description of the original material, and the lack of detailed information on the epidemiologic methods used for tracing, collection of clinical data, and identification of the patients make it difficult to show accurately just how selection may have taken place. Nevertheless some possibilities of bias do exist, and it is on the basis of these that Bruusgaard's critics have re-interpreted his results.

Sowder maintained that selection exists in regard to sex, neurosyphilitics, cardiovascular involvement, and the living and dead. He supported his claims with the following considerations:

Selection According to Sex. The sex distribution of the sample is different from that of the original material, as shown in table 3 taken from Sowder's article.

Thus, of the 2,181 patients, 1,388 (63.6 per cent) were females, and 793 (36.4 per cent) were males; in the investigated cases the sex distribution turned out to be: 260 (55 per cent) females, and 213 (45 per cent) males. On turning to the various sub-groups arranged according to duration of infection, Sowder points out that there are marked departures from the original proportion of males and females, females comprising 82 per cent in the 3—10-year group, and only 39.1 per cent in the 30—40-year group. He also points to the relatively low proportion of females among the dead, namely 44.5 per cent. He believes that this fact tends to increase the percentage of complications in the predominantly male groups, because males are more prone to develop complications than females. He adds that this factor could have been adjusted by making all comparisons on a sex-specific basis.

Selection of Neurosyphilis.

Here Sowder declares, «Another selective factor of great importance is the search that was made by Bruusgaard of all the insane asylums in that part of Norway for neurosyphilitics.» and he goes on to quote Bruusgaard's own statement on neurosyphilis (given on p. 8 in this paper). Sowder continues: «. . . This statement by Bruusgaard indicates that the percentage occurrence of neurosyphilis should be based on the original 2,181 cases rather than on the 473 cases followed. Furthermore, Bruusgaard includes in his tables, without much amplification, 6 cases of psychosis. These conditions may or may not have been due to syphilis, but in classifying them separately from paresis, tabes, and cerebrospinal syphilis, Bruusgaard evidently registered his belief that they were not due to syphilis. At least one is definitely called paranoid dementia. A consideration of these factors reduces the number of neurosyphilitics to 30 of the original 2,181 cases, or 1.4 per cent. This percentage, of course, is a minimum figure and too low, but it probably approaches the true percentage among Bruusgaard's cases more closely than a figure based on the 473 followed cases . . .» Table 4, also from Sowder, shows these proportions.

By stating that he had found the majority of cases with tabes and paresis Bruusgaard has invited Sowder to draw this conclusion. However, the very low percentages obtained by using the original number of patients (2,181) as the denominator rather than Bruusgaard's followed group (473), strongly indicate that Sowder's assumption must be wrong, and that the use of the smaller number as originally used by Bruusgaard as a denominator, is more correct. Furthermore, due to the migrant nature of young unmarried persons with early syphilis, it seems very probable that a considerable number of the original group might have left Oslo in the interim, making it more reasonable to assume that the 473 patients (with and without complications), followed-up by Bruusgaard, have been residents of the City of Oslo, and that 473 rather than 2,181 should be used as a denominator.

Selection of Persons with Cardiovascular Disease.

Sowder gives his opinion on this point as follows, «There were 69 cases of cardiovascular disease, including cerebral apoplexy and arteriosclerosis, among

Table 4.

Cases of Possible Clinical Neurosyphilis With Percentage Based on 473 Investigated Cases and 2,181 Original Cases

	No.	Percentage	
		Based on 473 Investigated Cases	Based on 2,181 Original Cases
Total	36	7.6	1.7
Total with neurosyphilis	30	6.3	1.4
General paresis	13	2.7	0.6
Tabes dorsalis	6	1.3	0.3
Cerebrospinal syphilis	11	2.3	0.5
Psychosis	6	1.3	0.3

Reproduced from Sowder, W. T.: An Interpretation of Bruusgaard's Paper on the Fate of Untreated Syphilitics, Am. J. Syph., Gonor. & Ven. Dis., 24: 684, 1940.
(Sowder's table III).

the 473 patients followed; 48 of these were among the 164 dead. In 42 of these cases cardiovascular disease was given as the cause of death. In some of these patients syphilis was definitely the etiologic agent, but in the majority of cases it was merely assumed that, since the patients had had syphilis, this was the cause of death. There is no reason to suppose, however, that a syphilitic person, even when untreated, may not have nonsyphilitic cardiovascular disease, a very common condition in all persons. Official Norwegian figures show that during the period covered by Bruusgaard's paper 1 death out of 6 (16 per cent) in persons between the ages of 20 and 70 years in the general population was due to diseases of the heart or blood vessels. Of course, some of these were undoubtedly due to syphilis, but even in the United States where the disease is supposed to be more prevalent than in Norway the usual estimate is that about 10 per cent of all deaths from cardiovascular disease are due to syphilis. Since among Bruusgaard's dead 1 out of 4 deaths (26 per cent) was due to cardiovascular disease, it would seem more reasonable, in the absence of better evidence, to ascribe only those deaths in excess of 16 per cent to syphilis. This would certainly be more logical than to credit all the cardiovascular deaths to syphilis. This consideration along with the selective factors previously mentioned leads us to believe that the 14 per cent given by Bruusgaard is too high for the occurrence of detectable syphilitic cardiovascular disease in untreated syphilis. At least this percentage is not substantiated by a study of the material which he presents.»

This opinion seems valid enough as far as it goes but it must be kept in mind that Bruusgaard may have found among the living *too few* cases of cardiovascular syphilis. This does not seem too improbable considering the relatively great number of living patients examined after rather short periods of 3 to 10 years or 10 to 20 years after infection (i.e. 145 out of 309 patients, or 46.9 per cent). Thus, considering these possibilities of bias, too many cases of cardiovascular syphilis among the dead and too few among the living, it is difficult to determine to what extent they balance each other and therefore whether the 14 per cent may be too high or too low.

Selection among Living and Dead.

Sowder comments on this possible bias in the following way, «Another factor that would materially alter the results is the inclusion in the group followed of an undue proportion of the original patients who had died, for it is evident that among the dead as a group would be found a higher percentage of serious syphilitic lesions than would be found among the living. By computations based on Bruusgaard's figures it seems clear that his followed group included a greater proportion of dead than would be expected in a random sample of the original patients.» In Table 5 «. . . are shown the number and percentage of the dead among those followed. It might be expected that the death rate from syphilis would be higher among persons who had had the disease for ten to twenty years than among those who had survived with the infection for longer periods. But it will be noted under the column of those dead from causes other than syphilis that there is a considerably larger proportion of persons who died from causes other than syphilis in the ten-to-thirty-year group, than in the thirty-to-forty-year group, which is just the converse of what would normally be expected. Moreover, if it is assumed that the average age of acquiring syphilis in Bruusgaard's original group was twenty-five years, then the expected number of deaths among the followed group, computed on a person-year experience using the age specific mortality rates, is 88, or only about one-half the actual number of deaths (164). The evidence strongly suggests, therefore, that Bruusgaard's figures were unduly weighted with those persons among his original group who had died up to the time the analysis was made.»

The first point made by Sowder in this connection seems very well taken. However, the comparison he makes between the observed and the expected number of deaths computed on the basis of the age-specific mortality rates of the whole United States,[1] may tend to yield misleading results, inasmuch as the difference is apt to become too great. The reason is that syphilitics taken as a group generally are members of lower socio-economic classes and consequently, in addition to syphilis have higher general morbidity from a

[1] As the rates for Norway were not available at the time, the U.S. rates, which were slightly higher for the years in question, were used.

Table 5.

Number and Percentage of Investigated Patients Who Died From All Causes and From Causes Other Than Syphilis According to Duration of Infection

Duration of Infection	All Investigated Cases Living and Dead		Dead All Causes		Dead from Causes other than Syphilis	
	No.	%	No.	%	No.	%
Total	473	100	164	34.7	115	24.3
3 to 10 yr.	92	100	13	14.1	11	12.0
10 to 20 yr.	124	100	58	46.8	45	36.3
20 to 30 yr.	163	100	63	38.7	42	25.8
30 to 40 yr.	94	100	30	31.9	17	18.1

Reproduced from Sowder, W. T.: An Interpretation of Bruusgaard's Paper on the Fate of Untreated Syphilitics, Am. J. Syph., Gonor. & Ven. Dis., 24: 684, 1940.
(Sowder's table IV).

variety of conditions and will show higher mortality rates from all causes than would be expected in the population at large. This fact may, at least in part, account for the very marked difference found by Sowder (164 observed deaths as contrasted with 88 expected deaths), and Bruusgaard's figures may not have been as weighted with those persons who had died as Sowder's comparison indicates.

Sowder also points to possible selection as to time of infection and mentions especially the three-to-ten-year group, but it is evident that Bruusgaard himself was fully aware of the possible bias introduced by this group since he suggested that it be left out. Bruusgaard writes: «Leaving out the group examined three to ten years after the infection, the total number of patients followed-up is 230, or, including the 143 dead, a total of 373 patients. This only changes the different groups slightly; the total picture remains unchanged.» It is noteworthy none the less that if this group were omitted, however justified it might be, the final follow-up would comprise only 17 per cent of the total, something which naturally would add to the suspicion voiced by so many investigators, that Bruusgaard's sample hardly can have been representative.

In justifying his critical stand (see above) on the Bruusgaard figures Harrison has occupied himself with the question of the use of the Bruusgaard material in the determination of the prognosis of syphilis in three publications (1931, 1940 and 1941). In the last one (a review of Sowder's paper) Harrison refers to Sowder's discussion of the possibilities of selection and comments specifically on the statement by Sowder that the Bruusgaard sample presents a gloomier picture than would be given by follow-up of the whole 2,181 patients. As a comment on this Harrison says: «This may have been the case with regard to other late effects but, for reasons given above, the percentage of cases of G.P.I. given by Bruusgaard was probably much too low.» In support of this conclusion Harrison, using as did Sowder the 2,181 patients as a denominator, presents the following argument (taken from his 1931 review of Bruusgaard's paper): «. . . Thus, there were 8 cases of G.P.I. in an original material of 1,388 females and 5 males in an original of 798, making percentage incidences of 0.57 and 0.63 respectively. If the figures are correct some revision of existing notions of the differing incidence of G.P.I. in syphilitics of the two sexes seems necessary because it is commonly believed that the incidence of G.P.I. in syphilitic females is much lower than in syphilitic males. One would be inclined to think that this be the case in Norway also, as the official records show the following numbers of deaths from G.P.I. in that country from 1914 to 1928: Males: 472, Females: 105. Analysed by five-year periods the figures are: 1914—1918: M: 169, F: 48, 1919—1923: M: 182, F: 29, 1924—1928: M: 121, F: 28. Incidentally, the proportion of males to females was rather similar to that in England and Wales from 1914 to 1928, where it was as 4.5 to 1. The low ratio of females to males might be due to a low ratio of female infections to male, but with regard to cases of acquired syphilis reported to the authorities, the figures given by Haustein in Jadassohns Handbuch d. Haut & Geschlechts-krankheiten v. 22, 491, for the 25 years 1900 to 1924 show in Oslo a ratio of 2.3 males to 1 female. When one considers that a lower proportion of the actual syphilis in females comes to light than in males, in other words, that this ratio of 2.3 males to 1 female is very probably higher than it would be if every case were detected and reported, it is difficult to escape the conclusion that the incidence of G.P.I. in female syphilitics is considerably less than in males, so that Bruusgaard's ratio of 0.57 G.P.I. in his female syphilitics to 0.63 per cent in his male (which compares with the ratio of 1 to 4.6 in the Norwegian figures of mortality from G.P.I.) means that at least an important number of his male G.P.I. cases must have escaped his search. Further, one would have expected it to be much more difficult to trace females than males, and this difficulty is expressed by Bruusgaard as a reason for the fact that in the living cases he was able to report on the later histories of a larger proportion of his males than of his females. If this applies also to the identification of G.P.I. cases, it follows that some of the females in this category also must have been missed . . .»

Harrison continues with a very interesting explanation for the lack of follow-up in Bruusgaard's material. «. . . In this connection it may be significant that according to figures kindly obtained from the Bureau of Immigration, U.S.A., by Dr. Vonderlehr, U.S. Public Health Service, the number of Norwegian immigrants to the U.S.A. in the years 1881 to 1910 was 285,520 and in the years 1911 to 1920 it was 66,395. Dr. Vonderlehr calculates that 50 per cent of these immigrants would be in the age period 21 to 30, and at least 80 per cent between 16 and 35. The population of Norway in the year 1900 was 2,242,995.»

Harrison again (1940) mentions Bruusgaard's work and bases his critisism chiefly on the same evidence as quoted from his review of 1931. He adds among other things: «Another point of interest in Bruusgaard's statistics relates to the number of cases found in later years to have no sign whatever of syphilis. The numbers were 132 living patients with no sign and negative Wassermann reactions and 14 dead of cancer or of tuberculosis more than 20 years after infection in whom autopsy revealed no sign of syphilis. These figures have been quoted as evidence of spontaneous recovery from syphilis, but they would have carried more weight if the original diagnosis had been supported by laboratory tests. Most of these cases were dealt with first in Boeck's clinic before the advent of laboratory aids, and we know how often in that era the very elect were mistaken. I do not say that the 132 and the 14 did not suffer from syphilis but that in most of them the infections were non-proven according to modern standards of diagnosis.[1] *For the reasons which I have given I do not propose to make any use of Bruusgaard's figures.*»[2]

Harrison undoubtedly is right in his belief that the very small difference in the incidence of G.P.I. between the two sexes strongly indicates some bias in Bruusgaard's material. If we make use of the followed 473 cases as a denominator instead of the total material of 2,181 cases — which in the present author's opinion is more reasonable — the following results are obtained: females: 8 out of 260 followed, or 3.1 per cent, and males: 5 out of 213, or 2.3 per cent. These figures even more strongly suggest selection. There is no reason to believe that the incidence of G.P.I. in the two sexes should be any different from that which is the general experience, particularly when taking into consideration that the majority of these patients are hospitalized.

It is possible that the opinion of many syphilologists in various parts of the world was expressed by Sowder (1940) as follows: «It is to be regretted that the death of Bruusgaard (he died in 1934) cut short his studies of the course of untreated syphilis, but it is sincerely to be hoped that his successors will find it possible to continue the follow-up study of the 2,181 patients with early syphilis seen originally in Boeck's clinic. Probably nowhere else in the world is there a similar group of carefully studied patients who received no antisyphilitic treatment during the early stages of the disease. The extraordinary difficulty in studying the course of syphilis, due to its chronicity, is emphasized by the fact that the study of a single group of patients has already consumed the lifetimes of two men, Boeck and Bruusgaard. Many of these persons are probably still alive, offering a mine of information to anyone who continues to study them.»

[1] This question will be discussed in a later section.

[2] Italicized by the present author.

Chapter II

OTHER INVESTIGATIONS ON THE OUTCOME OF UNTREATED SYPHILIS

Since the beginning of modern treatment for syphilis any series of untreated syphilitics is for the most part self-selected either because of no knowledge of syphilis infection on the part of patients, or because of recalcitrance in following medical advice. In so far as this author has been able to ascertain from a careful search of the literature, there have been reported only two groups of syphilitics deliberately denied specific treatment and these for two totally different reasons: a) the Boeck group, untreated because of deep scientific conviction as to effects of treatment; and b) the «Alabama» group left untreated for investigative purposes in comparing the effects on health and longevity of an untreated syphilitic population with one non-infected (Vonderlehr et al., 1936; Heller and Bruyere, 1946; Deibert and Bruyere, 1946; and Pesare et al., 1950).

These facts indicate three methods or techniques by which information on the outcome of untreated syphilis may be obtained:

1. From anamnestic data obtained from patients seen for the first time in late stages of syphilis. Many contributions to the literature present such groups of patients and attempt to draw sweeping conclusions as to effects of various amounts of treatment or of no treatment.
2. From a specific group of untreated patients studied in retrospect such as the Bruusgaard study and the present one.
3. From a retrospective plus a prospective «no treatment» study such as the «Alabama» series.

To these may be added a fourth technique, that used by Rosahn (1947) in his very interesting «Autopsy Studies in Syphilis».

Each of these four techniques is fraught with sources of potential bias and these should be carefully considered in making statements about the prognosis of untreated syphilis. The shortcomings of the first technique, which incidentally is more frequently used than any of the others, are quite apparent. These patients are highly selected and the groups studied rarely include patients whose courses were so benign as to require no medical attention. Bias is likely to be in the direction of unfavorable outcome. The second technique and its sources of error is the subject of this monograph. The third («Alabama») and fourth (Rosahn) deserve further discussion at this point.

The study, under the auspices of the United States Public Health Service started in 1932, is being conducted currently in a Southern State of the U.S.A., (Alabama). The «Alabama» material originally described by Vonderlehr et al. (1936) consisted of 399 syphilitic Negro males 25 years of age or older who had been left untreated, and 201 presumably non-syphilitic Negro males serving as controls, these being selected so as to make the persons in each age-group comparable. The material was culled from a serologic survey of 1,782 male Negroes in a rural county in Alabama. The 399 syphilitic patients were chosen from the 472 persons who had a second positive serologic test. The 201 non-syphilitic controls were chosen from the 1,782 found to be serologically negative, and in so far as possible the choice was made on a comparable and non-selective basis.

Deibert et al. (1946) write about the objectives of the investigation: «... Briefly, the study is a continuing attempt to follow the natural history of syphilis, uninfluenced by treatment, in adult male Negroes, with special attention to its effect on the cardiovascular system». This special attention to the cardiovascular system was due to a finding in the first study that the cardiovascular system was most commonly involved in these patients.

The first paper (Vonderlehr et al., 1936) deals in the main with a variety of morbidity rates in the untreated presumably latent syphilitics as compared with those in the non-syphilitic controls. In the former group the proportion with evidence of morbid processes of all types was 84 per cent as compared with 39 per cent in the latter. Furthermore, 46.6 per cent of the syphilitics showed evidence of circulatory disease, whereas only 23.9 per cent of the non-syphilitic group were so affected. It is particularly striking that of 174 syphilitic individuals under the age of 40, 25.3 per cent had definite manifestations of cardiovascular disease, as compared with 5.7 per cent of 87 individuals in the same age-group among the controls. The difference is considerable although not so pronounced in individuals over 40, showing 63 per cent with cardiovascular disease among 225 untreated syphilitics against 37.7 per cent of 114 controls. It must be emphasized that the authors are not referring to cardiovascular syphilis in particular, but to cardiovascular disease in general. On the basis of these data they concluded that syphilis in the age-period under 40 tends to greatly increase the frequency of cardiovascular disease. Information as to type of cardiovascular disease or the frequency of cardiovascular syphilis itself is not given.

As to central nervous system syphilis the results were as follows: Of the 399 untreated syphilitics 7.8 per cent had definite evidence of central nervous system syphilis, and an additional 18.3 per cent showed asymptomatic neurosyphilis. Of these 7.8 per cent 3 per cent showed a relatively benign parenchymatous type, whereas the remaining 4.8 per cent had all other forms of central nervous system involvement. It is very interesting to note that no typical cases of general paresis or tabes dorsalis were found. Nine per cent had syphilis of the bones and joints; less than 1 per cent syphilis of the skin; and 2 per cent a combination of syphilis of the skin and bones.

The second paper (Heller et al., 1946) deals with a comparison of the mortality of the untreated syphilitics with that of the controls, and the most important findings were that the excess mortality among the syphilitics was about 75 per cent as compared with the controls, and that the life expectancy was about 20 per cent less. This study is limited to a 12-year period, and up to the end of 1944, 101, or 24.6 per cent, out of an original group of 410 syphilitics had died, as contrasted with only 28, or 13.9 per cent, of the 201 controls. Out of the 129 who had died, 93 cases were examined post mortem.

About the third paper (Deibert et al., 1946) the authors say: «Paralleling the first paper in the series, the purpose of the present analysis is to determine whether or not there are indications that syphilis constitutes a predisposing factor to disease regardless of whether the observed pathologic condition can be directly attributed to syphilis . . .» The details of this study will not be discussed here, but in general the findings support those of the 1936 study. The authors in summarizing emphasize these results, «The above findings viewed as a whole lead to the conclusion that an untreated syphilitic population exhibits appreciably more morbidity than an uninfected population of similar characteristics and environment.»

In sharp contrast to the usual run of such follow-up studies, these investigators maintained control over the types of examinations to be employed from time to time, rather than struggle with a great variety of methods used by others over whom they had no jurisdiction. Unfortunately, even under more or less ideal circumstances uniformity of methods was not possible to obtain, and in the third paper the authors stress the fact that «. . . no direct comparison of the two sets of findings is possible either on a case-by-case basis or through analysis of the material as a whole . . .» The following facts are mentioned as tending to invalidate comparisons:

1. «. . . In the first place, different clinicians carried out the two sets of examinations . . . The observations requiring a graded but not actually measured recording are not reported in the same manner by different individuals; and in addition, even where quantitative measurements are involved, the clinicians responsible for the respective examinations, because of their particular training and interests, made their measurements in slightly different fashions.»

2. »Furthermore, the emphasis of the second examination was intentionally somewhat different from that of the first. Because of the significant cardiovascular findings in the first examination, the well-known high incidence of cardiovascular syphilis in the Negro race and the controversial questions involved in the diagnosis of early uncomplicated syphilitic aortitis, the second examination placed relatively far more emphasis on the examination of the circulatory system than was true of the first examination . . .»

It is evident that the investigators in both the first and the second examinations and in the analysis of the results constantly had in mind the fact that high incidence of cardiovascular syphilis among Negro syphilitics was to be expected. This in itself undoubtedly can introduce a certain unconscious bias. Because of the uncertainty connected with the early diagnosis of cardiovascular disease, and in particular cardiovascular syphilis (especially as regards the x-ray findings), it is conceivable that a good many borderline cases will be encountered, and that bias might very well operate in the direction of classifying some of these as «definite cardiovascular disease».

The third examination (Pesare et al., 1950) confirmed the findings of the previous one that cardiovascular *disease* was more common among syphilitics than non-syphilitics, still not classifying according to etiology. Definite conclusions, therefore, should await the results of the analysis of the autopsies. Judging from the number of autopsies up to the end of 1944, the autopsy rate is going to be very high, and thus will give a much better basis for conclusions than do the clinical examinations. Despite the infrequent occurrence of general paresis among syphilitic Negroes, it is strange that not one single case of paresis or tabes dorsalis has been found in this series. The question arises as to whether preoccupation with cardiovascular disease has biased these findings in another direction.

Another problem deserving consideration is the establishment of the control group. When picking out the syphilitic part of a certain population group, is it not possible that we are making a selection which involves other factors than the syphilitic infection itself? Why is it that the seronegative have avoided being infected with syphilis? Furthermore, is it not possible that the selection of 201 individuals out of more than 1,200 seronegative individuals might have introduced some unrealized bias? The possibility that the syphilitics are different from the controls in other respects must be very seriously considered in view of the findings made hitherto, which are indeed surprising, especially as regards the very high excess morbidity rates of cardiovascular disease under the age of 40, but also in view of the all-over results, showing that the syphilitic can expect to experience more manifestations of ill health of all kinds than do the uninfected. True enough, the present author has not been able to point to any specific selection in connection with the establishment of the controls in the «Alabama Study», neither by reading the papers nor by talking over the problems with the public health nurse and others who have been with the study group of the United States Public Health Service ever since the investigation was started back in 1932. (The author made a visit to Alabama in 1951 and had an opportunity to discuss the various questions with the investigators then preparing the next follow-up of the patients.) However, syphilitics as a group frequently represent individuals who in many respects differ from the so-called normal population, and in our opinion it is necessary to produce convincing sociologic and other evidence of similarity between the syphilitics and the controls after the fact has been established that one group is seronegative and the other seropositive for syphilis.

Another important point is that the «Alabama Study» comprises males only. If a similar study had been made involving females, we would have had an opportunity to study the results on a sex-specific basis. Knowing that syphilis is prone to give more serious complications in males than in females it would have been interesting to note whether females would have given the same excess morbidity rates compared with controls as apparently males did. Such a comparison might probably have furnished valuable information as to the validity of the findings in the present material.

The duration of the syphilitic infection is not given and evidently reliable information on this point is not available. This is an essential drawback because it excludes the possibility of studying the important question of time relationship in untreated syphilis through this investigation. There is little doubt that the «Alabama Study» is the best controlled experiment ever undertaken in this particular field, and the difficulties encountered only emphasize once more how complicated the problems are when it comes to gathering information on the prognosis of untreated syphilis.

Even more difficulties in interpretation are encountered in studies of autopsied *hospital* populations such as the one made by Rosahn (1947). About these investigations Rosahn writes (p. 54): «... The present report utilizes a third[1] technic, heretofore not employed. All cases with historical, laboratory, or morphologic evidence of syphilis were selected from a large autopsy series, which has been described in previous chapters. The clinical record of each of these patients was reviewed and classified according to the kinds and amounts of therapy. The group of syphilitic patients for whom no evidence of therapy could be found is described in the present communication. This, then, is a retrospective study, and similar in this regard to the work of Bruusgaard. However, since the group was culled originally from an autopsy population, each individual in it was studied by post-mortem examination.»

[1] Fourth according to our discussion above.

Three fundamental epidemiologic features characterize Rosahn's series:

1. the patients belong to a hospital population,
2. they represent that part of it who died in the hospital,
3. and finally they are confined to that part of the dead on whom autopsies were performed.

The post-mortem rate during the period chosen by Rosahn for study is 48 per cent (4,371 post-mortems on 9,162 deaths of both sexes).

It is generally accepted that a hospital population is not representative of the population from which it is drawn, and similarly it is questionable whether an autopsy population is representative of the hospital population. It is highly probable, therefore, that selection may have taken place in such a way that an excess of patients with serious ailments have been included, for non-syphilitic as well as for syphilitic diseases. Therefore, when the patients are culled from a hospital population the number of healthy patients, who completely have overcome their syphilitic infection, with negative or positive serologic tests, is apt to become too low.

The sex distribution in Rosahn's material is also of considerable interest in this connection. He found a total of 198 untreated syphilitics, of whom 129, or 65.2 per cent, are males, and 69, or 34.8 per cent, are females. The analysis of the results was not made on a sex-specific basis, and in a material where males comprise about two-thirds of the patients, the number of serious complications will tend to become too high because males, as is well known, are more prone to develop late syphilitic lesions than females.

In one other respect this material is biased, as pointed out by Rosahn himself. He writes (p. 57): «. . . The New Haven Hospital, a general hospital for acute diseases does not make a practice of admitting the deteriorated patient with central nervous system syphilis. These patients ultimately reach the various State hospitals, and to this extent our material is biased.» In other words, patients with general paresis are not included in Rosahn's material, and here the selection works in the opposite direction: the number of serious lesions tending to become too small. How much weight should be given to the specific factors of selection is practically impossible to decide, but because the number of paretics developing in any group of syphilitics is comparatively small, it is still probable that selection in this material is in the direction of too many cases with serious syphilitic complications.

Rosahn's final results are presented in table 6. It will be seen that in 23.2 per cent of the cases syphilis was the primary cause of death, whereas another 15.7 per cent showed syphilitic lesions but with death occurring from some other disease process, and in 61.1 per cent no anatomic lesions were present. A little more than two out of ten syphilitics died as a result of syphilis, while as

Table 6.

End results in 198 untreated syphilitic patients.

End result	Number		Per cent	
Anatomic lesions present	77		38.9	
Primary cause of death		46		23.2
Subsidiary findings		31		15.7
Anatomic lesions absent	121		61.1	
STS positive		80		40.4
STS negative		35		17.7
STS doubtful or not known		6		3.0
Total	198	198	100.0	100.0

Reproduced from Rosahn, P. D.: Autopsy Studies in Syphilis, Ven. Dis. Inform., Suppl. 21, Wash., D. C., 1947.
(Rosahn's table 40).

many as six out of ten died with no evidence of syphilis at all, and a little less than two out of ten died of unrelated causes but with syphilitic lesions present. The fact that 61 per cent of the syphilitics in Rosahn's material showed no anatomic lesions at autopsy undoubtedly in itself is a very important finding, and it is the more striking if we take into consideration the possibilities for selection, which, as pointed out above, tend to give a greater number of serious lesions than would ordinarily be expected.

Table 7 gives another example of the use made of the Bruusgaard data. Rosahn compares his own results and those of Bruusgaard, showing a remarkable similarity when it comes to number of patients with syphilitic lesions in the two series, namely 35.1 per cent in Bruusgaard's and 38.9 per cent in Rosahn's. Rosahn, as already mentioned, fully realizes the fact that his series comprises no deteriorated patients with central nervous system syphilis (in the main presumably thinking of paretics), in contrast to that of Bruusgaard, in which the paretics are included. After having discussed this factor, he says in conclusion (p. 57): «We have no method of evaluating the influence of this sampling error on our end results, but the general agreement between our findings and those of Bruusgaard suggests that it is not excessive».

A comparison between the ratio of positive and negative serologic results, as also pointed out by Rosahn, is not too valuable, the reason being that an evaluation of the serologic tests used in the two investigations is practically impossible, because of different techniques and the large number of patients in Bruusgaard's material where the serologic tests for syphilis are not known. Otherwise, one would expect to find a considerably higher percentage syphilitic

Table 7.
Summated comparison of end results of untreated syphilis in Bruusgaard's and the Yale series

	Bruusgaard		Yale	
	Number	Percent	Number	Percent
Organic syphilitic disease	166	35.1	77	38.9
No evidence of syphilis, STS+ ..	68	14.4	80	40.4
No evidence of syphilis, STS—	132	27.9	35	17.7
No evidence of syphilis, STS not known	107	22.6	6	3.0
Total	473	100.0	198	100.0

Reproduced from Rosahn, P. D.: Autopsy Studies in Syphilis, Ven. Dis. Inform., Suppl. 21, Wash., D. C., 1947.
(Rosahn's table 42).

lesions in a 100 per cent autopsy material than in Bruusgaard's, where only 8.5 per cent of the patients have been autopsied.

Two explanations why the results have turned out fairly similar in spite of this are the following: Paresis accounts for about 3 of the 35 per cent syphilitic lesions found in Bruusgaard's series. To make the two series comparable up to this point, then, these 3 per cent paretics would have to be subtracted, leaving us with 32 per cent as contrasted with Rosahn's 39 per cent. Furthermore, in Bruusgaard's series 13 per cent of the lesions are «benign» tertiary manifestations of the skin, mucous membranes and the bones, the majority of which presumably were diagnosed in still living patients. Not one single case of «benign» tertiary syphilis is listed among Rosahn's anatomic findings, which include serious lesions of the cardiovascular and central nervous systems, and other internal organs exclusively, (gummata in the various internal organs not being classified as «benign» tertiary syphilis). Irrespective of other dissimilarities between the two series, therefore, a comparison taking the above factors into account, would give as its result that Rosahn has found 39 per cent serious syphilitic lesions among his patients as contrasted with Bruusgaard's 19 per cent, quite a considerable difference. In fact, there seems to be no general agreement between Rosahn's and Bruusgaard's findings, which is only what would be expected. Even after these corrections have been made, the two series can not be compared legitimately.

However, this is a very interesting use of Bruusgaard's figures, and again we have an example which shows how complicated such comparisons really are when different epidemiologic methods have been used in the establishment of the materials.

Chapter III.

DESCRIPTION AND CHARACTERISTICS OF STUDY GROUP

Professor Caesar Boeck, M.D., and His Policy of Treatment as Regards Early Syphilis.

This present large series of patients untreated for early syphilis is available to us because of the unorthodox opinions of Caesar Boeck. Attention was first directed to them by his successor Bruusgaard.

Boeck's concept of the treatment of syphilis is summarized by Bruusgaard as follows (Bruusgaard, 1929 b), «The immune mechanism of the body is the most important factor in combating this disease. The specific drugs must be considered as adjuvants only; they are not potent enough to exterminate the disease completely — — the anti-body formation is disrupted, the course of the disease becomes atypical, and serious complications may result. Specific drugs should only be used in cases where the body does not seem able itself to overcome the disease — — they should then be used in great quantities and over a long period of time. You are at the mercy of the drugs.» Between 1889 and 1910 mercury was very seldom administered in Boeck's department, whereas potassium iodide became the drug of choice in all cases where the clinical course indicated its use. According to modern concepts of what constitutes a specific drug, therefore, Boeck with rare exceptions, left the patients with primary and secondary syphilis, and secondary relapse, untreated. And he showed remarkable steadfastness in view of the fact that the majority of syphilologists in Norway and abroad did not share his opinions on the treatment of syphilis. His policy of treatment had been firmly established by January 1st 1891, and it was followed in the department until August 26th 1910, when the first injection of 606 was given. During the latter part of 1910 salvarsan was gradually introduced, and in 1911 the «Boeck period» of no specific treatment, which had prevailed for more than twenty years, came to an end. Thus, there were recorded in the archives of the Department of Dermatology & Venereology, University Hospital (Rikshospitalet), Oslo, Norway, approximately 2,000 instances of untreated primary and secondary syphilis, hospitalized between

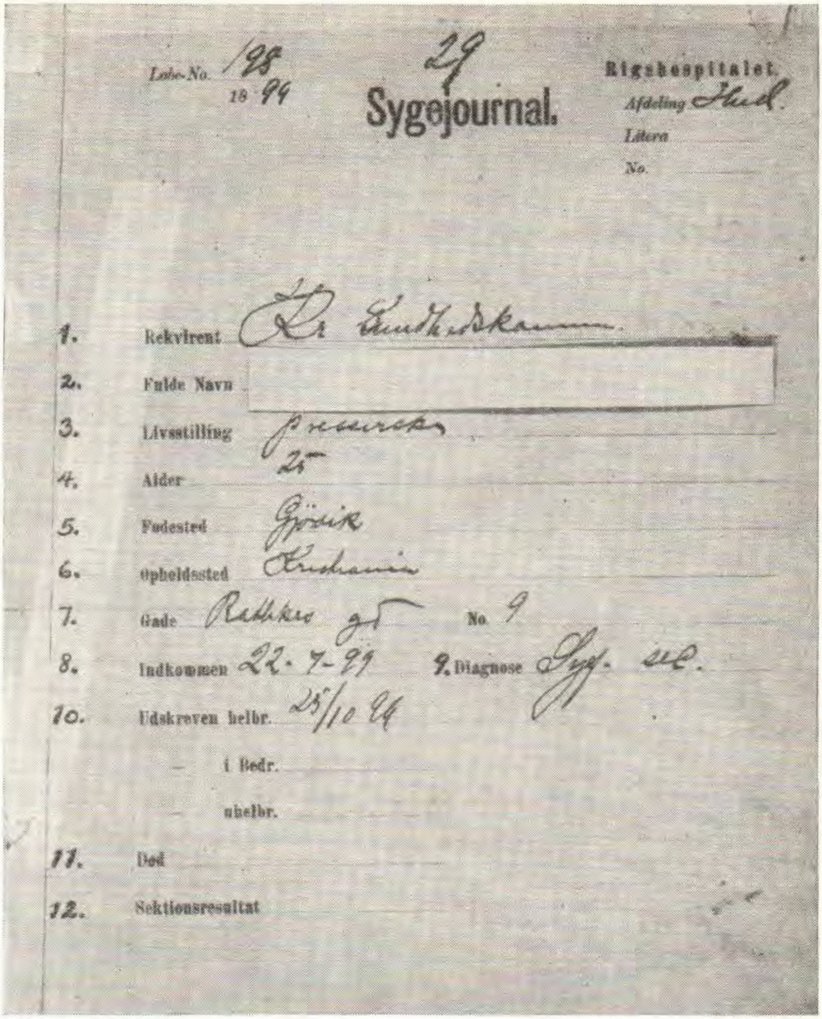
January 1st 1891 and December 31st 1910. These are the object of the present investigation.

Basic Records Available in the Department of Dermatology and Syphilology at the Rikshospital.

Bound Chronological Hospital Admissions.

Conventional hospital record forms have been bound chronologically into books by date of discharge, by month and year, there being a single book for each month. The books contain the records of all patients treated in the department, both dermatologic and venereal disease cases. Subsequent admissions of the same patient are bound at the point in time of the actual admission, an abstract of the previous record usually having been entered. A photostatic copy (Fig. 1) of the front page of the record form is given here so as to illustrate which identifying data are available on each patient. The text naturally is in Norwegian, and therefore, we have numbered each line and translated it into English, together with a few explanatory notes for some of the items. The remaining are self-explanatory.

1. *Admitting agency.* This refers to the institution which was financially responsible for hospitalization expenses, and consequently in the majority of cases its records provided considerable information on the patients, helpful in location and identification.
2. *Full name.* This is very important, particularly for tracing and identification, but unfortunately in many instances the full name was not recorded.
3. *Occupation.* This is in itself self-explanatory, but the following should be noted: There was no specific line or item for marital status, but in the case of married females, however, this item was utilized to record the family supporter's occupation, for example «carpenter's wife», «seaman's wife» and so on. For unmarried females it can usually be concluded that they were single because their own occupation was entered. In respect to males, however, there is no information on marital status on the cover page of the records, but information on this point can very often be found in the history in connection with questioning on contacts etc. This pertains to all adult patients for that matter.
4. *Age.* It will be noted that line 4 says «Age» and thus does not provide the exact date and year of birth, which is so important for tracing and identification. The lack of it must be considered an essential shortcoming in the records. This system of entering age instead of date and year of birth was consistently followed throughout the period 1891—1910, and longer for that matter, and it pertained not only to the various records, but also to documents and the like containing information on the patients.



Løbe-No. 198
18 99
29
Sygejournal.
Rigshospitalet.
Afdeling Hud
Litera
No.
1. Rekvirent
2. Fulde Navn
3. Livsstilling
4. Alder 25
5. Fødested Gjövik
6. Opholdssted Kristiania
7. Gade Rathkes gt No. 9
8. Indkommen 22·7-99 9. Diagnose Syph. rec.
10. Udskreven helbr. 25/10 99
— i Bedr.
— uhelbr.
11. Død
12. Sektionsresultat

Fig. 1.
Example of the Front Page of the Record Form Used in Boeck's Clinic.

5. *Place of birth.*
6. *Place of residence.*
7. *Street and number.*
8. *Date and year of admission.*
9. *Diagnosis.* Admitting diagnosis is entered here, this subsequently having been changed, however, in cases where the clinical observation justified it.
10. *Date and year of discharge* including *Cured, Improved, No improvement.*
11. *Death: Date, Year, Time.*
12. *Post-mortem findings.* This included a brief summary of the findings.

Then follow history, physical examination, progress notes, treatment, etc. in the usual order. The records are fairly complete even judged by modern standards. It is important to remember that the hospital (the Rikshospital), including the Department of Dermatology & Venereology, is a University hospital, and as such also serves as a teaching and research institution.

The «Syphilis Registry» or the «Syphilis Protocols».

These are large ledgers with numbered pages. A photostatic copy of two such pages (Fig. 2) is reproduced here, but not translated into English. All syphilitics were recorded chronologically by the discharge date with the following information: Name, place of birth, place of residense, age, date of admission and discharge from hospital, established diagnosis, resumé of clinical findings and treatment. In addition there was in most instances a note as to subsequent admissions and follow-up. Furthermore, Bruusgaard entered his 1925—27 findings in this Registry.

The entries in this Registry were ordinarily written by Boeck's deputy, frequently dictated by Boeck himself. The diagnosis was recorded at discharge and as such was the department's final one. This Registry was not limited to early syphilis but was a record of syphilis of all types, entered in a similar manner. It was exceedingly rare for a patient to be discharged without entry here.

Out-patient Records.

These are also in large ledgers about the same size as the «Syphilis Protocols», and contain records of visits with name, age, occupation, any new address, date or dates of examination, diagnosis, and any treatment given. They do not play a very important part in defining the basic material, but were of considerable assistance in follow-up and identification. It is not necessary to present a photostatic sample of these pages, as the principles of recording should be sufficiently clear through the above information.

Choice of Study Group.

Before undertaking the follow-up of the Boeck patients, careful analysis of the basic material of the Syphilis Registry had to be made as well as explorations into tracing procedures and the sources of data needed for significant results.

The Syphilis Registry has served as the basis for the choice of the patients to be followed. All patients with primary and secondary syphilis, and secondary relapse, recorded there during the period January 1st 1891 to December 31st 1910 were utilized, and their names and other identifying data were entered on numbered index cards, these numbers serving to identify the patients throughout our investigations. Cases where Boeck's own department had questioned the diagnosis were omitted. There were only four of these. However, on counting our cards it was found that only 1,978 patients with primary and secondary syphilis, and secondary relapse, meeting the above criteria had been discharged from Boeck's department during the 20-year period. This considerable discrepancy between the number meeting our criteria (1,978) and those of Bruusgaard (2,181) is not easy to explain, because no detailed description of the original material is given in Bruusgaard's paper. Neither has it been possible to find notes among the records which might have explained just how he chose this number. There are three possible explanations which occur to us:

1. *Duplications.* Since some patients were found to have been entered twice in the Registry for the same admission (reason unknown), it is possible that if the larger number was obtained by actual count of entries, these would have counted more than once.
2. *Inclusion of other stages and doubtful diagnoses.* Bruusgaard may have included some cases with congenital or tertiary manifestations, since these were also to be found in the Registry. There were also some cases of doubtful diagnosis which we have excluded and he may have included in his total.
3. *Inclusion of patients discharged during the year 1890.* We excluded all of those discharged before January 1st 1891.

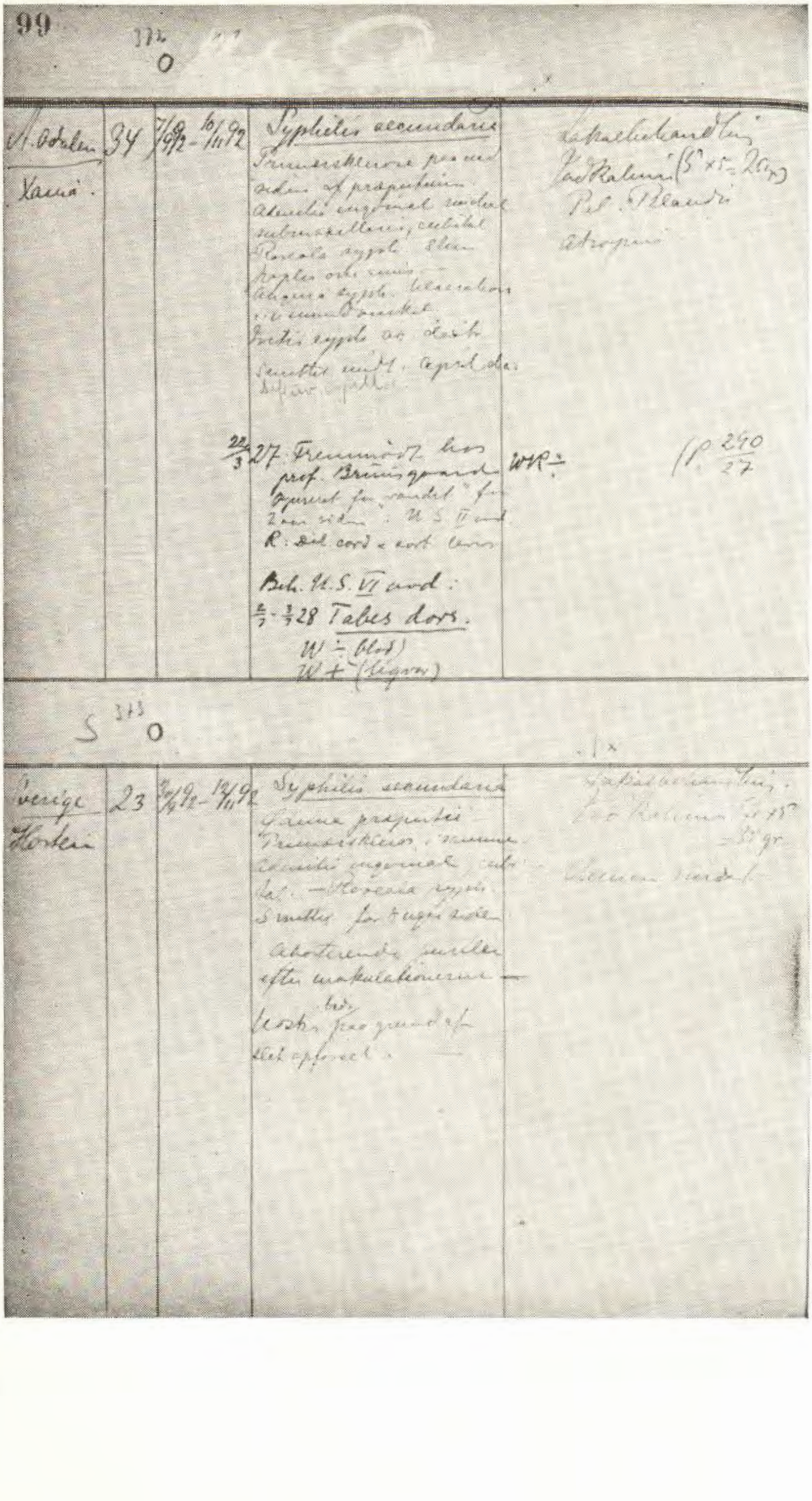
If these explanations do not account for the difference we are at a loss to explain it. We have endeavored to avoid similar pitfalls by giving each patient an index card and individual number. Furthermore, each hospital record has been transcribed in full, and in this way we feel that we have avoided including any patient with congenital or tertiary manifestations as well as duplications. On each index card the year of discharge was entered as part of the identifying data, and thus patients from 1890 can not have been included.

The number of patients actually included in the studies was 1,404, a group made uniform by the exclusion of 574 non-Norwegians and non-residents of Oslo. This choice was made without bias, in so far as we could determine, and it simplified tracing in some degree, and provided a more satisfactory basis for comparison with possible controls.

During the planning stages of the investigation, when sources of information were being determined by using small exploratory samples it was learned that there were three well defined admitting agencies for these patients: 1) The Oslo Bureau of the Indigents;[1] 2) The Oslo City Health Department, V.D. Division;[1] and 3) Similar institutions outside the City of Oslo. The admitting

[1] Discussed in detail on pp. 57—59.

Fig. 2.
Example of Ledger Pages from the «Syphilis Registry» Used in Boeck's Clinic.



100

278
0

Lobebehandling

Fredsted [illegible] Hanna	20	16/9 92 – 12/11 92	Syphilis secundaria. Ulcus induratum paa h. side af underlæben. Submaxillarglandler [illegible] langs [illegible] sterno-cleido-mastoid. paa h. side – supraclaviculære gl. paa samme side. Roseola syph. [illegible] [illegible] [illegible] [illegible] [illegible] paa grund af [illegible]	Lokalbehandling; [illegible] [illegible] Brandt
[illegible] Hanna	17	[illegible] – [illegible]	Syphilis secundaria [illegible] Blenorrhoea [illegible] [illegible] Roseola [illegible] [illegible] [illegible]	Lokalbehandling Emplastr. hydrargyri [illegible] Palmdén
		1/3 – 9/4 94	Scrofulo-glandler, ulcus [illegible] [illegible] Sympt. (Pediculosis, blennorrhagia)	

28/11 23 död av Cancer mammae.

Table 8.

1950-Status «Known» (Living and Dead), «Partially Known», and «Unknown» of Sample of 395 Patients, by Sex.

Part A. Admitting Agency: The Oslo Bureau of the Indigents.

Tracing Status		Male		Female		Total	
		No.	%	No.	%	No.	%
«KNOWN»	Living	8	11.6	11	9.2	19	10.1
	Dead	50	72.5	61	51.3	111	59.0
	Subtotal	58	84.1	72	60.5	130	69.1
«PARTIALLY KNOWN»		3	4.3	10	8.4	13	6.9
«UNKNOWN»		8	11.6	37	31.1	45	23.9
TOTAL		69	100.0	119	100.0	188	100.0

Part B. Admitting Agency: The Oslo City Health Department, V.D. Div.

Tracing Status		Male		Female		Total	
		No.	%	No.	%	No.	%
«KNOWN»	Living	9	21.9	23	23.7	32	23.2
	Dead	19	46.3	44	45.4	63	45.6
	Subtotal	28	68.2	67	69.1	95	68.8
«PARTIALLY KNOWN»		2	4.9	6	6.2	8	5.8
«UNKNOWN»		11	26.8	24	24.7	35	25.4
TOTAL		41	100.0	97	100.0	138	100.0

Part C. Admitting Agency: Institutions Outside the City of Oslo.

Tracing Status		Male		Female		Total	
		No.	%	No.	%	No.	%
«KNOWN»	Living	9	26.5	8	22.9	17	24.7
	Dead	18	52.9	13	37.1	31	44.9
	Subtotal	27	79.4	21	60.0	48	69.6
«PARTIALLY KNOWN»		4	11.8	0	0.0	4	5.8
«UNKNOWN»		3	8.8	14	40.0	17	24.6
TOTAL		34	100.0	35	100.0	69	100.0

Explanation of terms:

«KNOWN» — Patients with definitely classifiable «end points» — alive during investigation period or time of death established.
«PARTIALLY KNOWN» — Patients with one or more observations during the years following discharge from Boeck's department, but not to same «end point» of the «KNOWN».
«UNKNOWN» — No observations following discharge from Boeck's department.

agency was in general determined by the residence of the patient. Most of the patients hospitalized through the Oslo Bureau of the Indigents were residents or potential residents of the city. The majority of the patients admitted by the Oslo City Health Department were also residents of the city. On the other hand, according to the Norwegian Health Act of 1860, the Health Department was also responsible for out-of-town persons suffering from communicable diseases, and consequently a certain number of these patients might have come from other cities, towns or rural areas. Those admitted through institutions outside of Oslo, however, were generally non-residents, but were admitted to the Rikshospital (Boeck's department) because this hospital as a federal hospital, served the entire country, and because they usually came from areas located relatively close to the City of Oslo, or had happened to be visiting the city just when the disease appeared.

Foreigners and non-residents of Oslo comprised a total of 574 persons (women 289 and men 285), and among these were 249 foreigners (women 126, men 123), admitted through all of these agencies. It was perfectly clear that the collection of data on non-residents and foreigners would prove extremely difficult. This was particularly true of the latter, many of whom doubtless had returned to their native countries. Although some of the foreigners were seamen of various other nationalities, the vast majority of them were Swedish. Up to 1905 Sweden and Norway were united, and a good many Swedes settled in Norway for a shorter or longer period of time. Some of them undoubtedly became Norwegian citizens and stayed on in Norway, while others went back to Sweden. We were in no position, however, to determine whether a foreign-born person became a citizen of Norway or not, nor could we determine whether he had returned to his own country. For those born in countries other than Sweden, it was expected that most of them were aliens with intentions to leave Norway after a time. In order to contribute to uniformity, therefore, anyone who had been born in a foreign country was classified as a foreigner, and was omitted from the study. These 249 persons were fairly well distributed among the three admitting agencies and there is no evidence that omission could possibly bias the final results.

It was our belief also that by limiting the study group to residents or potential residents of Oslo we would not prejudice the results, but before making this decision we used data from our 20 per cent random sample[1] to determine this point. These patients were followed carefully according to prearranged plans and the results tabulated according to our rather rough measure of residence — the admitting agency (table 8, Parts A, B and C).

[1] Sample of 395 chosen at random from 1,978 patients according to tables of Fisher & Yates (1948). This sample, taken early in the course of the investigation, fortified the decision to complete the study. (Danbolt, Clark, Gjestland, 1954.)

It can be seen from this table that for the totals the proportions «Known» were similar in the three groups (69.1 per cent, 68.8 per cent and 69.6 per cent), as were the «Partially Known» and the «Unknown». There is a difference, however: According to sex, a larger proportion of male «Known» in Parts A and C than in Part B, and a larger proportion of female «Known» in Part B than in Parts A and C. It seemed clear from this table that the omission of patients in Part C (from outside Oslo) would not prejudice the material in so far as tracing was concerned. Thus, since this group required considerably more effort than the others it was decided to eliminate non-residents in the follow-up of the total material. As described previously, foreigners too were omitted for the same reason, thus limiting the study to 1,404 residents and potential residents of Oslo at the time of Boeck.

Table 9.

Sex and Age Distribution of Patients in Study Group.

(1,404 patients)

Age-groups	Male		Female		Total	
	446 — 31.8 per cent		958 — 68.2 per cent		1404 — 100.0 per cent	
	No.	Per cent	No.	Per cent	No.	Per cent
0— 4	23	5.2	25	2.6	48	3.4
5— 9	6	1.3	10	1.0	16	1.1
10—14	3	0.7	6	0.6	9	0.6
15—19	56	12.6	218	22.8	274	19.5
20—24	152	34.1	373	38.9	525	37.4
25—29	103	23.1	159	16.6	262	18.7
30—39	68	15.2	109	11.4	177	12.6
40 and over*	35	7.8	58	6.1	93	6.6
Total	446	100.0	958	100.0	1404	100.0
Mean age	25.6 years		24.3 years		24.8 years	
Mean age 15—39	25.4 years		23.7 years		24.2 years	

* Average age males over 40: 48 years.
« « females over 40: 46.4 years.
« « total over 40: 47.2 years.

The elimination of the above groups of patients resulted in a shift in the sex distribution inasmuch as a relatively larger number of males than females came to be omitted. The ratio males to females in the original material of 1,978 patients was 36.5 per cent to 63.5 per cent, whereas the ratio in the present study group of 1,404 is 31.8 per cent to 68.2 per cent. But this deviation can not be considered serious, since the analysis is to be made on a sex-specific basis. One of the reasons for it is to be found in the fact that both among group C and the foreigners there were quite a number of seamen.

Sex and Age Distribution of Patients in Study Group.

In table 9 will be found the sex and age distribution of the 1,404 persons comprising our study material. First of all it will be noticed that there are far more female than male patients, 958 females (68.2 per cent) and 446 males (31.8 per cent). The proportion males to females is here 1 to 2.1 which does not conform to the sex distribution of cases reported to the Oslo City Health Department for the same period of time. This latter proportion is exactly the opposite, averaging 2.1 males to 1 female (see table 10). The only explanation we have been able to discover is the fact that during the period in question the capacity of the female ward in Boeck's department was twice that of the male section (Sinding-Larsen, 1926). This in itself should not affect generalizations based upon these data as long as they are made on a sex-specific basis. On comparing the age distribution according to sex (table 9), it will be seen that the group where the difference is most marked is among the 15-to-19-year olds, where the ratio of females to males is 4 to 1. This is quite in line with general experience from studies on venereal diseases, and is presumably in the main a result of the earlier sexual maturity in females.

As regards age, it will be noted that the mean age for the total group is 24.8 years, with a mean of 25.6 years and 24.3 years for males and females respectively. Further it will be observed that the age-groups 0-to-4, 5-to-9 and 10-to-14 years (children) together account for 73 patients (5.1 per cent of the total), and the group over 40 years 93 (6.6 per cent), whereas the central age-groups 15-to-39 years embrace the great majority of the patients with 1,238 (88.2 per cent of the whole material). The children were patients with acquired, not congenital, syphilis, usually infected in the home, either by another member of the family, or by someone from the outside through handling or nursing. They were often admitted to the hospital together with their mother or father, or both, and not seldom together with one or more brothers and/or sisters. In the majority of these cases the whole family group suffered from secondary syphilis. In other words these are examples of small epidemics of infectious syphilis in the homes, a consequence of poor economic status and the resulting low, almost primitive, hygienic standards.

Table 10.

Notified Cases of Acquired Syphilis in the Oslo City Health Department 1891—1910, by Sex.*

(11,221 cases)

Year	Male	Female	Total	Ratio Male/Female
1891	272	160	432	1.7 — 1
1892	330	188	518	1.8 — 1
1893	259	198	457	1.3 — 1
1894	316	176	492	1.8 — 1
1895	518	206	724	2.5 — 1
1896	498	235	733	2.1 — 1
1897	450	233	683	1.9 — 1
1898	565	259	824	2.2 — 1
1899	543	221	764	2.5 — 1
1900	457	195	652	2.3 — 1
1901	432	208	640	2.1 — 1
1902	368	196	564	1.9 — 1
1903	431	183	614	2.4 — 1
1904	355	154	509	2.3 — 1
1905	340	128	468	2.7 — 1
1906	302	129	431	2.3 — 1
1907	251	123	374	2.0 — 1
1908	278	134	412	2.1 — 1
1909	315	142	457	2.2 — 1
1910	332	141	473	2.4 — 1
Total	7612	3609	11221	Average: 2.1 — 1

* From «Beretning om Folkemængden og Sundhedstilstanden i Kristiania i Aaret 1900» (1901), and from «Beretning fra Oslo Helseråd fra året 1929» (1930).

(Ratio male/female figured out by the present author).

Marital Status and Occupation of Patients in Study Group.

Marital Status.

As mentioned in the preceding description of the basic data, marital status is not entered on the cover page of the hospital admission records, but in the case of female patients a fairly reliable picture of their status may be had by making use of the information found under the heading «Occupation». For

Table 11.
Marital Status of Women in Study Group.
(894 individuals)*

Marital status	No.	Per cent
Single	750	83.9
Married	120	13.4
Widowed and divorced	24	2.7
Total	894	100.0

* 64 children omitted.

married women the husband's occupation was recorded here, for single women their own occupation. In table 11 will be found 894 adult women classified according to marital status (64 girls omitted).[1] As will be noted unmarried women are in the majority. A relatively small number are married, and an even smaller number widowed or divorced. This is just what would be expected in a material of this nature. It is very important to keep this distribution in mind, for the following reasons: It must be expected that quite a considerable number of the unmarried will, sooner or later during the period of observation, change their name through marriage, and the fact that they are unmarried will also to no small degree mean instability as regards place of residence. Both these factors naturally play an important part in tracing and identification.

As for men, we have, as previously mentioned, no data on marital status on the cover page of the hospital record, and the information in the history has not been found reliable enough to warrant setting up a distribution according to marital status. It would seem very likely, though, that the majority of the male patients also are single, when we take into account the age distribution and the type of patients with which we are dealing.

Occupation.

The tables are set up by sex, with females (table 12) divided into three groups: single, married (including widowed and divorced), and girls; and males (table 13) into two groups, adults and boys. The occupation listed is that entered on the cover page of the hospital admission record. At the time these observations were made it is not likely that there was particular interest in a precise and systematic classification of occupational data. Our object at this time is to

[1] These comprise 41 persons under 15 years of age, and 23 presumed adolescents classified according to occupation of father. See p. 49.

Table 12.

Occupational Status of Patients in Study Group.
Females (958 patients)

Part I. Single

Occupation	Number		Per cent	
Domestic worker (housemaids, charwomen, waitresses, etc.)	511	732	68.1	97.6
Industrial worker (all forms)	131		17.5	
Sewing-room and laundry worker (sewing-room girls and laundresses)	90		12.0	
Office worker, and sales personnel	14	18	1.9	2.4
Miscellaneous	4		0.5	
Total		750		100.0

Part II. Married (inclusive widowed and divorced)

«Breadwinner»'s occupation	Number		Per cent	
Unskilled labourer	66	94	45.8	65.2
Seaman	17		11.8	
Teamster	11		7.6	
Skilled labourer (including apprentices)	41	50	28.5	34.8
Office worker, and sales personnel	9		6.3	
Total		144		100.0

Part III. Girls

«Breadwinner»'s occupation	Number		Per cent
Unskilled labourer	27	43	67.2
Seaman	6		
Housemaid	5		
Teamster	5		
Skilled labourer (including apprentices)	17	21	32.8
Office worker, and sales personnel	4		
Total		64	100.0

elucidate the all-over picture of the socio-economic status of the patients through their occupations, rather than give a detailed description of the various occupational categories, and for this purpose the information found in the records is considered adequate.

Table 13.

Occupational Status of Patients in Study Group.
Males (446 patients)

Part I. Adults				
Occupation	Number		Per cent	
Unskilled labourer	138	270	33.5	65.6
Seaman	88		21.4	
Teamster	28		6.8	
Waiter	16		3.9	
Skilled labourer (including apprentices)	115	142	27.9	34.4
Office worker, and sales personnel	20		4.8	
Miscellaneous	7		1.7	
Total		412		100.0

Part II. Boys			
«Breadwinner»'s occupation	Number		Per cent
Unskilled labourer	14	24	70.6
Housemaid	5		
Teamster	2		
Seaman	1		
Errand-boy (own occupation)	2		
Skilled labourer (including apprentices)	8	10	29.4
Office worker, and sales personnel	2		
Total		34	100.0

The larger number of patients classified as «boys» and «girls» in these tables than the number under 15 given in our table 9, is due to the fact that some patients over 15 years were found to have been registered in the terms applying to children («labourer's daughter», «teamster's son», etc.). Usually these were

4

adolescents with no occupation of their own, who lived in their parental home and were supported there. On these grounds it was decided that the «boys» and «girls» group should not be limited to the under 15 years category.

As regards single females (see table 12, Part I) it is to be noted that an overwhelming majority (97.6 per cent) fall within three occupational categories: domestic, industrial, and sewing-room and laundry worker. The two other categories, office worker and sales personnel, and miscellaneous, are of minor import in that they comprise only 2.4 per cent. At the time these patients were infected (1891—1910) women in such occupations (particularly those in the three first groups) worked long hours for low wages. Working conditions were poor, and living quarters not much better. They had little time off, and little or no chance of recreation or entertainment. The socio-economic conditions under which they lived obviously must place them among the underprivileged in society, and under such circumstances the road to prostitution or promiscuity was for many of them rather short.

Part II of table 12 discloses that 65.2 per cent of married women belonged in the unskilled worker, seaman, and teamster occupational categories (classified according to the «breadwinner's» occupation), while 34.8 per cent have their place in the skilled worker, office worker and sales personnel groups. Part III of this same table reveals about the same ratios for «girls» belonging to the various occupational groups as were described for Part II.

It is noteworthy that table 13, Parts I and II, adult males and boys, shows an occupational distribution which is practically identical with that found for married women and girls. This is to be expected, since virtually all of them came from the same environment. The general impression is that the patients listed in table 12, Parts II and III, married women and girls, and those covered by table 13, Parts I and II, adult men and boys, belonged to the same socio-economic stratum as single females. Thus, that the main body of the patients in all groups, judging from their occupational status, had their place among the underprivileged.

Place of Residence in Oslo of Patients in Study Group.

The patients have been grouped according to localization of actual place of residence in an attempt to give a more complete picture of their social and economic status, and also as a possible aid in the selection of appropriate controls for this study of the prognosis of untreated early syphilis.

Our regional classification of domicile is based on the following considerations: The City of Oslo is divided into parishes, each with a parish minister in charge, who, among other things, is responsible for the registration of data of vital statistics such as births, marriages, deaths, and so on.

In addition, this city can be separated in the manner of other European cities, into two distinct parts, an East End and a West End. The greater part of the population domiciled within the eastern zone belongs to the working class, whereas the residents of the western part of the city in the main consist of the well-to-do and middle classes. It is evident that such a division of a city never can be but an approximate way of distinguishing the population groups according to social and economic status, but it is our opinion that the following grouping of the parishes of the City of Oslo (1891—1910) fairly well answers the purpose:

East:		*West:*
Gamlebyen	Petrus	Fagerborg
Grønland	Sagene	Frogner
Jacob	Vålerenga	Gamle Aker
Kampen	Vår Frelser	Trefoldighet
Paulus		Uranienborg

By and large, classifying a parish within one of the two mentioned categories is rather simple. In a very few cases, however, a parish can only be described as a border parish, containing elements from both population groups, although as a rule they will inhabit separate parts of it. Among the parishes, two in particular can be designated as border parishes, namely Vår Frelser and Trefoldighet. Vår Frelser has been placed East because only a relatively small section of it can be said to comply with our definition of West. By far the greater part of it is in the immediate vicinity of the large railroad stations and the docks, and bears the impress of this proximity. It is a bit more difficult to define the parish of Trefoldighet. Quite a substantial part of it is inhabited by working class people, whereas other sections of about the same size must be regarded as typical middle-class areas. Because of this Trefoldighet has been classified arbitrarily as a western parish.

It is emphasized that this division of the City of Oslo is not based on thorough sociological investigations — which certainly would have been desirable — and also that the socio-economic structure of the different sections of a city changes constantly, however slowly. Blighted areas develop in a city's so-called western parts, and slum clearance and modern housing projects alter sections of the eastern part.

As set forth in the first paragraph of this section (page 50) our aims are not only to study the place of residence as an index of socio-economic status, but also to determine if these patients are drawn largely from a fairly well defined population group within the city. If such is the case it may be possible to utilize this population group as controls in our studies of longevity and of causes of death. The use of this control group rather than the entire urban population is of particular importance if there is a statistically valid difference in the

Table 14.

Place of Residence in Oslo of Male Patients in Study Group.
(446 patients)

Parish East:	No.	Per cent
Gamlebyen	14	
Grønland	64	
Jakob	60	
Kampen	17	
Paulus	28	
Petrus	28	
Sagene	5	
Vålerenga	21	
Vår Frelser	77	
Subtotal	314	
Without fixed abode	36	
Streets since razed	12	
Shipboard	16	
Østre Aker parish	4	
Subtotal	68	
Total East	382	85.6
Parish West:		
Fagerborg	7	
Frogner	4	
Gamle Aker	7	
Trefoldighet	17	
Uranienborg	4	
Subtotal	39	
Vestre Aker parish	2	
Bærum parish	3	
Subtotal	5	
Total West	44	9.9
Out-of-town	19	
Miscellaneous	1	
Subtotal	20	4.5
Grand total	446	100.0

mortality rates of the two population groups. This latter point is taken up in the section The Establishment of Controls, p. 88.

Tables 14 and 15 show the distribution of the patients in the study group based on the above described division of the City of Oslo into one eastern and one western zone. The tables require some explanation. The addresses used for the construction of these tables are those given by the patients on admittance. All patients who declared they were without fixed abode have been grouped East. Practically without exception these were alcoholics, vagabonds and prostitutes, and their social and economic status placed them among the most distressed individuals of the entire material. Those persons who inhabited streets that have since been razed through slum clearance and city regulations have all been placed East, for the simple reason that all the streets with which we are concerned in this category, actually were located within the East side according to our definition. Patients from Østre Aker, a parish bordering closely on the eastern sections of the city, have also been placed East, while those from Vestre Aker and Bærum have been placed West because these two parishes are located in the vicinity of the western parts of the city. This more or less arbitrary method of allocation may be open to some criticism, but numerically these groups play a minor role and their classification is actually of little, if any, consequence.

Patients who worked on shipboard without definite address, have been classified East, with basis in their socio-economic status, because these occupations are largely drawn from the eastern population.

Of the male patients (table 14) 85.6 per cent lived in the eastern sections of the city, as compared with only 9.9 per cent in the western parts. It is fairly typical that a substantial number of the 44 male patients living West (more than one-third of them) are found in the so-called border parish of Trefoldighet, whereas the others are scattered all over the western parishes. Most of the male patients who gave out-of-town addresses (only 4.5 per cent) are seamen.

For females the all-over picture is much the same, with 78.5 per cent residing East. It will be observed, however, that an appreciably larger percentage females lived in the western parishes, namely 18.7 per cent, as compared with 9.9 per cent of the males. Here too we find that the border parish of Trefoldighet has more of these patients than any other western parish, namely 74 out of 179 (about four out of each ten). The remainder of this group were scattered all over the western zone. Furthermore, if we classify females living West according to occupation, this will in part explain why they resided West and not East: 132, or 73.7 per cent, of these 179 fall within the following occupational categories:

domestic worker	108
industrial worker	13
sewing-room girls and laundresses	11

The rest of them belong in the other occupational categories listed under distribution according to occupation. It seems fairly obvious that most of these persons, seen from a socio-economic point of view, belonged East and only temporarily lived West because they earned their living there, and this goes

Table 15.

Place of Residence in Oslo of Female Patients in Study Group.

(958 patients)

	No.	Per cent
Parish East:		
Gamlebyen	18	
Grønland	156	
Jakob	74	
Kampen	35	
Paulus	79	
Petrus	79	
Sagene	30	
Vålerenga	36	
Vår Frelser	173	
Subtotal	680	
Without fixed abode	33	
Streets since razed	31	
Shipboard	5	
Østre Aker parish	3	
Subtotal	72	
Total East	752	78.5
Parish West:		
Fagerborg	18	
Frogner	11	
Gamle Aker	48	
Trefoldighet	74	
Uranienborg	21	
Subtotal	172	
Vestre Aker parish	2	
Bærum parish	5	
Subtotal	7	
Total West	179	18.7
Out-of-town	25	
Miscellaneous	2	
Subtotal	27	2.8
Grand Total	958	100.0

particularly for those who did domestic work. The proportion of female out-of-town patients is 2.8 per cent.

A definite correlation between social and economic status and place of residence has been demonstrated, and this goes nicely in hand with the conclusions drawn from the distribution of the patients according to occupation. We are dealing with the underprivileged in society both as regards housing and occupation, and this allows us to underline Smillie's characterization of syphilis, «. . . It is truly a social disease — a disease of ignorance, poverty, carelessness, and negligence — an associate of crime, social maladjustment, war, and other disturbed social conditions . . .» (Smillie, 1946 — p. 289).

Year of Discharge from Boeck's Department of Patients in Study Group.

In table 16 the patients are shown according to year of discharge from Boeck's department by five-year periods from 1891 to 1910, and by sex. It will be seen that roughly three-fourths of the males and two-thirds of the females were discharged during the first decade and that the number steadily declined towards 1910. The number of cases in the material is 1,404 and the number of notified notified cases in the main reservoir, the City of Oslo.

Table 16.

Distribution of Patients in Study Group According to Year of Discharge from Boeck's Department, by 5-year Groups and by Sex.

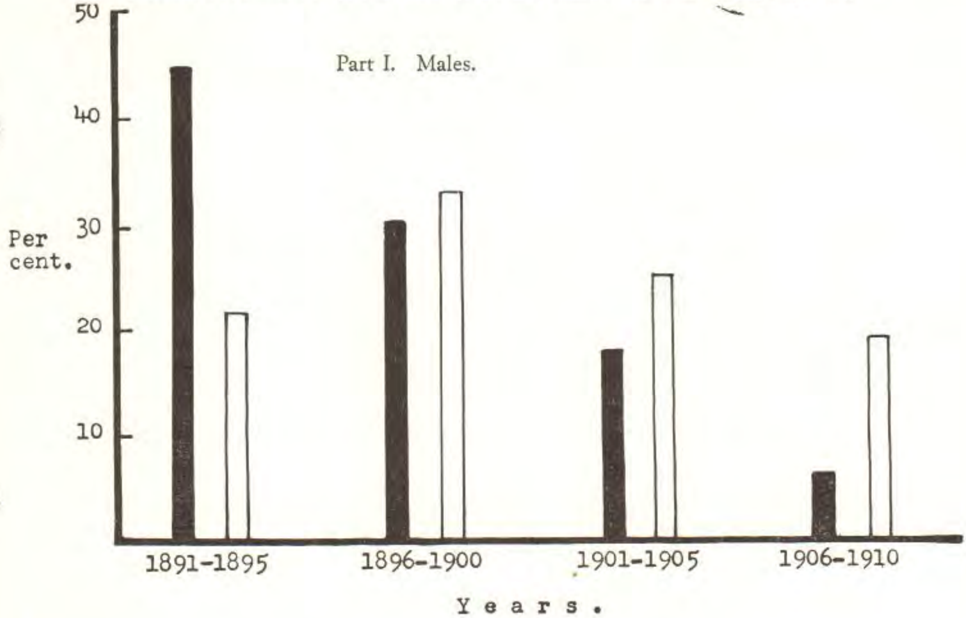
(1,404 patients)

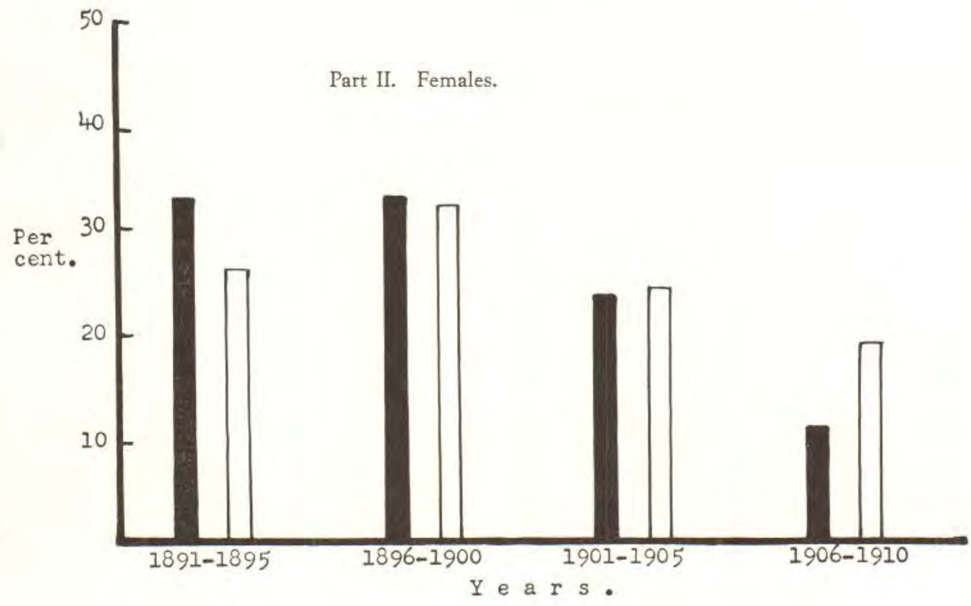
Year of Discharge	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
1891—1895	200	44.8	317	33.0	517	36.8
1896—1900	135	30.3	314	32.8	449	32.0
1901—1905	82	18.4	224	23.4	306	21.8
1906—1910	29	6.5	103	10.8	132	9.4
Total	446	100.0	958	100.0	1404	100.0

Fig. 3 presents a comparison between the percentage distribution of patients in our material and the percentage distribution of notified cases in the Oslo City Health Department computed on a five-year basis from 1891 through 1910. The number of cases in the material is 1,404 and the number of notified cases of acquired syphilis in Oslo over the same period is 11,221. The diagram illustrates that the trend is the same in both groups. The decrease is more pronounced, however, in our material, and this can probably be explained as follows: The Rikshospital is first and foremost a federal hospital and as such it serves the entire country. In earlier years a relatively large number of patients from the City of Oslo was admitted to the Rikshospital, but as the Municipal Hospital of Oslo expanded, this state of affairs changed, and fewer and fewer patients from Oslo proper were received at the Rikshospital, whereas the

Fig. 3.

Comparison between Proportions of Cases in Study Group (1,404 patients) and of Notified Cases of Acquired Syphilis in the Oslo City Health Department (11,221 cases), by 5-year Periods 1891—1910, in Per Cent of Total Number in Each Group, by Sex.





Legend :

■ Cases in study group.

□ Notified cases of acquired syphilis in the Oslo City Health Department.

Municipal Hospital of Oslo admitted always increasing numbers of these patients. This undoubtedly applied to cases of venereal diseases as well.

When studying the diagram, however, it is also worth keeping in mind that the numbers representing cases of acquired syphilis reported to the Oslo City Health Department do not include only new cases of early syphilis, but also old cases not previously notified. But this would hardly influence the common trend, and by and large there is reasonable accord between the two groups as illustrated by the diagram.

Admitting Agency for Study Group Patients.

The importance of the admitting agency is two fold; as an index of socio-economic status and, as will be seen later, a significent factor in tracing and identification. These agencies requisitioned hospitalization and were responsible for hospitalization expenses. There are three groups of admitting agencies which figure in this material:

1. The Oslo Bureau of the Indigents.
2. The Oslo City Health Department, V. D. Division.
3. Other institutions, the patients themselves, etc.

Table 17 shows the proportions of males and females sponsored by the various agencies according to 5-year periods and for the total period. The majority (61.6 per cent) was admitted by the Oslo Bureau of the Indigents (Part I). During the first 5-year period, 1891—1896, approximately 98 per cent of both sexes was admitted by this agency (Part II). During the next 5-year period the relation shifted somewhat, the Oslo City Health Department evidently taking over the responsibility for an increasing percentage of patients, although the greater number still were admitted through the Oslo Bureau of the Indigents. The third 5-year period shows the Oslo City Health Department as admitting agency for most of the patients, and in respect to females this also holds true for the fourth and last 5-year period. Males, however, were again being admitted to a somewhat larger degree by the Oslo Bureau of the Indigents. It is to be noted that only a very small number of patients were not admitted through some official institution (40 patients, or 2.8 per cent of the total).

The patients admitted by the Oslo Bureau of the Indigents did not necessarily need to be indigent in the strict sense of the word, but as soon at individuals from the working class were in need of hospitalization most of them immediately became medically indigent, and the Bureau was obliged to take care of hospitalization expenses. Norway at this time had no compulsory sick-insurance, something which was first established in 1911.

Beginning in 1898—1899 the Oslo City Health Department started to assume responsibility for patients suffering from venereal diseases, evidently on the basis of «The Norwegian Health Act of 1860», which, because of its general

Table 17.

Distribution of Patients in Study Group According to Admitting Agency, by Sex.

Part I. For Total Period 1891 — 1910.

Admitting agency	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Oslo Bureau of the Indigents	308	69.1	557	58.1	865	61.6
Oslo City Health Dept. V.D. Div.	117	26.2	382	39.9	499	35.5
Others. (The patient himself etc.)	21	4.7	19	2.0	40	2.8
Total	446	100.0	958	100.0	1404	100.0

Part II. By 5-year Periods.

Admitting agency	1891 — 1895				1896 — 1900				1901 — 1905				1906 — 1910			
	Male		Female		Male		Female		Male		Female		Male		Female	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Oslo Bureau of the Indigents	196	98.0	312	98.4	86	63.7	221	70.4	12	14.6	7	3.1	14	48.3	17	16.5
Oslo City Health Dept. V.D. Div.	0	0.0	1	0.3	42	31.1	85	27.1	65	79.2	214	95.5	10	34.5	82	79.6
Others. (The patient himself etc.)	4	2.0	4	1.3	7	5.2	8	2.5	5	6.1	3	1.3	5	17.2	4	3.9
Total	200	100.0	317	100.0	135	100.0	314	100.0	82	100.0	224	100.0	29	100.0	103	100.0

wording, gives the Board of Health wide powers when it comes to combating disease and promoting health. This is particularly true of communicable diseases, including, of course, V.D.

Stage of Disease of Patients in Study Group.

This distribution is found in table 18. The diagnoses are the final ones, that is, those listed by the department at discharge, after the patients had been under observation throughout the period of hospitalization. If a patient, for instance, was admitted with a primary chancre and developed secondary manifestations during his stay in the hospital, and likewise if a patient was admitted with both primary and secondary syphilis, the final diagnosis became primary *and* secondary syphilis.

On studying the table it is readily observed that a diagnosis of primary syphilis alone was made in only 7 instances, one-half of one per cent of the total number of patients. Actually the patients with this diagnosis were persons who did not develop secondary manifestations within a reasonably long period or who were discharged for non-medical reasons before sufficient time had elapsed for symptoms or signs of secondary syphilis to develop. In any case the number is practically negligible. The rest of the patients admitted with primary syphilis were all kept in the hospital beyond the primary stage, and thus fall into the category primary *and* secondary syphilis. This group is relatively large, and it is noteworthy that a considerably higher percentage of males than females is listed in this category (42.6 viz. 20.5 per cent), something which is in accordance with general experience, early syphilis as a whole being diagnosed later in females. Secondary syphilis comprises the largest group in both sexes and here the percentage distribution of males and females is 52.2 and 73.6 per cent. The order of magnitude in percentage distribution between the two sexes

Table 18.

Distribution of Patients in Study Group by Stage of Disease and by Sex.

Stage of disease	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Primary syphilis	4	0.9	3	0.3	7	0.5
Primary *and* secondary syphilis	190	42.6	196	20.5	386	27.5
Secondary syphilis	233	52.2	705	73.6	938	66.8
Clinical secondary relapse	19	4.3	54	5.6	73	5.2
Total	446	100.0	958	100.0	1404	100.0

is about the same when it comes to clinical secondary relapse. However, this group is small, and does not play any great role numerically. It represents patients previously observed elsewhere for secondary syphilis, with or without treatment, whose symptoms and signs had disappeared only to reappear with manifestations characteristic of secondary relapse. The validity of the diagnoses in these cases is discussed later (p. 67).

Treatment of Patients in Study Group.

As already mentioned few if any at all of Boeck's contemporaries shared his opinions on the treatment of syphilis. We were thus obliged to take into account that some patients possibly could have received treatment elsewhere, either before admittance to Boeck's department or immediately after discharge. The former occurred in a portion of those classified as secondary recurrence (table 18). The latter possibility would be relevant to those very rare instances where the patient had been discharged before all symptoms and signs had disappeared. We know from the records that some — but not very many — were expelled from Boeck's department for disciplinary reasons. The Oslo City Health Department was on these occasions as a rule instrumental in getting these patients hospitalized in the V.D. Department of the Municipal Hospital of Oslo, or its own V.D. Division took care of a small number on an ambulatory basis. As regards patients who had received any form for treatment prior to admittance, we have good, though not always complete, information in Boeck's records. This is not surprising in view of the great interest Boeck himself naturally took in this point. For those discharged as a disciplinary measure, on the other hand, no information is available in the original material itself, except the fact that lesions were still present at discharge.

The basis for the setting up of the tables on type of treatment for early syphilis, therefore, was expanded to include information gathered through various other sources to be discussed later (in the main the Oslo City Health Department's records and those of the Municipal Hospital of Oslo, V.D. Division).

Table 19, Parts I and II, takes into account all treatment received prior to, during, and immediately after hospitalization by Boeck. Thus it represents the sum of all treatment for this manifestation. Part I reveals that the vast majority of the patients (96.4 per cent) received no specific treatment whatever during the early stage of the disease, and that there is no appreciable difference between the sexes in this respect. It is further to be noted in Part I that quite a substantial proportion was given potassium iodide, about 40 per cent of the total, whereas only 3.6 per cent received mercury in any form. It does not, therefore, seem wholly correct when Bruusgaard in his paper — quoted again and again by other authors — states that only a *small* number of the patients received the

Table 19.

Part I. *Distribution of Patients in Study Group According to Type of Treatment, by Sex.*

(1,404 patients)

Treatment	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
General*	244	54.7	552	57.6	796	56.7
Potassium iodide	179	40.1	379	39.6	558	39.7
Subtotal	423	94.8	931	97.2	1354	96.4
Mercury inunctions	20	4.5	23	2.4	43	3.1
Mercury, other	3	0.7	4	0.4	7	0.5
Subtotal	23	5.2	27	2.8	50	3.6
Total	446	100.0	958	100.0	1404	100.0

Part II. *Distribution of Patients in Study Group Treated with Mercury, According to Amount by Bi. Units and by Sex.*

(50 patients)

Treatment by Bi. Units.	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
15 and over	2	—	0	—	2	—
10 to 14	2	—	2	—	4	—
5 to 9	2	—	7	—	9	—
Subtotal	6	26.1	9	33.3	15	30.0
1 to 4	12	—	9	—	21	—
Mercury, other	3	—	4	—	7	—
Amount unknown	2	—	5	—	7	—
Subtotal	17	73.9	18	66.7	35	70.0
Total	23	100.0	27	100.0	50	100.0

* Includes bed rest, baths, iron pills, cod-liver oil, etc.

specific drugs of that day, potassium iodide and mercury. As regards mercury the statement is valid, but it does not apply to potassium iodide. According to today's concept of the term specific, the *majority* of the patients was given no specific treatment. Boeck himself, as mentioned previously, considered potassium iodide a specific drug. As far as we now know this is not so, in spite of its effect on so-called «benign» tertiary manifestations. Whether potassium iodide interferes with the immune processes during the early stages of the disease in any way, is not known. In any case it has been accepted as a fact that potassium iodide is not a specific drug, and by and large it can therefore be said of the great majority of the patients in this material that they were left untreated. To the limits set by the above mentioned reservations Bruusgaard's statement on this point is correct.

Concerning the amount of mercury given the 50 patients who received this drug in any form at all, we see that 7 of them, or 0.5 per cent of the total, had such treatment as mercury pills, bichloride of mercury baths, and the like. It is certainly not going too far to say that this treatment was of near to no consequence. For the remaining 43 patients the amount of mercury administered varied, but was as a rule relatively small, as seen in Part II, table 19. Arbitrarily we have set 6 mercury inunctions as equalling 1 Bi. unit, and on this basis table 19, Part II, has been prepared. As can be seen only 6 men and 9 women had more than 5 Bi. units or 30 inunctions of mercury, while the remainder of the treated patients received 4 or less Bi. units, or 24 or less mercury inunctions. Only 3 out of the total 50 patients were given mercury by Boeck himself, the rest of them having been treated before admittance to Boeck's department or immediately after discharge from there.

Thus, it seems quite safe to state that we are concerned here with a group of patients with primary and secondary syphilis, and secondary relapse, of which the great majority were left untreated during the early stage of the disease and a small number grossly inadequately treated, even measured with the standard of that day as to the necessary number of mercury inunctions.

Another consideration which introduces itself is the fact that we are unable to produce absolute proof that no one received mercury at some later time during the early stage of the disease, though it can be said to be credibly established that this must have occurred very seldom, except in instances of relapses. In the light of the above we have therefore not removed this group of inadequately treated patients from the material.

Length of Stay in Hospital of Study Group.

The hospital admission records from Boeck's department as well as the records of the Oslo City Health Department, V.D. Division, point to the fact that isolation was considered one of the most potent weapons in the fight against the spread of venereal diseases at that time. Quite a substantial number of syphilitics were hospitalized in special V.D. wards, either at the Rikshospital (Boeck's department) or at the Municipal Hospital of Oslo (V.D. ward). Excepted from this practice were patients the Health Department had reason to believe could be trusted. And, too, the socio-economic status was doubtless taken into account, the more affluent being referred to private practitioners for ambulatory treatment rather than hospitalization. No figures on the ratio of those hospitalized to those treated by private practitioners are available.

Further, the Health Department requested that patients once hospitalized should be kept in the hospital until all symptoms and signs had disappeared. This rule was very strictly adhered to, and only occasionally did the Health Department permit a patient to leave the hospital before he was completely symptom-free. In such cases an application in which the patient stated his reasons for wanting to be discharged against the recommendation of the clinicians (family trouble, possibility of losing his job, etc.), was forwarded to the Health Department, and the written approval of the public health authorities was necessary before the hospital could release the patient. Before he was permitted to be released from the hospital the patient was obliged to sign a legal document. This practice pertained to all patients with early syphilis. A photostatic copy of this form (fig. 4), signed by one of our patients, is reproduced here, and in translation it reads as follows:

> I hereby acknowledge that through Dr. N.N. it has been brought to my attention:
>
> 1. that I am suffering from syphilis,
> 2. that my illness is infectious at least for 4—5 years,
> 3. that it is under penalty of the law that I expose any other person to infection.
>
> Kristiania (Oslo) 15. 7. 03.
>
> Witnessed:
> (signature) Patient's signature (deleted).

It is obvious that the Oslo City Health Department in this way waged a rather intensive campaign against the spread of venereal diseases, and it is equally clear that, in view of the methods of treatment available at the time, this policy was remarkably farsighted.

The document, incidentally also shows that the clinicians at Boeck's time were fully aware of the possibilities of infectious relapse, and in line with their experience set a time limit for such a possibility. The time limit found in these documents varied from two to five years, presumably dictated by the approximate age of the infection and the clinical picture. This conforms closely with the concept of most syphilologists even today.

The length of stay in hospital was certainly determined by the Health Department's policy of isolation. In table 20 length of stay in hospital is presented by sex and in relation to stages of disease. The median stay in the hospital for our entire group is 3.2 months, or 95.1 days, quite a considerable length of time, and a hardship in many respects for patients and physicians alike. It is also interesting to note the marked difference between the two sexes, males showing a median of 2.5 months, or 74 days, as compared with a median of 3.6 months, or 107.1 days, for females. It will be seen also that during the development of the infection, the earlier the patient was admitted the longer the period of hospitalization. And also that the sex difference is maintained through all stages. For primary *and* secondary syphilis the median length of stay was: males 3.1 months (93.3 days), females 4.4 months (132.2 days); for secondary syphilis males 2.1 months (64.3 days), and females 3.5 months (104.1 days).

Table 20.

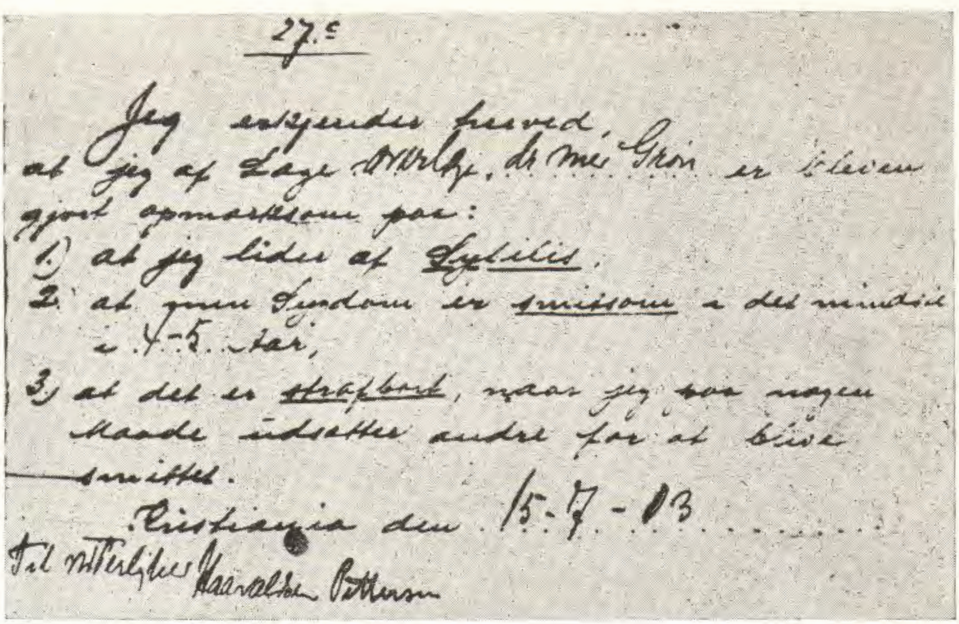
Distribution of Patients in Study Group According to Length of Stay in Hospital, by Stage of Disease and by Sex.

(1,404 patients)

Length of Stay in Hospital. Months	Male				Sub-total	Female				Sub-total	Total
	L. I.**	L. I. & II.	L. II.	L. II. R.		L. I.	L. I. & II.	L. II.	L. II. R.		
0*	0	17	44	9	70	0	6	21	11	38	108
1	0	32	64	6	102	0	16	111	16	143	245
2	4	41	60	3	108	1	32	152	13	198	306
3	0	46	33	1	80	2	24	146	3	175	255
4	0	28	12	0	40	0	49	103	7	159	199
5	0	15	7	0	22	0	25	74	2	101	123
6	0	4	5	0	9	0	17	29	0	46	55
7	0	4	5	0	9	0	11	27	2	40	49
8	0	1	0	0	1	0	5	19	0	24	25
9	0	2	1	0	3	0	4	8	0	12	15
10	0	0	1	0	1	0	3	9	0	12	13
11	0	0	1	0	1	0	4	6	0	10	11
Total	4	190	233	19	446	3	196	705	54	958	1404
Median length of stay	not given	3.1 m. (93.3 days)	2.1 m. (64.3 days)	1.1 m. (32.5 days)	2.5 m. (74 days)	not given	4.4 m (132.2 days)	3.5 m. (104.1 days)	2.0 m. (60 days)	3.6 m. (107.1 days)	3.2 m. (95.1 days)
Mean length of stay	not-given	3.2 m. (96 days)	2.5 m. (75 days)	1.3 m. (40 days)	2.7 m. (81 days)	not given	4.6 m. (135 days)	3.9 m. (117 days)	2.4 m. (72 days)	3.9 m. (117 days)	3.6 m. (108 days)

* 0 under 1 month.
1 between 1 and 2 months.
2 between 2 and 3 months. etc.

** L. I Lues primaria.
L. I. & II. Lues primaria & secundaria.
L. II. Lues secundaria.
L. II. R. Lues secundaria recidevans.



27.e
Jeg erkjender herved,
at jeg af Læge Overlæge Dr. med. Grøn er bleven
gjort opmerksom paa:
1) at jeg lider af Syphilis,
2) at min Sygdom er smitsom i det mindste
i 4-5 Aar,
3) at det er strafbart, naar jeg paa nogen
Maade udsætter andre for at blive
smittet.
Kristiania den 15-7-13

Fig. 4.
Example of Legal Document Signed by Patients at Discharge from Hospital.

Apart from the control of infectiousness, it is of the greatest importance that the patients were kept under observation for such a long time; it gave the clinicians ample opportunity to study the course of untreated early syphilis, and correspondingly increased the probability of correct diagnoses. This is particularly true of the time when diagnoses had to be made on a strictly clinical basis, no laboratory methods being available. There seems to be general agreement among syphilologists that the diagnosis of primary *and* secondary syphilis combined can be made with a considerable degree of accuracy even on a clinical basis, because this combination of signs and the history of their development are hardly to be found in any other disease. It is also commonly held that the diagnostic difficulties encountered in secondary syphilis alone are comparatively greater. But, in cases left untreated the difficulties are certainly in inverse proportion to the length of the observation period. Thus, even with the shortest median period of observation, 64.3 days for males diagnosed secondary syphilis, it seems safe to assume that the number of nonsyphilitics included by such well-trained syphilologists must have been negligible.

The number of secondary relapses is relatively small, but by and large the same considerations as to the possibility for correct diagnoses should be valid here, the period of observation being a median of 1.1 months and 2.0 months for males and females respectively.

The next question that comes up in connection with the sex difference found

5

in relation to length of stay in hospital, is whether symptoms and signs of untreated early syphilis really persist for a longer period of time in females than in males. On the one hand we must take cognizance of the fact that it would not appear unreasonable if the clinicians as an extra safe-guard had kept females hospitalized a bit longer than they did males, because many of these women were more or less unreliable, and the danger of further spread of the infection could not be ignored, something which increased the responsibility the doctors of the hospital took on declaring these patients symptom-free. On the other hand we know that all experts agree that females ordinarily come under observation for early syphilis later than do males, and it is about certain, therefore, that these females as well had had their syphilitic infection for a longer period of time before hospitalization. These two factors work in opposite directions, and the one may compensate for the other; however, we have no data available to determine the weight of either of them.

If we are willing to accept the above assumptions the implication is that the notably longer period of hospitalization found in females, and through all phases of the early disease, really does mean that symptoms and signs of untreated early syphilis persisted for a longer period of time in females than in males, which again would be indicative of a difference in the response of males and females already at this early stage of the infection.

The length of stay in the hospital of our patients may also give an indication as to course and duration of symptoms and signs in untreated early syphilis of both sexes. If we consider the two groups primary *and* secondary, and secondary syphilis it has been demonstrated that there was, as would be expected, a wide range of durations from less than one month to between eleven and twelve months, varying among other things with age of infection at time of admittance. We are not able to determine precisely for how long the patients had had their disease before coming under observation, but it would seem safe to assume that those with primary who developed secondary under observation, and those who had both on admission, had had their infection for a shorter time than those admitted with secondary syphilis alone. Despite the lack of homogeneity among the primary *and* secondary group, this group lends itself best to an approximate estimate of the duration of symptoms and signs in early untreated syphilis. The median length of stay in the hospital among these patients is 4.4 months and 3.1 months respectively for females and males. Since the *average* duration of hospitalization (table 20) was 4.6 and 3.2 months respectively this can be considered the average period of time in which symptoms and signs persist in early untreated syphilis.

It is also interesting to note that patients admitted in secondary relapse had a median length of stay in hospital of 2 months for females and 1.1 months for males. This period of potential infectiousness is minimum since we have no information on the duration of the lesions prior to hospitalization.

The long duration of symptoms and signs in all the groups very strongly demonstrates how dangerous untreated early syphilis is in the spread of infection. This is a well-known fact, but here we have found for the first time in so far as we are aware, a numerical expression for it.

On the Validity of the Original Diagnoses.

A discussion of this material cannot be terminated without a consideration of the validity of the original diagnoses, since scepticism in this respect has prevailed especially among those not familiar with all of the circumstances. It is true, of course, that the diagnosis of syphilis in Boeck's department was based entirely on clinical examinations and observation all through the period 1891—1910; neither darkfield examinations nor serologic tests for syphilis were employed before 1910.

The validity of these diagnoses is supported by the following facts and by some complementary data to be presented in later sections.

1. Boeck himself was an expert of international reputation.
2. Boeck and his deputies were experienced dermato-syphilologists and the activities of the department were based on many years of solid traditions in the diagnosis of syphilis.
3. Since the department was part of a University Hospital, teaching and research formed an essential and important feature of its activities, thus increasing the requirements for exact diagnostic work beyond that of an ordinary hospital.
4. The physicians of that day were competent clinicians, and with no modern laboratory methods available, they were obliged to develop their clinical abilities to a degree of perfection which is probably seldom found among present-day physicians.
5. The art of description was highly developed in these times and Boeck's records were no exception. From the descriptions of signs and course there can be little doubt that these patients had early syphilis.
6. Finally, Boeck and his assistants were not compelled to make their diagnoses on the basis of the symptoms and signs the patient showed on admittance, but had a unique opportunity to follow the daily course of the disease for some months without having to take into account the effects of treatment (see p. 65).

Summary and Conclusions.

1. In the archives of the Department of Dermatology and Venereology, University Hospital (Rikshospitalet), Oslo, Norway, there were recorded

approximately 2,000 cases of untreated primary and secondary syphilis, hospitalized between 1891 and 1910. These cases are the object of the present investigation.

2. This large series of patients untreated for early syphilis is available to us because of the unorthodox opinions of Caesar Boeck.
3. The «Syphilis Registry» of the Department of Dermatology and Venereology at the Rikshospital served as a basis for the choice of the patients to be followed.
4. After a careful analysis of the basic material of the «Syphilis Registry», it was found that a total of 1,978 patients with primary and secondary syphilis, and secondary relapse, had been discharged from Boeck's department during the 20-year period 1891—1910.
5. The discrepancy between the number meeting our criteria (1,978) and the number originally given by Bruusgaard (2,181) was discussed. It is indicated that the 203 in excess of Bruusgaard's material may be due to duplications in registration, inclusion of other stages of syphilis in the total, or perhaps inclusion of some discharged in the year 1890.
6. The study group was reduced from 1,978 to 1,404 by the exclusion of 574 non-Norwegians and/or non-residents of Oslo. This procedure was tested by a 20 per cent random sample; no bias was found to have been introduced.
7. In the study material there were more females (68.2 per cent) than males (31.8 per cent), the ratio females to males being about 2 to 1. The ratio males to females among notified cases in Oslo during same period was about 2 to 1, or just the opposite.

   The reason for this excess of females over males in the study material is thought to lie in the fact that the capacity of the female ward in Boeck's department was twice that of the male section during the period in question. It is held that this in itself should not affect generalizations based upon these data as long as they are made on a sex-specific basis.
8. The mean age for the total group was 24.8 years, with a mean of 25.6 and 24.3 years for males and females respectively. Patients under 15 (children) account for 5.1 per cent, and those over 40 for 6.6 per cent of the total. The central age-groups, 15—39, embraced the great majority of the patients (88.2 per cent).
9. The patients were attempted classified according to marital status. The majority of the women were unmarried, a relatively small number married, and an even smaller number widowed or divorced. The importance of this distribution for tracing and identification is emphasized.

   On the information available, the males could not be classified according to marital status but it is held likely that the majority of them were single.

10. The all-over picture of the socio-economic status of the patients was elucidated through their occupations.

Further, in an attempt to get a more complete picture of their social and economic status, the patients were grouped according to localization of actual place of residence.

The City of Oslo was separated into two distinct parts, the East End and the West End. It is pointed out that the greater part of the population domiciled within the eastern zones belongs to the working class, whereas the residents of the western part of the city in the main consist of the well-to-do and middle classes.

It was found that the great majority of the patients (85.6 per cent of the males and 78.5 per cent of the females) lived in the eastern sections of the city.

It is concluded that the main body of the patients in all groups, judging from occupational status and place of residence, belonged to the under-privileged in society, and was drawn largely from a fairly well-defined population group within the city.

11. Distribution of the patients according to year of discharge from Boeck's department by 5-year periods from 1891—1910, showed that roughly three-fourths of the males and two-thirds of the females were discharged during the first decade, and that the number steadily declined toward 1910.

After 1900, there was also a general decrease in the number of notified cases in the main reservoir, the City of Oslo, and this fact is held partly responsible for the decrease in the number of patients discharged from Boeck's department during the same period.

12. The admitting agencies for the study group patients were described.

These admitting agencies are considered important as an index of socio-economic status and as a significant factor in tracing and identification.

13. The patients were grouped according to stage of disease. The diagnoses were the final ones, that is, those listed by the department at discharge, after the patients had been under observation throughout the period of hospitalization.

Primary syphilis alone was diagnosed in 0.5 per cent of the instances; primary *and* secondary syphilis in 27.5 per cent; secondary syphilis in 66.8 per cent; and secondary relapse in 5.2 per cent.

It was noteworthy that a considerably higher percentage of males than females fell in the category primary *and* secondary syphilis (42.6 versus 20.5 per cent), showing that in accordance with general experience, early syphilis was diagnosed later in females. Secondary syphilis comprised the largest group in both sexes (52.2 per cent in males and 73.6 per cent in females). In secondary relapse the percentage distribution in the two sexes was about the same.

14. The treatment status of the patients was analysed. All treatment administered prior to, during, and immediately after hospitalization by Boeck was taken into account.

It is concluded that we are here dealing with a group of patients with primary and secondary syphilis, and secondary relapse, of which the great majority were left untreated during the early stage of the disease, and a small number grossly inadequately treated, even measured with the standards of that day.

15. Because of requirements of the City Health Department the patients were as a rule kept in hospital until *all symptoms and signs had disappeared.*

The mean length of stay in hospital for our entire group was 3.6 months, with a range from less than 1 month to 12 months.

It is held to be of the greatest importance that the patients were kept under observation for such a long time. Apart from the control of infectiousness, it is stressed that it gave the clinicians ample opportunity to study the course of the disease, and thus correspondingly increased the probability of correct diagnoses.

There was a marked difference between males and females as to length of stay in hospital (2.7 versus 3.9 months for the totals) and the sex difference was maintained through all stages of the disease.

The implication is that the notably longer period of hospitalization in females, and through all phases of the early disease, really does mean that symptoms and signs of early syphilis persist for a longer period of time in females than in males. Although nothing definite can be stated with the data available, it is felt that these findings may be indicative of a difference in response of males and females already at this early stage of the disease.

The primary *and* secondary group of this material was used to make an estimate of the duration of symptoms and signs in early untreated syphilis. Since the average duration of hospitalization among these patients was 4.6 and 3.2 months in females and males respectively, this is considered an approximation of the average period of time that symptoms and signs persist in early untreated syphilis.

It is emphasized that the long duration of symptoms and signs in all phases of early syphilis strongly demonstrates the danger of leaving the disease untreated. This is a well-known fact, but, as far as we are aware, we have here for the first time numerical expression for it.

16. The validity of the original diagnoses was considered.

It is concluded that although the diagnoses were based entirely on clinical examinations and observations in all instances, the evidence is that the number of nonsyphilitics included must have been negligible.

Chapter IV

AIMS OF INVESTIGATION AND PLANS OF STUDY

This is an epidemiologic investigation and in its planning and execution a more or less generally accepted epidemiologic method of approach has been followed (Leavell and Clark, 1953; Gordon, 1952; and Felix, 1950). The problem of the outcome of untreated early syphilis is an important one since more than one-half of the persons who acquire syphilis do not reach medical attention until after early lesions have disappeared. An appraisal of existing information relating to the subject reveals no specific quantitative answers to the question of prognosis under circumstances of no treatment for early syphilis. Qualitatively the course of untreated syphilis and its potential damage to health is well known, but the quantitative aspects are actually unknown, the various hypotheses being based upon the studies mentioned in Chapters I and II.

Our study is an attempt to obtain these quantitative data and to contribute further information on the natural history of syphilis. The present knowledge of the natural history of syphilis has been reviewed recently (Leavell and Clark, 1953) according to the following concepts, on which this present investigation is based: Disease is the result of multiple causes acting through disease agents, the human host, and the environment; in order to understand disease in its entirety *information must be sought that will disclose its «natural history»*. Natural history in this sense includes not only pathogenesis in the human host, but also the factors in the environment which lead to its initiation and perpetuation in man. Given an individual disease or disorder, an *epidemiologic approach* to a definition of its natural history would include a consideration of all the agent factors, the characteristics of the human host, and the factors in the environment which contribute to the disease process in the individual or in the community. This concept emphasizes that *disease is a process* and not a static entity, that the process is acted upon by multiple causes. It follows then, that the interception of any of these causes may have its effect on the process by preventing its further development.

In this disease we have considerable knowledge of a great many of the factors involved relative to the agent, the host and the environment. But due to the fact that no groups of untreated syphilitics have actually been followed for a sufficient length of time, we know very little about the quantitative features of the natural course[1] of this disease. Consequently, evaluation of interception at various points in its development has been made correspondingly difficult. Based on the above concept of disease as a process, an attempt will be made to show the natural course of syphilis according to as many indices as the material will allow, and thereby contribute to a better understanding of the prognosis and perhaps establish a base-line for interpretation of the huge mass of information we already possess. These are the principal aims of the investigation. Thus, at the outset, we have asked the following questions which we hoped might be answered from this material:

I. Relating to the natural course of the disease:

  In untreated or highly inadequately treated secondary syphilis,
    with no subsequent treatment,
    or, with some subsequent treatment,
    or, with unknown subsequent treatment.

  A. What is the frequency (or the probability) of:

    1. clinical secondary relapse?
    2. «benign» tertiary syphilis?
    3. cardiovascular syphilis?
    4. neurosyphilis?
    5. other late syphilis?
    6. having no inconvenience as a result of the disease?
    7. spontaneous «cure»?

  B. 1. What are the causes of death at various ages?
    2. Are the causes of death same as among nonsyphilitics?
    3. What are the probabilities of death at various ages?
    4. What is the life expectancy?
    5. What is the frequency of syphilis as direct or contributory cause of death?

  As compared with controls.

II. A. Does age at time of infection influence outcome?
  B. Does sex influence outcome?

[1]Natural course as used in the monograph refers strictly to the process in man from infection to ultimate outcome; whereas natural history takes into account in addition the factors in the environment which lead to the transmission of syphilis. This distinction is essential in epidemiology and preventive medicine.

III. Is morbidity from conditions other than syphilis greater than among normals or controls?

IV. A. What is the result on subsequent pregnancies?

B. Do pregnancies protect against serious late complications?

V. In autopsied patients:

A. What is the frequency of morphological evidence of syphilis?

B. What is the frequency of syphilis as direct cause of death or contributory cause of death?

C. Are causes of death same as among nonsyphilitics?

As compared with controls.

None of these questions has been omitted from consideration during the course of tracing and in the analysis of the data, but as the study progressed it became obvious that answers could not be provided for each and every one of them. The reasons for this lie in the material itself and in the extent to which complementary data could be obtained. These specific reasons for the omission of certain questions will be discussed in appropriate sections to follow.

The principal objectives in order to reach these aims can be formulated as follows:

1. To trace as many patients as possible to an «end point» defined as the last observation whether living or dead.
2. To collect a maximum amount of clinical data (including data on treatment) on each patient from the date of his original discharge from Boeck's department, all through the interim period and up to the «end point».
3. To determine the cause of death through study of post-mortem examinations, hospitalizations, death certificates etc., with the maximum amount of accuracy.
4. To examine at the Rikshospital as many living patients as possible and to employ as complete examinations for syphilis as circumstances would permit, and to have examined elsewhere, according to the same principles, those patients who, for some reason or other, could not be brought to the Rikshospital.

Sources of Information for Tracing and for the Collection of Clinical Data.

The first requirement in the fulfilment of these objectives was to establish an orderly and as practical and as simple as possible a plan of investigation. There were potentially great difficulties of tracing and of identification to be certain that the data recorded from the various sources referred to our patients, but such difficulties are not insurmountable provided a workable system of identification could be established and a logical plan of search of available sources set up. This was accomplished as will be clear from the discussion in this section.

A number of sources of tracing data and clinical information was known to us, but at the beginning a few explorations were made with small samples to determine other places where information could be obtained. While these explorations were in progress we were also engaged in constructing our basic record system and in transcribing all of the original personal and clinical data to these records. Then came the process of identification by means of search of Population Registers, of the records of admitting agencies, of the files of the church, of the vital statistic records and of hospitals. Upon proper identification, clinical data were added to our files from extensive searches of hospital and physicians' records.

Record and Filing System.

The filing system consisted of two parts: a) an index card file, and b) a clinical record folder file.

The index file. Each patient was given a card and an identification number. On the card space was provided for the following data:

1. Basic information as found in the original records:
   Name, (maiden name if given),
   Year of birth (exact date and year of birth was not noted in the original records; year of birth was figured out on the basis of age by the subtraction method),
   Place of birth,
   Marital status if given,
   Occupation,
   Address,
   Name and age of children,
   Original number and year of discharge (taken from the «Syphilis Registry»),
   Admitting agency.
2. Hospitalizations, visits to out-patient clinics and private practitioners.
3. Date, year and place of death,
   post mortem done, or not done.
4. Pertinent information on relatives, and other data serving tracing and identification.
5. Blank space on the reverse of the card for a brief record of the tracing process.

All information collected from our own hospital records, out-patient registries, the «Syphilis Registry», and so on, was typed in *black*, whereas all subsequent information gathered was typed in *red*, in order to facilitate identification.

These cards were divided into males and females and alphabetically arranged within each group.

The clinical record folder. Each patient was given a single folder. These were filed according to the patient's identification number as given on the index card. All clinical records — whether from our own hospital or another one — and death certificates, were completely transcribed for these folders. In principle the transcriptions were done *in toto.* Thus there was recorded in our own files complete available information on each patient included in the study. This was particularly important since the records were of multiple types and a uniform abstract at the time the record was available for study would have been impossible. All records which could be taken to the Rikshospital itself, were brought in and copied there by the secretaries of the study. If for some reason a hospital was not willing to, or could not, forward the original record, the transcription was done at that hospital, either by one of our secretaries (if in Oslo or vicinity), or by one of the secretaries of the hospital in question. When this work was not done by our own secretaries, an unabridged transcript was always requested. Naturally there is much not related to syphilis in such records, but the above described system ensured uniformity, and more important, it enabled the investigator to study all available clinical and identifying information at any time it was needed during the analysis. Even the slightest information may aid in identification. There were frequent referrels to these records during tracing and the study of the material. Furthermore, the fact that this entire material is unique, the possibility of its use in later studies, in the author's opinion justified this very thorough and complete record system.

Tracing and Determination of a «Search Order».

Although the processes of tracing and the collection of clinical data could not be categorically separated and had to go hand in hand, they are separated in the discussions of sources of information which follow. Practical considerations in this respect had to be kept in mind constantly in order to save time and effort.

As mentioned previously the original records lacked information on the date and year of birth. The difficulties which could be expected in tracing and identification due to lack of such vital information, would be further aggravated by the fact that quite a number of the patients had very common names, and that full name was not always given. Finally, since the majority of the women in the material were single, we could anticipate change of name through marriage in a substantial number of instances. It was obvious that our «search order» had to be constructed in a manner which would enable us to surmount these obstacles. Only by setting up some type of an orderly and strict «search order» could we achieve uniformity throughout, and relative to our chief sources of information, the tracing would have to be as consistent and rigorous as possible.

Population Registers.

By Act of Parliament in 1946 decision was passed that each municipality in Norway have a so-called Population Register, and today this register forms the natural starting-point for any tracing process. Prior to 1946 it had been left to each municipality to decide for itself whether to run a Population Register or not. The main functions of these registers can briefly be described as follows: Registration of the members of each household within the community, with accurate identifying data such as full name, date and year of birth, place of birth, marital status, occupation and address. Registration of births, deaths, marriages and divorces. Recording changes of name of both men and women, and keeping an index file containing both the new and the old names. (In the case of women changing name through marriage, the index file is to contain both maiden and married names). Registration of movements to and from, and also within, the borough, if permanent, with date and year entered each time change of address takes place. In addition to the day-to-day recording of the above data together with other data not mentioned here, the Population Register, among other functions, also is responsible for the Census.

The Population Register of Oslo was established in 1906, fifteen years after the first patients of our series were hospitalized. Oslo's large neighbor, the borough of Aker, did not get its Register until 1917. On the other hand Census had been taken at regular intervals also prior to the establishment of these registers, and all Census lists for the City of Oslo are filed with the city's Population Register. The lists in question, however, are not as accurate as we know them today. At that time they carried name, year of birth, occupation and address of the breadwinner, and as a rule similar information on the other members of the household.

At first an effort was made to trace our patients through the Oslo Population Register by means of the identifying data available in the original hospital records, without supplementary information. After a relatively short exploratory period of tracing, it became apparent that satisfactory results could not be obtained without better identifying data, and that sources which could furnish more accurate information would have to be found.

Admitting Agencies.

On going through the admitting agencies it was immediately observed that the majority of the patients, or 61.6 per cent (see table 17, Part I, p. 58), had been admitted through the Oslo Bureau of the Indigents. This institution, being financially responsible for the patient's hospitalization, could be expected to have on file pertinent data provided its archives were intact and in good order. This turned out to be so. As regards the identifying data on the patients the registration there was generally very accurate, not only in connection with hospitalizations, but also in regard to other aid given, such as relief for various reasons, unemployment aid, and the like. All persons who had received aid in some form or another were recorded in the institution's main registry, and those who had been hospitalized were in addition registered in the so-called «Sick Registry», large ledgers where admittances to hospital were entered chronologically. In the latter registry were to be found the following information: full name, date and year of birth, name of hospital, diagnosis, and dates of admittance and discharge. Starting out with date and year of admittance to Boeck's department at the Rikshospital and the name, the patients were relatively easy to find in the «Sick Registry», and identification close to 100 per cent definite. Besides hospitalizations in Boeck's department, hospitalizations in other wards of the Rikshospital, the Municipal Hospital of Oslo, and other hospitals in or outside Oslo, also were recorded. The patients were cross-indexed to the main registry, and from there again to the archives of the Bureau of Old Age Pensions. Until 1911 the main registry too consisted of large ledgers, wherein information was entered chronologically, but from then onwards the Oslo Bureau of the Indigents has had a modern filing system with index cards, based on year and date of birth as the leading principle, with name as the secondary principle. As a rule the main registry contained such data as: date and year of birth, place of birth, occupation, addresses (often over several years, since the Bureau was interested in determining legal residence), and likewise name, year of birth, occupation and address of parents and/or other relatives. Furthermore, there was information on children, marriages and divorces, death of supporter, and so on. In addition there was often attached correspondence with other Bureaus of the Indigents all over the country containing information on financial aid granted the patients for various reasons, among others hospitalizations outside the City of Oslo. Naturally the amount of information varied somewhat from patient to patient all according to his need of financial support through the years. Some patients were only to be found in connection with their stay in Boeck's department, whereas others could be followed in the registry right up to their death and still others were discovered to be alive in Oslo or elsewhere. The data which can be found in the archives of an institution such as the Oslo Bureau of the Indigents are of course manifold, and the description given here can only cover a fraction of them, but we have endeavored to include those considered the most important from the point of view of the special tracing job which faced us. It does not seem an exaggeration to state that the whole investigation would have been in danger of foundering at the outset if this invaluable source of information had not been found.

For patients admitted through the Oslo City Health Department, V.D. Division (35.5 per cent) (see table 17, Part I, p. 58), the situation was somewhat different. During the period from about 1898 to about 1908, the Health Department did not enter detailed identifying data on their patients, but employed the same principles of registration as did Boeck's department, which meant among other things, that it used age and not date and year of birth. In 1907—08 however, the more precise method of recording date and year of birth had its beginning, and for patients admitted during the remainder of the period through 1910, this kind of identifying information could be had through the records of the Health Department. However, as shown previously (table 16, page 55), relatively few of our patients were admitted during the last few years of the period 1891—1910. And also, the very same information could be provided by the Oslo Population Register (established in 1906). For patients admitted through this same agency during the period 1898—1908 it was necessary to employ another technique in order to gather identifying data. These patients were checked against the Census lists mentioned under the description of the Oslo Population Register, the Census coinciding with or falling nearest to the year of admittance being used. This method gave satisfactory results in a fair number of instances, although as a rule we got only year of birth, not date, but in addition often valuable information on relatives.

Marriage Registers and Church Records.

When the above mentioned sources (the Oslo Bureau of the Indigents, the Oslo Population Register, the Oslo City Health Department, V.D. Division) did not yield suitable identification, the parish minister at patient's birthplace was contacted. (The State Church of Norway is responsible for the registration of births, and incidentally there is some overlapping between the Church and the Population Registers when it comes to the recording of vital statistics). These records furnished accurate information on name and date and year of birth on a substantial number of individuals, and often additional information such as name, year of birth and occupation of parents.

Since single women made up the majority of the patients, the possibility of their having changed their names through marriage had to be kept in mind. To find information clarifying this point was essential. Marriages performed in the City of Oslo were registered with the Central Bureau of Statistics, and it was decided that all our female patients be checked for identifying data against the Marriage Registry for the years 1891—1910 (containing about 40,000 marriages). After 1910 the files of the Oslo Population Register could be counted on to provide such information. In this manner a considerable number of women, although not all, who had changed name through marriage were found (simultaneously with name, year and place of birth, occupation and address of the husband). Many of the patients had only recently settled in Oslo, and still had their parental homes in other cities and towns or rural areas. It being quite a common practice in Norway to have the marriage ceremony performed in the bride's home town, a good number of marriages were thus recorded outside the City of Oslo.

Other Sources.

In addition to the sources mentioned above, it was obvious that one would have to contact a variety of supplementary sources, according to need and to the extent indicated in each instance. The most effective of these supplementary sources was without question the relatives or kin of the patient. As already mentioned we had often found information on such relatives in the Oslo Bureau of the Indigents, the Oslo Population Register, the Marriage Registry for Oslo, and through the parish ministers. It was not exceptional, for instance, to manage to locate relatives through the Population Register, and, though the patients themselves were not found, in this manner to procure necessary information on them both as regards identifying data and data on their further fate. It was likewise often possible through inquiries sent to local sheriffs to locate one or more members of a patient's family, who had continued to live at the patient's place of birth or in the area where he resided just prior to settling in Oslo. At times such family members could furnish the needed identifying data, and frequently they could provide vital information on the patient's later whereabouts. In many instances inquiries also were sent to local Bureaus of the Indigents and local Population Registers all over the country, either in order to provide data on the patient himself or in order to locate relatives who in turn could furnish such data.

Collection of Clinical Data.

In connection with the collection of clinical data on complications and treatment, emphasis was laid on the fact that the entire period of time from the date of discharge from Boeck's department until the «end point» was important.

As noted above, the first step was the recording of all existing information from the Dermatologic ward of the Rikshospital where the patient had been hospitalized at the outset. Not only were the original admission data recorded, but also data covering the entire period from 1891 to 1951. This was a relatively easy task because practically all information on these patients was entered in the «Syphilis Registry» at the place where each originally figured. Here were to be found notes from Bruusgaard's follow-up study 1925—1927. Bruusgaard also made entries covering the period of his investigation in the registry of the out-patient department.

Another source of clinical information was the V.D. Division of the Municipal

Hospital of Oslo, the only other hospital ward in the City of Oslo where venereal disease patients were taken care of. It seemed reasonable to assume that a good many of the patients at one time or another would be in need of a stay at the Municipal Hospital of Oslo, V.D. Division, especially in view of the fact that residents of Oslo increasingly became dependent upon the city's own facilities. Therefore, all of our patients were checked against the records of the Municipal Hospital of Oslo, V.D. Division, for the whole period 1891—1951.

The third clinical source was another institution which also took care of venereal disease patients, although on an ambulatory basis, the Oslo City Health Department, V.D. Division. Both clinical and tracing data were available here since this institution carried two sets of registries. The one contained the notifications of cases of venereal diseases, including description of the sources of infection and notes on the contact tracing of the department, all such data chronologically entered in special ledgers. The other was the so-called «Treatment Registry», wherein were entered persons who had been summoned to the department for examinations or who had sought medical advice voluntarily. These data also were in large ledgers and chronologically recorded. In 1921 the Health Department abandoned the ledgers and shifted to an alphabetical index card system, built up according to date and year of attendance. From a public health point of view the first years of the infection would be the most important ones and consequently the greater amount of information in all probability would have to do with the early phases of the disease. But it could also be anticipated that a good many women would have been summoned after having given birth to children with congenital syphilis, and that a number of patients would have appeared for blood tests and diagnosis of late manifestations down through the years. It was therefore found necessary to go through the various Health Department records mentioned above, from 1891 up to and including 1951.

As for the two last mentioned institutions, the Municipal Hospital of Oslo, V.D. Division, and the Oslo City Health Department, V.D. Division, the checking there assumed even greater importance because we knew that the doctors in charge had not shared Boeck's opinions on the treatment of early syphilis, and had used mercury inunctions as their method of choice.

There were other clinical data to be had from the records of hospitalizations in asylums for the insane, psychiatric, neurologic, medical and other wards. This information was collected more or less indirectly through the various methods mentioned in this section rather than through direct checking of our cases against all of the records of many hospitals. This seemed to be the only method which could be employed, as the practical difficulties of going through the complete archives of all these hospitals and asylums for a period of fifty to sixty years obviously would be almost insurmountable during the time available.

Data from death certificates. When it came to the dead, the death certificate was collected as soon as date, year and place of death had been ascertained. For deaths having occurred in the City of Oslo these certificates were gathered through the Oslo City Health Department's files (the same method was used in cases where legal residents had died outside the city). For deaths having occurred elsewhere in the country, the Central Bureau of Statistics was the natural source of information. When the death certificate contained information on the patient's last hospitalization (i.e. if the patient had died in a hospital), the records of that hospital were collected and transcribed. For those who had not died in hospital other sources — first and foremost the Oslo Bureau of the Indigents, including the Bureau of Old Age Pensions, the Sick-Insurance Offices, and relatives — were contacted to endeavor to find out if the patient had been hospitalized at some time close to or further from, as the case might be, the time of death, and if so, to procure name of hospital and ward, and date and year of admittance and discharge.

Data relating to living patients. For both those who refused to come in for examination and those who were examined we found it helpful to go back to the history of previous examinations wherever they were performed, as a starting-point for collecting information. This meant that we frequently had to return to the Oslo Bureau of the Indigents for data on these patients. (The same procedure was also used for those who were located by death certificates). The value of this lies in the fact that the socio-economic status of the majority of these patients was such that illness practically always necessitated some kind of aid from the Bureau of the Indigents. This was true after as well as before our compulsory sick-insurance system was established in 1911. Even if the patient in question was insured and hospitalization expenses thus taken care of, his dependents in case of illness very often became indigent. Neither was the sick-insurance system by any means as comprehensive at the beginning of its operation as it is today. For patients incapacitated either by illness or old age, or who became eligible for old age pension, the Bureau of the Indigents or the Bureau of Old Age Pensions took care of expenses in connection with hospitalizations and other forms of medical care.

The «Search Order».

As soon as the multiple sources of information were discovered it became apparent that all sorts of information would be provided, some pertinent to our objectives, some misleading. It was clear that with so many sources and with such similarity of names, even in a small country the process of identification (see next section) had to be made as objective as possible. A name and a date are not sufficient for identification for tracing individuals over such a period of time as is involved here. To ensure the objectivity of our search we set up

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an order which was to be followed in getting data on our patients — a «Search Order». This was determined as a matter of convenience and practicality. It is shown in fig. 5.

The «Search Order»

Chief Sources of Information.	Supplementary Sources of Information
1. The Department of Dermatology & Venereology of the Rikshospital.	
2. The Oslo Bureau of the Indigents.	3. Bureaus of the Indigents elsewhere.
4. The Central Bureau of Statistics' Marriage Registry for Oslo (women only).	
5. The Oslo Population Register.	
6. The Oslo City Health Department, V.D. Division.	
7. The Municipal Hospital of Oslo, V.D. Division.	
	8. Parish minister, sheriff, or local Population Register at patient's place of birth.
	9. Parish minister, sheriff, or local Population Register at patient's place of residence prior to his settling in the City of Oslo.
	10. Individual sources, especially relatives of the patient, but also many others not specified.
11. The Oslo Bureau of the Indigents, second, or later, checkings.	
12. The Oslo Population Register, second, or later, checkings.	
13. The Oslo City Health Department and the Central Bureau of Statistics (for collection of death certificates).	
	14. Mental hospitals, Psychiatric wards, Neurological and other hospital wards, (Private practitioners), as indicated.

Fig. 5.

Against the sources listed under the heading «Chief Sources of Information» the entire series with some essential omissions was checked. However, it is to be noted that in practice the order in which the various sources of information were listed was of necessity changed at times, because it was constantly necessary to take steps to meet the practical issues of the moment. In a great many cases supplementary sources were utilized, and with the new information gathered the person was again checked against one of our chief sources, especially then against the files of the two institutions which had proven themselves to be the most important in our «search order», namely the Oslo Bureau of the Indigents and the Oslo Population Register.

The Identification Process.

In all follow-up studies, and particularly in those where the observation period is extensive, it is necessary, as shown in the preceding section, to draw information from a vast number of sources in order to locate the patients and collect clinical data. Each step in the process poses problems of identity. A subjective element will always be present when problems of identity are up for decision, inasmuch as the result in each case is dependent on the investigator's interpretation of the various factors which go into determining whether identification is definite or not. However, by constructing a form containing a fixed set of rules on which the various data can be collated for each comparison made, the process of identification can be made as nearly objective as is possible. This method was adopted here and a model of the form used is reproduced (see fig. 6). The form contains patient's name and identification number, followed by the sources of information employed, the latter being marked with Roman numerals which correspond to columns in the figure itself. In the figure will be found such data on and around which identification generally revolved, together with data of more occasional nature applied according to need. Information taken from the original record is covered by the first column, and each item is marked with a V for present or an O for absent. In the next column, marked with the Roman numeral I, we find the information from source I. When information from source I was identical with the original data the item was marked with a D for Definite. If the information was contradictory the item was marked with a C. Between the two extremes we used the designations P for Probable and Q for Questionable. New data not previously on record were marked with V for present, and items on which data still were lacking continued to be marked O for absent. At the bottom of the column was entered the rating or end result of the comparison of information from source I with the original data, which was noted with Definite, Probable, Questionable or Contradictory. When identification had been judged to be Definite, any additional information which had come in was utilized in the subsequent comparisons. When a comparison had given Contradictory as the end result it generally meant that at some time during the tracing process we had lost our original patient and picked up some other person, making the information gathered at that step valueless. The process was then cut short at that point and we returned to the last definite step

Fig. 6.

Identification Process

Name: No.:

Original record compared with:

I. Information from the Oslo Bureau of the Indigents.
II. Inf. from I. and the Municipal Hospital of Oslo, V.D. Dept.
III. Inf. from I. and II. and death certificate.
IV.
V.
VI.

Details of Comparison

Identifying Data	Original	Sources of Information					
		I	II	III	IV	V	VI
Name	V	D	D	D			
Date & year of birth	O	O	V	D			
Year of birth	O	V	D	—			
Age	V	D	D	—			
Place of birth	V	D	D	D			
Residence. City	V	D	D	D			
Street address	V	D	P	D			
Marital data	O	V	O	D			
Name of spouse	O	O	O	O			
Name of children ..	O	O	O	O			
Occupation	V	O	P	O			
History from patient	V	D	O	O			
History of syphilis ..	V	D	O	O			
History Boeck	V	D	O	O			
Syphilis diagnosed ..	V	D	O	O			
Other:							
End result identification		D	D	D			

V: Present. O: Absent. D: Definite. P: Probable. Q: Questionable.
C: Contradictory.

and sought new paths of tracing. However, when the end result of a comparison had had to be termed Probable — or even Questionable — the process went on past this point and was continued for a time along the same pathways because additional information coming in during the further tracing work had proved in a substantial number of cases that we had actually found the right individual. It is to be noted that mistakes of numerous kinds may creep into the archives of the various sources, and allowances have to be made for such eventualities.

Date of birth for instance, may vary from source to source, and a good many of the data may change from year to year for natural reasons, such as occupation, marital status, and of course address and residence.

The process continued in this manner, step by step, from one comparison to the next, (marked II, III, IV and so on), each comparison reverting to all accessible data from every preceding collation. As a result of this method of identification we have included only those persons in the analysed material whose identification could be termed satisfactory, the rest of the patients coming into the group «Unknown». It is emphasized that it is not possible to give a detailed and full description of the great variety of ways and means made use of in this rather complex identification work, but it is felt that as impartial a stand as was possible has been taken all through the process. We have no specific definition of what constitutes identification but believe by this system that objectivity is at its maximum.

Examination of Living Patients.

It seemed wise from the beginning to make an immediate effort to bring in for examination as many as possible of the patients still alive. The median age of these patients if alive in 1949 would be between 70 and 74 years. Clearly then, this effort should be made at once before their numbers were further diminished. Aside from actual tracing two factors had to be taken into account: a) the precautions to be observed in recalling an unfortunate experience ot many years ago; and b) the details of the examination procedure when they were persuaded to cooperate with us.

Plainly it would be a most delicate matter to confront patients who at some earlier period of their life had suffered from syphilis. Only a most carefully planned and tactfully executed approach could be expected to produce satisfactory results. First of all it would be essential to avoid embarrassing situations for the patients as regards curious family members who through carelessness on our part might get a hint of the actual purposes of our examinations. Furthermore, we would have to be aware of the possibility of misidentification, even if we did have reason to believe that our identification process would prove adequate. In addition, the patients would have a legitimate claim to an acceptable explanation as to why they were being called-in for examination so many years after infection, whatever form this explanation were to have. Also, we had to take into account the matter of making appointments as to time and place, and because so many of the patients were of considerable age, the means of transportation to and from the hospital had to be considered. Lastly came the question of a small remuneration for appearing at the hospital, and particularly for those who had jobs and would lose time from work.

All of these points precluded the possibility of mailing a written summons to each one of the patients. Thus it was decided to base this part of the work to the greatest extent possible on personal contact. Before seeking contact we tried in each case to ascertain with whom the person lived, the marital status, if grown children were residing at home, and also if the patient or marital partner were working. Such information was gathered simultaneously with the other data we needed for tracing through the sources previously mentioned.

As a rule one of our nurses was asked to contact the patient either at home or at the place of work, after the problem of how best to avoid embarrassing situations with possible relatives had been discussed thoroughly. She would take along with her a standard letter of introduction from the hospital (signed by the Chief of the Department of Dermatology & Venereology). If the patient agreed to show up at the hospital, an appointment was made and transportation to and from the hospital by car was arranged. After a number of patients had been called-in and examined in line with the fixed standards, it was found that each would be obliged to spend about three hours at the hospital before all examinations would be finished. This proved trying to the patience of these elderly persons, and thus it was necessary that one of the nurses continuously be in attendance while they were on the hospital grounds, and render assistance in taking them from one department to the other.

When the nurse did not manage to persuade the patient to come to the hospital — something which surprisingly enough very seldom happened — the author personally contacted the patient and made a new try. All patients who then refused to appear for examinations, either at the Rikshospital or elsewhere as the case might be, were again rigorously and exhaustively checked through appropriate files for additional leads which might give the desired information. In every instance an effort was made to discuss the situation personally with each living patient, whether examined or not.

As regards out-of-town patients who for some reason or other could not be visited by our nurses, a doctor at their place of residence was asked to interview them and persuade them to come in for examinations, as arranged by him and according to his facilities. We also, through various means, attempted to get clinical information on patients residing in foreign countries. Information was forthcoming in a number of instances as a result of examinations, interviews and actual transcriptions of records. As a last resort extensive effort was made in the case of unexamined living patients to use their relatives as a source of information regarding state of health. These were either questioned directly, if living in or near the City of Oslo, or by letter, if living elsewhere in the country or abroad.

By utilizing these channels as indicated we counted on being able to collect adequate information on most of those patients who would still be alive at the time of the investigation (1949—1951). The complete accuracy of the data on unexamined persons might vary somewhat, but due to the long duration of infection it is unlikely that anything of a serious nature would be overlooked. Most of the living, however, were examined.

Principles of the Examination.

To ensure the greatest possible uniformity in the examinations, detailed guide sheets for history and physical examinations were formulated. These forms (modified from Stokes et al., 1944) are reproduced in Annex II.

The following items comprised the complete plan of examination of each patient:

1. History.
2. Ordinary physical examination.
3. Complete neurologic examination.
4. X-ray of the heart and the aorta.
5. Serologic tests blood (one complement-fixation test and one precipitation test).
6. Spinal fluid examination.
7. Examinations by eye and ear-nose-throat specialists and internists etc. whenever indicated.

The history and the physical examination was done by the author, who also collected the samples of blood and spinal fluid. During the first months of the investigation the neurologic examinations were performed by the various doctors of the policlinic of the Department of Neurology, later by one of the senior residents there, who assumed this special task so that we might obtain uniformity. The x-rays were done by the Rikshospital's X-ray Department, and the findings discussed in the presence of the author at the department's weekly demonstrations. Serologic tests of blood and spinal fluid were done at the Bacteriological Institute of the Rikshospital. The other examinations of the spinal fluid were carried out at the laboratory of the Department of Dermatology & Venereology.

It was obvious that in a material such as this we would discover some of our patients to be living in areas — in Norway and abroad — inaccessible to our own examination team. In order to produce results as uniform as possible we sent our examination forms or detailed instructions to those responsible for the examinations. Blood and spinal fluids were examined when possible in our laboratories and all findings, clinical, radiologic and laboratory, were reviewed carefully at the Rikshospital according to the standards originally established.

Establishment of Controls.

From the list of questions which might be asked of the present material (pp. 72—-73) it will be noted that a comparison with controls was found desirable in order to illuminate many of the most important problems as to the natural course of the syphilitic infection. The establishment of satisfactory controls, however, obviously would be no easy task, and the final solution was arrived at only after careful consideration of several possibilities, such as:

I. *Sample of patients similar to the study group in age, sex, socio-economic status, and locale, without a diagnosis of syphilis, attending the Rikshospital during the same period.*

A. Patients from the hospital as a whole. This is not a good control group, the chief reason being that it will represent persons with other, often serious, forms of illness, and not the general population.

B. Neither would patients hospitalized by Boeck constitute a good control group for the same reasons as mentioned under point A, although the illnesses in question on an average probably can be considered as being less serious in a dermatologic department than in most others.

C. Patients from the dermatologic out-patient department. In addition to the fact that these patients were suffering from other illnesses, we also had to take into account that the basic data were not as complete in the out-patient department records as in those of the hospital itself, something which might seriously hamper identification and tracing.

In view of these considerations it did not seem wise to use the above mentioned patient groups as controls.

II. *Controls obtained by «Pairing».*

A. Identify birth certificates of patients and use as a control the next person in the same area, of the same sex, and born on the same day. This would provide excellent controls, but to be satisfactory each control must have been alive at the time the diagnosis of syphilis was made in the patient with which it was compared. It was obvious, however, that retrospective identification of birth certificates and prospective identification of the individuals in the control, particularly the latter, would be very difficult, if not impossible. Further, the method of procedure would be time-consuming to no small extent: we knew that our patients mostly came from the lower socio-economic classes and that they lived through a period of time when not only infant mortality, but also mortality during the first years of childhood and during adolescence, was relatively high. It was therefore to be expected that a fair proportion of the individuals in the control group had died before they had reached the required ages. In all such instances another person would have had to be picked out, and again we would have had no guarantee that this person also had not died before reaching the required age.

Finally, even if we had succeeded in establishing a control group by this method, there was another and very important shortcoming connected with it. Since the individuals in the control group would be drawn from the same socio-economic stratum as the patients, we would have to anticipate a rather high proportion of the former sooner or later to contract syphilis, and we would be unable to determine to what extent this might have taken place. Under these circumstances, we felt that this method of procedure offered no satisfactory solution to our problem and had to be discarded.

B. «Pairing» by age, sex, socio-economic class (occupation) and locale at time of diagnosis on patients in study group. Theoretically, this would seem to be the best method of all, but the question of just where the «pairing» information might come from immediately arose. If the Oslo Population Register had been in operation all through the period in question (1891—1910), the files of that institution might have formed the starting-point for providing the necessary data. As mentioned previously, however, the Register was not established until 1906, and the Census lists available could not be utilized because Census was naturally only taken at relatively long intervals. (For a detailed description of the Population Registers and the Census lists mentioned here see p. 76). As far as we were able to ascertain there was actually no way of providing the desired «pairing» data, and if only for this reason the method had to be discarded. However, even if it would have been possible to establish a control group by this method, the use of it would have been connected with such serious difficulties that it probably would have had to be discarded under all circumstances. First, by picking controls so close to the patients as to socio-economic status and other indices, it is obvious that we would have to expect a fair proportion of the individuals of the control group to be syphilitics, or at least potential syphilitics. As mentioned previously, the median age of the patients in the study group was calculated to be 70—74 years at the time of the investigation (1949—1951) (see p. 85), and thus we could anticipate that the majority of them would have died during the intervening years. And this, of course, would also be true of the individuals in the control group. Therefore, it would be extremely difficult, not to say impossible, to rule out syphilis (treated or non-treated) among these persons, something that would again bring into the picture an unknown factor of considerable importance and subtract from the value of the comparisons, especially if the control group was of the same size as the study group. Second, if we had chosen to study the total material (the 1,404 patients in our study group) the method would have necessitated the inclusion of a control group of the same size, making a total of no less than 2,808 persons to be traced and identified according to an elaborate and strict «search order». The difficulties of tracing persons over such long periods of time could easily be anticipated, and also that it would be time-consuming to no small extent. With the relatively limited time at our disposal, tracing such a great number of persons would have been impossible. The only way out then, if we had chosen this method. would have been to cut the study group in half and pick out the same number of controls. This, it seems, would have been a rather risky procedure in view of the fact that sub-grouping according to such factors as for example sex and age is so essential in the study of syphilis, and we might very well have found ourselves in a position where the figures were too small for significant comparisons.

C. «Pairing» according to similar indices as those mentioned under point B by means of the records of the admitting agencies. (See pp. 57—59 for detailed description of admitting agencies). As for the Oslo Bureau of the Indigents, which was the admitting agency in the majority of instances (61.6 per cent), it might have been possible to find individuals who were similar to the syphilitics in most respects, but here again we would have to reckon with a relatively great proportion of syphilitics or potential syphilitics in the control group, and for reasons already discussed, probably more so than in the control possibilities discussed under points A and B. And, we would have no way of finding out to what extent. Furthermore, we had to take into account the remaining 35.5 per cent of the patients who were admitted by the Oslo City Health Department, V.D. Division. Even if we could exclude syphilis in the individuals of this control group with a fair degree of accuracy at time of diagnosis on our own patients, it is obvious that these V.D. patients were potential syphilitics to such an extent that they could not be utilized as controls under any circumstances. The method was discarded on the basis of these considerations.

III. *Comparison of life experience with that of the population from which the patients came.*

After the methods discussed in the foregoing had been discarded, the possibility of using the general population as contrôls occurred to us as the only way out. That possibility was considered on the basis of the following important facts:

1. Our study group had been limited to patients residing in the City of Oslo, or in its close vicinity, at the time of diagnosis.
2. The great majority of the patients lived in the eastern sections of that city. (For a detailed description of the distribution of the patients according to residence see pp. 50—55.)
3. They belonged to the lower socio-economic strata of the population.

Official mortality rates are given separately for «all cities in Norway», which includes Oslo, and «all rural areas of Norway». One might think of using the former for eventual comparisons, but in view of the fact that our study group was drawn almost exclusively from the City of Oslo, it seemed desirable to limit the controls to residents of that city. However, the population of a city is not homogeneous as to socio-economic status, and there is every reason to believe that differences in this respect are also reflected in the mortality rates. Since our patients came mostly from the eastern sections of the city and belonged to the lower socio-economic strata of the population, it was felt that even better controls could be obtained if we limited ourselves to the population among which the patients lived, rather than using the total population of the city. In order to justify this method of procedure and test the above hypotheses as to mortality and socio-economic status in the various parts of the city, it would be necessary to have age, and sex, and cause-specific mortality rates, by decades, for both the eastern and the western parts of Oslo. (For details on the division of the city into one eastern and one western part, see pp. 50—51.) Since a comparison along these lines between the western and eastern population groups of Oslo had never been done, and no figures grouped according to our principles existed, it was decided to do a regional study of the mortality of the City of Oslo by age, sex, cause and decade, comparing the western and eastern populations, and at the same time provide mortality data for appropriate study group and eastern population comparisons.

Chapter V.

GENERAL RESULTS

Tracing.

In table 21 is presented the outcome of our tracing efforts when the investigation was closed (August 1951). It will be seen that a little more than two—thirds of the total number of patients (67.8 per cent) have been classified as «Known» (males 74.2 per cent and females 64.9 per cent). When those on whom limited follow-up information is available are added (the «Partially Known») the total observed rises to 81.6 per cent (males 83.8; females 80.7). While many of the «Partially Known» have not been followed over any great length of time, they are of no small importance in connection with the course of the untreated disease in the early years of the infection. The «Unknown» group constitutes close to one-fifth of the total (18.3 per cent) with no appreciable difference between the sexes (16.1 and 19.3 per cent for males and females respectively).

There are many reasons why the «Known» groups are no larger. The many difficulties in retrospective studies requiring the tracing of patients over long periods are well known. Of particular importance in our series of patients are their socio-economic status and the effect of improperly functioning registration during the early years. The socio-economic status of these individuals was generally such that instability as to type and place of work, together with residence, had to be expected, something which again would result in movements within the country itself, and, for a substantial number, in emigration, particularly to the United States at the turn of the century. (See quotation from Harrison, p. 25). It is further reasonable to assume that this instability to some extent contributed to poor registration, which of course, plays a very important role in view of the very many years (forty to sixty) which have elapsed since the patients were first discharged from our hospital. Lack of accurate registration, naturally, would make tracing more complex, and the difficulties were no doubt aggravated by the fact that the Population Registers, with their systematic recordings, were developed only after fifteen years of the period with which we are concerned (1891—1910) had already passed.

Table 21.

1951-Status «Known» (Living and Dead), «Partially Known», and «Unknown» of Study Group of 1,404 Patients, by Sex.

Tracing status		Male		Female		Total	
		No.	Per cent	No.	Per cent	No.	Per cent
«KNOWN»	Living	72	16.1	187	19.5	259	18.4
	Dead	259	58.1	435	45.4	694	49.4
	Subtotal	331	74.2	622	64.9	953	67.8
«PARTIALLY KNOWN»		43	9.6	151	15.8	194	13.8
Subtotal		374	83.8	773	80.7	1147	81.6
«UNKNOWN»		72	16.1	185	19.3	257	18.3
Total		446	100.0	958	100.0	1404	100.0

Explanation of terms:

«Known» — Patients with definitely classifiable «end points» — alive during the investigation period or time of death established.

«Partially Known» — Patients with one or more observations during the years following from Boeck's department, but not to same «end point» of the «Known».

«Unknown» — No observations following discharge from Boeck's department.

The lower proportion of «Known» in females could be anticipated. The great majority of our female patients being single, it was only natural that change of name through marriage would take place in a considerable number of cases, and this factor in all probability accounts for the greater part of the difference found.

Table 22.

Sex Distribution of Original Material Compared with That of Study Groups «Known» and «Known» plus «Partially Known».

	Males		Females		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Original material	446	31.8	958	68.2	1404	100.0
Study Group: «Known»	331	34.7	622	65.3	953	100.0
Study Groups: «Known» plus «Partially Known»	374	32.6	773	67.4	1147	100.0

Table 23.

Age Distribution of Original Material Compared with That of Study Groups «Known» and «Known» plus «Partially Known».

Part I. Males.

Age — groups	Original material		Study Group «Known»		Study Groups «Known» + «Partially Known»	
	No.	Per cent	No.	Per cent	No.	Per cent
0 — 4	23	5.2	20	6.0	22	5.9
5 — 9	6	1.3	5	1.5	5	1.3
10 — 14	3	0.7	3	0.9	3	0.8
15 — 19	56	12.6	43	13.0	50	13.4
20 — 24	152	34.1	108	32.6	123	32.9
25 — 29	103	23.1	72	21.8	83	22.2
30 — 39	68	15.2	52	15.7	57	15.2
40 and over*	35	7.8	28	8.5	31	8.3
Total	446	100.0	331	100.0	374	100.0
Mean age	25.6 years		25.5 years		25.5 years	
Mean age 15 — 39	25.4 years		25.4 years		25.3 years	

Part II. Females.

0 — 4	25	2.6	24	3.9	25	3.2
5 — 9	10	1.0	8	1.3	9	1.2
10 — 14	6	0.6	6	1.0	6	0.8
15 — 19	218	22.8	131	21.1	173	22.4
20 — 24	373	38.9	225	36.2	292	37.8
25 — 29	159	16.6	105	16.9	127	16.4
30 — 39	109	11.4	78	12.5	89	11.5
40 and over**	58	6.1	45	7.2	52	6.7
Total	958	100.0	622	100.0	773	100.0
Mean age	24.3 years		24.3 years		24.2 years	
Mean age 15 — 39	23.7 years		24.1 years		23.8 years	

* Average age: Original material — 48 years.
Study Groups:
«Known» — 47.9 years.
«Known» plus «Partially Known» — 48.3 years.

** Average age: Original material — 46.4 yars.
Study Groups:
«Known» — 43.5 years.
«Known» plus «Partially Known» — 44.4 years.

Representativeness of «Known» and «Partially Known» of the Study Group Based on Comparisons with the Original Material.

The following comparisons have been made in order to determine whether the tracing process utilized here has resulted in a group about which it can be said that the basic characteristics of the original material have been retained to such a degree that no appreciable selection has taken place, especially with reference to the sex and age distribution, the distribution according to year of discharge from Boeck's department and the distribution relative to length of stay in hospital.

Turning to the sex distribution (table 22) it will be seen that there is only a small deviation from the original material in the study group «Known», and that the sex distribution of the combined groups «Known» plus «Partially Known» is practically identical with that of the original material. The similarity is also seen when these groups are compared according to age, the mean age for the three groups being respectively 25.5, 25.5 and 25.6 years in males, and 24.3, 24.2 and 24.3 years in females (see table 23, Parts I and II).

Table 24.

Distribution of Patients According to Year of Discharge from Boeck's Department, by 5-year Groups and by Sex. (A Comparison between the Original Material and Study Groups «Known» and «Known» plus «Partially Known»).

Part I. Males.

Year of Discharge	Original material		Study Group «Known»		Study Groups «Known» + «Partially Known»	
	No.	Per cent	No.	Per cent	No.	Per cent
1891—1895	200	44.8	145	43.8	167	44.7
1896—1900	135	30.3	101	30.5	113	30.2
1901—1905	82	18.4	61	18.4	68	18.2
1906—1910	29	6.5	24	7.3	26	6.9
Total	446	100.0	331	100.0	374	100.0

Part II. Females.

1891—1895	317	33.0	181	29.1	249	32.2
1896—1900	314	32.8	199	32.0	248	32.1
1901—1905	224	23.4	156	25.1	180	23.3
1906—1910	103	10.8	86	13.8	96	12.4
Total	958	100.0	622	100.0	773	100.0

Table 25.

Distribution of Patients According to Length of Stay in Hospital, by Sex. (A Comparison between the Original Material and Study Groups «Known» and «Known» plus «Partially Known»).

Part I. Males.

Length of Stay in Hospital. Months	Original material	Study Groups	
		«Known»	«Known» + «Partially Known»
0*	70	51	58
1	102	72	81
2	108	81	92
3	80	62	70
4	40	28	32
5	22	16	19
6	9	8	8
7	9	7	8
8	1	1	1
9	3	3	3
10	1	1	1
11 and over	1	1	1
Total	446	331	374
Median length of stay	2.7 months	2.8 months	2.8 months

Part II. Females.

0*	38	26	32
1	143	90	107
2	198	134	163
3	175	103	140
4	159	115	139
5	101	66	79
6	46	32	37
7	40	22	30
8	24	18	21
9	12	5	7
10	12	6	9
11 and over	10	5	9
Total	958	622	773
Median length of stay	3.9 months	3.8 months	3.9 months

*0: Less than one month.
1: Between one and two months.
2: Between two and three months. etc.

Table 24, Part I, covering the distribution of male patients according to year of discharge from Boeck's department, reveals good agreement between the original material and the groups of the analysed sample in this respect too. It will be noticed, however, that among the female patients (Part II) we have found comparatively fewer of those discharged during the period 1891—1895 and a relatively larger number of those from the last period 1906—1910. The differences among females are small and hardly of importance. Otherwise there is satisfactory accordance between the original material and the «Known» and «Partially Known» of the study group. By and large the results reveal that year of discharge has only influenced the tracing results to a minor extent, if at all.

With reference to length of stay in hospital (table 25, Parts I and II) comparisons along the same lines show that the median length of stay in hospital is practically identical in the three groups. Hence the study group has not been unduly weighted with patients who might have had a somewhat longer, or shorter hospital stay originally, and who therefore might have differed also in respect to the course of the disease during the early stages of the infection.

As far as the above comparisons go, it can be concluded that the tracing process has not led to any important degree of selection as regards basic characteristics such as sex and age distribution, year of discharge from Boeck's department or length of stay in hospital, and the group studied, therefore, can be considered as being representative within the limits set by the indices used.

Collection of Clinical Data.

A. *Number of Observations.*

Table 26 shows a frequency distribution of the number of observations on the patients classified as «Known» and «Partially Known» and has in the main been constructed to illustrate quantitatively rather than qualitatively the extent to which these patients have come under medical observation. It will be seen that the mean number of observations in the «Known» group of patients is 3.8 (approximately 4), whereas the mean number of observations on patients we have only followed for a limited period of time (group «Partially Known») is 2.7, or about one observation less.

These means include the original observation of Boeck. In order to get an idea of the number of observations exclusive of the original and the final, these means are adjusted and it is found there were on the average two observations per person during the interim period.

B. *Treatment.*

The question of the time, type and amount of specific treatment received by the patients in this series, is an important one if we are to answer questions

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Table 26.
Number of Observations on Patients in Study Groups «Known» and «Partially Known».

Number of observations.	«Known»		«Partially Known»		Total	
	Number of patients.	Number of observations.	Number of patients.	Number of observations.	Number of patients.	Number of observations.
1	—	—	—	—	—	—
2	326	652	106	212	432	864
3	220	660	58	174	278	834
4	160	640	23	92	183	732
5	86	430	2	10	88	440
6	65	390	2	12	67	402
7	41	287	1	7	42	294
8	15	120	2	16	17	136
9	23	207	—	—	23	207
10	6	60	—	—	6	60
11	4	44	—	—	4	44
12	4	48	—	—	4	48
13	—	—	—	—	—	—
14	2	28	—	—	2	28
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	—	—	—	—	—	—
18	1	18	—	—	1	18
Total	953	3584	194	523	1147	4107
Mean no. of observations.	3.8		2.7		3.6	

as to the natural course of this disease. Our basic question in this respect (p. 72) was: What is the natural course of untreated or highly inadequately treated early syphilis, with no subsequent treatment; with some subsequent treatment; or with an unknown amount of subsequent treatment? Two questions are implied here: Are we dealing with patients left untreated during the earliest stage of the infection? And, to what extent have these patients received treatment during the period between the first discharge from Boeck's department and the last observation?

As shown in the section on treatment in the Chapter «Description and Characteristics of Study Group», it can safely be said that these patients for all practical purposes were left untreated during the earliest phase of the infection. To answer the second question is considerably more intricate, and conclusive proof that the patients have not received treatment in the interim can hardly be provided. However, it is possible to introduce a chain of circumstances which give evidence that any treatment received by these patients was highly inadequate as judged by acceptable standards. This evidence both circumstantial and factual is convincing and consists of two parts: a) the historical development of available «adequate» treatment; and b) the actual amount of treatment known to have been received by our patients.

a) *Outline of the varying possibilities for specific treatment of syphilis in Norway during the periods of time through which our patients may possibly have lived.*

1891—1910: Mercury alone. In the majority of the cases as mercury rubs, but also in the form of Hg. pills (calomel), Hg. injections (bichloride of mercury), and mercury «bibs». Amounts according to clinical response rather than according to fixed schedules.

1910—1920: 1. Arsenicals and 2. Mercury. The arsenicals introduced during the latter half of 1910, but at first employed in relatively small quantities, either alone or combined with mercury rubs. Amounts determined by clinical development, varying between three and six injections, rarely exceeding six (Krefting, 1913).

1920—1930: 1. Arsenicals, 2. Bismuth and 3. Mercury. Combined courses of arsenicals and mercury used. Courses consisted of 12 to 15 injections of arsenicals plus 80 to 100 mercury inunctions in females, and 12 to 15 injections of arsenicals plus 15 injections of mercuric salicylate in males. Two courses usually given. Bismuth not frequently employed, although slowly replacing mercury through this period (Bruusgaard, 1932).

1930—1946: 1. Arsenicals, 2. Bismuth and 3. Mercury. About 1930 introduction of combined intermittent courses consisting of 16 injections of arsenicals and 16 injections of Bismuth to the course, and two or more courses according to serologic response. Mercury very rarely employed (Bruusgaard, 1937).

1947—1950: 1. Arsenicals, 2. Bismuth and 3. Penicillin. Combined intermittent courses the method of choice until January 1947, at which time penicillin was first introduced in Norway (Danbolt, 1950). At first a combined therapy, with arsenicals and Bismuth added, as follows: 6 million units of penicillin, 6 injections of arsenicals and 12 of Bismuth. This schedule in operation until January 1951, when penicillin alone became standard treatment.

In the period 1891—1910 mercury was the only specific drug available, and this excludes the possibility of any of the patients having received adequate treatment during these years, even under maximal conditions.

During the decade 1910 until about 1920 we had the arsenicals, but their use was in the experimental stage and doses were far from adequate, even though this was presumed to be remedied to a certain extent through combination with mercury.

In the following decade, 1920—1930, the doses of arsenicals were increased considerably, but the standard treatment employed can hardly be called adequate, although the practice of giving two courses and the combination with mercury probably gave fairly good results.

From 1930 on it can be said that treatment was potentially adequate, without bringing up the issue of whether the British-Scandinavian intermittent treatment schedules were less efficient than the consistent treatment recommended by American syphilologists.

In 1947 penicillin became available, but this is only of slight importance to us, because those of our patients who had survived would now have had their infection for about forty to sixty years.

This outline covers such treatment as was generally given for fresh syphilis at any given period, thus constituting maximal treatment. Before 1930, patients with latent syphilis, «benign» tertiary, cardiovascular or neurosyphilis were not as a rule given as much treatment as described above, these manifestations usually being treated according to the clinical picture, regular courses rarely being employed. In 1930, however, it gradually became common practice, at least among leading syphilologists, to treat all cases of late syphilis (except perhaps cardiovascular) with doses equalling or coming very close to those used in fresh syphilis, and also according to fixed schedules. But by 1930 our patients had already had their infection from twenty to forty years. And there seems to be sufficient grounds for counting on our patients having received each period's potential maximal treatment only in rare instances, because at the time their manifestations would be diagnosed, the infection would usually have progressed far into the late stages. Theoretically, therefore, there is little probability that any great number of these patients, even under maximal conditions, have received treatment which, according to present-day definitions, can be called adequate.

b) *Amount of treatment found to have been given our patients.*

In order further to illuminate the problem of treatment, table 27 has been constructed. Only the group «Known» has been included, and the information on treatment is based on the data found among the close to 3,600 clinical observations gathered on the patients. (See table 26.) By treatment is here meant the sum of all treatment given each patient from the onset of the infection until the final observation. As mentioned in the section on treatment in Chapter III (p. 62) 6 Hg. inunctions have arbitrarily been set as equalling one Bismuth unit. In this table it should be remembered that the aggregate does not take into account that the treatment may have been received with intervals

Table 27.

«Known» Patients Grouped According to Sum of All Treatment Found to Have Been Given from the Onset of Infection to the «End Point», by Sex, and by Amount for Those Treated.

Status		Male No.	Male Per cent	Female No.	Female Per cent	Total No.	Total Per cent
Patients not found to have received treatment		276	83.4	519	83.5	795	83.4
Patients found to have received treatment	No. of As and/or Bi. Units						
	40 and over	4	—	11	—	15	—
	20—39	9	—	15	—	24	—
	10—19	14	—	19	—	33	—
	Subtotal	27	8.2	45	7.2	72	7.6
	1—9	28	8.4	58	9.3	86	9.0
Total		331	100.0	622	100.0	953	100.0

of many years, and without any kind of regularity; in fact this seems to have been the case in the majority of instances. The table discloses that for 83.4 per cent of the patients we have not been able to ascertain that any treatment has been given, while the remaining 16.6 per cent have received some form of treatment. A bit more than one-half (or 9 per cent of total) of the latter group have only received highly inadequate treatment: 1 to 9 injections of arsenicals and/or Bismuth. This method of illuminating the problem leaves us with 7.6 per cent of whom it can be said that they have received adequate or near to adequate treatment. No appreciable difference between the sexes has been found. These figures lend weight to the assumption made on a theoretical basis in the forgoing paragraph, namely that it can be stated with relative safety that we are dealing with a group of syphilitics who — broadly speaking — have been left untreated during the earliest phase of the infection, and that the same patients in the great majority of cases probably were left untreated — or at least were highly inadequately treated — also in the interim period or period of observation. In other words, it seems as if treatment could only to a relatively small degree have interfered with the natural course of the infection in our series, and in these times of almost universal treatment of syphilis such a material will in all likelihood never again be available for study. To what extent the treatment given has affected the end results, however, is close to impossible to determine, but the problem will be dealt with in considerably more detail in the following sections on the various complications.

Summary and Conclusions.

1. The present investigation was closed in August 1951.
2. The outcome of our tracing efforts was:

   More than two—thirds of the total number of patients (67.8 per cent) were classified as «Known» (74.2 per cent of the males, and 64.9 per cent of the females).

   When those on whom limited information was available (the «Partially Known») were added, the total observed rose to 81.6 per cent (83.8 per cent of the males, and 80.7 per cent of the females).

   The remainder (16.1 and 19.3 per cent of the males and females respectively) represented total loss.
3. The problem of loss from observation was discussed.

   It is held that emigration, migratory movements within the country itself, and poor registration, are factors possibly responsible for losses.

   Males were easier to locate than females. Difficulties in tracing of females due to change of name through marriage in all probability accounted for the greater part of this difference.
4. The «Known» and the «Partially Known» of the study group were compared with the original material with reference to sex and age distribution, the distribution according to year of discharge from Boeck's department, and the distribution relative to length of stay in hospital.

   It is concluded that the tracing process has not led to any important degree of selection as regards these basic characteristics, and the group studied, therefore, is considered as being representative within the limits set by the above indices.
5. The extent to which the patients had come under medical observation was considered from a quantitative point of view.

   Total number of observations on the patients classified as «Known» and «Partially Known» was 4,107. The mean number of observations in the «Known» group was 3.8, and in the «Partially Known» group it was 2.7. Excluding the original and the final observation, there was on an average 2 observations per person during the interim period.
6. Finally it was discussed to what extent the patients might have received specific treatment between the time of original discharge from Boeck, and the time of final observation.

   It is concluded that we are here dealing with a group of syphilitics who, broadly speaking, was left untreated during the earliest phase of the infection, and that the same patients in the great majority of instances, probably were left untreated — or were highly inadequately treated — also in the interim period, or period of observation. The indication is, therefore, that treatment can only to a relatively small degree have interfered with the natural course of the infection in the present series.

Chapter VI

CLINICAL SECONDARY RELAPSE

There are three *early* indications of the effectiveness of antisyphilitic treatment: The rapidity of healing of lesions, serologic tests and freedom from early relapsing lesions. Although there is considerable literature on relapse following various types and amounts of treatment, no extensive data are available as to what happens in untreated syphilis. The public health importance of this is obvious and an attempt will be made with this material to show just how important clinical secondary relapse is among patients who receive *no* treatment for secondary syphilis.

I. Excerpts from and Comments on the Literature.

Stokes et al. (1944 — p. 622) leave no doubt as to the importance of this manifestation, «Syphilis, as we have already remarked, is the relapsing disease par excellence. The ability to recognize relapse, to know when and where to look for it, to understand its influence on the transmission of the disease, and to control it, becomes an essential part of the equipment of every physician who assumes charge of a syphilitic patient.»

Causes and Definition.

We do not know the quantitative aspects of the natural course of the syphilitic infection in its entirety, and here we are confronted with a similar lack of knowledge. The reasons for this limited information has been given a very precise formulation by Moore (1944 — pp. 22—23): «There is no information available as to the incidence of infectious mucosal relapse in untreated syphilis because no observer ever has followed, or will be able to follow, a large series of untreated patients with *frequent*[1] recheck examinations. Since 1493, most patients with early syphilis, if recognized, have received some form of treatment. Those who were not treated were unrecognized; if recognized, were not followed.» The concepts of the causes of clinical secondary relapse, therefore,

[1] Italicized by Moore.

are almost entirely based on results arrived at through observations of treated patients, and it is not at all surprising that inadequate or irregular treatment forms an essential part of practically all the definitions given by modern authors. Stokes et al. (1944 — p. 629): «. . . This brings out the fundamental essential of any working definition of cutaneous and mucosal relapse, which is *an appearance or reappearance of lesions after treatment has been suspended*».[1] They continue (ibid. pp. 629—630): «Without previous treatment, relapse for the purpose of general definition does not exist, all other lesions being regarded as progression.» Kampmeier (1943 — p. 194): «Clinical relapse, or recrudescence, is uncommon in untreated acute syphilis. By far the majority of cases of relapse result from inadequacy of antisyphilitic treatment . . .» Thomas (1949 — pp. 9—10): «As a matter of fact, I have never seen true clinical relapses of secondary syphilis except in patients who had had insufficient treatment during the early stages of the disease. I do not believe that relapses occur in the untreated stage of secondary syphilis. During the untreated secondary stage lesions may appear progressively in different sites, but the progressive manifestations are not evidences of relapse but of a persistence of secondary syphilis.» Thomas continues (ibid. p. 10): «From a *clinical*[2] point of view secondary syphilis terminates when all demonstrable secondary lesions have completely disappeared . . .» Marshall (1948 — p. 173): «Muco-cutaneous relapse may occur during treatment, especially if this is irregular or intermittent. This is commonest in patients beginning treatment in the primary sero-negative stage, less frequent in primary sero-positive cases, and least in secondary cases. The development of cutaneous immunity probably explains this finding, which is paradoxical in that, with regular adequate treatment, the sooner this is begun the better the prognosis in early syphilis. Such relapses usually occur during a phase of treatment with a heavy metal alone.»

In earlier textbooks, however, differing concepts of the causes of clinical secondary relapse are expressed, an example being Meirowsky and Pinkus (1923 — p. 58): «Wenn wir den 2—4 Jahre ausfüllenden Ablauf der sekundären Syphilis an Haut und Schleimhaüten zu überblicken versuchen, so können wir einen recht regelmässigen periodischen Ablauf konstruieren, der an die Entwicklungsperiode tierischer Parasiten, besonders der Trypanosomen erinnert. Wie die erste Eruption etwa ein Vierteljahr zur vollen Ausbildung braucht, *so scheint es auch mit den Recidiven zu sein.*[3] Diese Erfahrung der alten Kliniker bildet die Grundlage der chronisch intermittierenden Quecksilberbehandlung. Alle drei Monate vermutete man die in ein Ruhestadium verfallenen Syphiliserreger, die von der vorigen Behandlung nicht erreicht worden waren, im neuen Anwachsen. Die Amplitude der Spirochätenentwicklung scheint drei Monate

[1] Italicized by Stokes.
[2] Italicized by the present author.
[3] Italicized by the present author.

zu betragen, öfter aber an Höhe zu wechseln, so dass nicht immer ein dreimonatlicher, sondern nur ein sechsmonatlicher, auch einmal ein neunmonatlicher Rhytmus hervortritt. *Er erscheint oft in reinster Form, wenn kein Eingriff der Behandlung die sichtbaren Erscheinungen beseitigt hat.*[1] In diesem Fall, wenn ein derberes Exanthem länger als drei Monate zur Selbstheilung braucht, sind zu gleicher Zeit alte Reste der einem mit frischen Erscheinungen der nächsten Eruption zusammen aufzufinden. Die im allgemeinen kürzere Zeit der Selbstheilung der Exantheme bringt aber *meistens eine symptomlose Pause zwischen zwei Hauteruptionen hervor.*»[1] The authors continue (ibid.): «*Auf diesen Rhytmus hat die Behandlung keinen nennenswerten Einfluss . . .*»[1]

It is noteworthy how strongly modern authors emphasize treatment in their definitions of clinical secondary relapse, and the only reservation made lies in the statements that all later lesions which occur (i.e. without treatment) must be regarded as progression. Meirowsky and Pinkus on the other hand, stress the rhytmic course of secondary syphilis and the relapses, maintaining that this rhytmic course is found in its purest form in untreated cases, and also that treatment has no appreciable effect on it. There is a possibility that clinicians at the time of Meirowsky and Pinkus had an opportunity to observe more cases of untreated syphilis than have modern authors, and certainly they saw more cases influenced little by treatment (such as by mercury inunctions and small doses of salvarsan). These facts may have led to their concept as to the course of the infection at this stage of the disease. However, these beliefs of Meirowsky and Pinkus evidently are not based on the observation of a series of untreated patients, but rather on clinical impressions gained through the study of individual cases (as demonstrated by the fact that no figures are given). Consequently this concept rests on a more or less hypothetical background and must be judged accordingly. Their theory, nevertheless, demonstrates a considerable divergence of opinion on the causes of clinical secondary relapse as expressed by modern and earlier authors.

If we accept the hypothesis that the course of the syphilitic infection at this stage of the disease really is rhythmic in character, symptoms and signs disappearing and reappearing with symptom-free intervals without treatment, this means we shall have to consider the possibility that clinical secondary relapse develops as part of the natural course of the disease and is not caused by inadequate or irregular treatment in itself. The validity of this hypothesis can be tested in the present material.

Occurrence.

As already mentioned we do not know the incidence of clinical secondary relapse in untreated syphilis, and the figures found in the literature are all

[1] Italicized by the present author.

Table 28.

Clinical relapses of early type in cases receiving different amounts of treatment, reported by Stokes, Usilton et al. Co-operative Clinical Group, U. S. A. (1934)

Treated with	Cases	Per cent Relapsed		Total
		Muco-cutaneous	Ocular	
Less than 10 doses arsphenamine*	4094	7.7	1.0	8.7
10 to 19 doses As.*	1645	4.0	0.2	4.2
20 to 29 doses As.*	754	3.6	0.3	3.9
30 to 39 doses As.*	244	1.2	—	1.2
40 or more doses As.*	94	1.1	—	1.1

* Presumably Bi og Hg. also given.
Reproduced from Harrison, L. W.: Venereal Diseases and Life Assurance, Brit. J. Ven. Dis., 16: 1, 1940.
(Harrison's table II).

based on groups of patients treated with differing amounts and kinds of treatment. Several modern authors present certain aspects of the findings of the Cooperative Clinical Group, and the figures vary somewhat from author to author. It is not clear why this is so, but it may be a reflection of difficulties in interpretation of the C.C.G.[1] data, differing approaches in studying it, or shortcomings of the data themselves. Table 28 on the relation of clinical relapse to treatment is taken from Harrison (1940), who has reproduced C.C.G. material from Stokes, Usilton et al. Stokes et al. (1944 — p. 623) write: «Statistical estimation of the incidence of infectious recurrence and mucocutaneous relapse is influenced greatly by the stage of syphilis represented by the material under consideration. For example, if patients under observation for less than six months are excluded, it was found in the Cooperative Clinical Group surveys that the proportion of mucocutaneous relapse to the total of cases was materially affected. In the collected material of this group, among 5952 cases, regardless of observation period, mucocutaneous relapse occurred in 6.05 per cent of patients . . . In patients observed for six months or more, the incidence was 12.1 per cent . . .» Moore (1944 — p. 25) says: «The data of the C.C.G. relate almost entirely to arsphenamine (606), but probably hold good

[1] «Cooperative Clinical Studies in the Treatment of Syphilis» is a comprehensive investigation started in the U.S.A. in the late 1920's by a committee consisting of five directors of important clinics together with four representatives (including one statistician) from the U.S. Public Health Service. This committee has come to be known as the Cooperative Clinical Group (C.C.G.).

for other arsphenamines and for mapharsen (arsenoxide). They are presented graphically in Fig. 2.[1] Since the incidence of infectious mucocutaneous relapse in untreated patients is unknown, no comparison can be made as between treated and untreated groups. Among treated patients the incidence of infectious relapse shown in Fig. 2 is a minimum, for it represents only patients actually observed; because of the triviality of relapsing lesions, many (perhaps most) such patients are not observed at the time. Of those who receive only 1—4 injections of an arsenical drug, however, nearly 65 per cent later develop infectious relapse. When 5—9 injections are given, the proportion drops to about 12.5 per cent; with as many as 30 injections (now, of course, with concomitant heavy metal) to about 1.2 per cent.» It will be noted that in table 28 ocular forms of relapse have been included, whereas the figures given by Stokes et al. relate to mucocutaneous relapse, and Moore's to infectious relapse, probably meaning that some of the non-infectious forms have been omitted by the last authors. It is not quite clear, however, whether Moore's figures have to do exclusively with proven darkfield positive lesions or include also potentially infectious forms, whereas Stokes' use of the expression mucocutaneous relapse may indicate that he has taken in all lessions of the skin and the mucous membranes irrespective of infectiousness. Otherwise Stokes et al. (1944 — p. 672) in discussing the prognostic significance of secondary and serologic relapse, write: «Cooperative Clinical Group results (Stokes and coworkers) (observation period too short) showed a relapse expectancy of 19.7 per cent including all forms, of which, when observed for more than six months, 12.1 per cent was mucocutaneous, 3.4 per cent asymptomatic neurosyphilis, 4.1 per cent symptomatic neurosyphilis, and 0.9 per cent cardiovascular syphilis.» Kampmeier (1943) reports 6.9 per cent recurrent manifestations among 1,837 cases of acute syphilis diagnosed at the Vanderbilt University Hospital Syphilis Clinic. For occurrrence of clinical secondary relapse in patients treated with different amounts and types of penicillin see subsequent section in this chapter on time relationships.

There is general agreement that the relapse rate in early syphilis is dependent not only on treatment but also on stage of the infection at the time treatment is begun. Moore (1944 — p. 23) presents the following table (our table 29) and writes: «As is shown by the data of the C.C.G. (Table 1), infectious relapse is paradoxically more frequent in primary than in secondary syphilis under identical conditions of treatment. This is surely due to the fact that by the time the patient has developed the generalized tissue reaction of secondary syphilis, his own resistance against the infection is enhanced. The data are convincing evidence that in this respect, at least, primary syphilis should be treated as energetically and for as long a time as secondary syphilis.»

[1] Figure not reproduced.

Table 29.

Incidence of Infectious Relapse as Related to Stage of Disease at the Start of Treatment

(Data of the C. C. G.)

Stage of disease	Total cases observed	Percentage of patients developing infectious relapse
Seronegative primary	342	16.4
Seropositive primary	585	20.2
Early secondary	2252	9.5

Reproduced from Moore, J. E.: «The Modern Treatment of Syphilis», 2nd ed. Charles C. Thomas, Springfield, Ill., 1944.
(Moore's table 1, p. 23).

The incidence of secondary relapse in Copenhagen, Denmark, as reported by Lomholt (1936), for two different periods during the salvarsan era, is presented in tables 30 and 31. Lomholt remarks about the findings in the first table (p. 33): «In the first years of salvarsan therapy infectious relapse was observed in more than one-fifth of treated syphilitics. Pontoppidan has rendered an account of the materials from the Rigshospital and from Rudolph Bergh's Hospital (table 2[1]). The patients were given a combined salvarsan-mercury treatment consisting generally of 2—3 salvarsan injections and a single series of mercurial inunctions (30—50). In several cases 6—10 calomel injections were given instead of the inunctions. Only a small percentage of these patients have been under any protracted, intermittent course of treatment.» About table 30 Lomholt says (ibid. p. 6, Part II): «Probably in some of these cases it was a matter of reinfection or superinfection rather than a relapse. Most of the clinical skin manifestations that have occurred after the treatment, however, have been relapses. As in most instances it is not possible clinically to differentiate between relapse and reinfection, they are all put down under the designation «recurrence». Undoubtedly this gives no essential shift of the figures . . .» In connection with table 31 he writes further (ibid. p. 33): «After the venerologists went on to give more and stronger doses of salvarsan (6—7) in connection with a strong, often combined (salv. +Hg or Bi) intermittent treatment in the first years of the infection, the contagious relapses have decreased considerably in number. This is illustrated very strikingly in an account of a large material from the Rigshospital and Rudolph Berg's Hospital (1797 cases from 1920—27) as shown in Table 3 (in comparison with Table 2) . . .» It is notable that these findings do not seem to corroborate the concept that secondary relapse is to be

[1] Reproduced in table 30.

Table 30.

Frequency of Clinical Recurrences in 727 Cases of Fresh Syphilis, Treated in the Rigshospital and Rudolph Bergh's* Hospital between 1910 and 1914, by Stage of Disease at Start of Treatment.*

(After B. Pontoppidan's investigations)

Stage of disease	Total number of cases observed	Patients developing clinical recurrence	
		No.	Per cent
Seronegative primary	142	16	11.3
Seropositive primary	139	32	23.0
Secondary	446	112	25.1

* Copenhagen, Denmark.

Note: Among the total of 727 patients there were also found 87 serologic relapses (12.0 per cent), and among the 446 treated during the secondary stage 75 serologic relapses (16.8 per cent). The serologic relapses have been omitted from the present table.

Adapted from Lomholt, E.: «Course of Changes in the Spinal Fluid of Syphilitics. A Clinical and Catamnestic Study», Acta psychiat. et neurol., Suppl. XI, Levin & Munksgaard, Ejnar Munksgaard, Copenhagen, 1936.

(Lomholt's table 2, Part II, p. 6).

found more frequently in primary than in secondary syphilis. In the first series (table 30) the opposite has been found to be the case; in the second series, the figures are only slightly higher for primary syphilis and the differences are probably not statistically significant.

Multiple outbreaks. Kampmeier (1943 — p. 201) writes about this question: «Though secondary relapse usually occurs but once, multiple relapses may occur. Among the 80 cases in our clinic, 89 per cent experienced one relapse, 9.6 per cent two relapses, and 1.4 per cent three relapses . . .» Stokes et al. (1944 — p. 623) refer to the results from the Cooperative Clinical Group series: «. . . 86 per cent of them relapsing once, 11 per cent twice, 2 per cent three times and 1 per cent four times . . .» Neither of the authors gives any information as to possible re-treatment given the patients for their various multiple outbreaks, and how this may have affected the frequency.

Sex, and Age at Infection.

As to the influence of age in clinical secondary relapse Stokes et al. (1944 — p. 623) write: «. . . Relapse tends to be more frequent in the younger patient (33.3 per cent for patients under sixteen years and 30.9 per cent for patients between sixteen and twenty years; as compared with 23 per cent in patients over forty) . . .» The figures are taken from Cooperative Clinical Group and the University of Pennsylvania Studies and the differences do not seem striking.

Table 31.

Frequency of Clinical Recurrences in 1797 Cases of Fresh Syphilis, Treated in the Rigshospital and Rudolph Bergh's* Hospital between 1920 and 1927, by Stage of Disease at Start of Treatment.*

Stage of disease	Total number of cases observed	Patients developing clinical recurrence	
		No.	Per cent
Seronegative primary	217	16	7.4
Seropositive primary	339	16	4.7
Secondary	1241	51	4.1

* Copenhagen, Denmark.

Note: Among the total of 1797 patients there were also found 170 serologic relapses (9.5 per cent), and among the 1241 treated during the secondary stage 149 serologic relapses (12.0 per cent).
The serologic relapses have been omitted from the present table.

Adapted from Lomholt, E.: «Course of Changes in the Spinal Fluid of Syphilitics. A. Clinical and Catamnestic Study», Acta psychiat. et neurol., Suppl. XI, Levin & Munksgaard, Ejnar Munksgaard, Copenhagen, 1936.
(Lomholt's table 3, Part II, p. 6).

It is possible that the number of patients under sixteen and over forty was relatively small, so that the differences very well may be due to chance. In addition comes the question of treatment, the effect of which is close to impossible to evaluate in this connection. Also, on the basis of the results in the above mentioned studies Stokes et al. maintain that clinical secondary relapse is more frequent in males than in females. Kampmeier (1943 — p. 197) says among other things: «... The influence of sex and race on the incidence of mucocutaneous relapse is not of great significance. The factors influencing the apparent incidence in these respects are greater ease of recognition of genital recurrences in the male than in the female, ...»

Forms and Sites of Lesions.

Stokes et al. (1944 — p. 622) list the following forms of secondary relapse, and the frequency with which they occur:

«1. *Mucocutaneous relapse.*
2. *Serological Relapse.* — These two exceed all others in frequency and constitute, according to the large material of the Cooperative Clinical Group, 12.1 and 15.1 per cent respectively of the total number of early cases studied and under treatment for six months or more (3244).
3. *Ocular recurrences* (3.3 to 0.3 per cent depending on method of treatment)

include iritis, iridocyclitis, keratitis, neuroretinitis. The form of ocular relapse seen most often in Negroes is iritis.

4. *Neurosyphilitic relapse* either in the form of neurorecurrence in the strict sense (see p. 617) (2.9 per cent) or of asymptomatic neurosyphilis develops following a previous normal spinal fluid (3.4 per cent).
5. *Bone and joint lesions* (0.4 per cent), as forms of relapse, include particularly periostitis and osteitis . . .»

«6. *Visceral lesions* (0.03 per cent), especially hepatitis.

7. *Birth of a syphilitic child* to an apparently healthy and serologically negative mother who has syphilis.
8. *Infection of a sex partner with syphilis* in the absence of detectable clinical or serological relapse in the patient. The relative frequency of these forms of relapse can only be partly estimated but the percentage data given here from the Cooperative Clinical Group investigation are believed to be representative.»

Table 32.

Sites of Mucocutaneous-relapse Lesions

Site	Number
Genitalia only	18
Genitalia and buccal mucosa	8
Genitalia and skin	6
Genitalia, buccal mucosa, and skin	4
Buccal mucosa only	6
Buccal mucosa and skin	6
Skin only	29

Reproduced from Kampmeier, R. H.: «Essentials of Syphilology», J. B. Lippincott Company, Philadelphia, 1943.
(Kampmeier's table X, p. 201).

About the lesions of secondary relapse Kampmeier (1943 — p. 201) writes: «These may consist of either skin manifestations or moist erosions or mucous patches of the anogenital region or of the mouth and throat. A comparison of the type and distribution of secondary lesions with the same features of relapse lesions indicates that, if anything, the latter present a greater public-health hazard than the former. The site of the lesions in clinical secondary recurrence in our group was such that 62 per cent of the cases were potentially infectious. (This frequency is identical with that found by Stokes; namely, 61 per cent in 56 cases.) . . .» He continues (ibid.): «. . . The distribution — very similar to that described by Stokes in 56 cases — is shown in Table X.», which table is reproduced here (table 32).

Time Relationships.

Moore (1944 — p. 23): «Disregarding the factor of the kind and amount of treatment given, however, Fig. 1[1] shows the time relationships of infectious mucocutaneous relapse, based on our own experience and the monumental data of Fournier and of the C.C.G. Curve A represents the cumulative percentage likelihood of appearance of infectious relapse lesions as related to duration of infection. It shows that approximately 25 per cent of all relapses may be expected in the first six months, 55 per cent within the first year; 84 per cent by the end of the second, and 95 per cent by the end of the third year of infection . . .» Stokes et al. (1944 — p. 624): «The American figures of Moore and Kemp compare very closely with our own as to the time of relapse in cutaneous and mucosal lesions in early syphilis. These authors, in 55 cases (our series 56 cases) found that the average lapse from treatment was 8.1 months (University of Pennsylvania series 8.5 months) . . .» Stokes continues (ibid.): «In our Pennsylvania series 24 per cent relapsed in the first six months after onset of the infection and 31 per cent in the second six months, making a total of 55 per cent within the first year of the infection and 93 per cent before the end of the second year of the infection.» On a theoretical basis Thomas (1949 — p. 10) discusses the time relationship of clinical secondary relapse at considerable length: «. . . In an immunologic sense, the secondary stage of syphilis terminates only when the body tissues have attained a permanent refractory state toward early infectious lesions.» He continues (ibid.): «To understand the foregoing statement, it is necessary to know that, within 2 years after infection, *untreated*[2] syphilis produces immunologic changes in the host which, with rare exceptions, are permanent and make it impossible for the tissues to react to subsequent infection with the development of early syphilitic lesions. Thus, after the immunologic changes have become established, regardless of whether or not the syphilis is subsequently cured, reinfection may occur, but it occurs without the development of primary or secondary lesions. On the other hand, if the patient is treated before the refractory state is permanently established, reinfection or relapse is usually followed by the development of new early lesions.» . . . «The period required for the attainment of the refractory state in untreated individuals undoubtedly varies greatly and may be as long as 2 years in some cases. In most individuals permanent «immunity» to the re-development of early lesions probably occurs in much less than 2 years, but one cannot be certain in all cases that the refractory state is established by the time clinical signs of secondary syphilis can no longer be demonstrated.» Thomas continues (ibid. p. 11): «Such observations lead to the conclusion that individuals who receive no antisyphilitic treatment for 2 years following

[1] Not reproduced.

[2] Italicized by the present author.

infection, with extraordinarily rare exceptions, will never again react to the syphilitic virus with early dark-field positive lesions, even though reinfected or superinfected with heterologous treponemes ...» He states further (ibid. p. 13): «Prior to the advent of rapid treatment of early syphilis, infectious relapses were frequently seen during the course of irregular treatment with heavy metal and arsenical drugs. Patients who failed to receive treatment for several weeks or months and patients who received very small doses of arsenical drugs often suffered repeated infectious relapses. In some cases relapses recurred over as long a period as 4 or 5 years. Because infectious relapses were not uncommonly observed up to 5 years after infection, during irregular treatment, most syphilologists in the past taught that secondary syphilis might relapse over a period of 4 to 5 years. Actually, the delay in the development of this immunologic change beyond 2 years was due to the interference of inadequate and irregular treatment ...» Thomas further states (ibid.): «... This train of events in some cases continued for at least 4 to 5 years, provided patients had not lapsed from all therapy for at least 2 years ...» And finally he says (ibid.): «... Therefore, irregular or inadequate treatment of early syphilis prolongs the period of relapsing infectious lesions long after a permanent refractory state would have been established without treatment.»

Thomas' opinions on these problems can be briefly summarized as follows:

1. Clinical secondary relapse in the form of infectious lesions does not exist except in cases which previously have received inadequate or irregular treatment.
2. In untreated cases what Thomas calls the refractory state toward early infectious lesions usually is established within two years after infection, in the majority of cases much earlier.
3. Inadequate or irregular treatment may delay the development of the refractory state up to four to five years, provided the patient has not been left untreated for as long as two years.
4. In untreated individuals the refractory state ordinarily is established by the time clinical signs of secondary syphilis no longer can be demonstrated. (On this point, however, Thomas expresses himself somewhat cautiously, saying that one cannot be certain in all cases that the refractory state has been reached by the time the signs of secondary syphilis have disappeared.)
5. If the immunologic changes leading to the refractory state have taken place, the patient will not react with new early lesions on reinfection, but if he has been treated before the immunologic changes have become permanent, the reinfection or relapse will develop in the form of early infectious lesions.

Table 33.

Cumulative Relapse and Reinfection Rates at 18 Months Post Treatment

Treatment (Penicillin in million units)	Texas clinics Negroes		New York and Chicago clinics			
			Negroes		Whites	
	Cum. percentage relapse	Cum. percentage reinfection	Cum. percentage relapse	Cum. percentage reinfection	Cum. percentage relapse	Cum. percentage reinfection
0.3 Am. P.* Aq.†	18.0	9.6				
0.6 Am. P.* Aq.†			15.9	4.0	17.6	2.2
1.2 Am. P.* Aq.†	16.6	9.6	13.5	4.1	15.1	2.3
2.4 Am. P.* Aq.†			13.1	4.2	8.8	2.4
4.8 Am. (POB)°	4.1	10.6	8.1	4.3	2.1	2.4
2.4 or 4.8 G§ Aq.†	3.4	10.7	6.5	4.3	1.2	2.5
1.2*† + 0.32 Gm. As.			12.9	4.2	5.3	2.4
1.2*† + 0.6 Gm. Bi.	5.9	10.8				

* Amorphous penicillin.
† Aqueous solution.
° Peanut-oil-beeswax.
§ Crystalline penicillin G.

Reproduced from Merrell, M.: Estimates of Relapse and Reinfection Rates in Early Syphilis Treated with Penicillin, Am. J. Syph., Gonor. & Ven. Dis., 35: 532, 1951. (Merrell's table IV).

After penicillin was introduced in the treatment of syphilis, studies on relapse rates in patients treated with varying amounts of penicillin have been published (Merrell, 1951). The treatment was given at several cooperating clinics in the United States as part of a planned prospective evaluation study, through which an attempt was made to determine the efficacy of varying doses of penicillin as expressed by the relapse rates. Only *clinical* failures within eighteen months have been included in Merrell's evaluation. The follow-up is described by Merrell as follows: «... In the follow-up of cases, an attempt was made to see everyone every 4 weeks for the first year, every 3 months during the second year, and every 6 months thereafter. This was not accomplished, of course, and in setting up incidence rates for failures it was necessary to make certain assumptions. It was assumed that a person not actually observed in a given month, but observed later and found not to have failed, would have been a success if he had been observed in the intervening months. It was further assumed that the occurrence of any failure was within the month of discovery. These assumptions operate in the direction of minimizing the failure rates, but it has been found by checking the rates so determined against those for persons actually observed in consecutive months that there is no appreciable discrepancy.» The results are summarized in Merrell's table IV, which is reproduced here (table 33). In this table will be found the amounts and types of penicillin given and the relapse rates (rather than retreatment rates) in relation to treatment and time (18 months). It is readily seen that the smaller dosages and the less refined penicillins are associated with a higher relapse rate. Further, it is noteworthy that the relapse rates are in general about the same for the same schedule of treatment at the various clinics in the time limits of this report.

Prognostic Significance.

About the dangers of inadequate or irregular treatment Thomas (1949 — p. 15) says: «The point to fix firmly in mind with respect to the somewhat confusing phenomena of relapsing early syphilis is that inadequate treatment during the early stages of infection interferes with the production of permanent «immunity» to the development of early lesions and probably with that of other immune reactions in the host. As a result, patients may have infectious relapses and later may develop serious late lesions of syphilis, if the relapse was undetected. This fact explains the old dictum that inadequate therapy of early syphilis may do more harm than good, and also explains why it is so essential to keep patients under observation for long periods after treatment is completed.»

The unfavorable prognostic significance of secondary relapse was demonstrated in Padget's series of 534 patients with early syphilis, 14.6 per cent of whom relapsed (Padget, 1940). His table XII is reproduced here (table 34). Padget emphasizes the fact that only 28.2 per cent among the relapsers achieved «cure» as contrasted with 73.2 per cent among the non-relapsers. And it is

Table 34.

Comparison of Final Outcome in 78 Patients Who Relapsed and 456 Treated Patients Who Were Not Observed to Relapse

	No. of patients	«Cure» (%)	Positive STS (%)	Benign late syphilis (%)	Cardio-vascular syphilis (%)	Neuro-syphilis (%)	Multiple late manifesta-tions (%)	Treatment-resistant syphilis (%)
No observed relapse	456	73.2	16.0	1.7	2.0	6.1	0.7	0.2
Intermediate relapse observed ..	78	28.2	10.3	12.8	7.7	35.9	5.1	—
Total	534							

Reproduced from Padget, P.: Long-term Results in the Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis., 24: 692, 1940.
(Padget's table XII).

noticeable that other manifestations of late syphilis also are found more frequently among those who suffered relapse. The amount and type of treatment given originally to the 78 and to the 48 who were subsequently treated during the first two years of infection was not mentioned. «... Efforts to evaluate treatment before and after relapse in so small a group gave meaningless results...» (Padget, ibid.). It should be noted also that in this connection no breakdown as to sex was made and it was not stated how large a percentage of the cases with neurosyphilis constituted asymptomatic neurosyphilis. In the material as a whole asymptomatic neurosyphilis comprises about fifty per cent of the cases listed as neurosyphilis. Furthermore, the proportions of uncomplicated aortitis in the two groups of cardiovascular syphilis were not given. The seriousness of prognosis may depend on the above factors.

II. Present Investigation.

Introductory Remarks.

As a basis for the study of clinical secondary relapse in untreated secondary syphilis, we have chosen a total of 1,035 patients (335 male and 700 female). We started out with the patients belonging to the main groups «Known» and «Partially Known», which totalled 1,147 patients, or 374 males and 773 females (see table 21, p. 93), and from this number we removed 112 patients as follows: Those admitted to Boeck's department *in* secondary recurrence, comprising 17 males and 47 females, or a total of 64 patients. Those known to have received any kind of specific treatment before, during, or immediately after hospitalization in Boeck's department (comprising 22 males and 26 females, or a total of 48).

Before proceeding to the description of the findings it is important that the points given below be borne in mind:

1. The vast majority of the patients had shown symptoms and signs of *secondary* syphilis before discharge; we are dealing with only a negligible number of patients discharged during an earlier phase of the infection.
2. These patients were under close clinical supervision for their secondary syphilis for a considerable length of time.
3. With very rare exceptions they were not discharged until all symptoms and signs had disappeared, as judged from the clinical picture.
4. For the majority of the patients who developed clinical secondary relapse the same policy of isolation was employed as that described for the patients originally. These patients were either hospitalized in Boeck's department at the Rikshospital or at the V.D. ward of the Municipal Hospital of Oslo, and only occasionally observed on an ambulatory basis by the Oslo City Health Department, V.D. Division. It can therefore safely be assumed that the quality of the diagnoses was uniform and as good as the original.

5. The individuals in whom clinical secondary relapse was observed were found not to have received treatment elsewhere between the termination of the secondary syphilis and the outbreak of the first relapse, whereas a few are known to have been given treatment, either for the first relapse or one or more of the subsequent ones (see later).
6. The period of time between the termination of secondary syphilis and the outbreak of secondary relapse is here calculated as the interval between the date of original discharge from Boeck's department and the date of readmittance either to the same department or to the Municipal Hospital of Oslo, or the Oslo City Health Department. This seemed the only procedure which could secure uniformity, the patient's own information as to onset of symptoms and signs usually not being reliable enough for estimates of time relationship. The outbreaks of clinical secondary syphilis, therefore, may have been recognizable for a shorter or longer period of time before the diagnosis actually was made, but we have no way of determining the length of this period, a drawback we have in common with most investigators analysing similar problems.

When it comes to the estimates of time relationships the material has been limited to the central age-groups 15 to 39, the groups under 15 and over 39 having been omitted. It is felt that omission of these groups is not necessary for the study of clinical secondary relapse inasmuch as the period of time in question is comparatively short, relapses usually occurring within the first, second, and up to approximately the fifth year of infection. However, for the study of the longer time relationships in «benign» tertiary, cardiovascular and neurosyphilis, it is essential that the material be composed of individuals whose ages do not differ markedly. It is felt that the time-relationship problem should be treated on a similar basis through all phases of the disease and identical methods utilized so as to allow for evaluation from period to period. This is the reason why the above mentioned age-groups have been omitted from the beginning, and the principle has been maintained in all tables dealing with time relationships, in order to assure uniformity throughout.

As mentioned above, we are here necessarily dealing with clinical secondary relapse occurring after the *healing of lesions of the original outbreak of secondary syphilis*, which forms the starting-point for our time-relationship estimates as contrasted to most series described in the literature, where the starting-point is the onset of infection, or to be more exact, the onset or termination of treatment. Thus direct comparisons as relates to time relationship can not be made without that fact being taken into consideration. It is possible, however, roughly to estimate the interval between the onset of infection and the outbreak of clinical secondary relapse also in our material. What we have to take into account is the period of time during which the patients show symptoms and signs of their secondary syphilis. In our series this period can be estimated to be approximately identical with the length of stay in hospital. For secondary syphilis (see table 20, p. 64), the median is 3.5 months for females and 2.1 months for males. True enough, we do not know the interval of time between the onset of symptoms and signs and the original hospitalization, but the variations found in the duration of stay in the hospital probably express variations in the duration of the infection prior to admittance. Thus the median length of stay in the hospital can be used as an approximate index of the duration of symptoms and signs of secondary syphilis, as already mentioned. For patients with primary *and* secondary syphilis the median hospital stay is 4.4 months for females and 3.1 months for males, or about one month longer for each group. Thus, if we wish to use onset of infection as our starting-point instead of termination of the secondary syphilis, we shall have to add on the average about one month to the medians for secondary syphilis. Thus, the time from onset to discharge is estimated as about three months for males and about four and one-half months for females. In this way the time-relationship figures for our series should at least roughly be comparable with those where the onset of infection has been used as the starting-point. It is fairly obvious that possible comparisons under these circumstances should be limited to broad trends rather than to details.

7. From the standpoint of comparisons of type and sites of lesions it is to be remembered that the lesions found in this group of patients with clinical secondary relapse do not represent only those diagnosed on admittance, but also any lesions which developed during the period of hospitalization. In this respect our patients differ from those where treatment is administered as soon as the diagnosis has been made, something which in the majority of such cases would prevent further progression of the disease.
8. Except for more recent prospective studies for the evalution of treatment (especially penicillin) most data on secondary relapse have been obtained in retrospect. This study is no exception. These patients have either sought medical advice because of some suspicious symptoms or signs, or, as in some cases, have been called-in by the Oslo City Health Department as possible contacts. This, of course, bears on both the incidence and time-relationship estimates and must be considered as being very important also in eventual comparisons with other series.

Occurrence.

Table 35 presents by sex and by age at infection our findings relative to the occurrence of clinical secondary relapse in untreated secondary syphilis. It shows that 23.6 per cent of the patients, or close to one out of four, after a longer

Table 35.

Proportions Developing Clinical Secondary Relapse, by Sex and Age at Onset of Infection.

(244 patients)

	Males			Females			Total		
	Number of Patients Observed	Patients Developing Clinical Secondary Relapse		Number of Patients Observed	Patients Developing Clinical Secondary Relapse		Number of Patients Observed	Patients Developing Clinical Secondary Relapse	
		No.	Per cent		No.	Per cent		No.	Per cent
	335	76	22.7	700	168	24.0	1035	244	23.6
Age-groups*									
0—4	19	2		25	4		44	6	
5—9	5 } 27	0 } 3	11.1	8 } 38	1 } 6	15.8	13 } 65	1 } 9	13.8
10—14	3	1		5	1		8	2	
15—19	47	10	21.3	157	45	28.7	204	55	27.0
20—24	110	29	26.4	250	57	22.8	360	86	23.9
25—29	74	15	20.3	121	21	17.5	195	36	18.5
30—39	47	11	23.4	84	26	31.0	131	37	28.2
40 over	30	8	26.7	50	13	26.0	80	21	26.3
15—39	278	65	23.4	612	149	24.3	890	214	24.0

* Age at infection.

or shorter symptom-free interval, developed clinical secondary relapse. This figure is certainly a minimum for it represents only patients who have been actually observed. Other patients who have relapsed, although presumably not very many, will have seen private practitioners, and these cases will neither have been reported to the proper authorities nor will they have been admitted to hospital or clinic. Also, by paying the expenses themselves, the patients will have escaped registration by official institutions, such as for instance the Bureau of the Indigents. In others, particularly in females, the lesions may have been so trivial as to go undetected by patient and physician alike. And some, of course, may have been observed — and possibly recorded — outside the City of Oslo.

Multiple outbreaks. Among the 244 patients who developed clinical secondary relapse 189, or 77.5 per cent, experienced only one outbreak; 46, or 18.9 per cent, two; 8, or 3.3 per cent, three, and one, or 0.4 per cent four outbreaks. (See table 36.) It is to be noted that the figures are suggestive of a difference in the two sexes in this respect, females showing a higher percentage of second, third, and fourth, outbreaks than do males, but they are too small to permit definite conclusions.

Table 36.

Clinical Secondary Relapse with Reference to Number of Outbreaks Experienced.

(All ages)

Number of outbreaks experienced	Males		Females		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
One	65	85.5	124	73.8	189	77.5
Two	10	13.2	36	21.4	46	18.9
Three	1	1.3	7	4.2	8	3.3
Four	—	—	1	0.6	1	0.4
Total	76	100.0	168	100.0	244	100.0

When considering the frequency of multiple outbreaks of clinical secondary relapse, treatment again enters the picture. Treatment may either prevent further outbreaks, or — if we accept the irregular or inadequate treatment theory — cause new outbreaks. Altogether 20 of the patients in question received specific treatment for one or another relapse. Of the 189 patients experiencing only one outbreak, 11 (6 female and 5 male) received treatment for this outbreak. Among the 46 with two outbreaks, 5 (3 females and 2 males) were treated for their first outbreak, and 3 (2 females and 1 male) for their second.

Of the 8 experiencing three outbreaks, only 1 (a female) had received treatment for her first outbreak. The treatment consisted of mercury inunctions only, and the doses were comparatively small, much smaller than those given for primary and secondary syphilis, and they were given according to the clinical picture rather than according to any fixed schedule, so that treatment in the majority of these cases certainly was highly inadequate. Also the question of whether mercury inunctions are effective at all in preventing relapse comes up. Moore (1944 — p. 24) says: «. . . Mercury probably has no effect at all; patients treated with it relapse in about as high a proportion as if no treatment had been given . . .» By and large, therefore, it should be safe to assume that the treatment given some of these patients has not substantially affected the figures for multiple secondary relapse. The figures of treatment and non-treatment are too small for significant conclusions.

Sex, and Age at Infection.

According to the results arrived at here there is no appreciable difference in the two sexes in this respect either in the material as a whole or in the 15—39-year age-groups (table 35). (Relapses in total males 22.7 per cent, females 24.0 per cent; in 15—39-year ages 23.4 and 24.3 per cent respectively. These differences are not statistically significant.) There is the possibility that diagnoses of secondary syphilis and secondary relapse are made more frequently in males than in females, but any attempt at a numerical evaluation of this factor must be considered futile, and in the present material not even a trend in this direction can be demonstrated. On the contrary, females show a slightly higher (if not statistically significant) percentage of cases with clinical secondary relapse than do males.

As to age at infection (table 35), it will be seen that clinical secondary relapse occurred in all age-groups presented in the table. The distribution, however, is uneven and the difference[1] no greater than would be expected by chance. Thus, with the data available, nothing definite can be stated as to the influence of age at infection on the frequency of these lesions. Also, it is difficult to point to any trend, but it is interesting to note that no tendency towards decreasing proportions was found in the higher age-groups (those over 30).

Sites and Types of Lesions.

The sites and types of lesions in clinical secondary relapse are of considerable interest both from a clinical and a public health point of view. It is important to know where to look for the signs of relapse and no less important to know to what extent the lesions are potentially infectious. Table 37, Parts I and II,

[1] Tested by χ^2 on total.

Table 37.

Sites and/or Types of Lesions in Clinical Secondary Relapse According to Potentially Infectious or Non-infectious Forms, by Outbreak Number and Sex.

(All ages*) (244 Patients — 309 outbreaks)

Part I.

Sites and/or Types of Lesions	Outbreaks of Clinical Secondary Relapse								
	First		Second		Third		Fourth		Total
A. Infectious or Potentially Infectious	Males	Females	Males	Females	Males	Females	Males	Females	
	No.	No.	No.	No.	No.	No.	No.	No.	No.
Anogenital alone	11	40	0	18	0	3	0	0	72
Anogenital plus:									
Mouth-throat	16	27	5	5	0	1	0	1	55
Mouth-throat + skin ..	9	17	1	0	0	0	0	0	27
Skin	6	11	0	2	0	0	0	0	19
Iritis	0	0	0	2	0	0	0	0	2
Keratitis	0	2	0	0	0	0	0	0	2
Mouth-throat + iritis ..	0	2	0	0	0	0	0	0	2
Mouth-throat + periostitis	0	1	0	0	0	0	0	0	1
Hepatitis + skin	1	0	0	0	0	0	0	0	1
Mouth throat + hepatitis + skin	1	0	0	0	0	0	0	0	1
Hepatitis	0	1	0	0	0	0	0	0	1
Periostitis	0	2	0	0	0	0	0	0	2
Mouth-throat alone	10	19	4	7	0	1	0	0	41
Mouth-throat plus:									
Skin	13	13	0	3	0	1	0	0	30
Skin + iritis	1	2	0	0	0	0	0	0	3
Iritis	0	1	0	0	0	0	0	0	1
Periostitis	0	2	0	0	0	0	0	0	2
Subtotal	68 (89.5 %)	140 (83.3 %)	10 (90.9 %)	37 (84.4 %)	0	6 (75.0 %)	0	1 (—)	262 (84.8 %)

B. Potentially Non-infectious									
Iritis alone	2	12	0	2	0	1	0	0	17
Iritis plus keratitis	0	1	0	0	0	0	0	0	1
Chorio-retinitis	0	1	0	0	0	0	0	0	1
Subtotal	2 (2.6 %)	14 (8.3 %)	0	2 (4.4 %)	0	1 (12.5 %)	0	0	19 (6.1 %)
Skin alone	2 (2.6 %)	9 (5.4 %)	0	3 (6.7 %)	0	1 (12.5 %)	0	0	15 (4.9 %)
Skin plus:									
Iritis	1	1	0	1	0	0	0	0	3
Chorioiditis	0	0	0	1	0	0	0	0	1
Iritis + periostitis + neuroreccurrence ..	0	1	0	0	0	0	0	0	1
Hepatitis	1	0	0	0	0	0	0	0	1
Periostitis	0	2	0	0	0	0	0	0	2
Periostitis + arthritis ..	0	0	1	0	0	0	0	0	1
Arthritis	1	0	0	0	0	0	0	0	1
Periostitis alone	0	1	0	0	1	0	0	0	2
Arthritis alone	1	0	0	0	0	0	0	0	1
Subtotal	4 (5.3 %)	5 (3.0 %)	1 (9.1 %)	2 (4.6 %)	1 (—)	0	0	0	13 (4.2 %)
Total	76 (100 %)	168 (100 %)	11 (100 %)	44 (100 %)	1 (—)	8 (100 %)	0	1 (—)	309 (100 %)

* Age at infection.

Note: Figures too small for significant comparisons in many of the sub-groups.
Percentages given for completeness.

have in the main been constructed to illustrate these points. In Part I the lesions have been grouped as to potentially infectious and non-potentially infectious. By anogenital and mouth-throat is here meant mucous patches or moist erosions in the anogenital and mouth-throat regions. The other designations are self-explanatory.

The table (37, Part I) shows the lesions as they occurred, as solitary type-site or concomitant type-site manifestations, in 244 individual patients (with a total of 309 outbreaks). It will readily be observed in the total column that lesions of the anogenital and mouth-throat regions play a dominant role, occurring as solitary or concomitant manifestations in 84.8 per cent of the outbreaks. There is no marked difference between males and females, and the picture remains practically unchanged throughout the different outbreaks. Next in importance come solitary ocular occurences, with 6.1 per cent of the total number of outbreaks, iritis being the most common form. Eye lesions seem to be more predominant in females than in males, but the figures are too small to permit conclusions. Solitary lesions of the skin represent 4.9 per cent of the total and the remaining lesions 4.2 per cent. There is no appreciable difference in the sexes in these groups.

Table 37, Part II, shows the distribution of the total number of lesions (508) diagnosed in the 244 patients, according to site-type and irrespective of whether the lesions were solitary or concomitant. It will be seen that anogenital and mouth-throat lesions account for a bit more than two-thirds, or 68.5 per cent, of the total number observed; skin about one-fifth, or 20.9 per cent; and ocular (all forms) approximately 7 per cent. Other manifestations play a relatively minor role numerically. Because of the difficulties in differential diagnosis prior to the use of x-ray it is probable that the periostitis group comprised cases of osteitis as well. It is interesting to note there was one outbreak of neurorecurrence in the strict sense of the definition, asymptomatic neurosyphilis not being diagnosed during the period in question as no spinal punctures were performed. This is in keeping with the concept that neurorecurrence is related to irregular or inadequate treatment. The most striking observation, however, regardless of whether we consider the individual cases, the various outbreaks, or the individual manifestations, is the predominance of lesions of the anogenital and mouth-throat regions. These lesions will be infectious or potentially infectious in practically all instances, and in regard to possible spread of infection, they constitute an extremely dangerous form of early syphilis. The importance to public health can hardly be over-estimated and it is essential that the clinician dealing with early syphilis be aware of these facts. They are well known, but they deserve to be emphasized in view of the theories held by some modern syphilologists, who point out that in *untreated secondary* syphilis the refractory state towards early infectious lesions is usually reached by the time clinical manifestations have completely disappeared.

Table 37.

The Total Number of Individual Sites or Types of Lesions in Clinical Secondary Relapse, According to Outbreak Number, by Sex.

(all ages*) (244 patients — 508 sites or types)

Part II.

Sites or Types of Lesions	Outbreaks of Clinical Secondary Relapse															
	First				Second		Third		Fourth		Subtotal 2nd + 3rd + 4th.				Total	
	Males		Females		M	F	M	F	M	F	Males		Females			
	No.	Per cent	No.	Per cent	No.	No.	No.	No.	No.	No.	No.	Per cent	No.	Per cent	No.	Per cent
Anogenital	44	31.7	103	37.1	6	27	0	4	0	1	6	28.6	32	45.7	185	36.4
Mouth-throat	50	36.0	84	30.2	10	15	0	3	0	1	10	47.6	19	27.1	163	32.1
Skin	36	25.9	56	20.1	2	10	0	2	0	0	2	9.5	12	17.1	106	20.9
Ocular: Iritis	4	2.9	20	7.2	0	5	0	1	0	0	0	0	6	8.6	30	5.9
Ocular: Keratitis	0	0	3	1.1	0	0	0	0	0	0	0	0	0	0	3	0.6
Ocular: Chorioretinitis	0	0	1	0.4	0	1	0	0	0	0	0	0	1	1.4	2	0.4
Periostitis	0	0	9	3.2	1	0	1	0	0	0	2	9.5	0	0	11	2.2
Hepatitis	3	2.2	1	0.4	1	0	0	0	0	0	1	4.8	0	0	4	0.8
Arthritis	2	1.4	0	0	0	0	0	0	0	0	0	0	0	0	3	0.6
Neurorecurrence	0	0	1	0.4	0	0	0	0	0	0	0	0	0	0	1	0.2
Total	139	100.0	278	100.0	20	58	1	10	0	2	21	100.0	70	100.0	508	100.0

* Age at infection.

Table 38.

Interval of Time Between Termination of Secondary Syphilis and First Outbreak of Clinical Secondary Relapse, by Sex.

(Ages 15 — 39*)

Part I.

Time interval	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Weeks 0	2	—	0	—	2	—
1	2	—	2	—	4	—
2	2	—	6	—	8	—
3	4	—	8	—	12	—
Subtotal	10	15.4	16	10.7	26	12.1
Months 1	15	—	27	—	42	—
2	9	—	14	—	23	—
3	5	—	7	—	12	—
4	5	—	20	—	25	—
5	3	—	13	—	16	—
Subtotal	37	56.9	81	54.4	118	55.1
6	3	—	5	—	8	—
7	5	—	3	—	8	—
8	4	—	9	—	13	—
9	1	—	7	—	8	—
10	0	—	6	—	6	—
11	0	—	2	—	2	—
Subtotal	13	20.0	32	21.5	45	21.0
12	2	—	1	—	3	—
15	0	—	3	—	3	—
18	0	—	1	—	1	—
21	1	—	5	—	6	—
Subtotal	3	4.6	10	6.7	13	6.1
Years 2	1	—	8	—	9	—
3	1	—	0	—	1	—
4	0	—	2	—	2	—
5	0	—	0	—	0	—
Subtotal	2	3.1	10	6.7	12	5.6
Total	65	100.0	149	100.0	214	100.0

Interval of Time Between Termination of Secondary Syphilis and Second and Third
Part II. *Outbreaks of Clinical Secondary Relapse, by Sex.*

Time interval	Outbreaks				Total	
	Second		Third			
	Male	Female	Male	Female		
	No.	No.	No.	No.	No.	Per cent
Weeks 0	0	0	0	0	0	—
1	0	0	0	0	0	—
2	0	0	0	0	0	—
3	0	0	0	0	0	—
Subtotal	0	0	0	0	0	—
Months 1	0	0	0	0	0	—
2	1	0	0	0	1	—
3	1	2	0	0	3	—
4	2	2.	0	0	4	—
5	0	4	0	0	4	—
Subtotal	4	8	0	0	12	20.7
6	0	2	0	0	2	—
7	0	3	0	1	4	—
8	1	2	0	0	3	—
9	0	2	0	0	2	—
10	0	4	0	1	5	—
11	0	1	0	1	2	—
Subtotal	1	14	0	3	18	31.0
12	0	3	0	0	3	—
15	0	3	0	0	3	—
18	0	3	0	2	5	—
21	0	3	0	0	3	—
Subtotal	0	12	0	2	14	24.1
Years 2	0	6	0	0	6	—
3	2	3	0	0	5	—
4	0	0	0	2	2	—
5	0	0	0	0	0	—
6	1	0	0	0	1	—
Subtotal	3	9	0	2	14	24.1
Total	8	43	0	7	58	100.0

* Age at infection.

Time Relationships.

To illustrate the problems of time relationships in clinical secondary relapse, two sets of tables have been constructed: one showing the frequency distribution of secondary relapses by time (table 38) according to first, second and third outbreaks, and one probability table (table 39) including the first outbreaks only. The figures for multiple outbreaks are too small to justify the setting up of probability tables.

Table 38, Part I, reveals that the first outbreak of clinical secondary relapse may occur fairly soon after symptoms and signs of secondary syphilis have disappeared. Some of the patients have already experienced relapses within the first week, and we find them all through the first month with 12.1 per cent of the total in this period. At the end of the next five months another 55.1 per cent is added, making a total of 67.2 per cent, or a little more than two-thirds within the first half-year.

During the following six months 21 per cent more of the outbreaks develop, so that at the end of the first year after the termination of the secondary syphilis, 88.2 per cent, or close to nine out of ten, of the relapses have occurred. In the course of the second year the number of relapses is relatively small, totalling 6.1 per cent bringing the total up to 94.3 per cent at the end of this period, whereafter another 5.6 per cent develops during the following years, the majority of the latter being between the second and third years.

It is noteworthy that no case of first outbreak of clinical secondary relapse has been observed after the end of the fifth year. And also that there is no appreciable difference between males and females neither as to frequency nor as to period of time in which secondary relapse has been diagnosed.

Table 38, Part II, shows the time relationships for 51 second and 7 third outbreaks of clinical secondary relapse. The results in regard to multiple outbreaks can be summarized as follows: About one-half of the outbreaks, or 51.7 per cent, have been observed within the first year, and at the end of the second year we have reached about three-fourths, or 75.8 per cent. During the following years, up to between six and seven, another fourth, or 24.1 per cent, is added, with the majority of the outbreaks experienced between the second and fourth years.

In table 39 are given the calculations for the probability of developing clinical secondary relapse, and in fig. 7 the results are demonstrated graphically.

In the table the period of time has been calculated according to the principles mentioned in Introductory Remarks in this section (p. 117, point 6) only differing from the frequency distribution table 38 in that the first four weeks have been put together and called «Less than one month» (column one). In column two it will be noted that the word «Observed» has been used. This does not mean that the patients in question have been examined clinically within

Table 39.

Calculation of the Probability of Developing Clinical Secondary Relapse, First Outbreak.

Part 1. Males. (65 patients) (Ages 15—39*)

Observation period. Months and years † x to x + n	Number observed this period or later.	Number lost from observation in this period.		Number found positive †† this period.	Probability of a person not previously found positive being found positive in this period. $\frac{(4)}{(2)-\frac{(3)}{2}}$ †††	Probability of a person not previously found positive remaining negative †† in this period. 1 — (5)	Cumulative probability of a person remaining negative from beginning of observation to x + n. (6) x (7)	Cumulative probability of a person becoming positive between beginning of observation and x + n. 1 — (7)
(1)	(2)	(3)		(4)	(5)	(6)	(7)	(8)
		Dead	Living last seen					
Months 0	278	0	0	10	0.03597	0.96403	0.96403	0.03597
1	268	0	0	15	0.05597	0.94403	0.91007	0.08993
2	253	1	0	9	0.03564	0.96436	0.87764	0.12236
3	243	0	2	5	0.02066	0.97984	0.85951	0.14049
4	236	1	0	5	0.02123	0.97877	0.84126	0.15874
5	230	1	0	3	0.01307	0.98693	0.83026	0.16974
6	226	0	0	3	0.01327	0.98673	0.81165	0.18835
7	223	0	0	5	0.02242	0.97758	0.79345	0.20655
8	218	0	0	4	0.01835	0.98165	0.77889	0.22111
9	214	1	0	1	0.00468	0.99532	0.77524	0.22476
10	212	0	0	0	0	1.00000	0.77524	0.22476
11	212	0	0	0	0	1.00000	0.77524	0.22476
12 to 15	212	0	1	2	0.00946	0.99054	0.76791	0.23209
15 to 18	209	0	0	0	0	1.00000	0.76791	0.23209
18 to 21	209	0	0	0	0	1.00000	0.76791	0.23209
21 to 24	209	0	0	1	0.00478	0.99522	0.76424	0.23576
Years 2	208	1	0	1	0.00482	0.99518	0.76056	0.23944
3	206	3	2	1	0.00491	0.99509	0.75683	0.24317
4	200	1	1	0	0	1.00000	0.75683	0.24317

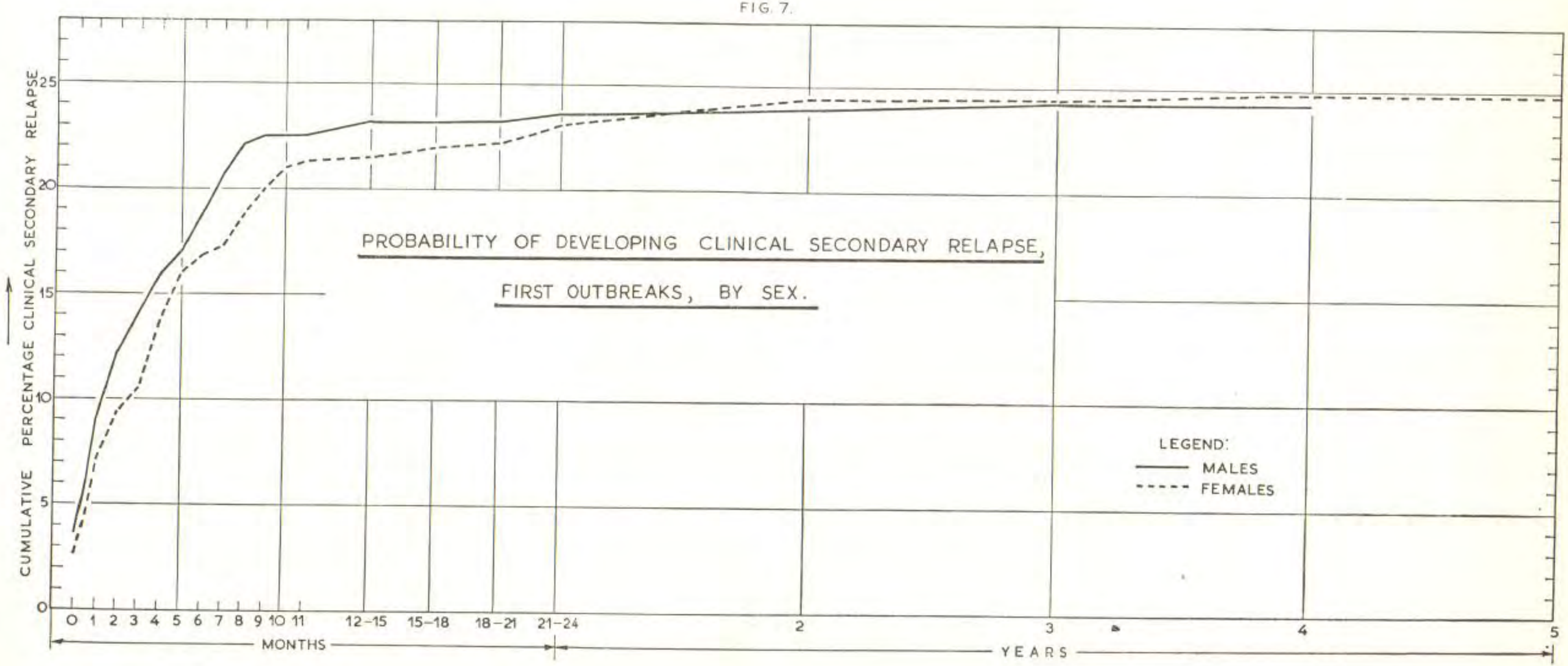
9

Part II. Females. (149 patients)

Months	0	612	3	0	16	0.02621	0.97379	0.97379	0.02621
	1	593	1	0	27	0.04557	0.95443	0.92941	0.07059
	2	565	0	1	14	0.02480	0.97520	0.90636	0.09364
	3	550	1	1	7	0.01275	0.98725	0.89480	0.10520
	4	541	0	0	20	0.03697	0.96303	0.86172	0.13828
	5	521	0	1	13	0.02498	0.97502	0.84019	0.15981
	6	507	1	4	5	0.00991	0.99009	0.83186	0.16814
	7	497	0	0	3	0.00604	0.99396	0.82684	0.17316
	8	494	0	1	9	0.01824	0.98176	0.81176	0.18824
	9	484	1	0	7	0.01448	0.98552	0.80001	0.19999
	10	476	0	2	6	0.01263	0.98737	0.78991	0.21009
	11	468	1	1	2	0.00428	0.99572	0.78653	0.21347
	12 to 15	464	3	0	1	0.00216	0.99784	0.78483	0.21517
	15 to 18	460	0	0	3	0.00652	0.99348	0.77971	0.22029
	18 to 21	457	0	2	1	0.00219	0.99781	0.77800	0.22200
	21 to 24	454	0	0	5	0.01101	0.98899	0.76943	0.23057
Years	2	449	4	9	8	0.01808	0.98192	0.75552	0.24448
	3	428	5	8	0	0	1.00000	0.75552	0.24448
	4	415	3	5	2	0.00487	0.99513	0.75184	0.24816
	5	405	3	4	0	0	1.00000	0.75184	0.24816

* Age at infection.
† 0 — less than 1 month.
1 — between 1 and 2 months.
2 — between 2 and 3 months. etc.
2 — between 2 and 3 years.
3 — between 3 and 4 years. etc.
†† Positive — clinical secondary relapse.
Negative — no clinical secondary relapse.
††† Assumes all still under observation, but not examined at this time, are clinically negative.

FIG. 7.


PROBABILITY OF DEVELOPING CLINICAL SECONDARY RELAPSE,
FIRST OUTBREAKS, BY SEX.
CUMULATIVE PERCENTAGE CLINICAL SECONDARY RELAPSE
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11
12–15 15–18 18–21 21–24
MONTHS
2 3 4 5
YEARS
LEGEND:
MALES
FEMALES

the period of time set up in the table. It has been assumed that those not found to have developed clinical secondary relapse (through the manifold methods of collecting clinical data employed) have remained symptom-free, and only in this sense have they been kept under observation. (See also note under table 39, column five, and point eight, p. 118 in Introductory Remarks.) Column three gives the numbers known to have been lost from observation (dead or alive). The remaining column headings are self-explanatory. Positive and negative in these columns refer not to tests but to these terms as applied to this table — developing or not developing clinical secondary relapse.

The cumulative probability of developing clinical secondary relapse as demonstrated by this material (fig. 7), is about 24 per cent at the end of three years after symptoms and signs of secondary syphilis have disappeared. It is about the same for males and females. The percentage is slightly higher than that arrived at through ordinary frequency estimates, which was to be expected since the denominator steadily decreases with time. By and large this way of demonstrating the incidence certainly gives a more correct picture of the development than does an ordinary frequency distribution table. It is further to be noted that the curves are fairly steep in the first year, the one for males climbing a bit faster and higher than the one for females, reaching 22.5 and 21.3 respectively. After the first year the increase is very small and the curves correspondingly gradual, the one for females being a bit steeper than that for males. Between the third and the fourth years the curves for the two sexes have reached a point where they are practically identical (about 24 per cent).

Prognostic Significance.

This question is discussed in Chapter XI, The Prognostic Significance of Clinical Secondary Relapse and «Benign» Tertiary Syphilis, pp. 332—337.

III. Discussion.

Causes and Definition.

It has been shown that symptoms and signs in untreated *secondary syphilis* disappear after a period of a few weeks to twelve months. This is then followed by a period of clinical latency, which in a minimum of 25 per cent of the cases is interrupted by new demonstrable lesions, or, symptoms and signs of clinical secondary relapse. Of these patients again a little more than one-fifth will experience from one to three additional outbreaks, likewise occurring after periods of clinical latency. *This development, therefore, must be considered as part of the natural course of the disease.* It has been held that the reaction of the skin and the mucosal membranes (and probably also of the eye, the bones etc.) is dependent upon the multiplication of the spirochetes at any given time, the rate of which is in turn determined by the status of the struggle between the immune forces of the body and the invading organisms. In our relapsers the immune forces presumably have not been able to subdue the multiplication of the spirochetes sufficiently to prevent a new crop of lesions from developing, the majority of which are infectious or potentially infectious. In other words, the theory held by so many modern syphilologists, that clinical secondary relapse is in itself mainly caused by inadequate or irregular treatment which interrupts the natural development of «immunity», has not been confirmed. If unsuccessful treatment of *secondary syphilis* results in the development of a certain percentage of relapses, it could better be put this way: The treatment has not been sufficiently adequate to prevent the natural course of the disease as expressed by the occurrence of clinical secondary relapse. Whether irregular or inadequate treatment during the secondary stage may result in a greater frequency of secondary relapse is a different matter, but so far there is no evidence pointing in this direction. On the contrary, it seems that under these circumstances even inadequate treatment is able to prevent secondary relapse to a certain extent.

When it comes to unsuccessful treatment of syphilis in the *primary stage* (seronegative or seropositive), it is, in the present author's opinion, much more reasonable to assume that interference with the immune-mechanism actually takes place to an extent which may cause the development of relapse phenomena. In untreated patients the primary stage is followed by the clinical picture of ordinary secondary syphilis in close to 100 per cent of the cases. If the irregular or inadequate treatment did not interfere with the natural course of the disease, we would expect a similar development to take place, but usually what we see is the relapsing type of secondary syphilis. By interfering it seems that we have changed the immunological conditions so that the ordinary secondary stage, so to say, is by-passed, and, judging from the clinical findings, a later stage, namely that of secondary relapse, follows. To what extent we get the clinical picture of ordinary secondary syphilis or the relapsing type is probably dependent on the degree of interference. It seems natural to believe that the less interference the greater the similarity with the ordinary type, with secondary lesions in approximatly 100 per cent, which denotes the natural course in untreated primary syphilis.

In view of the above considerations, it is felt that the definition of clinical relapse can not be based exclusively on the concept that it is caused by irregular or inadequate treatment. If we consider secondary syphilis as terminated when clinical lesions no longer can be demonstrated (Thomas, 1949), all subsequent secondary type lesions occurring after a sypmtom-free interval should be called clinical secondary relapse, whether this development is the result of failure on the part of the immune forces of the body or a combination of this and irregular or inadequate treatment. Clinically speaking, the terms progression and/or persistence of secondary type lesions should be reserved for the period during which secondary lesions appear progressively or persist without symptom-free intervals, a period which in untreated secondary syphilis may last for as long as twelve months as shown previously (see section on length of stay in hospital, p. 62).

By and large, the results arrived at in this study agree very well with the concept held by Meirowsky and Pinkus (1923), namely that the syphilitic infection during the early years tends to take a rhythmic course, which is most clearly demonstrated in untreated syphilis. On the other hand, it seems reasonable to believe that clinical secondary relapse also may follow inadequate or irregular treatment, particularly when interference takes place during the primary stage. Any definition, therefore, should take both possibilities into account, as follows: Clinical secondary relapse is the reappearance of secondary type lesions after a period of clinical latency. It may either be a part of the natural course of the disease following the termination of the secondary syphilis, or it may follow irregular or inadequate treatment during the early stage of the infection.

Unfortunately we know very little about the immune-conditions existing behind the various clinical pictures. To answer authoritatively the many questions arising in connection with the confusing phenomena of secondary relapse in treated syphilis, we shall probably have to await the development of specific serologic methods by means of which the status of the immune-apparatus can be measured under various circumstances and correlated with the clinical findings. It is possible that the differences in opinion in regard to this phenomenon may be due to actual differences in the immune-mechanism created on the one hand in clinical secondary relapse following inadequate treatment and on the other, that associated with the clinical secondary relapse observed in the natural course of the untreated disease.

Occurrence.

It has been found that at least one out of every four patients (23.6 per cent) with untreated secondary syphilis sooner or later develop clinical secondary relapse. This is a minimum, for reasons mentioned previously. In other words, we have been able to establish an approximate base-line for comparisons with figures arrived at through the analysis of treated cases.

It is obvious, however, that such comparisons are a complicated matter due to the many basic epidemiologic factors which have to be taken into account. When it comes to the incidence of clinical secondary relapse in treated series, the following are generally held as essential points in the evaluation of the relapse rates: First, there is the question of kind, amount and method of treatment. Second, the stage of infection at time of treatment. Third, the efficiency of follow-up and the length of the period of observation. Fourth, the forms of relapse included. And finally, the distinction between reinfection and relapse.

Whenever we are obliged to disregard one or more of these factors, comparisons with the relapse rates found in untreated syphilis may lead to misinterpretations. In the following pages some of the difficulties one can expect to encounter will be demonstrated through examples, and also an attempt will be made to show why conclusions have to be drawn with great caution in these matters. For the comparisons there have been chosen series of treated cases thought to be sufficiently representative for this purpose, and covering various periods of time in the development of the treatment of syphilis.

The two series referred to by Lomholt (1936) seem to lend themselves best for comparisons (Tables 30 and 31, pp. 109—110). Kind, amount and method of treatment is known, and likewise the stage of infection at the time treatment was given. The methods of follow-up were not discussed, but in all probability the efficiency was as great as in any similar series. The period of observation seems to be approximately the same as in the Bruusgaard study judging from the table presented, but not knowing anything about the follow-up method, it is difficult to evaluate this. Lomholt's two series, however, also comprise a certain proportion of serologic relapses (12.0 and 9.5 per cent respectively for the total number of patients, and 16.8 and 12.0 per cent respectively for those treated during the secondary stage). (Notes, tables 30 and 31, pp. 190—110.) These patients were presumably re-treated, and we do not know how many of them eventually would have come down with clinical relapse if left untreated. The weight of this factor, therefore, can not be determined, but in all probability it worked in the direction of minimizing the number of clinical relapses. The question of relapse versus reinfection or superinfection was discussed, and it was concluded that the great majority of the cases probably were relapses and not reinfections, something which it is reasonable to assume in view of the relatively small doses of salvarsan and Hg. used for treatment. His tables are ordinary frequency-distribution tables corresponding in this respect to our table 35, p. 119.

Turning then to the cases treated during the secondary stage in the first series (table 30, minimum treatment, p. 109) it will be seen that the relapse rate is 25.1 per cent as compared with 23.6 per cent in ours, the order of magnitude being practically identical. As our figure is certainly a minimum, but the follow-up probably better in Lomholt's series, a comparison would indicate that the treatment given his patients has only to a relatively small degree interfered with the natural course of the disease as expressed by the percentage of relapse. As soon as the dosages are increased, however (see table 31, cases treated during the secondary stage, p. 110), there is a marked drop in the percentage of relapses (4.1 per cent) showing that the closer the treatment is brought towards adequacy the less relapses, even if treatment employed is still far from sufficient as measured by usual standards (20 injections of arsenicals plus 20 injections of Bismuth). It is dubious, however, whether the figures referred to by Lomholt can be accepted at their face value, and this goes particularly for the relapse rate in the second series, which is surprisingly low compared with those found in other series where considerably more adequate treatment has been employed. On the other hand a trend has been demonstrated and the reasoning is based on this fact rather than on the figures themselves.

A comparison between the relapse rates in Lomholt's two series and that found in untreated syphilis, therefore, seems to indicate that inadequate treatment during the secondary stage neither causes secondary relapse in itself nor does it increase its frequency. On the contrary, in the first instance (Lomholt's first series) it has only resulted in relapse rates which are about the same as expected in untreated cases, and in the second instance (Lomholt's second series) it has been sufficient to prevent the development of a certain number of relapses. But, we can not disregard the question of what would have happened to the serologic relapsers if left untreated, and thus definite conclusions are not possible.

We now turn to a consideration of the relapse rates found in the Cooperative Clinical Group series. As already mentioned these results have been presented in a number of ways by various authors, but evidently the most complete analysis has been done by Moore (1944), and therefore the following comparisons with the rates found in untreated syphilis are in the main based on the figures given by him. The kind of treatment given is discussed by Moore, who writes that it almost exclusively relates to arsphenamine (as many as thirty injections, with concomitant heavy metal). In that material relapses have been grouped according to amount of treatment, without regard to stage of infection (see p. 107), and to identical conditions of treatment without regard to amount (see table 29, p. 108). It seems however, that Moore has only included the infectious forms of relapse and omitted all others. The efficiency of follow-up was also mentioned in that Moore has stated that the incidence of infectious relapse represents a minimum. As far as one can see, the problem of reinfection versus relapse was not taken up.

From table 29 (p. 108) it will be seen that the infectious relapse rate in treated early secondary syphilis was 9 per cent, as compared with the close to 25 per cent in this untreated series. If Moore had included also the non-infectious forms of secondary relapse, his figures probably would have been somewhat higher. It is also possible that the efficiency of follow-up was somewhat better in the Cooperative Clinical Group series, but it is difficult to evaluate to what extent this may have influenced the results. Furthermore, we do not know what treatment these cases of early secondary syphilis have received. There is another factor of importance in comparing clinical secondary relapse among modern series of treated patients with the present untreated series. The treatment of *serologic* relapse, which in a certain number of instances precedes clinical relapse, will doubtless reduce the proportion of clinical relapses which might otherwise occur. This possibility does not exist in a series of untreated patients. (According to Stokes et al. (1944) the serologic relapses among the Cooperative Clinical Group cases constituted 15.1 per cent, see p. 110.)

With the reservations made necessary by the above considerations, it is nevertheless fairly safe to assume that the treatment given these patients with early secondary must have been sufficiently adequate to prevent a certain number of relapses from developing, but the circumstances do not permit any definite conclusions as to the magnitude of the difference between the treated and the untreated cases.

When it comes to the results of the Cooperative Clinical Group series relative to patients treated in the primary stage (a 16.4 and 20.2 per cent relapse rate for primary seronegative and primary seropositive respectively, table 29, p. 108), the same reservations as mentioned above should be made. These figures are nearer to those found in untreated secondary syphilis. In the present author's opinion, however, the relapse rates found after irregular or inadequate treatment in primary syphilis are not directly comparable with those found after the termination of secondary syphilis in untreated cases. If we accept that the relapse rates in primary syphilis under the given conditions of treatment, as referred to by Moore, are near to those expected in untreated secondary syphilis, then what has happened is actually this: the treatment has prevented a substantial number of patients from developing the clinical picture of ordinary secondary syphilis which would have occurred in practically 100 per cent if they too had remained untreated, and instead it has resulted in a much smaller percentage of cases with the relapsing type of secondary syphilis. The results following treatment of primary syphilis are poorer than those found following treatment of early secondary syphilis, under identical conditions of treatment (according to Moore, see p. 107[1]), but on the other hand, they are decidedly better than those found when primary syphilis is allowed to go untreated, which usually results in close to 100 per cent secondary syphilis. Furthermore, under the latter condition an additional 25 per cent secondary relapses may be expected to occur. The relapse picture is completed by the fact that one-fifth of the relapsers experience multiple episodes. The public health implications of this are obvious.

Moore's figures relative to the incidence of relapse after varying amounts of treatment (p. 107) are hard to interpret. One to four injections of arsenicals was followed by as high a relapse rate as 65 per cent, and this figure is far from being in accord with those given by Lomholt both for primary and for secondary syphilis. There is also a surprisingly marked drop in the relapse rates, from

[1] This refers to results arrived at during the study of patients treated with the arsenicals and the heavy metals. In treatment with penicillin results are better in primary than in secondary.

65 to 12.5 per cent when five to nine injections of arsenicals were given. These groups of patients are presented with no mention of the relative distribution of primary and secondary syphilis in the two groups, nor is there any way of knowing whether the first group was predominantly one-treatment patients and the latter predominantly nine-treatment patients. Without breaking down the figures in this manner it is hardly possible to offer an explanation of such high relapse rates on the one hand, and of such precipitous decline on the other.

Finally we have the results arrived at during the modern studies of patients treated with varying amounts and types of penicillin, as exemplified by Merrell's paper of 1951. The relapse rates have been figured out according to the same principles employed in our own probability estimates. The reinfection rates have been calculated on a sound statistical basis as well, thus convincingly eliminating this disturbing factor of reinfection from the evaluation of the relapse rates. The study is part of a well-planned experiment, where the treatment schedules have been adhered to, and where the time relationships rest on relatively safe ground. On the other hand, there are several dissimilarities in basic epidemiologic factors which must be borne in mind before comparisons are attempted with the rates found in untreated syphilis, even along broad lines. Some of these are as follows:

1. Merrell's material comprises both primary and secondary syphilis with no indication of the relative proportions of each, whereas in our material practically all patients had secondary syphilis.
2. The Merrell patients were subjected to a periodic follow-up system, whereas ours were not. This would have the effect of increasing the number of relapsers found.
3. Secondary relapse among Merrell's patients may well have been influenced by treatment of serorelapse which may precede clinical relapse. This would have the effect of reducing the occurrence of clinical relapse, and the follow-up system was conducive to this possibility. Although Merrell's concern was with clinical relapse only, 30 per cent of the total relapses in the material was serologic.
4. The time relationships in Merrell's material began at the termination of treatment, whereas ours are calculated from the time of complete disappearance of secondary symptoms and signs. This is the only one of these factors for which we can offer a correction: by increasing ours to the extent of the median duration of hospitalization, 3.2 months for example, an 18-month observation in her material would compare with 21 months in ours. There is no way of determining the relative weight of the other factors, and therefore comparisons as to incidence of clinical secondary relapse should be along broad lines, with due consideration to the dissimilarities between these series.

If we consider the groups in Merrell's series where the smaller dosages of penicillin have been employed (see table 33, p. 114) the cumulative percentage relapse at 18 months were as follows:

For 0.3 million units of penicillin: 18 per cent (Negroes only); for 0.6 million units of penicillin: 15.9 per cent (Negroes), 17.6 per cent (whites); for 1.2 million units of penicillin: 16.6 per cent and 13.5 per cent (Negroes), 15.1 per cent (whites). (Incidentally, there is no appreciable difference between Negroes and whites in this respect.)

With increasing dosages Merrell has found decreasing relapse rates. It is noteworthy that the figures given for the groups where the smaller dosages have been employed are not as high as those found in untreated secondary syphilis. Thus, if we take into account that the difference in the relapse rates in penicillin-treated and untreated cases, in all probability is a minimum, for reasons mentioned in the foregoing, the comparison indicates that even small amounts of penicillin are sufficiently adequate to prevent a certain number of relapses from developing, or at least do not seem to cause higher frequency than would be expected. Whether this would also be true if the doses were lowered still more, or the method of administration changed, is a different matter.

Multiple outbreaks. A direct comparison between treated and untreated cases relative to the frequency of multiple outbreaks of clinical secondary relapse is close to impossible, the reasons being: The figures given by authors who have analysed this phenomenon in treated patients are broken down neither according to stage of infection when treatment was first administered, nor according to amount of treatment given for the multiple outbreaks as such. Furthermore, the efficiency of follow-up has not been discussed, and there is no breakdown by sex. It is obvious that a great many of those patients who have been observed for a second or third outbreak of relapse have received treatment, which in turn has prevented further outbreaks from developing. Roughly speaking, however, there seems to be no great difference between the figures given for treated cases and those found in this material, inasmuch as the majority of the patients in both groups have experienced only one outbreak (89 and 86 per cent respectively in the series of Stokes et al. (1944) and Kampmeier (1943), as compared with 77.5 per cent in our material). Also, second, third, and fourth outbreaks have been observed in our series as well as in those analysed by the above authors. As a matter of principle, therefore, the picture is very much the same in treated and untreated cases, but due to the dissimilarities described, it is felt that we have to abstain from detailed comparisons relative to frequency. A certain trend can possibly be demonstrated nevertheless, pointing in the direction that multiple outbreaks are more frequently found in untreated syphilis, and this is in accordance with the belief that even inadequate or irregular treatment tends to a certain extent to prevent secondary relapse. Our figures also seem to show that multiple outbreaks are more commonly found in females than in males, but the figures are too small to permit definite conclusions in this respect.

Sex, and Age at Infection.

As far as incidence of clinical secondary relapse in the untreated syphilitics is concerned, no appreciable difference between males and females has been found, and this is in agreement with the opinions expressed by Thomas (1949) and Kampmeier (1943) on this point. The symptoms and signs of clinical secondary relapse have been considered as the result of hitherto unknown immunologic processes. Thomas for example, maintains that relapses are caused by inadequate or irregular treatment which «. . . interferes with the production of permanent «immunity» to the development of early lesions and probably with that of other immune reactions in the host . . .» (ibid. p. 15). If the occurrence of clinical secondary relapse is the same in untreated males and females, it seems reasonable to believe that the immune-reactions which have taken place are identical in the two sexes, resulting in correspondingly identical clinical manifestations. In other words, the factors usually held responsible for the milder course of the syphilitic infection in women (biochemistry of menstruation and pregnancy), do not seem to affect the natural development of the disease in this early phase, as judged by the clinical picture. If the development of clinical secondary relapse in itself as maintained by several authors, meant a change in the immune-mechanism which might lead to serious late lesions, it is rather surprising that the phenomenon is found as commonly in females as in males. At any rate, the possible change in the immune-processes can hardly play a *decisive* role for the later occurrence of serious manifestations, when we take into account the preponderance of late lesions in males. But, even if this change in the immunological picture takes place to the same extent in both males and females, it cannot be excluded that the more unfavorable outcome in males may have to do with the fact that females are protected by a mechanism which acts during the later development of the infection, irrespective of what may have happened during the early phase. Of course, if secondary relapse passes undetected, the patient is exposed to the risk of subsequently developing serious late manifestations because treatment has not been sufficient to prevent the natural course of the disease, and not because of relapse itself.

To date the problems of clinical secondary relapse have been surprisingly seldom analysed on a sex-specific basis. However, if the syphilitic infection is «. . . milder in women to the point of being almost a distinctive disease . . .» as expressed by Stokes et al. (1944 — p. 30), it is evident that a breakdown by sex should be done for all phases of the infection, beginning with the secondary relapses, this being the only way of evaluating the course of the disease in its entirety in both sexes. To mention an example, it would have been of great interest to have had Padget's analysis (1940) of the prognostic significance of clinical secondary relapse on a sex-spesific basis.

Sites and Types of Lesions.

By and large, the main clinical features demonstrated by authors who have analysed series of treated patients are similar to those found in untreated syphilis, the majority of the lesions of clinical secondary relapse both in treated and untreated cases being moist erosions and mucous patches of the anogenital and mouth-throat regions, and as such, infectious or potentially infectious (62 and 61 per cent respectively in Stokes et al. (1944) and Kampmeier's (1943) series as compared with 84.7 per cent in ours). It is only reasonable to expect a greater variety of concomitant lesions in untreated patients because the development has not been interrupted by treatment. As a whole, the site of the manifestations other than the mouth-throat and anogenital lesions, generally seem to be the same in both groups, the only exception being that so-called neurorecurrence in the strict sense of the word (asymptomatic neurosyphilis not included) was diagnosed among the untreated patients in only one single instance. It is hard to explain why neurorecurrences play such a minor role in the untreated series, but two explanations may be offered: They have either been overlooked, which is doubtful, or this special form of secondary relapse is a product of inadequate or irregular treatment with arsenicals. The present author is inclined towards the latter possibility as the most plausible one. If this is so, it would be an example of such treatment being the cause of secondary relapse. Otherwise we find manifestations of the skin, the eye, the periostium, the joints, and the liver, in treated as well as in untreated cases. To evaluate the order of magnitude for these latter groups, however, is out of the question, the figures being too small to allow for comparisons. As relates to eye manifestations in clinical secondary relapse, iritis seems to be the most frequent form in untreated syphilis, which, according to Stokes et al. is also the case in Negroes (treated?). Whether eye lesions are to be found more frequently in females than in males can not be definitely established, but there seems to be a trend pointing in this direction among our untreated patients. The authors who have dealt with treated patients in this respect, and have been quoted here, have given no breakdown by sex, and thus a comparison which might corroborate our findings is not possible.

Time Relationships.

In this material it has been demonstrated that 67.2 per cent, or a little more than two-thirds, of the clinical secondary relapses in untreated syphilis occur within the first six months after the termination of the secondary stage, and that the vast majority, 88.2 per cent, or close to nine out of ten, occur within the first year, and 94 per cent within two years (see table 38, Part I, p. 126). Among the relapsers 77.5 per cent have experienced only one outbreak, whereas 22.5 per cent had two or more. Among those who had multiple outbreaks 78.5 per cent, or about three-fourths, were observed within two years after secondary syphilis, and about 25 per cent, or roughly one-fourth, were found between the second and the sixth years (see table 38, Part II, p. 127).

If it is desired to put these figures in relation to onset of infection instead of termination of secondary syphilis, it is necessary to add on an average three to four months to the time periods given above. It must again be emphasized that the time periods figured out in relation to onset of infection are only to be considered as approximate, as already mentioned under Introductory Remarks (point 6, pp. 117—118).

Generally speaking, Thomas (1949) has maintained that in untreated syphilis the refractory state towards early infectious lesions in the vast majority of cases is usually reached within two years after infection, but adds that one can not be absolutely certain that this state has been reached in all cases when secondary syphilis is terminated. Our results show that in about 75 per cent of the cases with untreated secondary syphilis, the refractory state apparently has been reached within two years, and in most of the patients much earlier, since they have not developed further symptoms and signs of early syphilis. Thus, up to this point our results have confirmed the concept held by Thomas. In another approximately 25 per cent of the cases, however, the refractory state evidently was not established by the time symptoms and signs of secondary syphilis could no longer be demonstrated. On the contrary, sooner or later, and after a symptom-free interval, these patients came down with demonstrable lesions of early syphilis, the majority of which are infectious or potentially infectious. Again, most of the relapses occurred within 15—16 months[1] after infection, and in most of these patients as well the refractory state is established within the two-year limit, inasmuch as 77.5 per cent of them do not develop new lesions after the first outbreak of relapse. Among the patients experiencing more than one outbreak of secondary relapse, it has been found that the majority of these have occurred within the two to two and one-half year limit.[1] Thus, even among the patients who develop one or more outbreaks of secondary relapse the refractory state towards early infectious lesions in most of the cases is established within this period. The difference among these patients is that the disease has followed a rhythmic course, the refractory state being reached after an outbreak of clinical secondary relapse preceded by a symptom-free period, or after two to three outbreaks preceded by corresponding symptom-free periods.

[1] Three months have been added to the figures given above.

Thomas (1949) has also stated that infectious lesions developing after two years in untreated syphilis are extremely rare. It has been confirmed that they are rare, but 12 instances of the first outbreaks of secondary relapse and 14 of the multiple outbreaks were observed in our material after two to two and one-half years. (See table 38, Parts I and II, p. 126.) In other words, it does not seem that inadequate or irregular treatment in itself can be held responsible for this delay in the establishment of the refractory state.

In the section on occurrence we have already discussed the various basic epidemiologic factors that must be taken into account when it comes to comparisons between treated and untreated cases, and they are of no less importance in connection with the time-relationship question. Unfortunately, when presenting figures on time relationships of secondary relapse, most authors evidently have had to disregard these factors, either completely or in part.

Moore's (1944) figures on time relationships of infectious mucocutaneous relapse were based on the results arrived at in three different series («. . . are based on our own experience and the fundamental data of Fournier and of the Cooperative Clinical Group . . .», see p. 112), and this probably is the reason why he had to disregard the factor of kind and amount of treatment. It is further to be noted that breakdown as to stage of infection was not done, and that only infectious forms of secondary relapse were included.

The figures found by Stokes et al. (1944) through their analysis of the Pennsylvania series were presented in very much the same way, in that the results were not given according to amount of treatment or stage of infection and the material comprised only the mucocutaneous and cutaneous forms of relapse. It might be added that the number of relapses in this series is relatively small (55 cases). The method and efficiency of follow-up also bears on the time-relationship question, but how this factor may have influenced the figures in the above mentioned series is not clarified by the authors.

Finally, comparisons have been made even more complicated by the fact that our figures relate to the interval between the termination of secondary syphilis and the outbreak of the relapses, and thus only approximate estimates of the onset of infection can be given for purposes of comparison. Under these circumstances, therefore, an evaluation of the time relationships of secondary relapse in treated and untreated cases as based on comparisons between ours and the series above, are fraught with so many uncertainties that it must be considered close to valueless.

We turn now to the time relationships of secondary relapse in penicillin-treated cases (Merrell, 1951). The basic epidemiologic factors have been discussed previously (see section on occurrence). It is emphasized, however, that the lack of breakdown by stage of infection in Merrell's material probably forms the most serious obstacle when it comes to comparisons with the results arrived at in untreated syphilis. And again we have the question of using completion of treatment instead of termination of secondary syphilis as a starting-point, something which may further complicate the matter. However, it should be noted that in these two series time is reckoned from the disappearance of symptoms and signs, on the one hand as a result of treatment and on the other as a result of the natural course of the disease.

It is also to be noted that up to this point we have based the discussions on frequency distributions (table 38, p. 126), whereas for possible comparisons with Merrell's results, we shall have to use the figures presented in the probability table and figure (table 39 and fig. 7, pp. 129—131).

This latter way of demonstrating the rates undoubtedly gives a much more reliable picture of the development than does an ordinary frequency distribution table, inasmuch as the factor of the changing denominator with time is taken into account. But in this instance too, an evaluation of the time-relationship question can only be made with great reservations, and obviously has to be kept within the limits of broad principles, as the many dissimilarities prevent detailed comparisons. The main feature demonstrated by Merrell is that the cumulative probability of relapse at the end of 18 post treatment months in inadequately treated patients is 13.5 to 18.0 per cent depending on the amount and type of penicillin used. Furthermore the vast majority of relapses have occurred by the end of this time. In our series it was found that the cumulative probability at 18 months was 23.2 per cent and 22.0 per cent for males and females respectively, and similarly the vast majority have occurred by the end of this time.

As far as this comparison goes it seems that even small doses of penicillin will reduce the probability of relapse. The order of magnitude of the difference between treated and untreated cases will depend on the duration of infection at the time treatment is given. Since this is not known here no further comparisons can be made and it would not be wise to draw conclusions from these data alone. In principle, however, there does not seem to be any great difference between the penicillin-treated and the untreated cases, inasmuch as the vast majority of the relapses have been diagnosed within the first 18 months after the disappearance of symptoms and signs.

Summary and Conclusions.

1. The study group comprised a total of 1,035 untreated patients, the vast majority of whom were found to have been observed until clinical lesions of secondary syphilis could no longer be demonstrated.
2. Symptoms and signs of *untreated* secondary syphilis disappeared after a period of a few weeks to 12 months, thereafter followed a period of clinical latency, which in approximately 1 out of 4 patients was interrupted by

new demonstrable lesions, or symptoms and signs of clinical secondary relapse.

3. Among those who relapsed, a little more than one-fifth experienced from 1 to 3 additional outbreaks, likewise occurring after periods of clinical latency.
4. The findings demonstrate the rhythmic occurrence of this phenomenon, which must be considered as part of the *natural* course of the infection.
5. Our findings are at variance with the ordinary opinion that this phenomenon is related *only* to inadequate and/or irregular treatment, and therefore a new definition is suggested as follows: Clinical secondary relapse is the reappearance of secondary type lesions after a period of clinical latency. It may either be part of the natural course of the disease following the termination of the untreated secondary syphilis, or it may follow irregular and/or inadequate treatment during the early stages of the infection.
6. It is indicated that the immune-mechanism created in clinical secondary relapse following inadequate treatment may be different from that associated with the clinical secondary relapse observed during the natural course of the infection.
7. As far as incidence of clinical secondary relapse in untreated secondary syphilis is concerned, there was no appreciable difference between males and females. In other words, the factors usually held responsible for the milder course of the syphilitic infection in women (biochemistry of menstruation and pregnancy) do not seem to affect the natural development of the disease in this early phase. The importance of analysing the problem of clinical secondary relapse on a sex-specific basis is stressed.
8. The influence of age at infection on the frequency of clinical secondary relapse could not be determined with the data available. However, the lesions occurred in all age-groups listed and it was noted that no tendency towards decreasing proportions was found in the higher age-groups (those over 30).
9. As regards sites and types of lesions, those of the anogenital and mouth-throat regions played a dominant role, occurring as solitary or concomitant manifestations in 84.8 per cent of the outbreaks. Since these lesions will be infectious or potentially infectious in practically all instances, they constitute an extremely dangerous form of early syphilis. The importance of this is emphasized in view of the theories advanced by some modern syphilologists, who point out that in *untreated* secondary syphilis the refractory state towards early infectious lesions is usually reached by the time the clinical manifestations have completely disappeared.
10. In the strict sense of the concept only 1 case of neurorecurrence was observed in the study. The possibility is indicated that neurorecurrence

may constitute a form of relapse that is practically always related to irregular or inadequate treatment.

11. The time interval from healing of secondaries to first observed clinical relapse (without treatment) was such that about two-thirds (67.2 per cent) occurred within the first 6 months, the vast majority, or close to 9 out of 10 (88.2 per cent) within the first year, and practically all by end of the second year (94.3 per cent). The remaining 5.6 per cent developed during the following years, the majority between the second and third, the latest during the fifth year, and none afterwards.
12. The time interval between healing of secondaries and the occurrence of multiple outbreaks of clinical secondary relapse was as follows: about one-half of the outbreaks (51.7 per cent) developed within the first year, and three-fourths (75.8 per cent) within the first two years, whereafter the remaining fourth (24.1 per cent) developed during the following years, the majority between the second and fourth, the latest between the sixth and seventh year.
13. It was confirmed that infectious lesions developing after two years are rare, but 12 instances of first outbreaks and 14 of multiple outbreaks were observed in the present material after two to two and one-half years. Thus it does not seem that inadequate or irregular treatment in itself necessarily has to be responsible for this delay in the establishment of the refractory state towards infectious lesions.
14. The cumulative probability of developing clinical secondary relapse (one outbreak) was calculated and the following values were found in males and females respectively: 3.6 and 2.6 per cent by the end of 1 month; 18.8 and 16.9 per cent by the end of 6 months; 22.5 and 21.3 per cent by the end of 2 years; and 23. 9 and 24.4 per cent by the end of 3 years.
15. In respect to occurrence and time relationships it is concluded that we have been able to establish an approximate base-line for comparisons with figures arrived at through the analysis of treated cases.
16. The difficulties one can expect when such comparisons are attempted were discussed, and through examples it was shown why conclusions must be drawn with great caution.
17. As far as the comparisons go indication is that even inadequate treatment protects against clinical secondary relapse.

Chapter VII

«BENIGN» TERTIARY SYPHILIS

I. Excerpts from and Comments on the Literature.

Definition.

Formerly the definition of tertiary syphilis was based mostly on the pathologic-anatomical picture. However, this did not take into account the differences in diagnosis, treatment, and prognosis of lesions of various localizations. Thus, many clinicians found that tertiary syphilis of the skin, the mucous membranes, and bones and joints, could best be classified in one group termed *«benign»* tertiary syphilis, late «benign» syphilis, or tertiary syphilis of the skin, mucous membranes, bones and joints. The term «benign» tertiary syphilis was reserved for this group exclusively whereas lesions often of a similar pathologic-anatomical type (mostly gummata) in the brain, the liver and other internal organs were classified as neurosyphilis, visceral syphilis and so on. From a clinical point of view this seems to be the most logical classification, and it has been adopted by more and more of the modern syphilologists. But the system of classifying these lesions according to the pathologic-anatomical picture is still maintained to a certain degree by some authors. Kampmeier (1943), for instance, has listed visceral syphilis among the late «benign» lesions, whereas gumma of the brain has been classed as neurosyphilis. Nielsen (1950) has included his one case of visceral syphilis in the group «benign» syphilis. By putting the word benign in quotation marks, however, he has pointed to the necessity of distinguishing between the two groups.

Causes.

The development of «benign» tertiary lesions is in general thought to be related to an upset in the parasite-host relationship resulting from reactivation of remaining treponemes in a sensitized host. That such a reaction in a sensitized host can result from treponemes introduced from sources outside the host is suggested by superinfection experiments in laboratory animals and by observations of Grin (1953) on endemic syphilis in Yugoslavia. Grin (ibid. p. 40) describes both types as follows, «. . . First, there may be reactivation of residual treponemes in a sensitized allergic organism, upsetting the parasite-host relationship. This occurs in untreated or inadequately treated sporadic venereal syphilis; it may also occur in endemic areas, usually in the stationary or regressive period, but it is probably of secondary importance. Secondly, tertiary lesions may develop from superinfection of the host which is already in an allergic state as a result of prior infection. In such cases, any residual dormant treponemes in the host are likely to be of little importance; the essential features are the host's changed reactivity and allergic state».

Occurrence.

It is only natural from a public health point of view that the non-infectious «benign» tertiary lesions have been considered less important than secondary relapse, and likewise by both patient and physician have been looked upon as minor problems compared with cardiovascular, neuro- and other late syphilis. This, in addition to the steady decrease in occurrence after salvarsan was introduced, has certainly played a great role in the relative lack of interest in the problem of these manifestations, and in the scarcity of information relating to epidemiologic data in the literature.

Moore (1944), quoting Bruusgaard, gives the incidence as being about 12 per cent in untreated syphilis. Thomas (1949 — p. 190) writes: «The incidence of demonstrable late syphilitic lesions of the skin, mucous membranes, skeletal system, and viscera of patients observed at Bellevue Hospital has definitely declined in the past decade. This is probably due to improvement in case finding and treatment during the past 20 years. I doubt that statistics of the incidence of the so-called benign late lesions of syphilis have much significance at present. The incidence undoubtedly varies in different communities. In Bruusgaard's report of 473 untreated patients, the incidence of late lesions of the skin, mucosae, and bones was 12.2 per cent.» In the «Alabama Study» (Vonderlehr et al., 1936) the incidence of late involvement of the bones, joints and skin turned out to be 11.5 per cent, the majority of the patients (9 per cent) showing periostitis, osteitis and Charcot's joints, whereas only 2 per cent had both a late skin *and* bone and joint involvement, and less than 1 per cent syphilis of the skin alone. These figures evidently are based on the findings made in the original 1932 examinations (see description of the «Alabama Study», p. 28), and therefore represent prevalence of «benign» tertiary syphilis rather than incidence. Whether the lesions diagnosed relate to active or inactive forms, or both, is not clear. It is also to be noted that Charcot's joints have been included.

Nielsen (1950) made a follow-up study of 467 male patients treated for primary and secondary syphilis in the University Clinic of Dermato-Venereology of the Rigshospital in Copenhagen between 1913 and 1920. The period of observation ranged between 29 and 36 years, and the patients had received 1—3 gm. of salvarsan (Ehrlich 606) and about 50 inunctions of mercury, sometimes more. The results are of considerable interest in many respects, but particularly because they are based on patients treated during the early salvarsan era, or the period of development in the treatment of syphilis following upon that chosen for our study of untreated syphilis. The percentage incidence of «benign» tertiary syphilis in Nielsen's series is 1.1 per cent (one case of pulmonary syphilis included). Nielsen comments on this question as follows: «There were very few cases of benign syphilis which may possibly be explained by the fact that patients do not invariably seek medical attention for benign tertiary syphilis, as the symptoms frequently do not cause much inconvenience. Further, it is a common experience that tertiary syphilis of the skin has become a rare occurrence . . .»

As the possibilities for follow-up studies of syphilis in Denmark are probably unique in the world, and because we are coming back to Nielsen's findings on several occasions later, it is felt that a general description of his methods may as well be given here and then referred to when we discuss other phases of the infection. In a later paper Nielsen (1952) has described the background[1] for his follow-up studies as follows: «. . . In Denmark all serological tests for syphilis are made at one institution, viz. the State Serum Institute in Copenhagen. Since 1920 a Syphilis Registration Office has been in existence, covering all syphilitics in the country. Thus, any sample for examination (blood or spinal fluid) is sent to the Sero-Diagnostic Department accompanied by a card containing the following particulars about the patient in question: — Sex, year and date of birth, the initial letter of the surname, the date on which the diagnosis of syphilis was first established and the name of the physician or department that made the diagnosis. These so-called elements of identification make it possible to identify the individual patient and yet observe anonymity. Furthermore, the card is provided with the patient's reference number in the records of the physician or hospital in question and with details of any manifest or previously noted outbreaks of the disease. Thus, every time a sample of blood or spinal fluid obtained from a patient who is, has been, or is suspected of suffering from syphilis is submitted for examination, the registration office is automatically notified of the case. In this way information is received at intervals about the individual patient and entered in chronological order on his card in the registration office.» On the basis of the data he found in the archives of the Syphilis Registry of the State Serum Institute, Nielsen collected from physicians and hospitals throughout Denmark all the information available on the course of the disease during the 29 to 36 years that had elapsed since the patients in the study group were infected.

[1] It was also described in his 1950 paper, but we have chosen to quote from the later one.

It is of course difficult to evaluate the efficacy of this particular method of tracing and collection of clinical data, but the author refers to various quite extensive studies showing good agreement between the expected number and the number of patients actually found in the register. In any event, it is certainly safe to assume that this method is as good, or presumably better, than any other that can be utilized in the follow-up of syphilitics. Whether these patients received treatment in any form in the interim period, that is, between time of original discharge and the final observation, is not stated. Neither is there any description of their occupation or socio-economic status in general, which might have indicated something about their stability in respect to residence, which again might bear on the results of tracing and follow-up.

Grin (1953 — p. 35) offers a plausible explanation why treatment alone can not be held responsible for the decreasing incidence of «benign» tertiary lesions in sporadic syphilis, «. . . The influence of treatment, however, gives only a partial explanation, since there exist geographical areas in the world today with a high percentage of inadequately treated, or even untreated, endemic syphilis where tertiary lesions are comparatively rare and no more frequent than in areas with sporadic venereal syphilis.», and continues (ibid.), «It is important to bear in mind that, wherever tertiary manifestations are frequent in endemic areas, the reservoir of *T. pallidum* is always extensive, as is shown by the numerous fresh cases of early infectious syphilis that occur, and that the primitive living conditions afford repeated opportunities for the perpetuation of the disease by direct and indirect contact . . .»

Grin gives no figures on *incidence*, but the relationship of early clinical syphilis to active tertiary manifestations has been convincingly illustrated by examples drawn from his experience.

Among other examples were two villages where the *prevalence* of various forms of syphilis was recorded: In the village of Kosova the findings were: 17.3 per cent early infectious (secondary) and 60.9 per cent latent seropositive, whereas tertiary syphilis accounted for 21.8 per cent (of which 13.5 per cent had lesions of recent date and 8.3 per cent showed scars). In the village of Šije, on the other hand, the results were: 4.9 per cent infectious cases (secondary) and 2.9 per cent new cases with tertiary lesions, whereas 14.4 per cent showed signs of old tertiary manifestations. Studies in other villages gave similar results: where the prevalence of early infectious syphilis was high, the active late «benign» lesions were high, and vice versa.

Multiple outbreaks. Figures on the frequency of multiple outbreaks of «benign» tertiary syphilis have not been found in the textbooks and scientific papers available to the present author. The explanation is probably that most modern authors have had to base their studies on first outbreaks which have either been observed through out-patient clinics or have been hospitalized, and consequently the majority of the patients have received some form of treatment which has prevented or at least made multiple outbreaks relatively rare.

In Frazier and Li's series (1948) it is not directly stated whether the total number of patients with «benign» tertiary manifestations represent first outbreaks only or include also multiple outbreaks occurring in the same patient. This question may have some bearing on the sex distribution of «benign» tertiary syphilis. If multiple outbreaks occur more frequently in females, this phenomenon may, at least in part, be responsible for the preponderance of females over males in this respect. Whether it has influenced the findings in Frazier and Li's series is difficult to determine. About the Chinese patients in this latter study it is stated that they represent all admissions to the syphilis clinic of the Peiping Medical College from 1927—1937, which might indicate that they are dealing with number of outbreaks rather than with the actual number of patients. On the other hand, all of the patients were admitted to good hospitals or clinics and presumably treated, something which in the majority of the cases would probably prevent further outbreaks of «benign» tertiary manifestations, and therefore the number of such outbreaks can be assumed under all circumstances to be relatively small in Frazier and Li's series.

Sex, and Age at Infection.

Information on sex is either scanty or lacking, and this goes for practically all the leading textbooks on syphilology. Among the white patients (patients who were admitted to the Johns Hopkins during the twelve years 1920—1931) Frazier and Li (1948) found that females had more tertiary localizations in extraneural structures than did males. In considering this series as a whole, comprising in addition to the whites, Negroes and Chinese, these authors write about «benign» tertiary syphilis «. . . throughout the course of the disease, cutaneous and skeletal structures were more often actively involved in women than in men, but the reverse was true of the cardiovascular and central nervous systems».

The present author has not been able to find information in any of the above mentioned textbooks on the influence of age at infection in «benign» tertiary syphilis. That it occurs in children is mentioned by Grin (1953 — p. 34) in his work on endemic syphilis, «. . . Although frequent in children, they[1] also occur in all age-groups». No figures on the relative frequency in the various age-groups are given, however.

Age at manifestation. In Frazier and Li's (1948) white patients the mean ages at outbreak of cutaneous and skeletal manifestations of «benign» tertiary syphilis were as follows: males — cutaneous 41.5 years, and skeletal 42.0 years; females — cutaneous 37.1 years, and skeletal 43.5 years.

[1] Gummatous lesions.

Table 40.

Distribution of Late «Benign» Lesions as to Site and Race.

Site	Negro			White		
	No.		Per cent	No.		Per cent
Skeletal, all types		122	31.0		39	30.2
Skin		121	30.8		43	33.3
Upper respiratory (nose-throat, larynx)	49	90	22.9	18	33	25.6
Mucous membrane (mouth)	41			15		
Eye (all types)		43	10.9		11	8.5
Lymph nodes	7	17	4.3	0	3	2.3
Penis	3			2		
Genital tract, female	4			0		
Skeletal muscle	3			1		
Total		393	100.0		129	100.0

Adapted from Kampmeier, R. H.: «Essentials of Syphilology», J. B. Lippincott Company, Philadelphia, 1943.
(Kampmeier's table XX, p. 241).

Structures Involved.

Kampmeier (1943) has given the distribution of late «benign» lesions as to site and race as based on 561 cases from the Vanderbilt University Hospital Syphilis Clinic. The author particularly calls attention to the fact that his figures do not represent the actual frequency of such lesions since certain patients are more likely to be admitted to the hospital than to the clinic. Kampmeier's figures as modified for comparisons by the present author are given in table 40. We have taken out 39 patients who, according to our definition, are not classified as being «benign» tertiary syphilis (visceral, lower respiratory tract, mediastinum and testis). From this table it is seen that among whites the highest frequency is 33.3 per cent skin, and the next 30.2 per cent skeletal.

Grin (1953) in his work on endemic syphilis has stated that gummatous lesions are most frequently found on the skin, in the nasopharyngeal region and the osteoarticular system. He has emphasized that in some regions affections of the bones and joints constitute as many as 20 per cent of the cases, the most common forms being arthralgia and osteoperiostitis. Otherwise Grin gives no figures as to the relative frequency of localizations.

In table 41, modified from Frazier and Li (1948), it will be seen that among the white patients the skin was most commonly involved in both males and

Table 41.
Site of Lesions in «Benign» Tertiary Syphilis, by Race and Sex.

Clinical Phenomena	Chinese				White				Negro			
	Male		Female		Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cutaneous	263	36.9	84	41.0	99	42.1	78	43.6	138	27.4	215	32.8
Muscle and tendon	15	2.1	4	2.0	0	0	6	3.4	4	0.8	2	0.3
Upper respiratory	55	7.7	19	9.3	39	16.6	48	26.8	90	17.9	114	17.4
Skeletal	223	31.3	64	31.2	71	30.2	24	13.4	190	37.7	240	36.6
Ocular	112	15.7	30	14.6	16	6.8	22	12.3	63	12.5	70	10.7
Gland	44	6.2	4	2.0	10	4.3	1	0.6	19	3.8	14	2.1
Total	712	100.0	205	100.0	235	100.0	179	100.0	504	100.0	655	100.0

Adapted from Frazier, C. N., and Li Hung-Chiung: «Racial Variations in Immunity to Syphilis. A Study of the Disease in the Chinese, White, and Negro Races», The University of Chicago Press, Chicago, 1948.
(Frazier and Li's table 10, p. 54).

females (42.1 and 43.6 per cent respectively), skeletal comes next in males (30.2 per cent) and upper respiratory in females (26.8 per cent), then in males upper respiratory (16.6 per cent) and in females skeletal (13.4 per cent), whereafter follows ocular with 6.8 per cent in males and 12.3 per cent in females. The other localizations play a minor role (muscle and tendon and gland). The authors have furthermore found that solitary clinical phenomena were much more frequently observed in extraneural tertiary syphilis than were the combinations. Among whites for instance more than 90 per cent of the patients showed solitary lesions. It is to be noted that extraneural syphilis here means «benign» tertiary, cardiovascular and visceral syphilis. However, if we omit the two last mentioned categories from the material and figure out the percentage on the basis of the total number of «benign» tertiary manifestations the results turn out about the same, solitary lesions accounting for approximately 90 per cent. Finally the same authors point out that cutaneous and skeletal lesions usually are absent in patients with cardiovascular and neurosyphilis.

Time Relationships.

As to time relationships, Kampmeier (1943) writes that «benign» tertiary lesions usually occur from 3 to 10 years after infection, and also that precocious tertiaryism may occur at the end of the secondary stage. Furthermore, he says that in so far as one can determine by clinical examination or history, tertiary «benign» manifestations may develop as late as 35 to 40 years after infection. Thomas (1949 — p. 190) gives his opinion as follows: «Late cutaneous syphilides may develop at any time after the secondary stage. Precocious tertiary lesions of the skin may be noted within the first year or two of the infection, and it is not unusual for late syphilides to develop 20 or 30 years after infection.» Frazier and Li (1948) estimated the differences between mean ages at infection and at time of outbreak of «benign» tertiary manifestations and give the following figures: for white males — cutaneous 12 years and skeletal 12.6 years; for white females — cutaneous 11.5 years and skeletal 8.9 years. The differences between the sexes were not found to be significant. Grin (1953 — p. 40) has given no detailed data as to time relationships of «benign» tertiary lesions in endemic syphilis but has made the following general statement: «From the observations made and the results of the campaign in Bosnia, we may conclude that it (development of «benign» tertiary lesions[1]) is largely due to the environmental factors which influence the natural course of the disease in endemic areas, and which are the chief cause of reinfection and superinfection, *that the late manifestations af syphilis appear early, particularly tertiary lesions in already sensitized hosts*,[2] and that the frequency with which such lesions occur represents an epidemiological indication or index of the state of activity of the rural endemic foci, and of whether their origin is more or less recent.»

Prognostic Significance.

It has been the impression that «benign» tertiary lesions rarely have *preceded* cardiovascular and neurosyphilis, and also that concomitance of the «benign» and the serious lesions have been found infrequently. These impressions have evidently led to the belief that the development of «benign» tertiary lesions in a way represented a defence mechanism towards late serious complications. In this connection Stokes et al. (1944) emphasize that there is no logical reason to believe that visible lesions of the skin, mucous membranes or bones protect the central nervous system. In Frazier and Li's (1948) series the absence of skin and skeletal lesions in patients with cardiovascular and neurosyphilis was a noteworthy characteristic. Nicol (1950) reports on the experience in some clinics where concomitant «benign» tertiary and cardiovascular manifestations were found in about 5 per cent. Figures on the frequency with which «benign» tertiary lesions *precede* the development of cardiovascular or neurosyphilis have not been found in the literature available to the present author, and Frazier and Li write that their data do not permit any statement on this point, but emphasize that as a rule it must be considered a rare event.

[1] Present author's note.

[2] Italicized by the present author.

II. Present Investigation.

Introductory Remarks.

For the study of «benign» tertiary manifestations we have taken as a basis all patients belonging to the two main groups «Known» and «Partially Known», a total of 1,147 patients, 374 male and 773 female (see table 21, p. 93).

Before turning to the detailed findings the following points should be borne in mind:

1. The vast majority of the cases with «benign» tertiary lesions were hospitalized, either in Boeck's department at the Rikshospital or in the Municipal Hospital of Oslo, V.D. Division. A relatively small number were observed at the policlinic of Boeck's department, the Oslo City Health Department, V.D. Division, or in other hospitals, and a still smaller number were seen by private practitioners, mostly V.D. specialists. By and large, therefore, the diagnoses have been made by competent clinicians who have had an opportunity to follow the course of the tertiary outbreak for a shorter or longer period of time.
2. The patients are individuals who were observed and/or hospitalized after having seen their doctors because of some suspicious symptoms and signs, and thus the number of cases found is not the result of any follow-up system.
3. The 1,147 patients chosen for study comprise all cases of fresh syphilis (in the above mentioned groups) discharged from Boeck's department irrespective of original stage of infection, that is, in addition to the groups primary *and* secondary syphilis and secondary syphilis we have also included those seen originally in secondary relapse.
4. In contrast to the procedure adopted for the study of secondary relapse, we have *not* removed the patients who received some form of treatment prior to, during, or immediately after, hospitalization in Boeck's department (see p. 116). Furthermore, no patient was excluded who subsequently relapsed and was treated (see p. 121). Numerically these two groups play a minor role, and the treatment they were given must be considered highly inadequate in the majority of cases. However, we can not exclude the possibility that the treatment administered may have had some effect, and if so, it would tend to minimize the number of tertiary outbreaks somewhat.
5. As regards time relationships it is to be noted that we are dealing with the interval of time between date of the original discharge from Boeck's department and the date of discharge after the tertiary outbreak (except for the few patients observed on an ambulatory basis, in which cases the date when the tertiary lesions were first diagnosed has been used). Furthermore, in

the time-relationship estimates the age-groups under 15 and over 39 have been removed for reasons discussed in the foregoing section on secondary relapse. In addition to the patients in the above mentioned age-groups we have also omitted individuals in the central age-groups 15—39, where exact year of outbreak could not be determined by history, or where we had reason to believe that the outbreak observed in all likelihood was not the first one. *This* pertains to 2 male and 3 female patients, and explains the discrepancy between the frequency-distribution tables and the time-relationship tables. And finally, only first outbreaks have been included in the calculation of the probabilities of developing «benign» tertiary lesions.

Definition.

By «benign» tertiary syphilis we mean tertiary manifestations of the skin, mucous membranes, bones and joints (Charcot's joints not included). Gumma of the brain is classified under neurosyphilis, gumma of the liver under visceral syphilis, and so on.

Causes.

In this series we are in the main dealing with sporadic venereal syphilis. However, there were also instances of small epidemics of infectious secondary syphilis in some of the families, and non-venereal infection, particularly among the children, certainly has taken place, but these cases comprise only a small part of the total. In such families secondary relapse, developing later in one of the family members, may have been responsible for superinfection of others, leading to tertiary lesions. But again the numbers involved are probably too small to substantially influence the frequency of «benign» tertiary lesions in this material. Tertiary lesions may have resulted from the fact that a good many other patients exposed themselves to venereal superinfection after termination of the secondary stage or after secondary relapse. How often that may have happened is of course impossible to decide, but it is reasonable to assume that superinfection has played a minor role in the development of «benign» tertiary syphilis in our series, reactivation of residual treponemes being the main cause in the majority of the cases.

Occurrence.

We have found that a total of 15.8 per cent, or about one in every six of our patients, sooner or later developed «benign» tertiary lesions (table 42). In all probability this figure is a minimum, for the following reasons: Some of the patients have certainly left the City of Oslo before their first outbreak occurred and have been registered and observed elsewhere. We have information on a few of these, but it is possible that others in this category have escaped us.

Table 42.

Proportions Developing «Benign» Tertiary Syphilis, by Sex and Age at Onset of Infection

(181 patients)

	Males			Females			Total		
	No. of Patients Observed	Patients developing «Benign» Tertiary		No. of Patients Observed	Patients developing «Benign» Tertiary		No. of Patients Observed	Patients developing «Benign» Tertiary	
		No.	Per cent		No.	Per cent		No.	Per cent
	374	54	14.4	773	127	16.4	1147	181	15.8
Age-groups*									
0 — 4	22	2		25	0		47	2	
5 — 9	5 30	0 3	10.0	9 40	1 3	7.5	14 70	1 6	8.6
10 — 14	3	1		6	2		9	3	
15 — 19	50	4	8.0	173	29	16.8	223	33	14.8
20 — 24	123	12	9.6	292	46	15.8	415	58	14.0
25 — 29	83	18	21.7	127	22	17.3	210	40	19.0
30 — 39	57	9	15.8	89	21	23.6	146	30	20.5
40 over	31	8	25.8	52	6	11.5	83	14	16.9
15 — 39	313	43	13.7	681	118	17.3	994	161	16.2

* Age at infection.

Moreover, because of the good response to relatively simple methods of treatment (potassium iodide in particular) a certain number of these patients, including those remaining in Oslo, may have seen private practitioners for their «benign» tertiary lesions, and thus may have escaped registration by the official channels of information available to us. It is our impression, however, that the number of patients falling within the latter category must be comparatively small. References to treatment by private practitioners are rare in the numerous hospital records collected, and also among the official data found in institutions such as the Bureaus of the Indigents and the City Health Department. In this connection it must be remembered that the socio-economic status of the majority of the patients was such that hospitalization or treatment by official institutions like the City Health Department, became the more likely solution to their problems, rather than expensive treatment by private practitioners, particularly before the compulsory sick-insurance system was introduced (1911) and also during the first decades of its operation. Furthermore, the treatment given some of the patients during the early stages of the disease, however inadequate it may have been, also would work in the direction of minimizing somewhat the number of cases developing «benign» tertiary syphilis. To evaluate with any degree of exactness the influence of the above mentioned factors on the frequency of «benign» tertiary lesions in our series, is of course not possible, but by and large, it is safe to assume that the figure (1 in every 6) arrived at, represents a minimum.

As previously mentioned (p. 155) we have based our study of «benign» tertiary syphilis on the total number of patients in the two main groups «Partially Known» and «Known». Table 43 is presented in order to enable us to compare the proportions (by sex) developing «benign» tertiary lesions as calculated through the use of different denominators. First it will be seen that the use of the «Known» group as a denominator, rather than the combined groups mentioned above, will result in only a slightly higher percentage of «benign» tertiary manifestations, indicating that it matters little which one of the denominators we choose (17.2 and 16.4 per cent for females; 15.4 and 14.4 per cent for males). The reason for the differences, small though they may be, is probably to be sought in the group «Partially Known» where the percentage «benign» tertiary lesions is a bit smaller than expected, particularly in males. Evidently this is because we have not been able to follow the patients in question for as long a time as those in the group «Known». Finally, if we had taken the total number of patients in the study group as a denominator, we would have had to assume that none of the individuals in the «Unknown» group had developed «benign» tertiary manifestations. There is no reason to believe this and we rather prefer to assume that these behaved in the same way as the remainder. Consequently, percentages based upon the total will be too small.

Table 43.

Proportion of Patients Developing «Benign» Tertiary Syphilis as Calculated Through the Use of Different Denominators, by Sex.

(All ages*)

Group of Patients Used as a Denominator**	Male			Female			Total		
	Total Number Observed	Patients Developing «Benign» Tertiary Syphilis		Total Number Observed	Patients Developing «Benign» Tertiary Syphilis		Total Number Observed	Patients Developing «Benign» Tertiary Syphilis	
		No.	%		No.	%		No.	%
«Known»	331	51	15.4	622	107	17.2	953	158	16.6
«Known» plus «Partially Known»	374	54	14.4	773	127	16.4	1147	181	15.8
Total Patients in Study Group: («Known» «Partially Known» «Unkown»)	446	54	12.1	958	127	13.3	1404	181	12.9
«Partially Known»	43	3	7.0	151	20	13.2	194	23	11.9

* Age at infection.
** See table 21, p. 93.

Multiple outbreaks. Table 44 shows that a little more than two-thirds (68 per cent) of the patients with «benign» tertiary syphilis experienced only a single outbreak, while a little less than one-third (32 per cent) had 1 to 6 additional outbreaks, 16.6 per cent having two outbreaks, 5.7 per cent three, 4.0 per cent four, 2.9 per cent five, 2.3 per cent six, and 0.6 per cent seven.

On the basis of these findings it is probably safe to state that in general we can expect the majority of the patients who develop «benign» tertiary syphilis following no treatment or highly inadequate treatment for early syphilis, to experience only one outbreak of «benign» tertiary lesions. But the frequency of multiple outbreaks is to a large extent dependent on the type and amount of treatment given both for the first and the possible subsequent outbreaks. We know that some of our patients received specific treatment for their «benign» tertiary manifestations (see later section on treatment) and even if it was usually far from adequate as measured by modern standards, we have to assume that it may have had some effect, thus decreasing somewhat the number of

Table 44.

Patients with «Benign» Tertiary Syphilis According to Number of Outbreaks Experienced, by Sex.

(All ages*) (175 patients**)

No. of Outbreaks	Male		Female		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
1	38	74.5	81	65.3	119	68.0
2	5	9.8	24	19.4	29	16.6
3	1	2.0	9	7.3	10	5.7
4	4	7.8	3	2.4	7	4.0
5	0	0	5	4.0	5	2.9
6	3	5.9	1	0.8	4	2.3
7	0	0	1	0.8	1	0.6
Total	51	100.0	124	100.0	175	100.0

* Age at infection.
** 3 male and 3 female patients removed; outbreak number undetermined.

multiple outbreaks. It is therefore reasonable to believe that the figures of multiple outbreaks found in our series represent a minimum. It seems that multiple outbreaks occurred more frequently among females, but the distribution is uneven and the differences not significant, so with the data available nothing definite can be said on this point. It is felt, however, that this possibility should be borne in mind.

Sex, and Age at Infection.

In table 42 is presented the proportion developing «benign» tertiary syphilis according to sex and according to age at infection. No statistically significant difference between the two sexes can be demonstrated, the proportion being 14.4 per cent in males as compared with 16.4 per cent in females; and this also holds true for the age-groups 15—39, showing 13.7 per cent in males and 17.3 per cent in females. Relative to age at infection, we have found tertiary manifestations to occur in each of the age-groups presented in the table, with a tendency toward increasing proportions with age. The differences,[1] however, are no greater than would be expected by chance, and thus the influence of age on the frequency of these lesions can not be stated with the data available.

[1] Tested by χ^2 on the total.

Table 45.

Age at Time of Outbreak of «Benign» Tertiary Phenomena, by Sex. First Outbreaks.
(Ages 15 — 39*) (157 patients**)

Age at Outbreak of «Benign» Tertiary Phenomena	Male	Female	Total
	No.	No.	No.
15 — 19	0	0	0
20 — 24	0	19	19
25 — 29	9	30	39
30 — 34	14	24	38
35 — 39	6	12	18
40 — 44	4	7	11
45 — 49	1	10	11
50 — 54	6	5	11
55 — 59	1	2	3
60 — 64	1	3	4
65 — 69	0	3	3
70 — 74	0	0	0
Total	42	115	157
Mean age in years	36.8	34.9	35.7

* Age at infection.
** 3 male and 3 female patients removed; outbreak number undetermined.

Age at time of outbreak. In table 45 is found the distribution of cases with first outbreaks of «benign» tertiary syphilis according to age at emergence. It will be noted that only patients belonging to the age-groups 15—39 (at infection) are included, the under 15 and over 39 age-groups having been omitted for the same reasons as mentioned under Introductory Remarks, point 5, p. 156. Among the males the age at first outbreak varied from 25 to 65 years, with a mean of 36.8 years, whereas among the females it varied from 20 to 70 years, with a mean of 34.9. The mean for the total number of cases was 35.7 years.

Structures Involved.

Table 46 was set up in order to demonstrate the distribution of lesions in first and multiple outbreaks of «benign» tertiary syphilis according to structures involved. It will be noted that 175 patients experienced 291 outbreaks, and that the distribution is calculated on the basis of outbreaks rather than individuals.

In our series the predominant features were: First, solitary (single-structure) lesions were much more frequently diagnosed than were concomitant (more

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than one structure) ones, 90 per cent versus 6.1 per cent (3.8 per cent undetermined[1]). Second, solitary manifestations of the skin represent 70.1 per cent of all outbreaks, thus far outweighing all others in importance. Next come skeletal and mucous membranes with 9.6 and 10.3 per cent. The relationship of solitary and concomitant lesions and the preponderance of solitary skin lesions are by and large the same in males and females. When it comes to comparisons between the sexes in the various sub-groups (skeletal, mucocutaneous and those with concomitant lesions), the figures are too small to permit conclusions.

Treatment.

The treatment some of these patients received during the earlier stages of the infection has been considered previously (point 4, p. 155). As far as we have been able to determine on the basis of their records they had no other treatment between the termination of their fresh syphilis (secondary or secondary relapse), and the first outbreak of «benign» tertiary lesions. The majority, however, was treated for the various outbreaks of «benign» tertiary manifestations. This is an important point and an analysis of it will serve to illuminate further the questions raised in the section on treatment (p. 97) and may indicate whether the assumptions made therein are valid or not.

When we take into account that tertiary lesions most commonly occur during the first 10 to 15 years after infection, it would be reasonable to assume that the majority of such outbreaks in our series would be found within the first two decades of observation (1891—1910), a comparatively smaller part of them during the first decade after salvarsan was introduced (1911—1920), and a steadily diminishing number in the following decades which are characterized by an increasing degree of adequacy in the treatment of all forms of syphilis.

As will be seen from the percentages presented in the totals of tables 47 and 48 the results we have arrived at in fact confirm the above assumption both as regards first and later outbreaks. Again, the period of time within which these outbreaks occurred would also bear on the kind and amount of treatment administered, that is, according to the development of syphilo-therapy which can be briefly summarized as follows: During the period preceding the introduction of salvarsan: only potassium iodide, mercury inunctions or local treatment. In the following decade: potassium iodide, salvarsan usually in relatively small dosages, with mercury inunctions gradually disappearing. In the next decades: salvarsan in increasing dosages, Bismuth, either alone or in combination with salvarsan, and finally during the last half of the nineteen-forties, penicillin combined with arsenicals and Bismuth. Moreover, patients with «benign» tertiary manifestations usually would not receive the maximum

[1] Due to diagnoses without description.

Table 46.

Structures Involved in «Benign» Tertiary Lesions, by Sex and Outbreak Number.

(All ages*) (175 patients** — 291 outbreaks)

Outbreak Number	Solitary			Concomitant				Total
	Skin	Skeletal	Mucous membranes	Skin + skeletal	Skeletal + mucous membranes	Skin + mucous membranes	Structure undetermined	
Males:								
I	32	7	4	1	0	5	2	51
II	11	1	0	0	0	1	0	13
III	6	2	0	0	0	0	0	8
IV	7	0	0	0	0	0	0	7
V	2	1	0	0	0	0	0	3
VI	2	0	0	1	0	0	0	3
Subtotal	60	11	4	2	0	6	2	85
Per cent	70.6	12.9	4.7	2.4	0	7.1	2.4	100.0
Females:								
I	83	9	21	1	1	1	8	124
II	32	5	3	1	1	0	1	43
III	16	2	0	0	1	0	0	19
IV	8	1	0	0	1	0	0	10
V	4	0	0	1	1	1	0	7
VI	1	0	1	0	0	0	0	2
VII	0	0	1	0	0	0	0	1
Subtotal	144	17	26	3	5	2	9	206
Per cent	69.9	8.3	12.6	1.5	2.4	1.0	4.4	100.0
Total	204	28	30	5	5	8	11	291
Per cent	70.1	9.6	10.3	1.7	1.7	2.7	3.8	100.0
	$\underbrace{\hspace{6em}}$ 262 — 90.0 %			$\underbrace{\hspace{6em}}$ 18 — 6.1 %			$\underbrace{\hspace{2em}}$ 11 — 3.8 %	100.0

* Age at infection.

** 3 male and 3 female patients removed; outbreak number undetermined.

Table 47.

First Outbreaks of «Benign» Tertiary Syphilis According to Period of Time of Occurrence and Type and Amount of Treatment.

(All ages*)

Part I. Males. (51 patients** — 51 outbreaks)

Treatment Received for First Outbreak	First Outbreaks According to Period of Time					Total	
	1891 — 1910	1911 — 1920	1921 — 1930	1931 — 1940	1941		
Unknown	2	1	1	1	0	5	40 — 78.4 %
Local or none	7	1	2	0	0	10	
Potassium Iodide	20	4	1	0	0	25	
Mercury inunctions	2	1	0	0	0	3	11 — 21.6 %
As.	1[1])	2[2])	1[3])	0	0	4	
As. + Bi.	0	0	0	2[5])	0	2	
Bi.	0	0	1[4])	0	0	1	
Penicillin + As.	0	0	0	0	1[6])	1	
Total	32 — 62.7 %	9 — 17.6 %	6 — 11.8 %	3 — 5.9 %	1 — 2.0 %	51	100.0 %
Remarks	1) 1 inj.	1 pt. 5 inj. 2) 1 pt. 4 inj.	3) 4 inj. 4) 12 inj.	5) 1 pt. 10/10 inj. 1 pt. 12/12 inj.	6) Pen. 5 Mill. U. + 6 As.		

Part II. Females. (124 patients** — 124 outbreaks)

Treatment Received for First Outbreak	First Outbreaks According to Period of Time					Total	
	1891 — 1910	1911 — 1920	1921 — 1930	1931 — 1940	1941		
Unknown	5	1	1	0	0	7	107 — 86.3 %
Local or none	18	4	3	1	0	26	
Potassium Iodide	60	10	3	1	0	74	
Mercury inunctions	2[1]	0	0	1[5]	0	3	17 — 13.7 %
As.	0	6[2]	2[3]	0	1[7]	9	
As. + Bi.	0	0	0	1[6]	2[8]	3	
Bi.	0	0	1[4]	0	0	1	
Penicillin + As. + Bi.	0	0	0	0	1[9]	1	
Total	85 — 68.5 %	21 — 16.9 %	10 — 8.1 %	4 — 3.2 %	4 — 3.2 %	124	100.0 %
Remarks	1) 1 pt. 7 inunc. 1 pt. unknown.	2) 3 pts. 1 inj. 2 pts. 2 inj. 1 pt. 11 inj.	3) 1 pt. 2 inj. 1 pt. 9 inj. 4) 27 inj.	5) 12 inunc. 6) 35/45 inj.	7) 6 inj. 8) 1 pt. 4/13 inj. 1 pt. 15/35 inj. 9) Pen. 5 Mill. U. + 10 As. + 6 Bi.		

* Age at infection.

** 3 male and 3 female patients removed; outbreak number undetermined.

Table 48.

Multiple Outbreaks of «Benign» Tertiary Syphilis According to Period of Time of Occurrence and Type and Amount of Treatment.

Part 1. Males. (13 patients — 34 outbreaks)

Treatment Received for Multiple Outbreaks	Time Periods and the Occurrences of Multiple Outbreaks																									Total	
	1891 — 1910					1911 — 1920					1921 — 1930					1931 — 1940					1941 —						
	II*	III	IV	V	VI	II	III	IV	V	VI	II	III	IV	V	VI	II	III	IV	V	VI	II	III	IV	V	VI		
Unknown	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1											2	28—82.4%
Local or none	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0											1	
Potassium Iodide	9	6	6	1	1	1	0	0	1	0	0	0	0	0	0											25	
Mercury Inunctions	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0											3	6—17.6%
As.	0	0	1[1])	0	0	0	1[2])	0	0	1[3])	0	0	0	0	0											3	
As. + Bi.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0											0	
Bi.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0											0	
Penicillin + As.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0											0	
Total	28					5					1					0										34	
Per cent	82.4					14.7					2.9					0										100.0	
Remarks	[1]) 1 inj.					[2]) 6 inj. [3]) 3 inj.																					

Part II. Females. (43 patients — 82 outbreaks)

Treatment Received for Multiple Outbreaks	Time Periods and the Occurrences of Multiple Outbreaks: 1891 — 1910						1911 — 1920						1921 — 1930						1931 — 1940						1941 —						Total	
	II*	III	IV	V	VI	VII	II	III	IV	V	VI	VII	II	III	IV	V	VI	VII	II	III	IV	V	VI	VII	II	III	IV	V	VI	VII		
Unknown	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	61 — 74.4 %
Local or none	1	1	0	1	0	0	0	0	1	2	0	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	10	
Potassium Iodide	22	9	5	2	0	0	4	1	3	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	48	
Mercury Inunctions	1	3	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	21 — 25.6 %
As.	0	0	0	0	0	0	3[1])	1[2])	0	0	0	1[3])	3[4])	2[5])	0	1[6])	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	
As. + Bi.	0	0	0	0	0	0	0	0	0	0	0	0	1[7])	0	0	0	0	0	1[9])	0	0	1[10])	0	0	0	0	0	0	0	0	3	
Bi.	0	0	0	0	0	0	0	0	0	0	0	0	1[8])	0	0	0	0	0	0	1[11])	0	0	0	0	0	0	0	0	0	0	2	
Penicillin + As.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Total	47						18						12						4						1						82	
Per cent	57.3						22.0						14.6						4.9						1.2						100.0	
Remarks							1) 1 pt. 4 inj. 1 pt. 5 inj. 1 pt. 6 inj. 2) 5 inj. 3) 2 inj.						4) 1 pt. 13 inj. 1 pt. 10 inj. 1 pt. 6 inj. 5) 1 pt. 11 inj. 1 pt. 15 inj. 6) 2 inj. 7) 15/18 inj. 8) 22 inj.						9) 1/5 inj. 10) 20/20 inj. 11) unknown													

* II — Second Outbreaks.
III — Third Outbreaks. etc.

amount of treatment employed for fresh syphilis within the corresponding periods of time. At least it was not until the beginning of the nineteen-thirties that it became common practice to recommend for such patients courses of antisyphilitic treatment comprising about the same number of injections as used in fresh syphilis. By and large, the above outline of the development of treatment is reflected in the findings as demonstrated in tables 47 and 48. In table 47, showing first outbreaks, the number of patients is identical with the number of outbreaks, whereas in table 48 we are dealing with total number of outbreaks as experienced by the patients who had had two or more. If we consider first outbreaks of «benign» tertiary syphilis (table 47, Parts I and II), which numerically are most important, it will be noted that 86.3 per cent of the females and 78.4 per cent of the males were treated either with potassium iodide, with local remedies, or fall within our small group of «Treatment Unknown». In our opinion it is probable that the latter group was not very actively treated and, furthermore, most of these cases come within the first two decades of observation when the possibilities for specific treatment were limited to mercury in one form or another. It can be seen that 13.7 per cent of the females and 21.6 per cent of the males were found to have received specific treatment of various kinds.

Turning then to table 48, Parts I and II, showing multiple outbreaks, it will be seen that the picture remains much the same. Most of the outbreaks were treated with non-specific remedies (74.4 per cent of the females and 82.4 per cent of the males), while 25.6 and 17.6 per cent respectively were given specific treatment. In other words, according to present-day concepts of what constitutes specific treatment, the majority of the outbreaks of «benign» tertiary syphilis in our series were left untreated.

The tables presented, however, give only part of the story. If we are going to evaluate the specific treatment given and how it might possibly have changed the natural course of the disease, both in connection with the «benign» tertiary outbreaks themselves and later serious manifestations, it is necessary to analyse the cases in question in considerably more detail and according to the following indices: kind and amount of treatment, duration of infection at the time treatment was given, and finally the status of the patient relative to other syphilitic manifestations at time of occurrence of the «benign» tertiary outbreak. Furthermore, it must be borne in mind that patients who experienced more than one outbreak may have received specific treatment more than once, thus coming closer to adequacy than would otherwise have been the case.

In table 49 where the patients with «benign» tertiary manifestations are presented according to treatment, but irrespective of whether treatment was given for the first or later outbreaks, it will be seen that 31 of the females (25 per cent) and 12 of the males (23.5 per cent) were given specific treatment as contrasted with 93 (75 per cent) and 39 (76.5 per cent) respectively who

Table 49.

«Benign» Tertiary Syphilis According to Treatment — Specific or Non-Specific — by Sex.

(All ages*) (175 patients**)

Treatment	Males		Females		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Non-specific	39	76.5	93	75.0	132	75.4
Specific	12	23.5	31	25.0	43	24.6
Total	51	100.0	124	100.0	175	100.0

* Age at infection.

** 3 male and 3 female patients removed; outbreak number undetermined.

had non-specific treatment. Among the 31 females, 15 received specific treatment for their first outbreak and experienced no later outbreaks, while 2 received specific treatment for the first outbreak and, with 14 others, were given specific treatment for one or more of their subsequent outbreaks. Among the 12 males, 10 received specific treatment for their first outbreak and experienced no later outbreaks, while 2 had specific treatment for one or more of the later outbreaks. (See annex tables VII, VIII and IX.)

Of particular interest to us here are the following questions: Can it be assumed that the specific treatment has protected these patients with «benign» tertiary lesions against serious late complications? And, has the treatment given been sufficiently adequate to prevent later outbreaks of «benign» tertiary manifestations? When it comes to individual cases in a group of patients such as this it is practically impossible to answer these questions directly. What may prove adequate in one case may prove highly inadequate in another, and what constitutes adequacy in patients with «benign» tertiary manifestations at different times during the course of infection, is actually not known. We can, nevertheless, make certain assumptions based on the general concepts of adequacy, which clinical experience has taught us.

In Annex III an attempt has been made to provide answers to the above questions. The difficulties in such an analysis will be apparent from reading the discussion. However, the present author feels that there may have been some effect of the treatment received on the frequency of the development of subsequent multiple outbreaks in this particular group of patients. Thus, this is further evidence that our figures are minimum as mentioned previously. Furthermore, in regard to the effect on serious late lesions, it can be said that only a few patients received sufficient treatment and under circumstances which would be protective.

Table 50.

Duration of Infection at Time of First Outbreaks of «Benign» Tertiary Syphilis, by Sex.

(Ages 15 — 39*) (157 patients**)

Duration of Infection	Males		Females		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Months*** 0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	0	0	1	—	1	—
3	1	—	2	—	3	—
4	1	—	0	0	1	—
5	1	—	0	0	1	—
6	0	0	0	0	0	0
7	0	0	0	0	0	0
8	0	0	0	0	0	0
9	0	0	0	0	0	0
10	0	0	1	—	1	—
11	0	0	0	0	0	0
Subtotal	3	7.1	4	3.5	7	4.5
12	1	—	2	—	3	—
15	0	0	3	—	3	—
18	1	—	2	—	3	—
21	2	—	1	—	3	—
Subtotal	4	9.5	8	7.0	12	7.6
Years						
2 — 4	8	—	25	—	33	—
5 — 9	6	—	39	—	45	—
10 — 14	8	—	13	—	21	—
Subtotal	22	52.4	77	67.0	99	63.1
15 — 19	4	—	5	—	9	—
20 — 24	2	—	6	—	8	—
25 — 29	3	—	4	—	7	—
Subtotal	9	21.4	15	13.0	24	15.3
30 — 39	2	—	8	—	10	—
40 — 49	2	—	3	—	5	—
Subtotal	4	9.5	11	9.6	15	9.6
Total	42	100.0	115	100.0	157	100.0
Mean duration of infection in years	12.8		11.2		11.6	

* Age at infection.
** 3 male and 3 female patients removed; outbreak number undetermined.

*** 0 — Less than 1 month.
1 — Between 1 and 2 months.
2 — Between 2 and 3 months, etc.

Time Relationships.

In table 50 is presented the percentage distribution of *first* outbreaks of «benign» tertiary syphilis according to duration of infection. It will be noted that «benign» tertiary lesions occurred within a wide range of durations, from a few months and up to more than forty years after the termination of the secondary syphilis or secondary relapse. (See point 3, p. 155.) By the end of the first year we had found 4.5 per cent, with another 7.6 per cent added in the course of the second year, making a total of 12.1 per cent during the first two years (precocious tertiary lesions). The majority of the cases (75.2 per cent) was observed within the first 15 years, followed by another 15.3 per cent during the next 15 years up to 30, and 9.6 per cent in the subsequent years up to between 40 and 50. This picture can also be expressed through the mean duration of infection at first emergence of «benign» tertiary phenomena, which is 11.6 years. The difference between males (mean 12.8 years) and females (mean 11.2 years) is not significant.

In table 51 is given the percentage distribution of multiple outbreaks of «benign» tertiary syphilis according to duration of infection. As mentioned previously, the number of multiple outbreaks undoubtedly represents a minimum, one of the reasons being that about 25 per cent of the patients with «benign» tertiary syphilis received specific treatment for their first or later outbreaks. It is reasonable to believe that treatment may also have had some effect on the interval between outbreaks, but it is not known whether it delays or advances the emergence of tertiary phenomena, so this factor can not be evaluated in that connection. The important finding of this table is that the great majority of multiple outbreaks have occurred by the end of 15 years (males 93.9 per cent and females 68.4 per cent).

In table 52, Parts I and II, are presented the calculations of the probabilities of developing «benign» tertiary syphilis, and in fig. 8 a diagram showing these probabilities in per cent. It will be noted that no male cases were found between the 35th and the 46th year of infection, whereafter 2 cases developed in the 46th year, after the denominator had dropped to 67. In females, cases were found up to the 43rd year, the denominator still being close to 200. It has, therefore, been found reasonable to make the final comparison of males and females at 35 years. At 35 years the probability of developing «benign» tertiary syphilis in males was found to be 16.4 per cent as compared with 21.4 per cent in females. It will be seen that the cumulative percentage had reached 10.9 and 15.9 in the two sexes respectively at 15 years. During the next 15 years the increase was 4.8 per cent in males and 3.9 per cent in females, making a total of 15.7 and 19.8 per cent at 30 years respectively. Between 30 and 35 years we find an increase of 0.7 per cent in males, while females show an increase of 1.6 per cent, totalling 16.4 and 21.4 per cent respectively at 35 years. If we include the 2 cases among the males which developed at 46 years, the percentage

Table 51.

Duration of Infection at Time of Multiple Outbreaks of «Benign» Tertiary Syphilis, by Sex.

(Ages 15 — 39*) (53 patients — 112 outbreaks)

Duration of Infection in Years	Multiple Outbreaks												Total				Grand Total	
	II**		III		IV		V		VI		VII		Males		Females			
	M	F	M	F	M	F	M	F	M	F	M	F						
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	%	No.	%	No.	%
Less 2	0	3	0	1	0	0	0	0	0	0	0	0	0	—	4	—	4	—
2 — 4	5	9	2	5	1	1	0	0	0	0	0	0	8	—	15	—	23	—
5 — 9	6	8	7	5	3	2	2	2	0	0	0	0	18	—	17	—	35	—
10 — 14	1	9	0	4	1	5	1	0	2	0	0	0	5	—	18	—	23	—
Subtotal	12	29	9	15	5	8	3	2	2	0	0	0	31	93.9	54	68.4	85	75.9
15 — 19	1	2	0	2	0	2	1	0	0	0	0	0	2	—	6	—	8	—
20 — 24	0	1	0	1	0	2	0	1	0	1	0	1	0	—	7	—	7	—
25 — 29	0	2	0	0	0	0	0	2	0	0	0	0	0	—	4	—	4	—
Subtotal	1	5	0	3	0	4	1	3	0	1	0	1	2	6.1	17	21.5	19	17.0
30 — 39	0	5	0	1	0	0	0	0	0	0	0	0	0	—	6	—	6	—
40 — 49	0	1	0	0	0	0	0	0	0	1	0	0	0	—	2	—	2	—
Subtotal	0	6	0	1	0	0	0	0	0	1	0	0	0	0	8	10.1	8	7.1
Total	13	40	9	19	5	12	4	5	2	2	0	1	33	100.0	79	100.0	112	100.0

* Age at infection.
** II — Second outbreaks.
III — Third outbreaks, etc.

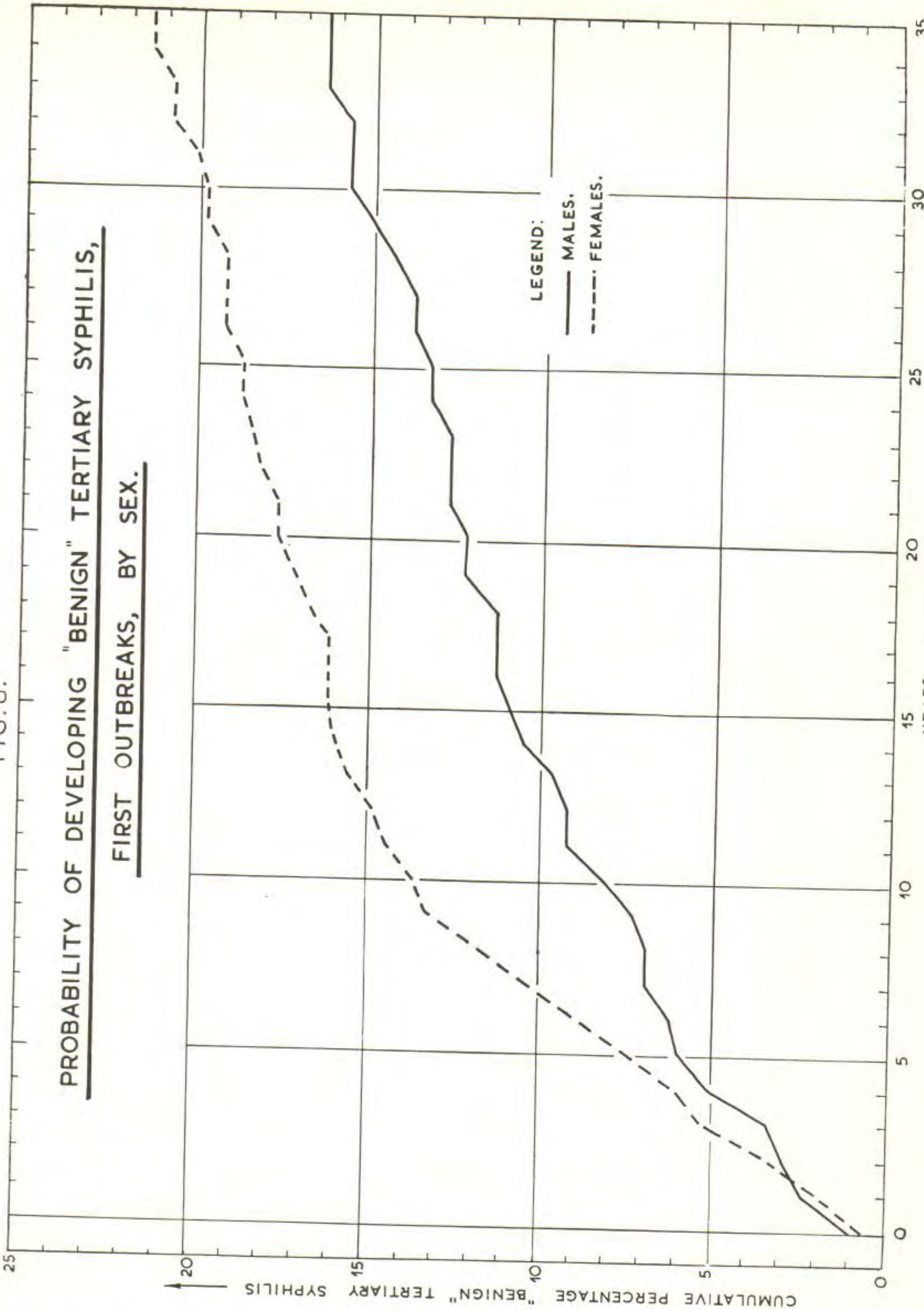
PROBABILITY OF DEVELOPING "BENIGN" TERTIARY SYPHILIS,
FIRST OUTBREAKS, BY SEX.
LEGEND:
MALES.
FEMALES.
YEARS
CUMULATIVE PERCENTAGE "BENIGN" TERTIARY SYPHILIS
0
5
10
15
20
25
30
35

FIG. 8.

Table 52.

Calculation of the Probability of Developing «Benign» Tertiary Syphilis,
First Outbreak.

(Ages 15 — 39*)

Part I. Males. (42 patients)

Observation period in years. † x to x + n.	Number observed this period or later.	Number lost from observation in this period.		Number found positive †† this period.	Probability of a person not previously found positive being found positive in this period. $\frac{(4)}{(2) - \frac{(3)}{2}}$ †††	Probability of a person not previously found positive remaining negative †† in this period. 1 — (5)	Cumulative probability of a person remaining negative from beginning of observation to x + n. (6) x (7)	Cumulative probability of a person becoming positive between the beginning of observation and x + n. 1 — (7)
		(3)						
(1)	(2)	Dead	Living last seen	(4)	(5)	(6)	(7)	(8)
0	313	4	15	3	0.00988	0.99012	0.99012	0.00988
1	291	0	1	4	0.01377	0.98623	0.97649	0.02351
2	286	1	0	2	0.00701	0.99299	0.96964	0.03036
3	283	4	2	1	0.00357	0.99643	0.96618	0.03382
4	276	1	2	5	0.01821	0.98179	0.94859	0.05141
5	268	2	1	2	0.00750	0.99250	0.94148	0.05852
6	263	4	0	1	0.00383	0.99617	0.93787	0.06213
7	258	3	1	2	0.00781	0.99219	0.93055	0.06945
8	252	2	1	0	0	1.00000	0.93055	0.06945
9	249	3	0	1	0.00404	0.99596	0.92679	0.07321
10	245	2	0	2	0.00820	0.99180	0.91919	0.08081
11	241	2	2	3	0.01255	0.98745	0.90765	0.09235

12	234	4	1	0	0	1.00000	0.90765	0.09235
13	229	5	1	1	0.00442	0.99558	0.90364	0.09636
14	222	7	0	2	0.00915	0.99085	0.89537	0.10463
15	213	3	1	1	0.00474	0.99526	0.89113	0.10887
16	208	5	2	1	0.00489	0.99511	0.88677	0.11323
17	200	3	0	0	0	1.00000	0.88677	0.11323
18	197	3	0	0	0	1.00000	0.88677	0.11323
19	194	1	0	2	0.01034	0.98966	0.87760	0.12240
20	191	8	0	0	0	1.00000	0.87760	0.12240
21	183	4	1	1	0.00554	0.99446	0.87274	0.12726
22	177	4	1	0	0	1.00000	0.87274	0.12726
23	172	4	0	0	0	1.00000	0.87274	0.12726
24	168	5	0	1	0.00604	0.99396	0.86747	0.13253
25	162	10	1	0	0	1.00000	0.86747	0.13253
26	151	3	0	1	0.00669	0.99331	0.86167	0.13833
27	147	2	0	0	0	1.00000	0.86167	0.13833
28	145	4	1	1	0.00702	0.99298	0.85562	0.14438
29	139	1	0	1	0.00722	0.99278	0.84944	0.15056
30	137	4	0	1	0.00741	0.99259	0.84315	0.15685
31	132	7	0	0	0	1.00000	0.84315	0.15685
32	125	4	0	0	0	1.00000	0.84315	0.15685
33	121	0	0	1	0.00830	0.99170	0.83615	0.16385
34	120	5	0	0	0	1.00000	0.83615	0.16385
35	115	5	0	0	0	1.00000	0.83615	0.16385
—								
46	63	1	3	2	0.03279	0.96721	0.80813	0.19127

Part II. Females. (115 patients)

Observation period in years. † x to x + n.	Number observed this period or later.	Number lost from observation in this period.		Number found positive †† this period.	Probability of a person not previously found positive being found positive in this period. $\frac{(4)}{(2) - \frac{(3)}{2}}$ †††	Probability of a person not previously found positive remaining negative †† in this period. 1 — (5)	Cumulative probability of a person remaining negative from beginning of observation to x + n. (6) x (7)	Cumulative probability of a person becoming positive between the beginning of observation and x + n. 1 — (7)
		(3)						
(1)	(2)	Dead	Living last seen	(4)	(5)	(6)	(7)	(8)
0	681	11	31	4	0.00606	0.99394	0.99394	0.00606
1	635	3	8	8	0.01271	0.98729	0.98131	0.01869
2	616	4	12	9	0.01480	0.98520	0.96679	0.03321
3	591	8	11	11	0.01892	0.98108	0.94850	0.05150
4	561	5	10	5	0.00903	0.99097	0.93994	0.06006
5	541	4	11	8	0.01500	0.98500	0.92584	0.07416
6	518	8	5	8	0.01564	0.98436	0.91136	0.08864
7	497	4	4	8	0.01623	0.98377	0.89657	0.10343
8	481	7	1	7	0.01468	0.98532	0.88341	0.11659
9	466	9	6	8	0.01745	0.98255	0.86799	0.13201
10	443	7	4	2	0.00457	0.99543	0.86402	0.13598
11	430	9	3	4	0.00943	0.99057	0.85587	0.14413
12	414	9	1	2	0.00489	0.99511	0.85168	0.14832
13	402	10	3	3	0.00759	0.99241	0.84522	0.15478
14	386	7	1	2	0.00524	0.99476	0.84079	0.15921
15	376	5	2	1	0.00268	0.99732	0.83854	0.16146
16	368	8	0	0	0	1.00000	0.83854	0.16146

17	360	5	1	0	0	1.00000	0.83854	0.16146
18	354	7	1	2	0.00571	0.99429	0.83375	0.16625
19	344	11	0	2	0.00591	0.99409	0.82882	0.17118
20	331	8	0	2	0.00612	0.99388	0.82375	0.17625
21	321	3	0	0	0	1.00000	0.82375	0.17625
22	318	2	2	2	0.00633	0.99367	0.81854	0.18146
23	312	4	0	1	0.00323	0.99677	0.81590	0.18410
24	307	5	1	1	0.00329	0.99671	0.81322	0.18678
25	300	3	1	0	0	1.00000	0.81322	0.18678
26	296	1	0	2	0.00677	0.99323	0.80771	0.19229
27	293	6	0	0	0	1.00000	0.80771	0.19229
28	287	8	1	0	0	1.00000	0.80771	0.19229
29	278	9	0	2	0.00731	0.99269	0.80181	0.19819
30	267	5	0	0	0	1.00000	0.80181	0.19819
31	262	3	2	1	0.00385	0.99615	0.79872	0.20128
32	256	5	0	2	0.00789	0.99211	0.79242	0.20758
33	249	4	0	0	0	1.00000	0.79242	0.20758
34	245	4	1	2	0.00825	0.99175	0.78588	0.21412
35	238	6	0	0	0	1.00000	0.78588	0.21412
36	232	3	0	1	0.00434	0.99566	0.78247	0.21753
37	228	4	0	1	0.00442	0.99558	0.77901	0.22099
38	223	6	0	1	0.00455	0.99545	0.77547	0.22453
39	216	3	1	0	0	1.00000	0.77547	0.22453
40	212	8	5	0	0	1.00000	0.77547	0.22453
41	199	9	6	2	0.01044	0.98956	0.76737	0.23263
42	182	2	4	1	0.00559	0.99441	0.76308	0.23692

* Age at infection.
† 0 — Less than 1 year.
1 — Between 1 and 2 years, etc.
†† Positive — «Benign» Tertiary Syphilis.
Negative — No «Benign» Tertiary Syphilis.
††† Assumes all still under observation, but not examined at this time, are clinically negative.

will be 19.1, and if we carry females up to the end of the 42nd year, it will be 23.7. This again demonstrates the fact that the majority of the cases occurred within the first 15 years (males cumulative percentage 10.9 at 15 as compared with 16.4 at 35 years; females cumulative percentage 15.9 at 15 years as compared with 21.4 at 35 years, the increase after 15 years being relatively small).

The difference between males and females, as shown by the graph, is rather marked and constant from about the 8th year on. By testing the differences at 10, 20, 30 and 35 years, it was found that the differences are statistically significant. That may indicate that «benign» tertiary syphilis occurs somewhat earlier among females, and the fact that the difference is retained up to 35 years may furthermore indicate that this manifestation actually has been found more frequently among the females in our series. It is true that we were not able to demonstrate any statistically significant difference between the sexes in our ordinary frequency estimates (13.7 versus 17.3 per cent respectively for the 15—39-year age-groups), but the probability estimates are considered more reliable because we here take into account the decreasing denominator, and therefore the above described difference may very well mean that «benign» tertiary syphilis occurs somewhat more frequently among the females in our series.

Prognostic Significance.

The prognostic significance of «benign» tertiary syphilis is discussed in chapter XI, pp. 337—342.

III. Discussion

Causes.

Grin (1953) has provided good evidence for the assumption that superinfection plays a major role in the development of «benign» tertiary manifestations in endemic syphilis. According to his findings the proportion of tertiary lesions decreases whenever the endemic foci of infectious syphilis (secondary) is on the wane. Also he has pointed to the fact that «benign» tertiary lesions occur early in endemic areas. Grin has not clarified exactly what is meant by early in this respect — there are no figures on time relationships — but presumably he is of the opinion that the occurrence of «benign» tertiary phenomena in endemic syphilis falls within the first few years of infection. As far as the figures[1] go (from the villages of Šije and Kosova), they relate to prevalence rather than incidence. It is stated that the percentage of tertiary lesions found in Kosova was 21.8, and of the 21.8, 13.5 per cent had active

[1] All percentages represent proportions of total syphilis.

lesions of recent date, while 8.3 per cent showed scars of lesions which had occurred some time before. In the village of Šije, on the other hand, where the proportion of infectious cases was much lower, the percentage active «benign» tertiary lesions was only 2.6, whereas 14.4 per cent showed signs of old lesions. It is conceivable, however, that the active cases found during the survey represent an accumulation, because open lesions in untreated syphilis are apt to persist for a shorter or longer period of time. We have, as far as the present author can see, no way of determining for how long such an accumulation can have taken place.

But, under all circumstances the percentage found in Kosova (13.5) is very high compared with the percentages found from year to year in our series where it has never exceeded two per cent in any one year, and usually has been lower than that even during the first decade of observation (see table 52, p. 174). As soon as the reservoir of infectious syphilis drops, as in the village of Šije, the percentage of active «benign» tertiary lesions comes much closer to the order of magnitude observed from year to year in our series, although it is still higher than would be expected. As far as this comparison goes, therefore, the results arrived at in our study of untreated sporadic syphilis seem to confirm the assumption made by Grin, that the causes of «benign» tertiary lesions are different in endemic and sporadic venereal syphilis, superinfection being the main cause in the former and reactivation of residual treponemes in the latter.

Occurrence.

As mentioned previously, the figures on incidence of «benign» tertiary syphilis in modern textbooks on syphilology are mostly those found by Bruusgaard (1929a) in his study of untreated syphilis, whereas figures based on the analysis of treated cases are practically non-existent. As far as the present author has been able to find out, the only systematic long-term follow-up studies of treated syphilitics, in whom the incidence of «benign» tertiary manifestations has been estimated, are those of Nielsen (1950) and Padget (1940), the latter also making a comparison between the frequency of these complications in successfully treated cases and those which developed secondary relapse.

Bruusgaard (1929a), quoted by Moore (1944), found the incidence in untreated syphilis to be 12.8 per cent. As we do not know the detailed epidemiologic methods employed by Bruusgaard a comparison between his figure and that found in the present study (12.8 versus 15.8 per cent) is difficult, but as the figures stand there is no marked difference in the order of magnitude. It is believed, however, that our figures can be considered more reliable, in view of the fact that a far greater percentage of the patients have been followed-up.

When it comes to Nielsen's study (1950) we have exact data on treatment given the patients during the early stages of the disease, and likewise detailed information on the methods of tracing and follow-up and period of observation (see p. 149). It is to be noted that Nielsen's study comprises male patients only, and that the treatment given the patients for their early syphilis must be considered highly inadequate as measured by modern standards (2 to 3 injections of Alt-Salvarsan plus some 50 inunctions of mercury), although it should be borne in mind that we know very little about what constitutes adequacy when it comes to prevention of «benign» tertiary manifestations. The percentage «benign» tertiary manifestations in Nielsen's series was 1.1. The author evidently was of the opinion that this figure represented a minimum, but did not elaborate on this problem at any length. He offered one explanation, namely, the possibility that the patients with «benign» tertiary syphilis had not invariably sought medical advice, and thus may have escaped registration in the Syphilis Registry. Speaking about the results of his follow-up study in general, Nielsen also pointed to the possibility that some cases of late syphilis may have escaped registration because they occurred before the establishment of the Registry in 1920. This seems reasonable to assume in view of the distribution of the 467 patients according to year of original treatment, which is as follows: 1913: 37, 1914: 73, 1915: 59, 1916: 62, 1917: 49, 1918: 58, 1919: 71, 1920: 58, and it would in all likelihood be particularly true of those outbreaks of «benign» tertiary syphilis which are apt to develop during the early years of infection. Refer to table 50, p. 170, for the findings in our series in respect to percentage distribution according to time. To evaluate how these factors may have influenced the figure in Nielsen's series is not possible, but in addition to the explanations given above for the relatively small number of cases with «benign» tertiary syphilis found, the possibility does exist that treatment may have played a decisive role. In all probability Nielsen's figure of 1.1 per cent represents a minimum, but so does ours of 14.4 per cent in males, and we also have to take into account that a little less than one-third of our patients had more than one outbreak. Therefore, the marked difference in respect to incidence in the two series suggests to the present author that even relatively inadequate dosages are sufficient to prevent the development of these complications in a considerable proportion of the patients.

Multiple outbreaks. As mentioned in the section on literature (p. 150), figures on the frequency of multiple outbreaks of «benign» tertiary syphilis have not been found in the textbooks and scientific papers available to the present author. Because of the relatively good response of these manifestations to a non-specific remedy such as potassium iodide, and to otherwise inadequate dosages of heavy metals, it is not surprising that multiple outbreaks have become so rare in modern times that nobody has been in a position to express numerically this phase in the development of the syphilitic infection. Only by studying untreated or grossly inadequately treated cases does it seem possible to get quantitative data on this point. We have found that a little less than one-third

(32 per cent) of the patients in whom «benign» tertiary lesions occured, in addition to their first outbreak, experienced from 1 to 6 more, and these figures represent a minimum for reasons described previously. This development, therefore, must be considered as part of the natural course of the disease, and the course, as was also the case during the secondary stage, shows a rhythmic tendency in a certain proportion of the cases. In order to evaluate what we accomplish by treatment, it must not be forgotten that we shall have to take into account also the multiple outbreaks of «benign» tertiary lesions occurring in untreated or inadequately treated syphilis.

Sex, and Age at Infection.

As regards the influence of *sex* on the frequency of «benign» tertiary lesions, we have not been able to demonstrate a significant difference on the basis of frequency data, although a certain trend in the direction of a more common occurrence among females was shown. There was, however, a significant difference between the sexes when the analysis was based upon calculation of probabilities. Thus we can not exclude the possibility that these manifestations actually are more frequent among females, as shown by Frazier and Li (1948) among others. It must be remembered, however, that the mentioned authors based their findings on a clinic or hospital material, and it is conceivable that females are more commonly hospitalized for these relatively «benign» lesions than are males. We have furthermore found that multiple outbreaks may be more common among females, although the distribution in this respect is not significant in our series. If multiple outbreaks do occur more frequently among females, this might also be an explanation of why some investigators, by counting outbreaks and not individuals, have found an excess of these manifestations among females. In, for instance, Frazier and Li's series this possibility is fairly remote for reasons discussed previously (see p. 151).

Age at Time of Outbreak.

Age at outbreak of «benign» tertiary syphilis is in any given series dependent, among other things, on the distribution of the patients at age of infection. It will be remembered that the mean duration of infection at time of first outbreaks of «benign» tertiary syphilis in our series was 11.6 years, which is roughly the same as that found by Frazier and Li (1948) among their white patients. There is, however, a rather marked difference between mean ages at time of emergence of «benign» tertiary lesions in the two series: as far as males are concerned 36.8 years in ours as compared with 41.5 years for cutaneous and 42.0 years for skeletal forms among the males of Frazier and Li's white patients. The age at infection among those of Frazier and Li's patients who later developed «benign» tertiary syphilis is not given, but if a fair proportion of patients with age 40 over at infection is included, this would tend to result in comparatively higher mean ages at time of emergence of «benign» tertiary phenomena. If we had included all patients over 39 at time of early manifestations, and omitted all under 15, the mean age at first outbreak of tertiary lesions for males would have come out as follows: 39.2 years, which is considerably closer to the figures found by Frazier and Li. Therefore, a possible explanation for the difference in age at time of «benign» tertiary manifestations in the two series, in spite of the fact that the duration of infection for this complication is about the same, would be that Frazier and Li's patients comprised a fair number of individuals whose age at infection was 40 and over, and a small number of individuals whose age at infection was under 15.

Structures Involved.

As will be recalled the skin was by far the most common site of «benign» tertiary manifestations in our series (70.6 and 69.9 per cent in males and females respectively). In Frazier and Li's (1948) material of *white* patients, skin accounted for 42.1 and 43.6 per cent in males and females respectively, and in Kampmeier's (1943) group of white patients (no breakdown by sex) skin was the site in 33.3 per cent. In the two last mentioned series the skin was also the structure most commonly involved, but the excess was much less pronounced than was the case in our material. Skeletal manifestations on the other hand, were found in only 12.9 and 8.3 per cent among our male and female patients respectively, as compared with 30.2 and 13.4 per cent in the same groups in Frazier and Li's series, and 30.2 per cent in Kampmeier's. Upper respiratory localizations accounted for 4.7 and 10.3 per cent in males and females respectively in our patients, as contrasted with 16.6 and 26.8 per cent for the two sexes in Frazier and Li's material, and 25.6 in Kampmeier's. What is particularly striking in the comparisons of ours with the findings in the two other materials, is the far greater percentage of skin lesions and the lesser percentages of skeletal and upper respiratory lesions encountered among our patients. Kampmeier has emphasized that he does not consider his findings representative of the usual distribution of sites of lesions in «benign» tertiary syphilis, because certain patients are more likely to be admitted to the hospital than to the clinic. He does not, however, mention specifically which type of patient is most commonly admitted to the clinic and which to the hospital and how this might have affected the distribution he presented. Whether Frazier and Li's (1948) results may be considered representative in this respect is difficult to determine. It was not stated directly whether the total number of patients with «benign» tertiary manifestations in this series includes both clinic and hospital cases, but presumably this is so (we are referring to their white patients only). If their sample also included hospitalized cases, this might offer an explanation for the relatively great frequency of skeletal and upper respiratory manifestations found, inasmuch as these complications are apt to present more difficult diagnostic problems than do skin lesions, and consequently such patients have a greater tendency to end up in a hospital. If the material includes ambulatory patients only, or patients who first came to the clinic and subsequently were admitted to the hospital, then the distribution found is more likely to be representative. But we might also question the representativeness of the patients coming to the clinic. It may very well be that here too we would have a greater chance of encountering comparatively more cases with diagnostic problems viz. skeletal and upper respiratory manifestations, than cases with skin lesions. Finally, the authors have mentioned that some of the patients received various amounts of antisyphilitic treatment before admission. How this might have affected the distribution of lesions in respect to site in cases with «benign» tertiary syphilis is of course, impossible to determine, but we can probably not exclude the possibility that it may have played a role. On the basis of the data presented by Frazier and Li we can not come to a definite conclusion on this point, and in the present author's opinion it is an open question whether the distribution of lesions in their material is representative or not.

When it comes to an evaluation of the representativeness of the findings in our own study, the following factors are considered important: In the first place, as a starting-point we utilized non-medical sources for the collection of information on hospitalizations and visits to clinics or practitioners, and only on the basis of that information did we search the records of the institutions in question. Access to additional data on hospitalizations etc. was procured through the history of the records found. The records of the V.D. departments of the area were an exception to this rule, however, as they were submitted to a special and careful search for data on the syphilitics. This undoubtedly may have resulted in a somewhat higher proportion of «benign» tertiary skin lesions in our study group than corresponds to the real distribution among the patients, because the V.D. departments first and foremost took care of dermatologic cases, while mucocutaneous and skeletal manifestations were not infrequently seen by the ear - nose - throat or surgical departments. True enough, through the indirect methods used in collecting clinical data we certainly got a considerable amount of information from these last mentioned departments as well, but it can not be excluded that this method may have biased our findings in the direction mentioned above. In the second place, it is possible that some cases of skeletal syphilis may have been overlooked or classified under other diagnoses than syphilis, in view of the fact that the majority of our patients had their «benign» tertiary lesions at a time prior to the development of the x-ray technique. It is, therefore, probable that the distribution of «benign» tertiary lesions in respect to site is not quite representative in our material either, but the chances are that it is more representative than that found on the basis of studies of clinic or hospital populations.

Time Relationships.

When it comes to time relationships of «benign» tertiary syphilis we have practically no figures based on treated cases with which the findings in our study could be compared. The reasons for this are obvious: even relatively inadequate treatment so reduces the number of «benign» tertiary lesions that a distribution of the cases over a period of several decades is not possible any more. Otherwise our figures seem to confirm the general impression gained by the clinicians, that «benign» tertiary lesions may develop shortly after the secondary period is over (precocious tertiaryism) and all the way through the duration of infection up to between 40 and 50 years. We have examples of «benign» tertiary manifestations developing within a couple of months after the secondary stage is terminated, and also examples of first outbreaks occurring after 46 yeas. Furthermore, we have been able to confirm the impression that this type of lesion is first and foremost a phenomenon of the first decade and a half after the secondary stage is terminated, 75 per cent of our cases having been observed within this period of time. The mean duration of infection at time of the outbreak of «benign» tertiary syphilis, has been estimated at 11.6 years, which is about the same as that found by Frazier and Li in their series of white patients. The present series indicates that not only does the majority (75 per cent) of first outbreaks occur within the first 15 years but also that most of the multiple outbreaks can be expected to appear in this period.

Summary and Conclusions.

1. The study group comprised a total of 1,147 patients, 374 male and 773 female.
2. «Benign» tertiary syphilis was defined to mean tertiary manifestations of the skin, the mucous membranes, and the bones and joints.
3. The causes of «benign» tertiary syphilis were discussed, and it is concluded that in the present series, superinfection has probably played a minor role in the development of these lesions, reactivation of treponemes being the main cause in the majority of cases.
4. A total of 15.8 per cent, or about 1 in every 6, of the patients sooner or later developed «benign» tertiary lesions.
5. A little more than two-thirds (68 per cent) of these patients had experienced only 1 outbreak, while a little less than one-third (32 per cent) had had 1 to 6 additional outbreaks.

   It is concluded that the occurrence of multiple outbreaks must be considered as part of the *natural* course of the disease, and that the course, as was also the case during the secondary stage, shows a rhythmic tendency in a certain proportion of instances.
6. On the basis of ordinary frequency estimates, no statistically significant difference between the sexes could be demonstrated, although a certain

trend in the direction of more common occurrence among females was shown (13.7 versus 17.3 per cent). However, when the analysis was based on the calculation of probabilities, there was a marked and constant difference in the same direction from the 8th year on. At 10, 20, 30 and 35 years the differences were statistically significant. The impression is, that «benign» tertiary syphilis occurs earlier and is more frequent among females.

7. «Benign» tertiary syphilis was found to have occurred in all age-groups listed, but the influence of age at infection on the frequency of these manifestations could not be determined with the data available.
8. In males the age at first outbreak varied from 25 to 65 years, with a mean of 36.8 years; in females it varied from 20 to 70 years, with a mean of 34.9 years. It is stressed that age at outbreak in any given series is dependent, among other things, on the distribution of the patients at age of infection. From a comparative standpoint, therefore, age at infection must be taken into account.
9. In respect to structures involved in «benign» tertiary syphilis, the predominant features in the present series were: firstly, solitary (single-structure) lesions were much more frequently diagnosed than were concomitant ones (more than one structure), 90 per cent versus 6.1 per cent (with 3.8 per cent undetermined). Secondly, solitary manifestations of the skin represented 70 per cent of all outbreaks, thus far outweighing all others in importance. Next came skeletal and mucous membranes with 9.6 and 10.3 per cent. These features were by and large the same in males and females. The representativeness of the above findings were discussed, and it is found that we can not exclude the possibility that our series, for various reasons, are weighted somewhat in the direction of too many cases with «benign» tertiary skin lesions.
10. The majority of the patients were found to have been treated for the various outbreaks of «benign» tertiary lesions. Among those who had experienced first outbreaks, 78.4 per cent of the males and 86.3 per cent of the females were treated either with potassium iodide, with local remedies, or fell within our small group of «treatment unknown». Most of the multiple outbreaks were also treated with non-specific remedies, 82.4 per cent of the males and 74.4 per cent of the females. Thus according to present-day concepts of what constitutes *specific* treatment, the majority of the outbreaks of «benign» tertiary in our series were left untreated.
11. Irrespective of whether it was given for the first or later outbreaks 12 of the males (23.5 per cent) and 31 of the females (25 per cent) were found to have received specific treatment for their «benign» tertiary manifestations. These cases were analysed to find out to what extent the treatment administered could be assumed to have protected the patients against

serious late complications. The difficulties connected with such an analysis were emphasized.

It is concluded that only a few of the patients had received sufficient treatment and under circumstances which would be protective.

12. «Benign» tertiary manifestations were found to have occurred within a wide range of durations, from a few weeks and up to more than forty years after the healing of secondaries. The majority of the cases (75.2 per cent) were observed within the first 15 years, followed by another 15.3 per cent during the next years up to 30, and 9.6 per cent in the subsequent years up to between 40 and 50. The mean duration of infection at first emergence of «benign» tertiary phenomena was 11.6 years (12.8 years in males and 11.2 years in females, this difference being statistically insignificant). The majority of the multiple outbreaks also occurred within the first 15 years (93.9 per cent in males and 68.4 per cent in females).
13. The probability of developing «benign» tertiary syphilis was calculated, and the percentage as found in males and females respectively, can be summarized as follows: by the end of 15 years, 10.9 and 16.1; by the end of 30 years, 15.7 and 19.8; by the end of 35 years, 16.4 and 21.4.
14. Since the present investigation represented a re-analysis of approximately the same material as that employed by Bruusgaard in his 1925—1927 follow-up study, it was natural to compare the incidence of «benign» tertiary syphilis in the two series. It is felt, however, that a comparison is difficult because we do not know the detailed epidemiologic methods used by Bruusgaard. As the figures stand (15.8 per cent in the present series versus 12.8 per cent in Bruusgaard's), there is no marked difference as to order of magnitude, but probably our figure must be considered as the more reliable, due to the fact that we found a far greater proportion of the original patients.
15. Figures on the incidence of «benign» tertiary syphilis based on the analysis of patients treated for their early lesions are seldom reported in the literature.
16. A comparison between the incidence as found in the present series of untreated cases with that found in one of the systematic follow-up studies of patients treated in the early phases of the infection, suggests that even relatively inadequate dosages are sufficient to reduce substantially the proportions developing «benign» tertiary manifestations.
17. When it comes to time relationships of «benign» tertiary we have practically no figures based on treated cases with which the findings in the present study can be compared. The reason for this is thought to be that modern treatment, both adequate and inadequate, so reduces the number of these lesions that a distribution of the cases over a period of several decades is no longer possible.

Chapter VIII.

NEUROSYPHILIS

I. Excerpts from and Comments on the Literature.

Definition.

The classification of neurosyphilis varies somewhat from one textbook to the other. Most modern syphilologists, however, base their classifications on a combined clinical and anatomic basis as exemplified by the following, originally given by Moore (1946), and with minor changes, adopted by Thomas (1949 — p. 241), from where it is reproduced.

«1. Asymptomatic.
2. Acute syphilitic meningitis of early syphilis.
3. Meningovascular syphilis, which includes arachnoiditis and all clinical syndromes which do not fit into some other recognizable classification.
4. Vascular neurosyphilis which is thrombosis or hemorrhage of cerebral vessels.
5. General paresis.
6. Tabes dorsalis.
7. Taboparesis.
8. Erb's spinal spastic paraplegia.
9. Syphilitic (nonparetic) epilepsy.
10. Gumma of brain or spinal cord.
11. Primary optic atrophy.
12. Eighth-nerve deafness.»

The general basis on which classification of neurosyphilis rests is reflected in the following statement by Moore (1944 — p. 356), «. . . This divides patients into four groups, depending on the extent to which the pathologic lesion is predominantly meningeal, vascular, or parenchymatous, the clinical picture predominantly on an inflammatory or a degenerative basis, as follows:

1. More or less purely meningeal neurosyphilis. This is almost always an early manifestation, occurring within the first two years of the infection. It includes acute syphilitic meningitis, most neurorecurrences, and early asymptomatic neurosyphilis.
2. More or less purely vascular neurosyphilis. This may occur early or late, usually the latter. It depends on the existence of a localized or widespread syphilitic cerebral endarteritis, sometimes with but often without associated meningeal or parenchymatous involvement. It is frequently found in association with cardiovascular syphilis, apparently as part of a widespread involvement of the blood vessels. It causes cerebral vascular accidents, hemiplegias, monoplegias, paraplegias, subarachnoid hemorrhage, etc.
3. Diffuse meningovascular neurosyphilis, in which the lesions are a mixture of meningeal and vascular involvement. Parenchymatous changes may or may not be present; if they occur, they are usually minimal and rarely enter into the clinical picture. This group includes such widely diverse clinical entities as brain gumma, syphilitic epilepsy, diffuse «cerebrospinal» syphilis, and late asymptomatic neurosyphilis.
4. More or less purely parenchymatous neurosyphilis, including tabes, paresis, and primary optic atrophy (whether or not associated with tabes).»

Although the classification suggested by Thomas certainly is a practical one from the point of view of the clinician who in his daily work deals with diagnosis, treatment, and prognosis of the various forms of neurosyphilis, a search of the literature readily reveals that this fine sub-grouping usually is not maintained when it comes to presenting quantitative data on these complications (see section on occurrence).

Occurrence.

The frequency with which neurosyphilis occurs has usually been estimated through either one of two different methods:

1. Through the study of syphilitics admitted to *clinics or hospitals*. All depending on which criteria were employed in establising the study group, it may consist of patients previously untreated, or having received various types and amounts of treatment for the early manifestations of the disease. Groups of studied have contained dead patients only (autopsied or non-autopsied), dead and living combined, or living only.
2. By doing *follow-up studies* at some later date of syphilitics known to have received either no treatment, or various types and amounts of treatment, during the earlier phases of the infection, and to determine the proportions which had developed central nervous system involvement. Such a material

will necessarily include dead patients (autopsied and non-autopsied), and living patients, hospitalized and non-hospitalized, etc.

For the purpose of quantitative measurement, the second method is preferable in our opinion for these reasons: Firstly, clinic or hospital populations tend to be weighted in the direction of more serious cases, because disease brought the patients under observation, and therefore, they are not representative of the «universe» from which they are originally drawn. Secondly, as a denominator for the calculation of proportional frequencies a part or all of the «syphilis universe» of the clinic or hospital in question necessarily must be employed. It is not possible to determine how closely the chosen denominator corresponds to the reservoir from which the patients originally came, and therefore, we have no way of evaluating the order of magnitude of the proportions. It follows that figures arrived at through this type of study are not very satisfactory for comparative purposes. True enough, there can be no denying that follow-up studies also have their serious shortcomings especially in regard to losses from observation, but they have one definite advantage over the clinic or hospital studies, namely that they permit us to start out with a well defined denominator. A description of the difficulties encountered in the analysis of figures found through the follow-up method is one of the objectives of the present investigation, and these will be discussed at considerable length later.

In his chapter on asymptomatic neurosyphilis, Moore (1944) states that *invasion* of the nervous system by treponemes probably occurs in all patients with syphilis, and that it takes place during the first year of the infection in all or most instances. This statement, the author continues, is based on the large proportions of abnormal spinal fluids found in patients with untreated early syphilis, some observers reporting percentages from 50 to 70. With respect to figures on spinal fluid changes in primary and secondary syphilis, Dattner (1944) specially calls attention to the wide discrepancies found in the literature. These discrepancies, the author writes, may have to do with such factors as varying concepts as to what constitutes an abnormal spinal fluid; stage of the infection during which examinations are performed, and size of study groups; but first and foremost it is essential to know whether examinations are done prior to or after treatment. In Dattner's opinion, there is namely the possibility that inadequate treatment may lower the resistance of the central nervous system, or at least that it may lead to the production of positive spinal fluids.

What particularly interests us here is the frequency of abnormal spinal fluids in *untreated* early syphilis. Dattner (1944) refers to a study made at Bellevue Hospital, by Thomas, Wexler and himself, including 567 untreated cases of primary and secondary syphilis, where 79 (13.9 per cent) were found to have positive spinal fluids. (If borderline cases were included the percentage rose to 18.6). This compares with the following findings taken from Lomholt's

(1936) series, also quoted by Dattner (1944): Abnormal spinal fluids were found in 24 (12.7 per cent) of a total of 204 cases with untreated primary syphilis, and in 197 (28.0 per cent) of a total of 693 cases with untreated secondary syphilis. There is general agreement that the proportion of positive spinal fluids in early syphilis increases with the age of the infection, secondaries usually showing higher frequencies than do primaries, as exemplified through Lomholt's figures among others. In our opinion, it would not be unreasonable to accept Lomholt's close to 30 per cent abnormal spinal fluids in early untreated syphilis as being representative of the natural course of the infection up to the point where the examinations were done, that is, some time during the secondary stage. This also agrees fairly well with a general statement by Dattner (1944) to the effect that at least 35 per cent of the patients with syphilis show spinal fluid changes in the first two or three years after infection. As far as we can judge, however, the latter figure represents only an approximate estimate, based on the numerous reports in the literature and arrived at through indirect methods, since there exists no group of *untreated* syphilitics followed with spinal punctures up to or beyond the time when the secondary stage is terminated. Whatever the true frequencies of abnormal spinal fluids in primary and secondary syphilis are, there is general agreement that this involvement is for the most part transitory. Moore (1944 — p. 344) writes: «. . . In spite of this apparent constancy of neuraxis invasion, however, relatively few patients later develop actual tissue involvement manifested by obvious clinical signs of neurosyphilis . . .».

Since the spinal fluid changes in untreated primary and secondary syphilis must be considered as being transitory in most instances, but not in all, the next question that arises is the following: What are the frequencies of asymptomatic neurosyphilis at various durations of infection after the termination without treatment of the secondary stage? This obviously is a most important question, since patients showing abnormal spinal fluids during the later stages of the infection, are the potential candidates for subsequent development of definite neuraxis lesions. In order to determine these frequencies, it would be necessary to follow a sizable group of patients with regular spinal punctures from the beginning of the period of early «latency» to the «end point». For this reason: the pathologic process, as reflected in the positive spinal fluids of patients with asymptomatic neurosyphilis, *in principle* must be assumed to be dynamic rather than static in character, meaning, that sooner or later, at varying durations of infection, it will either progress and result in clinically recognizable central nervous system lesions, or it will subside to the extent that the spinal fluid becomes negative.

Thus, depending on when during the course of the infection the examinations take place, we can expect to find four groups of patients in varying proportions according to the extent of central nervous system involvement:

1. Those showing clinical evidence of these complications, whether in an active form or so-called «burnt out» neurosyphilis.
2. Those still in the asymptomatic stage, who sooner or later are going to develop definite neuraxis lesions.
3. Those in the asymptomatic stage but in whom the pathologic process is not going to progress.
4. Those who have become negative.

So, if we consider the pathologic process behind the spinal fluid abnormalties in asymptomatic neurosyphilis as being dynamic in character, it follows that the proportions of the various forms listed above necessarily must change with the passage of time. Only by repeated clinical examinations with spinal punctures over a period of many years, is it possible, therefore, to determine the *incidence* of asymptomatic neurosyphilis, or the *prevalence* at varying durations of infection. No-one has ever followed a group of untreated syphilitics by means of spinal fluid examinations beyond the early stages of the disease; and even when it comes to treated syphilis practically all observers, who have attempted to do repeated spinal punctures over any length of time, have encountered great difficulties, and in most instances succeeded in repuncturing only a fraction of the cases, and lost an ever-increasing number of patients as the years went on. This being so, it is safe to state that the true incidence of asymptomatic neurosyphilis, or the true prevalence at varying durations of infection, whether in untreated or treated syphilis, is not known, and probably never will be.

When it comes to figures on the frequency of clinical neurosyphilis as found through the study of clinic or hospital populations, those presented by Moore (1944) have been widely quoted in the literature. The author writes (ibid. p. 357): «Grouping together all patients infected with syphilis, *disregarding*[1] the factors of race and sex, and whether untreated or treated by the older methods preceding the introduction of the arsphenamines, about 25 per cent will ultimately develop clinical evidence of involvement of the nervous system . . .». And he continues, «. . . The type of neurosphilis will be paretic in about 5 per cent of those infected, tabetic in about 5 per cent, and diffuse meningovascular in about 15 per cent . . .». On the basis of these figures Moore says that neurosyphilis is a more serious problem than cardiovascular, probably causing more deaths, and definitely causing more partial or complete disability. Although the source is not stated directly the figures apparently are an estimate based on Turner's (1930) statistical survey from the Johns Hopkins Hospital of the admission diagnoses of 6,420 patients with late *untreated* syphilis (table 53).

In describing the findings of this table, Moore calls attention to the fact that

[1] Italicized by the present author.

Table 53.

The Incidence of Neurosyphilis in Patients with Late Syphilis, by Race and Sex, based on 6420 Patients with Late Syphilis

(Turner)

Type of Neurosyphilis	Percentage of all patients with late syphilis developing specified type of neurosyphilis, by race and sex			
	White		Negro	
	Male	Female	Male	Female
General paresis and tabo-paresis	8.4	5.0	2.0	0.3
Tabes dorsalis	13.9	4.6	3.5	0.8
Vascular	1.3	0.3	2.4	0.6
Diffuse meningovascular	15.4	12.2	13.7	5.5
Total	39.0	22.1	21.6	7.2

Reproduced from Moore, J. E.: «The Modern Treatment of Syphilis», 2nd ed. 3rd printing, Charles C. Thomas, Springfield, Ill., 1944.
(Moore's table 76, p. 344).

sex and race definitely seem to influence the development of clinical neurosyphilis. Despite this, the author subsequently chose to disregard these important factors and presented total proportions not specific for sex or race. This nonspecificity necessarily detracts from the value of these data for comparative purposes. It is noteworthy also, that Moore's estimates frequently are made use of in the literature, both for descriptive and comparative purposes, with no mention of how they were actually established. If we hold to the original findings as shown in table 53, and limit ourselves to the whites, who particularly interest us in this connection, it will be seen that close to 40 per cent of the males and more than 20 per cent of the females with late syphilis were found to have developed serious central nervous system lesions of one kind or another. As they stand, these proportions seem remarkably high, especially as compared with those arrived at in the various follow-up studies (see later), and the question of representativeness as discussed on p. 189, enters into the picture. These are ill self-selected hospital and clinic patients.

Kampmeier (1943 — pp. 343—344) states: «. . . No accurate statistics are available (and probably never will be) as to the incidence of clinical neurosyphilis in untreated syphilis. All figures from clinics or hospitals represent selected cases since these places attract persons who have complaints. However, it is generally estimated that about 5—10 per cent of untreated syphilitic patients will develop neurosyphilis. *If anything, this figure probably needs to be graded downward.*»[1]

The only figures available on the occurrence of neurosyphilis as found through a *follow-up study* of patients left untreated (or at least highly inadequately treated) during the early phases of the infection, are those presented by Bruusgaard (1929a). Before proceeding to an appraisal of Bruusgaard's findings, however, it is necessary to clarify certain points.

From Bruusgaard's tables (see annex tables I—VI, pp. I—VI) it will be seen that there were in his series a total of *30* cases of neurosyphilis, of which 13 were diagnosed as general paresis; 6 as tabes dorsalis; and 11 as cerebro-spinal neurosyphilis. In summing up, the author gave only proportions relative to the two first mentioned types of central nervous system involvement as follows: general paresis 13 cases (2.7 per cent); tabes dorsalis 6 cases (1.3 per cent). There is no mention of patients with cerebro-spinal neurosyphilis, nor of total neurosyphilis. The proportions quoted were arrived at by using the 473 cases observed (directly or indirectly) as a denominator (see Introduction, p. 13). In the discussion on neurosyphilis (see p. 15) the author also made use of the original 2,181 patients as a denominator with the following results: general paresis 13 cases (0.60 per cent); tabes dorsalis 6 cases (0.27 per cent). In respect to the first of these conditions, he obviously felt justified in employing this method of calculation, since he was convinced he had found all, or practically all, of the patients with general paresis. In other words, there can be no doubt that Bruusgaard himself considered the 0.60 per cent as coming closer to the true frequency of general paresis than the 2.7 per cent mentioned above. When it comes to tabes dorsalis, he states that the situation is different, because only those with pronounced symptoms reach medical attention, while many abortive cases go undiagnosed, and he concludes that this figure (0.27 per cent) definitely represented a minimum.

For reasons discussed previously (see Introduction, p. 21), we are of the opinion that the 473 investigated cases rather than the original 2,181 cases should have been used as a denominator, and in the following discussions we are going to make use of the proportions calculated in this manner, as follows: Total neurosyphilis 6.3 per cent (30 cases); general paresis 2.7 per cent (13 cases); cerebro-spinal syphilis 2.3 per cent (11 cases); and tabes dorsalis 1.3 per cent (6 cases). See also table 4, p. 22.

To what extent Bruusgaard's figures on neurosyphilis are representative is an extremely difficult question to answer, mainly because we possess only limited information on the fundamental epidemiologic methods employed in tracing, identification, and collection of clinical data. There is reason to believe, however, that some unconscious bias must have been introduced, as shown by

[1] Italicized by the present author.

Harrison (see p. 25) who, by an analysis of the paretics on a sex-specific basis, found that, contrary to usual experience, there was practically no difference as to frequency of this complication between males and females (0.57 per cent in females versus 0.60 per cent in males, when the original 2,181 patients were used as denominator). By making use of the 473 investigated cases as denominator, we find proportions which even more strongly point in the direction of bias inasmuch as females then show an excess over males as follows: females: 3.1 per cent (8 cases out of a total of 260); males: 2.3 per cent (5 cases out of a total of 213). (See p. 26). If we go a bit further and analyse the other types of central nervous system involvement according to sex, we find that also cerebro-spinal syphilis was more commonly diagnosed among females than among males: 7 out of 260 females (2.7 per cent) as compared with 4 out of 213 males (1.9 per cent). Only in tabes dorsalis did males show an excess over females, with 4 cases out of 213 (1.9 per cent) versus 2 out of 260 (0.8 per cent). Finally, by sub-grouping the total number of cases with neurosyphilis according to sex, we get the following proportions: males — 13 cases out of 213 (6.1 per cent); females — 17 cases out of 260 (6.5 per cent), or, in other words, practically no sex difference as to the frequency of central nervous system involvement.

When it comes to follow-up studies of patients having received specific but inadequate treatment for their early manifestations, the most reliable figures on the frequency of neurosyphilis hitherto presented, are in our opinion, those found by the two Danish investigators Lomholt (1936) and Nielsen (1950). The reason for this lies first and foremost in the unique possibilities for follow-up studies of syphilitics created in Denmark by the establishment (in 1920) of the Syphilis Registration Office at the State Serum Institute in Copenhagen. (For details on the system we refer to pp. 148—150 and to pp. 266—268).

As mentioned in the chapters on «benign» tertiary and cardiovascular syphilis, Nielsen followed 467 *male* patients, who during the years 1913—1920 had received 2—3 injections of salvarsan, and some 50 inunctions of mercury for the early manifestations of the disease. The period of observation ranged from 29 to 36 years. Among these patients a total of 40 (8.6 per cent) were found to have developed central nervous system involvement in one form or another, the various types being distributed as follows: (the proportions represent per cent of the total number (467) investigated) General paresis — 20 cases (4.3 per cent); meningovascular and vascular neurosyphilis — 15 cases (3.2 per cent); and tabes dorsalis — 5 cases (1.1 per cent). Furthermore, there are 8 cases (1.7 per cent) listed separately under the heading Syphilis of the Special Organs of Sense: 7 with eye manifestations and 1 with an ear ailment. The latter was a case of syphilitic labyrynthitis, whereas the eye cases included some with primary optic atrophy and some with sequelae of iridocyclitis and chorioditis, but with no mention of how many belonged in each of the last mentioned groups. According to the definition quoted earlier (p. 187), both primary optic atrophy and syphilitic labyrynthitis represent types of neurosyphilis, and if so allocated, would have increased somewhat the total percentage (8.6) of central nervous system involvement in Nielsen's series. Due to the relatively small numbers involved, however, it does not make much difference which method of classification is chosen.

It is interesting to note that all of the 467 patients investigated by Nielsen were also included in a follow-up study of 538 cases made by Lomholt (1936) with *special reference* to the frequency of *general paresis*. Thus Nielsen started out with a study group similar to that chosen by Lomholt, except that he omitted from the material 71 patients in whom treatment for the early manifestations was presumably initiated with mercury instead of salvarsan. Lomholt too made use of the Syphilis Registration Office at the State Serum Institute in Copenhagen as a starting-point for tracing and identification of the patients. With a period of observation ranging from 14 to 23 years, Lomholt among the 538 cases, found 18 (3.3 per cent) with general paresis, which compares with 20 (4.3 per cent) found by Nielsen among his 467 patients followed from 26 to 39 years. The considerably longer period of observation in the last of the two otherwise practically identical investigations, is probably the chief reason for the increase in the proportion of general paresis. Lomholt, incidentally, was fully aware of the possibility that a somewhat longer period of observation probably would lead to an increase in the proportion of general paresis, and thus Nielsen's findings actually confirmed his viewpoint. However, the difference is not marked, and this in itself, in our opinion, adds to the reliability of the figures presented.

The best known of the older studies is probably that made by Mattauschek and Pilcz (1912 and 1913), who attempted to follow 4,134 Austrian Army officers infected during the period 1880—1900, and treated with mercury for their early manifestations. In the first publication (1912) the authors reported on their findings as of January 1st 1911 when the investigation was originally closed. After the patients had been followed for one more year (up to January 1st 1912), another set of data was published (1913). These were the figures on the frequency of neurosyphilis as presented in the second publication: general paresis — 4.75 per cent; meningovascular syphilis — 3.19 per cent; tabes dorsalis — 2.73 per cent, total — 10.67 per cent.

Originally (1912) the authors found 195 paretics among the 4,134 investigated cases (4.7 per cent). They chose, however, to omit from the material all patients observed less than 10 years after infection, amounting to 704 cases, including 35 paretics. This method of procedure left them with 160 paretics (4.67 per cent) among the remaining 3,430 investigated cases. It will be noted that the difference was negligible, and the reason for this is to be found in the surprisingly great number of paretics among the 704 followed for 10 years and less (35 —

4.97 per cent). The latter phenomenon, in our opinion, very strongly points in the direction of bias, although we are at a loss with the data available to explain how it was brought about.

Mattauschek and Pilcz, furthermore, sub-grouped their material according to period of time during which the patients were infected, comparing the frequencies of central nervous system involvement among those infected between 1880—1884 and those infected between 1895—1899, as follows:

1880—1884: total number infected: 617. Among these were found 60 cases of general paresis (9.72 per cent), and 15 cases of meningovascular syphilis (2.42 per cent).

1895—1899: total number infected: 1,139. Among these were found 37 cases of general paresis (3.25 per cent), and 28 cases of meningovascular syphilis (2.43 per cent).

The considerable decrease in the frequency of general paresis was interpretated by the authors as being due to better treatment of the early lesions in the latter of the two groups.

In a critical review of Mattauschek and Pilcz's material Aebly (1920), however, strongly opposed that interpretation. He pointed out that due to the relatively short period of observation in those infected between 1895—1899 (on an average about 14 years, as compared with an average of about 29 years in those infected between 1880—1884), the authors must have missed quite a considerable number of paretics among these patients. This, according to Aebly, was the chief reason why the proportion of general paresis turned out to be so much smaller among those infected between 1895—1899, and he therefore also felt justified in considering the percentage given for the total (4.75) as representing a definite minimum. In respect to frequency of meningovascular syphilis, it will be seen that there was practically no difference between the two groups in question (2.42 versus 2.43 per cent). Since meningovascular syphilis usually gives rise to symptoms and signs somewhat earlier during the course of the infection, Aebly felt that the authors had probably found all or practically all of the cases with that particular type of central nervous system involvement, even in the group with the shorter period of observation (about 14 years on a average). The findings relative to meningovascular syphilis were thus, in his opinion, in accordance with what one would expect and did not contradict what he had said about the figures on general paresis.

After having analysed the material further, Aebly stated that a proportion of about 10 per cent general paresis came closer to the true frequency in Mattauschek and Pilcz's series than the 4.67 and 4.75 per cent respectively presented by the authors themselves. He reasoned as follows: First, it was necessary to establish at least approximate values for the «period of incubation» in general paresis. On the basis of general experience, Aebly estimated the age at recognition to lie around 35—45 years, averaging 40 years, and the age at onset of infection somewhere around 20—25 years, averaging 22—23 years, thus making an average «period of incubation» of 17—18 years. Next, the spread around this mean had to be taken into account. Aebly emphasized that the distribution was not known, but he assumed the curve to be fairly symmetrical, the mean thus falling in the middle, between the two extreme values estimated at 2 respectively 30 years. In respect to the first group in the material, namely those infected between 1880—1884, Aebly found that the period of observation (average 29 years) was sufficiently long, so that all or practically all cases of general paresis could be expected to have developed within that period of time. He therefore felt that the proportion of general paresis (9.72 per cent) among these patients probably was more representative of the frequency in the material than the case was in the second group. In analysing the latter group (those infected between 1895—1899), he came to the conclusion that the proportion of general paresis given by the authors (3.25 per cent) definitely was too small, because of the relatively short period of observation (average 14 years). Assuming the spread around the mean to be fairly even, and the range to lie between 2 and 30 years, Aebly calculated one could only expect 24 per cent (or about one-fourth) of the cases with general paresis to have developed at the end of 14 years, and no more than 34 per cent (or about one-third) at the end of 16 years after infection. Thus, in his opinion, the proportion of 3.25 per cent among the patients in the second group, as found by the authors, had to be multiplied by 3—4 in order to get the true frequency of general paresis among them, which would then become 9.75—13.00 per cent.

Sex, and Age at Infection.

It can be considered an established fact that serious central nervous system involvement is more commonly found in males than females. According to Stokes et al. (1944) neurosyphilis, irrespective of form, is three times more frequent in males than in females, though abnormal spinal fluids are encountered to the same extent in both sexes during the early phases of the infection. Moore (1944) writes that all forms of late neurosyphilis are more frequent in males than in females (see table 53, p. 192).

The male-female ratios in neurosyphilis found in the literature usually refer to figures arrived at through studies of clinic or hospital populations, or, in some instances, especially as regards general paresis, to estimates based on mortality statistics. Both methods are characterized by the fact that the size of the reservoir from which the patients are originally drawn, for the most part in unknown. The figures can thus only be approximate, and there is no way of determining to what extent they are representative. Therefore, as would be expected, the ratios vary considerably from one series to another, probably reflecting differences in sources of data. In the data presented by Moore (1944) (table 53) the ratio males to females (white patients) for all types of neurosyphilis was 1.8 to 1, while the ratios for the specified types were as follows: general paresis — 1.7 to 1; tabes dorsalis — 3 to 1; meningovascular and vascular syphilis — 1.3 to 1. Kampmeier (1943) found these ratios (white patients, clinic population): general paresis — 8 to 1; tabes dorsalis 4 to 1. It should be emphasized that none of the above mentioned authors claimed their figures to be representative, and we have quoted the ratios just to exemplify how they may vary under varying circumstances. Most authors hold general paresis to be from 4 to 5 times more frequent in males than in females, and this ratio is commonly found when the estimates are based on mortality statistics. Harrison (see p. 25) on the basis of official records, showed that among those dead of general paresis, the proportion of males to females was 4.5 to 1 both in England and Wales as well as in Norway during the period 1914—1928. Källmark (1931), analysing Swedish figures, assumed 15 to 25 per cent of the paretics to be females, or a ratio of males to females of 4—6 to 1. The protective effects of pregnancies are usually held responsible for the milder course of the syphilitic infection in females as measured through the frequency of serious central nervous system involvement. Evidence in this direction was provided among others by Solomon (1926), quoted by Stokes et al. (1944), who found 44 per cent nulliparae among those having developed tabes dorsalis or general paresis, as compared with 26 per cent in syphilic women without neurosyphilis.

The Influence of Age at Infection. As far as we have been able to ascertain, there exist no reliable data as to the influence of age at infection on the frequency of neurosyphilis. The reason is mainly to be found in the fact that most of the materials studied, are based on cases picked from among hospital and/or clinic populations and are subject to the selective factors of such groups. This is exemplified through a statement by Meggendorfer (1921) among others, who wrote that the influence of age at infection on the frequency of neurosyphilis could not be determined on the basis of his material, because the study group comprised only that fraction of an unknown number of infected persons who later had developed central nervous system lesions. In investigations where the follow-up method of approach is utilized, the number of patients in the original study group naturally is limited, and since the proportion developing neurosyphilis is relatively small, it follows that the fine sub-grouping necessary to provide data on the influence of age at infection usually results in figures which do not allow for significant comparisons. Even Mattauscheck and Pilcz (1912), whose original study group consisted of more than 3,000 patients in whom the age distribution at time of infection was known, could not determine to what extent this factor had affected the outcome quantitatively.

It is a well-known fact that neurosyphilis is not infrequently seen in late congenital syphilis. Central nervous system lesions in patients infected during childhood (i.e. between 0 and 14 years) are, however, seldom reported in the literature, although they do occur. Whether this means that such patients are actually less commonly affected with neurosyphilis than those infected during adult life, is not known, but that possibility can not be excluded.

Treatment.

Ever since the introduction of the arsenicals, many syphilologists have been of the opinion that inadequate treatment during the early phases of the infection tended to increase the frequency of neurosyphilis. Just to mention an example, Dattner (1944), commenting on the wide discrepancies between the figures presented by Bruusgaard (1929a) and those arrived at by Mattauschek and Pilcz (1912—1913), indicated that an explanation probably could be found in the fact that the patients in the former series had been left untreated, whereas those in the latter had received various amounts of inadequate treatment in the form of mercury. Moore (1944), on the other hand, stated that even inadequate treatment[1] would markedly reduce the frequency of diffuse meningovascular syphilis, but that it would not materially influence the frequency of general paresis and tabes dorsalis in either direction. Adequate treatment,[1] he wrote, would in all probability eliminate diffuse meningovascular syphilis altogether, or at least reduce it to a very low figure, while it would affect a moderate reduction in the frequency of the two more serious forms of general paresis and tabes dorsalis. In conclusion Moore said (1944 — p. 359): «*Thus treatment, adequate or inadequate, appears to have no influence in increasing the incidence of any form of clinical neurosyphilis*[2] except acute syphilitic meningitis; . . .». Moore continued by stressing that treatment, especially if inadequate, definitely shortened the «incubation period» of neurosyphilis and presented the following evidence provided by Hopkins (1933) (table 54). Finally, it is noteworthy, that, according to Moore, treatment which practically eliminated the risk of getting cardiovascular, proved wholly inadequate for the prophylaxis of neurosyphilis.

Time Relationships and Age.

In connection with *time relationships* in neurosyphilis, it is important to bear in mind that the various types of central nervous system involvement manifest themselves at different durations of infection. Thus it is generally held that diffuse meningovascular neurosyphilis occurs earlier during the course of the infection than general paresis and tabes dorsalis. This was brought out, among

[1] This refers to treatment of early syphilis with the arsphenamines and the heavy metals.
[2] Italicized by the present author.

Table 54.

The Effect of Treatment on the Incubation Period of the Various Types of Neurosyphilis (Hopkins).

Type of neurosyphilis	Interval in years between infection and appearance of symptoms when the patient	
	Received no previous treatment	Was treated prior to the development of neurosyphilis
Diffuse meningovascular	13.9	10.4
Tabes	24.0	14.6
Paresis	19.5	15.3

Reproduced from Moore, J. E.: «The Modern Treatment of Syphilis», 2nd ed. 3rd printing, Charles C. Thomas, Springfield, Ill., 1944.
(Moore's table 80, p. 359).

others, by the figures presented by Hopkins (1933) and quoted by Moore (1944), (see table 54), where it will be noted that diffuse meningovascular showed a considerably shorter «period of incubation» than general paresis and tabes dorsalis, in treated as well as untreated cases. The durations of infection for the three types of central nervous system lesions, in the treatment and no treatment categories respectively, were as follows: diffuse meningovascular — 13.9 and 10.4 years; general paresis — 19.5 and 14.6 years; and tabes dorsalis — 24.0 and 14.6 years. The fact that meningovascular syphilis occurs earlier than the two serious forms of neurosyphilis, was also pointed out by Aebly (1920) (see p. 196). Therefore, it is essential, particularly from a comparative viewpoint not to lump all forms together when giving figures on time relationships in neurosyphilis.

Most authors agree that the mean «period of incubation» of general paresis in untreated cases lies around 18 years. As mentioned previously, Aebly (1920), on the basis of general experience, estimated the duration of infection at recognition to be from 16 to 18 years. The untreated paretics in Pette's (1920) series showed an average «period of incubation» of 18.3 years, as compared with an average of 17.6 years in Kral's (1933), and 19.5 years in Hopkins' (1933) untreated cases. Nielsen (1950) found 20 paretics among his 467 inadequately treated males, and the mean age of the infection at recognition was 16 years. Lomholt (1931 and 1936) among 315 male syphilitics admitted for general paresis to the St. Hans asylum for the insane in Denmark, found onset of infection to be known in 186 patients, in whom the mean duration of infection was calculated to be 18.6 years.

In tabes dorsalis the untreated group in Pette's (1920) series showed an average «period of incubation» of 16.7 years, which compares with Lowinsky's

(1911) average of 14 years, and Hopkins' of 24 years in untreated patients. The duration of infection in tabes dorsalis varies somewhat more from one series to the other than is the case in general paresis. This may, at least in part, have to do with the varying number of cases of so-called «burnt out» tabes included in the materials, since such cases on an average are likely to be recognized considerably later during the course of the infection than the active forms.

Finally, neurosyphilis as a whole, as pointed out among others by Frazier and Li (1948), is usually recognized earlier during the course of the infection than cardiovascular. «Of the tertiary phenomena, those of the cardiovascular system are usually the last to cause symptoms, and, when they occur, occupy the terminal position in the course of the disease, coming even later than degenerative affections of the spinal cord . . .» (ibid. p. 35). This is a feature which probably is characteristic of the natural course of the infection, but there are also other reasons for the differences found relative to duration of infection at recognition in the two main forms of late syphilitic complications. Suffice it to mention the great difficulties connected with the early diagnosis of uncomplicated aortitis, a factor which would tend to work in the direction of increasing the duration of infection at recognition in cardiovascular syphilis as compared with neurosyphilis, where spinal fluid examinations form a definite clue to an early diagnosis in a great proportion of instances.

Prognosis.

The prognosis of neurosyphilis will depend among other things on form of central nervous system involvement, and of course, on types and amounts of treatment. In this connection we are not going to consider the outlook of asymptomatic neurosyphilis, this form of neurosyphilis not having been diagnosed in our own material. Further, we are going to refer to prognostic considerations made in the pre-penicillin era, since penicillin-treated cases of neurosyphilis do not exist in our series. The prognosis of neurosyphilis in the pre-penicillin days, as based on Moore's (1944) review of the question, can briefly be summarized as follows:

Diffuse meningovascular syphilis. The author first stresses the wide variety of clinical pictures usually classified within this category of neurosyphilis, and expresses the opinion that this makes a statistical evaluation of the ultimate outcome practically impossible. Next he points to the fact that meningovascular syphilis seldom is the primary cause of death, and also that recovery from symptoms perhaps can be expected in most instances, either spontaneously or under the influence of comparatively small amounts of treatment. We must reckon with the possibility, however, that a certain proportion of the patients will become more or less incapacitated as a result of these lesions, and in some cases an underlying parenchymatous process may sooner or later lead to the development of general paresis. Adequate treatment can be expected to cause symptomatic relief and arrest of the pathologic process in about 80 per cent of the cases.

Tabes dorsalis. This complication, according to Moore, rarely causes death directly except from sphincter paralysis, cord bladder and ascending urinary infection. In about 90 per cent of all untreated tabetics, on the other hand, such manifestations as lightning pains, cord bladder, ataxia, gastric crises, Charcot's joints and optic atrophy, in that order of frequency, are apt to cause a more or less pronounced disability, whereas in only 10 per cent of the total the process is stayed for some hitherto unknown reason, and the patients may live on for many years with a so-called «burnt out» form of tabes. The results of treatment are less satisfactory than in any of the other central nervous system lesions except paresis, complete symptomatic relief and permanent arrest of progress being obtained in only about 30—40 per cent of those treated. Incidentally, it is not stated on which material or materials the above estimate of the frequency of «burnt out» tabes is based. In all probability it is an impression gained through the study of hospital and/or clinic populations. These «fortunates», to use Moore's expression, can be expected to reach hospitals and clinics in comparatively much smaller proportions than those showing more or less incapacitating manifestations of the disease, and therefore, one would be inclined to believe the true frequency of «burnt out» tabes to be greater than 10 per cent of the total.

General paresis. Without treatment the great majority of the cases end fatally within an average of 2 years after onset of symptoms. And, as pointed out by Moore, routine antisyphilitic treatment with the arsenicals and the heavy metals did not appreciably better the results. The introduction of fever therapy, however, completely altered the picture, and complete remissions were obtained in 30—40 per cent of unselected cases, and in an even higher percentage in carefully chosen series. The average duration of life was lengthened by many years.

II. Present Investigation.

Introductory Remarks.

1. For the study of neurosyphilis we have chosen to limit ourselves to the study group «Known», comprising altogether 953 patients, 622 females and 331 males. These patients were all followed to an «end point», that is, date and year of death were established, or, they were found to be alive at time of investigation (1949—1951). Possibly we might also have included some patients from the study group «Partially Known», but since the duration of infection in the various forms of symptomatic neurosyphilis varies quite considerably, it was practically impossible to decide for how

long these patients ought to have been followed in order to justify such inclusion. To secure uniformity, therefore, and because it was necessary to adopt the same procedure in respect to cardiovascular syphilis (see later), we chose not to make use in the present analyses, of the patients in the study group «Partially Known». Incidentally, no case of neurosyphilis was found to have developed among these latter patients. (For figures and explanation of terms relative to the various study groups, see table 21, p. 93.)

2. All patients in the study group «Known» were included irrespective of stage during which they originally were seen by Boeck, and irrespective of specific treatment received prior to, during, or shortly after, discharge from Boeck's department. Neither were patients, subsequently treated specifically for secondary relapse or «benign» tertiary syphilis, omitted. The principles employed are identical with those mentioned in the chapter on cardiovascular (see points 2 and 3 under Introductory Remarks, p. 275).
3. General factors relative to time relationships and age are discussed on pp. 229—231. When it comes to the definition of the intervals in the various time relationships and age estimates, this is identical with that used in cardiovascular (see Introductory Remarks, point 4, p. 275).

Definition.

As a matter of principle we have adhered to the classification of neurosyphilis suggested by Thomas (1949) (see p. 187). This does not mean that all the forms listed necessarily were found to have occurred in the present series; moreover, the small number of cases within some of the categories made the fine sub-grouping employed by Thomas impracticable for analytical purposes.

Types of Neurosyphilis and the Quality of the Diagnoses.

The types of neurosyphilis encountered in the present series are presented in table 55. As will be seen from the table, the cases are in principle classified into four main categories as follows: diffuse meningovascular neurosyphilis, general paresis, tabes dorsalis, and gumma of the brain; and, the calculation of the percentage distribution of the forms is based on this sub-grouping. For descriptive purposes and for future reference, however, the table is also constructed so as to show what goes into each one of these four categories.

On considering the total column, it will be noted that there were altogether 23 cases of diffuse meningovascular neurosyphilis, of which 18 are classified as meningovascular and 4 as vascular. It is a well-known fact that the two forms are not easily distinguishable, and therefore it seems logical, as commonly found in the literature, to group them together under one heading: diffuse meningo-

Table 55.

Distribution of the Forms of Neurosyphilis, by Sex.

(All ages*) (62 patients)

Forms of neurosyphilis**		Males No.		Males Per cent	Females No.		Females Per cent	Total No.		Total Per cent
Diffuse meningo-vascular	Meningovascular (Active)	6	12	38.7	5	11	35,5	11	23	37.1
	Meningovascular (Inactive)	5			3			8		
	Vascular	1			3			4		
General paresis	General paresis	9	10	32.3	10	10	32.3	19	20	32.3
	Taboparesis plus optic atrophy	1			0			1		
Tabes dorsalis	Tabes dorsalis (Active form)	2	8	25.8	3	9	29.0	5	17	27.4
	Tabes dorsalis (Forme fruste)	5			5			10		
	Tabes dorsalis plus optic atrophy (Active form)	0			1			1		
	Optic atrophy	1			0			1		
Gumma of brain			1	3.2		1	3.2		2	3.2
Total			31	100.0		31	100.0		62	100.0

* Age at infection.

** Categories mutually exclusive.

vascular. In the 4 cases listed here as vascular, the clinical and/or pathologic-anatomic picture was predominantly vascular (cerebral apoplexy), but actually it was either a question of both meningeal *and* vascular processes, or it could not be definitely established whether it was a purely vascular form or not. The 19 cases of meningovascular were also divided into active (11 cases) and inactive (8 cases) forms. The activity of the process relates to the time of recognition; and, by inactive is here meant that only sequelae of meningovascular could be demonstrated clinically or pathologically. This latter subgrouping is important, not only from a prognostic point of view, but also bears on the evaluation of the time-relationship and age estimates (see later).

Among the 20 cases of general paresis, there was 1 diagnosed as taboparesis with optic atrophy. It was found natural to classify this one case under general paresis.

Out of a total of 17 cases of tabes dorsalis, 10 fell into the category forme fruste, or «burnt out» tabes; the remaining 7 in the category active form. Here too activity relates to the time the lesions were first recognized, and again the sub-grouping must be considered essential from a prognostic viewpoint, as well as in connection with the evaluation of the time-relationship and age estimates.

Further, there were 2 cases of gumma of the brain, which according to accepted principles, were classified as a special type of neurosyphilis.

Finally, it should be noted that no case of asymptomatic neurosyphilis was found to have been diagnosed among our patients. The explanation for this phenomenon is partly to be sought in the fact that only a relatively small proportion of the total number of patients was found to have been subjected to spinal punctures, and partly in the fact that, when done, the examinations were in the majority of instances performed rather late in the course of the infection. For details on the quantitative aspects of the spinal fluid examinations we refer to Annex IV in which these questions are discussed.

For the calculation of the percentage distribution of the various forms of neurosyphilis, we have, as mentioned previously, sub-divided the cases into four main categories: diffuse meningovascular, general paresis, tabes dorsalis, and gumma of the brain, which were found to constitute 37.1, 32.3, 27.4, and 3.2 per cent of the total number in the series respectively. Among the forms listed in the table, gumma of brain was the least common form encountered, and this is in keeping with what we would expect. Relative to the three other forms, the trend — if any — would indicate diffuse meningovascular, general paresis, and tabes dorsalis to have occurred in that order of frequency. However, since the differences found are not significant, we are not in a position with the data available, to determine whether this distribution actually reflects the natural course of the infection or not. With the reservations made necessary by the small numbers involved, the findings also seem to indicate that, although neurosyphilis developed in higher proportions in males than females, there was practically no difference between the sexes as to frequency of the various forms of neurosyphilis diagnosed.

An evaluation of the quality of the diagnoses in these patients necessitates a rather comprehensive analysis of each single case. This analysis is found in Annex V, p. XXI, to which we refer for details.

By and large, the analysis showed that in the majority of instances the diagnoses, when made, rested on solid ground. A possible exception were the examinations done in some of the males diagnosed as having meningovascular syphilis. These must be considered as incomplete measured by modern standards, but taking into account the circumstances under which these diagnoses were made, we nevertheless felt justified in classifying the cases in question under meningovascular neurosyphilis.

Age at Infection.

In table 56 the patients with neurosyphilis are grouped according to age at infection. It will be noted that neurosyphilis in one form or another was found to have occurred in all age-groups listed in the table except in males 40 and over. There were 4 cases (3 males and 1 female) among patients infected before 15 years of age: 1 of general paresis (a male, infected at 2 years of age), and 3 of meningovascular neurosyphilis (2 males, infected at 2 and 14 years of age respectively, and 1 female, infected at the age of 2). Also, there were 2 cases, both females, among those infected at ages 40 and over.

The table readily reveals that we are in no position to determine how age at infection may have influenced the frequency of neurosyphilis in our series. The distribution of the proportions within the various sub-groups is such that not even a trend is discernible. The reason is obvious: the number of cases with neurosyphilis is far too small to permit the fine sub-grouping necessary for an analysis of this kind.

Finally, if we compare the totals for all ages, ages 15—39, and 15—40 and over, it will be seen that it matters little whether we include patients under 15 or over 39, or whether we limit ourselves to those aged 15—39 at infection. When it comes to comparisons with other studies, however, it would seem reasonable to assume that most materials of this kind will include only a few patients — if any — infected during childhood, whereas practically all of them will include some infected at ages over 39. For comparative purposes, therefore, we have chosen to limit our analyses to the proportions found in the group 15—40 over. The method of procedure is similar to that adopted for cardiovascular syphilis.

Occurrence.

Occurrence in the total study group «Known». From table 56 it will be seen that a total of 6.5 per cent of the patients observed was found to have developed neurosyphilis in one form or another (see lower section of table, total column, ages 15—40 over).

Since the various types of central nervous system lesions differ considerably, particularly from a prognostic point of view, table 57 is presented to show the proportions of males and females developing neurosyphilis, according to form. From the total column it will be seen that meningovascular plus vascular syphilis was found in 20 patients (2.3 per cent); general paresis in 19 (2.1 per cent); tabes dorsalis in 17 (1.9 per cent); and gumma of brain in 2 patients (0.2 per cent).

Table 56.

Proportions Developing Neurosyphilis, by Sex, and Age at Infection.

(62 patients)

Age at infection	Males			Females			Total		
	Number of patients observed	Patients developing neurosyphilis		Number of patients observed	Patients developing neurosyphilis		Number of patients observed	Patients developing neurosyphilis	
		No.	Per cent		No.	Per cent		No.	Per cent
0 — 14	28	3	10.7	38	1	2.6	66	4	6.1
15 — 19	43	2	4.7	131	6	4.6	174	8	4.6
20 — 29	180	20	11.1	330	20	6.1	510	40	7.8
30 — 39	52	6	11.5	78	2	2.6	130	8	6.2
40 over	28	0	—	45	2	4.4	73	2	2.7
Total	331	31	9.4	622	31	5.0	953	62	6.5
Ages 15 — 39	275	28	10.2	539	28	5.2	814	56	6.9
Ages 15 — 40 over	303	28	9.2	584	30	5.1	887	58	6.5

When it comes to evaluation of the representativeness of the above figures, we shall have to take into account the circumstances under which the final observation took place, as well as what may have happened to the patients in the interim, that is, the period between the original discharge from Boeck's department and the final observation. Furthermore, it is essential to consider each form of neurosyphilis separately. The general aspects of the quality of the diagnosis at final observation are discussed in Annex VIII, to which we refer. Here will be taken up questions of special importance for the evaluation of the quantitative data on neurosyphilis.

In respect to the circumstances under which the final observation took place, the material can be sub-divided into those found to be dead, and those still alive, at time of investigation (1949—1951). The dead, who comprise the great majority of the patients in the present series (694 out of a total of 953 — 72.8 per cent), were sub-grouped according to quality of diagnosis at final observation as follows (see annex table XX, p. XLIV):

1. 209 (30.1 per cent) were found to have been autopsied.
2. 200 (28.8 per cent) were found to have been examined in a hospital just prior to death.
3. 100 (14.4 per cent) were found to have been examined in a hospital a relatively short time prior to death, and the final diagnosis could be made on the basis of clinical information from the hospital plus the data found on the death certificate.
4. 146 (21.0 per cent) were found not to have been hospitalized during the last years before death, and the only information available at time of death was the death certificate.

Finally, there were 39 patients (5.6 per cent) in whom fact of death was established, but on whom no clinical information was available.

The average duration of infection at time of death was 26.8 and 26.0 years respectively in males and females (see annex table XXI, p. XLV).

Among the 259 patients alive at time of investigation, clinical data were available on 216 (83.4 per cent), and 43 (16.6 per cent) were found not to have been examined by others and could not be brought in for examinations by us (see annex table XXIII, p. XLVIII). Among the living the average duration of infection at time of investigation was about 50 years in both sexes (see annex table XXIV, p. XLIX).

On the basis of these data, plus both direct and indirect information from the interim period, an attempt will be made in the following to evaluate the representativeness of the proportions of the various forms of neurosyphilis as found in the present series.

Table 57.

Proportions Developing Neurosyphilis, According to Form, by Sex.

(Ages 15 — 40 over*) (58 patients)

Males				Females				Total			
Total number observed	Forms of neuro-syphilis**	No.	Per cent	Total number observed	Forms of neuro-syphilis	No.	Per cent	Total number observed	Forms of neuro-syphilis	No.	Per cent
303 (100 %)	Meningo-vascular plus vascular	10	3.3	584 (100 %)	Meningo-vascular plus vascular	10	1.7	887 (100 %)	Meningo-vascular plus vascular	20	2.3
	General paresis	9	3.0		General paresis	10	1.7		General paresis	19	2.1
	Tabes dorsalis	8	2.6		Tabes dorsalis	9	1.5		Tabes dorsalis	17	1.9
	Gumma of brain	1	0.3		Gumma of brain	1	0.2		Gumma of brain	2	0.2
	Total	28	9.2		Total	30	5.1		Total	58	6.5

* Age at infection.

** Categories not mutually exclusive. For principles employed in classification we refer to table 55.

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Representativeness of the figures on general paresis. Of the 694 dead, 509 patients (73.3 per cent) had been examined in a hospital either immediately prior to death or a relatively short time before death occurred. Under these circumstances — and taking into account the comparatively long average duration of infection at time of death — it is, in our opinion, fairly safe to assume that only a negligible number of cases with active general paresis (if any) can possibly have been overlooked among these patients.

When it comes to the 146 (21.0 per cent) on whom the death certificate data provided the only clinical information available at time of final observation, the following points need to be emphasized:

A. General paresis is seldom reported to be the cause of sudden death, the disease, if untreated, usually lasting for some time before it ends fatally. Moreover, in most instances the symptoms and signs are such as to bring the patients under medical observation, either in psychiatric wards or in hospitals for the insane. Also, if the patients come from the lower socio-economic strata of the population, as was usually the case with ours, a disease of the nature of general paresis can be reckoned with to make all, or practically all of them medically and/or otherwise indigent, which again would necessarily lead to official registration of examinations and hospitalizations. In view of the above considerations it is important to note that in the 146 patients in question we were unable to provide clinical data for the years preceding death, in spite of the most exhaustive search through the many channels of information open to us. Therefore, the chances seem remote that any significant number of cases with active general paresis have gone undiagnosed through the years elapsing before death.

B. In addition, there is practically no reason to believe that any of these 146 patients died primarily as a result of general paresis, unless the disease went undiagnosed, which, for reasons already discussed, appears unlikely. Provided this complication is the cause of death, the diagnosis will usually be found on the death certificate, since it can be stated accurately without utilizing such words as «syphilitic» or «luetic» to point out its specificity. This is in contrast to what we can expect in cardiovascular, where it is common practice to employ such general terms as «heart disease», «valvular disease», and so on, in order to withhold the specific diagnosis from relatives. Although the number of patients found to have died of general paresis admittedly is small in the present series (19 cases altogether), it is still noteworthy that a diagnosis of general paresis was noted on the death certificate in all but 2 instances.

Finally, there is among the dead a group of patients in whom we could only establish time of death, with no clinical data available. The group is, however, of minor importance numerically (39 patients — 5.6 per cent), and whatever they may have died of, it can hardly have influenced the end results significantly.

We have already stressed the important fact that the living patients in the present series had had their syphilitic infection for an average of about 50 years at time of final observation. Among the 216 (83.4 per cent), who had been submitted to examinations either at time of investigation (1949—1951) or shortly before, we feel convinced that no case of active general paresis was overlooked. When it comes to the remaining 43 (16.6 per cent) examined neither at time of investigation nor shortly before it took place, it must be emphasized that practically all of these were contacted — directly or indirectly — and were found to be well, or to have some more or less trivial disease. So, if any patients with symptoms and signs of active general paresis actually had existed among them, it would in all probability have been brought to our attention, either through official channels, or through relatives of the patients, or through personal interviews.

Now, even if it can be reasonably assumed that we found all — or practically all — of the patients showing symptoms and signs of general paresis at time of final observation, the next questions that arise are these: can it be credibly established that some of the patients who developed general paresis did not die of some other disease, because they had been treated successfully for the former condition in the interim? And, is it possible to prove that we have not missed some such cases due to lack of clinical data from the interim period? Our opinion is, that, although we have no means of proving that we have only missed a small number of paretics on this score, there is rather strong indirect evidence pointing in that direction, as will be shown in the following. The factors which must be taken into account in order to determine to what extent the patients in the present series may have been successfully treated for general paresis in the interim period, and thus may have escaped our search, are listed below:

1. *«Incubation period» of general paresis.* The average «incubation period» of general paresis in untreated syphilis is not exactly known, but generally it is held to be some 18 to 20 years. The spread around this estimate is also unknown, but cases, supposedly untreated for the early manifestations of the disease, have been reported from about 2 to about 50 years after infection.
2. *Possibilities of effective treatment of general paresis.* There was actually no treatment for general paresis until the malaria therapy was introduced.[1] Prior to that time the disease invariably ended fatally.

[1] Treatment of general paresis with malaria was first introduced in Norway in 1923 by H. G. Monrad-Krohn at the neurologic ward of the Rikshospital in Oslo (Lossius, 1926 and 1927), whereas malaria treatment of tabes dorsalis, according to Lossius (1954, personal communication to the present author), was begun somewhat later.

3. *Duration of syphilis at diagnosis of general paresis.* Here we are concerned with the study group «Known», comprising 953 patients (331 males and 622 females). For the purpose of this analysis the patients can be subgrouped as follows (we refer to table 24, p. 95):

   a) The majority, 626 patients (246 males and 380 females), 65.7 per cent of the total, infected during the period 1891—1900, had a duration in 1925 of 25—35 years.

   b) The 217 patients (61 males and 156 females), 22.8 per cent of the total, infected during the period 1901—1905, had a duration in 1925 of 20—25 years.

   c) The remaining 110 patients (24 males and 86 females), 11.5 per cent of the total, who contracted syphilis during the period 1906—1910, had a duration of 15—20 years in 1925 when malaria was introduced.

Since the spread around the usual «period of incubation» in general paresis is not known, we have no way of determining with any degree of accuracy how many of our patients could be expected to have shown symptoms and signs of general paresis as late as 1925 or later. But, considering the durations as of 1925 for the three groups listed above, the chances are that only a relatively small number of paretics could possibly have been recognized in a condition suited for treatment, and at the same time sufficiently late during the development of syphilotherapy to have been saved by means of malaria treatment. On the basis of these theoretical considerations we can not completely exclude the possibility that some of the paretics in the present series may have been treated successfully, but in order for us to have missed these cases, they must also have escaped our search for clinical data from the interim period. As will be recalled (see table 26, p. 98) there is an average of about two observations on each patient in the interim period, that is, between the original discharge and the final observation. If this fact is seen in context with the above considerations on the possibilities for successful treatment open to our patients, it is felt that the number of paretics missed because of treatment in the interim period, is so small as to have influenced the end results very little.

Now for the actual findings in the present series (see annex table XIII, p. XXII): Among the 20 paretics in the series, 6 (5 males — numbers 6, 7, 8, 9 and 10; and 1 female — no. 41) were found to have been recognized after 1925, that is, at a time when these patients might have profited from the introduction of malaria therapy. Any others developing after 1925 certainly would have had malaria therapy and a record would have been available to us.

One of the males (no. 8) is actually the only paretic found to have been saved by modern methods of treatment. He was infected in 1896 at the age of 2; general paresis was diagnosed in 1931, the duration of infection at that time being 35 years. The patient was treated successfully with malaria, tryparsamide and Bismuth, and at time of the present investigation (1949—1951) was found to be well. Among the remaining 4 males, 1 (no. 6) was diagnosed as having general paresis in 1927, 18 years after infection; was treated with malaria, tryparsamide and mercury inunctions, but died of general paresis in 1929. Two others (numbers 9 and 10) were recognized in 1932 and 1937, after 40 and 37 years duration of infection respectively. Both were considered too far advanced for treatment and died of general paresis shortly after the diagnoses were made. Finally, no. 7, who was diagnosed as having general paresis in 1927, 28 years after infection, also was considered unsuitable for treatment. Incidentally, he was found to be suffering from a syphilitic aortic insufficiency as well. This patient died of general paresis the same year the central nervous system lesion was diagnosed. The 1 female (no. 41) was recognized after 1925; was diagnosed as general paresis in 1927, 20 years after infection; was treated with malaria and tryparsamide, but died of general paresis shortly after treatment.

It is noteworthy that 4 of the patients recognized after 1925 showed considerably longer «incubation periods» than what is usually thought to be average in untreated cases: namely, no. 7 — 28 years; no. 8 — 35 years; no. 9 — 40 years; and no. 10 — 37 years; whereas 2 (numbers 6 and 41) were diagnosed at durations about average, namely at 18 and 20 years respectively.

So far the actual findings are in keeping with what one would expect according to the considerations made in the foregoing, and, on the basis of indirect evidence, therefore, we feel justified in maintaining that only a very small number of paretics can possibly have escaped our search because they were successfully treated in the interim.

To conclude, we are of the opinion that we have come fairly close to the true frequency of general paresis in our series.

Representativeness of the figures on tabes dorsalis. When it comes to an evaluation of the frequency of tabes dorsalis, the analysis of the representativeness of the figures will follow the same pattern as that demonstrated in the foregoing on general paresis.

As a basis for this appraisal of the figures, the following general features characterizing this type of central nervous system syphilis, are recapitulated from the section on prognosis (see p. 202):

1. Tabes dorsalis is only seldom the direct cause of death, but it frequently causes considerable disability from such manifestations as lightning pains, cord bladder, ataxia, gastric crises, Charcot's joints, and optic atrophy.
2. There is a certain tendency for the process to become stationary as shown by the discovery of the so-called «burnt out» forms.
3. Treatment is less satisfactory than in any other central nervous system lesion except general paresis.

Again we start with the 509 patients out of a total of 694 dead (73.3 per cent) who were examined in hospital immediately prior to death, or at least a relatively short time before death occurred. The chances are, in our opinion, that only a small number of cases — if any — with painful and disabling manifestations of the disease, can possibly have been overlooked in this group. There is still the remote possibility, however, that some cases of «burnt out» and some with incipient tabes have been missed, thus minimizing somewhat the total number of cases of tabes dorsalis in our series.

In connection with the 146 patients (21.0 per cent of the dead), in whom the death certificate formed the only clinical information available at time of death, we must again emphasize the fact that clinical data for the years preceding death was not found in spite of a most rigid search through the many sources of information open to us. Now, tabes dorsalis is seldom the cause of sudden death, usually the disease takes a more or less drawn-out course. Therefore, if any cases of incapacitating tabes had existed among the individuals of this group, the chances are that they would sooner or later have become hospitalized. Moreover, since the patients in question for the most part belonged to the lower socio-economic classes in society, such incapacitating lesions in the majority of instances necessarily would make the person indigent, medically or otherwise, which again would lead to registration of examinations and hospitalizations in the records of some official institution. Under these circumstances we are inclined to believe that the number of cases with tabes missed among these individuals must be small. We can, however, not exclude the possibility that a certain number of cases with «burnt out» tabes, or cases in the initial stage, can have been overlooked, something which would tend to minimize the total number of tabetics found in the present series.

In view of the above considerations, it would seem fairly safe to assume that of the 146 we can but have missed a negligible number of cases — if any — in whom tabes dorsalis was known to be the primary or contributory cause of death, because the diagnosis, like that of general paresis, is usually found on the death certificate of such patients, for the reason that it can be stated without directly disclosing to relatives of the patient, the specific nature of the disease. Among the very few patients in the present series, found to have died primarily as a result of tabes dorsalis, there was none in whom the diagnosis was not stated on the death certificate.

The last group among the dead (comprising 39 patients — 5.6 per cent), in whom fact of death was established without any clinical information being available, is so small that we cannot possibly have missed a number of tabetics among them sufficiently great to have influenced the end results significantly.

In respect to those found to be alive, they had, as pointed out previously, had their syphilitic infection for an average of about 50 years. Among those examined (216 — 83.4 per cent) we feel convinced that we have missed no case of tabes. But we shall have to reckon with the possibility that some cases with incipient tabes might have existed among these persons. In view of the long duration of infection, however, the chances are that the number of such cases would be small. This is exemplified by the fact that among those examined there was *one* person — a male (number 11, see annex table XIII, p. XXII) — found to be suffering from active tabes without pronounced symptoms and signs of the disease. The only incapacitating manifestation was an ataxia, which, up to the time of examination, had bothered the patient very little. Incidentally, he had been treated for tabes at the age of 52 with 10 injections of arsenicals plus 48 mercury inunctions, the duration of infection at that time being 16 years. Now he is 80 years of age, and has had his syphilitic infection for 44 years. Thus, the process must have been active all through the 28 years between treatment and final observation. He had received no additional specific treatment during this period.

As to the 43 (16.6 per cent) of the living found not to have been examined by others, and who, for some reason or other, could not be brought in for examinations by us, it should be recalled that we had contacted the majority, directly or indirectly, and found them to be well, or at least only suffering from more or less trivial diseases. Therefore, we are inclined to believe that no cases of real incapacitating tabes existed among them. On the other hand, it can not be excluded decisively that this group may have contained some scattered cases of tabes with only slightly incapacitating manifestations. But, for reasons discussed above, the number of such persons must under all circumstances be assumed to be small after so many years duration of infection. And thus we have probably missed no significant number of tabetics on that basis.

In summarizing, it is probably safe to assume we have found all or nearly all of the patients who showed symptoms and signs of *disabling* or painful tabes dorsalis at time of final observation, whereas we can not exclude entirely the possibility that we have missed some cases of early tabes, and also some with the so-called «burnt out» form of the disease.

The next questions we might ask are the following: to what extent may patients who developed tabes dorsalis have been treated successfully in the interim period, that is, between the original discharge from Boeck's department and the final observation? And, if so, does the possibility exist that we have missed some of these cases? These are the factors to be taken into account when attempting to answer the questions:

1. *The «incubation period» of tabes dorsalis.* The «incubation period» of tabes dorsalis in untreated syphilis is not exactly known, and, as mentioned previously (p. 201), the figures given in the literature vary somewhat from one series to another. If we assume that the disease is usually

recognized on an average some 15—20 years after infection, we are probably not too far from the truth, however.

2. *Possibilities for effective treatment.* During the early years of the salvarsan era, up to about 1925, and certainly during the period preceding the introduction of salvarsan (1910), the types and amounts of treatment employed in tabes dorsalis were probably in the majority of instances, not sufficiently adequate to control the symptoms and stop the progress of the disease. The only cases that might form an exception to this rule, would be those in whom the condition was recognized in the very early stage, that is, cases of incipient tabes. In such patients there is the possibility that even routine treatment usually administered at that time, may have caused relief from symptoms and arrest of the process, although there could hardly be a question of cure.

   About 1925 treatment became somewhat more effective through the use of the fever therapy, the trivalent arsenic, and the prolonged courses with ordinary arsenicals and the heavy metals. But, as late as the early nineteen-forties Moore (1944) nevertheless stated that treatment of tabes dorsalis was less satisfactory than in any other form of neurosyphilis except general paresis, and O'Leary (1938), quoted by Kampmeier (1943), maintained that the best results could be expected in patients with symptoms of recent appearance and with syphilis of no more than 10 years' duration.

3. *Duration of infection at time of diagnosis of tabes dorsalis.* As mentioned in the foregoing section on general paresis we are here concerned with the study group «Known», totaling 953 patients (331 males and 622 females). The patients were divided according to year of infection, and it was found that the majority, 65.7 per cent, were infected during the period 1891—1900; 22.8 per cent between 1901—1905; and the remaining 11.5 per cent between 1906—1910. (For details we refer to p. 208.)

Thus, about 1925, when methods of treatment for tabes dorsalis were improved — at least compared with the preceding years of the salvarsan era — the great majority of our patients (88.5 per cent), had had their syphilitic infection from 20 to 35 years, and the remaining 11.5 per cent for 15—20 years.

Not knowing the average «period of incubation» of tabes dorsalis in untreated syphilis, we shall have to base our considerations on the approximate average of some 15—20 years mentioned previously. The spread around this approximation is, of course, not known either, so we have no way of determining to what extent cases of tabes dorsalis could be expected to develop *after* 15—20 years.

Nevertheless, taking into account the above mentioned durations, we are inclined to believe that only a very small number of cases with incipient tabes possibly could have existed among these patients *after 1925*. In the majority of those having developed tabes, the process could at that time be expected to have become established with more or less pronounced tissue loss, resulting in more or less disabling manifestations of the disease. Under these circumstances the possibilities of any great number of tabetics having received treatment sufficiently effective to completely relieve their symptoms (and make the disease unrecognizable clinically) must be considered as being very small.

During the years *prior to 1925*, when the possibilities for treatment in the *early* stages of the disease actually existed among these patients, the types and amounts available and administered were usually not sufficiently effective to stop the manifestations from progressing. It can not be ruled out, however, that this treatment may have modified the course of the infection somewhat, particularly perhaps in those cases in which was present a tendency for the process to become stationary.

In view of the considerations made in the foregoing, it would seem reasonable to assume that only a relatively small number of tabetics in the present series could have been recognized under circumstances that would allow for successful treatment. Besides, in order for us to have missed any of these cases, they must also have escaped our comprehensive search for clinical data in the interim period. It should be remenbered that there is an average of about two observations on each patient between the original discharge from Boeck's department and the final observation (see table 26, p. 98). And, if any of the tabetics actually had been submitted to treatment which had proved to be sufficient, such treatment would in all likelihood have taken place in a hospital. Since the majority of the patients belonged to the lower socio-economic classes of society, the hospitalizations would in all probability have been registered in the records of one of the many official sources of information open to us (particularly the Bureaus of the Indigents), something which again in most instances, would have brought the event to our attention. Theoretically, therefore, the chances are that we have missed no significant number of tabetics because of successful treatment of the patients in the interim period.

Now for the actual findings in the present series. It will be recalled that among the 17 cases of tabes (see table 55, p. 204) there were 7 (3 males and 4 females) recognized in an active stage of the disease, while the remaining 10 (5 males and 5 females) were diagnosed as «burnt out» tabes. In this analysis we are going to consider only the patients of the former group, the question of the possible effects of previous treatment in the development of forme fruste of tabes being taken up later.

Four of the 7 patients who showed active manifestations of the disease at time of recognition, were diagnosed in 1925 or later (see annex table XIII, p. XXII): patients numbers 12 and 13 (both males) in 1925 and 1927, and patients numbers 45 and 47 (both females) in 1942 and 1950. The durations of infection in these cases were 34, 35, 37 and 40 years respectively. When these patients came under medical observation they were all in an advanced stage of tabes dorsalis, the disabling symptoms being: in no. 12 optic atrophy; in no. 13 paresis of the bladder; in no. 45 optic atrophy and pronounced ataxia; and in no. 47 paresis of the bladder. In the first of the two males (no. 12) the condition was considered too far advanced for specific treatment, whereas in the second (no. 13) treatment was attempted with arsenicals and Bismuth, but with seemingly no effect. The first of the females (no. 45) was started on a combined course of As. and Bi., but after having received 13 injections of each, treatment had to be discontinued because of a salvarsan dermatitis. As would be expected, this treatment had practically no effect on the symptoms, and the process progressed steadily, although slowly. In the second female (no. 47) penicillin-treatment was administered. Evidently this had no effect on the paresis of the bladder, although the general condition of the patient became somewhat improved.

The remaining 3 of the 7 patients diagnosed in an active or presumably active stage, were recognized prior to 1925. One (a male — no. 11) in 1923, and 2 (both females — numbers 42 and 43) in 1909 and 1915 respectively. All 3 of these were classified as incipient tabes, a relatively slight ataxia being the main symptom. The male (no. 11), who is identical with the patient described on p. 215, received, as mentioned previously, 10 injections of As. plus 48 mercury inunctions. No. 42 was given an unknown number of mercury inunctions, and no. 43, 3 injections of As. plus 70 inunctions of mercury.

During the 28 years that followed the treatment (see p. 215) the male had had practically no inconvenience from the disease, although at examination he still showed symptoms of an active tabes dorsalis. The 2 females (numbers 42 and 43) died 12 and 8 years respectively after treatment, of some disease other than syphilis. Since no spinal fluid examination was done at time of final observation, it can not be established whether the disease was still in an active stage or not, but the patients showed no disabling symptoms of tabes on ordinary physical examination.

It is, of course, not possible to determine whether the relatively favorable outcome in these 3 cases of incipient tabes was due to the treatment administered, or must be interpreted as exemplifying a tendency towards spontaneous remission, or slow progress, of the pathologic process in question. In view of the types and amounts of treatment employed, we would be inclined to believe the latter explanation to be the more plausible one. On the other hand we know very little of the long-term effects of inadequate treatment on incipient tabes, and therefore it can not be ruled out that such treatment at least may have slowed down the process and thus modified the course of the infection.

Though the number of patients diagnosed in an active stage of tabes is small, the findings in the present series are in keeping with what we would expect according to the theoretical considerations made in the foregoing, and therefore we believe we have missed no significant number of cases because of successful treatment in the interim.

In summarizing, we feel justified in maintaining that we have probably found practically all cases of real incapacitating tabes in the series, whereas there are chances that we have missed some patients with incipient tabes, and also some with forme fruste of tabes.

Representativeness of the figures on diffuse meningovascular neurosyphilis. When attempting to evaluate the representativeness of the figures on diffuse meningovascular syphilis, the following points must be borne in mind (some of them are taken from the section on prognosis pp. 201—202):

1. Generally speaking, the clinical picture is not as characteristic as that encountered in general paresis and tabes dorsalis.
2. The diagnosis, therefore, is to a greater extent dependent on whether spinal fluid examinations are done.
3. Recovery from symptoms can be expected in most instances, either spontaneously, or through the influence of otherwise seemingly inadequate treatment.
4. After the active stage is passed and one is dealing with sequelae of meningovascular, the clinical pictures are not easily distinguishable from those caused by non-syphilitic diseases producing similar symptoms and signs of central nervous system involvement, and this is particularly true in elderly patients.
5. Meningovascular syphilis is relatively seldom found to be the primary cause of death, the patients in question usually die of some other condition a shorter or longer period of time after the meningovascular neurosyphilis was present in an active stage.
6. When these patients are found to have died primarily of some disease outside the central nervous system, and an autopsy is performed, the brain is frequently left unopened, probably because the relatively vague symptoms and signs of sequelae of meningovascular *per se* do not indicate any necessity for such an examination.
7. Even in the instances where the brain is opened, either because the primary cause of death is thought to lie in the central nervous system, or because examination of the brain is a routine procedure in the particular pathology laboratory, the examiner is frequently apt to encounter considerable difficulties in diagnosing sequelae of meningovascular with accuracy, since the pathologic processes are often intermingled with those produced by non-syphilitic conditions. Again, this is particularly true in elderly persons.

From the points listed above, it follows that meningovascular constitutes a form of neurosyphilis that differs considerably from general paresis and tabes dorsalis. In the analysis of the representativeness of the figures on this particular form of central nervous system involvement, we have as a consequence chosen to follow a pattern somewhat different from that used in the discussion of the two other forms.

Before proceeding with the analysis, we find it important to emphasize the following: meningovascular is usually held to manifest itself relatively early during the course of the infection as compared with general paresis and tabes dorsalis. Although the «period of incubation» for meningovascular in untreated syphilis is not exactly known, we are probably not far from the truth when we assume that it lies somewhere around 10—15 years (see p. 200). Moreover, since the clinical pictures are often less characteristic than those encountered in general paresis and tabes dorsalis, the spinal fluid examination takes on added importance as an aid in diagnosis. If this is considered in relation to the fact that only a relatively small proportion of the patients in our series had had spinal fluid punctures done (209 out of a total of 953 — 22.0 per cent), and when done, these examinations were for the most part performed rather late during the course of the infection (none during the first decade of infection, and only 13 — 6.2 per cent of the total 209 — during the second decade), there is the possibility that a certain number of cases with meningovascular was overlooked and thus escaped our search. Generally speaking, therefore, this factor would work in the direction of minimizing the proportions of meningovascular in the present series, but it is practically impossible to determine to what extent it may have influenced the end results. (For further quantitative data on the spinal fluid examinations, we refer to Annex IV, p. XV).

We are here concerned again with the study group «Known» comprising altogether 953 patients (331 males and 622 females). The dead constitute the great majority of the cases (694 out of 953 — 72.8 per cent), whereas those found alive numbered 259 (27.2 per cent of the total).

First we are going to consider the 509 patients out of the total of 694 dead (73.3 per cent) who had been examined in a hospital at time of death or shortly prior to death, 209 (30.1 per cent) of whom had been submitted to autopsy. The average duration of infection at time of death among these patients was 28.0 and 26.3 years in males and females respectively, considerably beyond the usual 10—15-year duration of infection in meningovascular syphilis. It should be noted, however, that 56 males (28.9 per cent) and 131 females (41.6 per cent of the total of 694 dead) died within the first 20 years after infection (see annex table XXI, p. XLV).

Considering the circumstances under which the final observations of the examined patients took place, we are inclined to believe that most of the cases where meningovascular was the primary cause of death were discovered. We must, on the other hand, reckon with a certain number of patients — particularly among those found to have died within the first 20 years of infection — who may have died *of* some other condition, but *with* meningovascular, and whose central nervous system lesion may have been overlooked, chiefly because of the limited use of spinal fluid examinations in diagnosis.

The next group among the dead comprising 146 patients (50 male and 96 female — 21.0 per cent of the total of 694), is characterized by the fact that the diagnosis at time of final observation rested on the information as found on the death certificate. It is again emphasized, however, that in spite of the most exhaustive search through the many sources of information used in the present investigation, we were unable to provide clinical data on these patients for the period preceding death. The duration of infection in these cases was 23.6 and 26.3 years in males and females respectively. This also is considerably beyond the usual duration of infection in meningovascular.

Among the patients in this group, there is the possibility that we may have missed some patients in whom meningovascular syphilis was the primary cause of death, either because the condition was not recognized, or, if recognized, because the diagnosis was not stated on the death certificate. Taking into account the relatively long average duration of infection at time of death, and the fact that meningovascular comparatively seldom is the primary cause of death, there is reason to believe that the number of such patients was small. We can, on the other hand, of course not exclude the possibility that some of these patients may have died *of* some other condition, but *with* active meningovascular, and again this is particularly true of those who were found to have died within the first two decades of infection.

Finally, among the dead we have 39 patients —(5.6 per cent of 694 dead) in whom fact of death was established, but with no diagnosis. This group is so small that whatever the patients died of or suffered from at time of death, it can only have influenced the numerical results on meningovascular very little.

When it comes to possible instances of sequelae of meningovascular, an evaluation of the figures must be considered as futile because of the great uncertainties connected with the diagnoses. There is the possibility that a certain number of such cases have been missed within each one of the groups among the dead considered in the foregoing.

In respect to those patients found to be alive, 216, out of a total of 259 (83.4 per cent) had been examined at time of investigation or shortly before that. In view of the long average duration of infection in these patients (about 50 years in both sexes), the number of cases with active meningovascular existing among them necessarily must have been negligible, and therefore we feel justified in assuming that practically no such case was overlooked during the examinations. This is also borne out by the fact that not one single case of active meningovascular was diagnosed among those examined. When it comes to the

43 remaining patients (16.6 per cent of the total 259 living) who were not examined by us, and who were not found to have been examined by others within a reasonably short time prior to our investigation, the chances are that only a very small number of cases with active meningovascular could possibly have existed among them. First, because of the long duration of infection, and second, because most of these patients had been contacted by us, directly or indirectly, and found to be well or suffering from more or less trivial diseases. Thus we have probably missed very few if any, such cases among these patients.

Sequelae of meningovascular, on the other hand, may have been overlooked even among those examined, and may have existed among those not found to have been examined. Therefore, it seems natural to believe that we have missed a certain number of such cases among the living patients as well. We have, however, no way of estimating even approximately how many.

Up to this point we have attempted to illuminate the question of representativeness of the figures on meningovascular on the basis of the findings as related to time of final observation. From what is said in the foregoing, we came no closer to answering the above question than stating that our figures in all probability represented a minimum. In order further to analyse this problem, we tried to evaluate the findings as related to the data collected from the interim period, that is, between the original discharge from Boeck's department and the «end point». Such an analysis, however, proved futile, inasmuch as it permitted no other conclusions than those already arrived at, namely that we were dealing with minimum figures for this type of neurosyphilis. In other words, with the data available, we found ourselves in no position to exclude the possibility that we had missed a certain number of cases with meningovascular in spite of our rather comprehensive search for clinical information from the interim period. In our opinion, the factors chiefly to be held responsible for this are the following:

1. Meningovascular often produces clinical pictures that are not easily distinguished from those produced by non-syphilitic diseases of the central nervous system, unless spinal fluid examinations are used in diagnosis.
2. In the present series spinal fluid examinations were only employed to a limited extent, and this is particularly true of the first two decades of infection, during which meningovascular is most likely to occur.
3. Meningovascular syphilis shows a definite tendency towards remission of the pathologic process, either spontaneously or following seemingly inadequate treatment.

Generally speaking, it is extremely difficult to evaluate statistics on meningovascular syphilis, and the quantitative findings in the present series are no exception to this rule. We feel justified, however, in maintaining that our figures are minimum, but we have no way of determining to what extent this is so.

Representativeness of the figures on gumma of brain. We have only found 2 cases of gumma of brain in the present series, and it is, of course, not possible to determine whether our figures are representative or not. The only conclusion permissible is that this form of neurosyphilis evidently is rare as compared with general paresis, tabes dorsalis, and meningovascular.

In summary, the analysis of the representativeness of the figures on neurosyphilis gave the following results:

1. For *general paresis* we are inclined to believe the 2.1 per cent found (3.0 per cent in males, and 1.7 per cent in females) to represent a proportion which comes fairly close to the true frequency of this form of neurosyphilis in our series.
2. We are of the opinion that we have found most of the cases with truly disabling *tabes dorsalis*, whereas we can not exclude the possibility that we have missed some cases of incipient tabes and tabes dorsalis forme fruste. Thus the proportion of 1.9 per cent (2.6 per cent in males and 1.5 per cent in females) must be considered as representing a minimum.
3. For reasons already discussed in considerable detail, the 2.3 per cent *diffuse meningovascular neurosyphilis* (3.3 per cent in males, and 1.7 per cent in females) is definitely minimum.
4. *Gumma of brain* is a rare form of neurosyphilis, which numerically plays a minor role as compared with the others. Whether the 0.2 per cent found in the present series is representative or not can not be determined with the data available.

Considering the above points as a whole, it follows that the total, 6.5 per cent, neurosyphilis (9.2 per cent in males, and 5.1 per cent in females) is also minimum. It is worth emphasizing, however, that the cases missed for the most part must have been those which from a prognostic point of view were the least serious.

Occurrence in autopsy population. After having established that our figures on neurosyphilis represent minimums, the following question arose: Is it possible, by means of an analysis of the autopsy population, to establish maximum figures, and thus determine the range within which the true frequency of neurosyphilis in the present series actually lies? This method of approach is similar to that adopted for the study of the quantitative aspects of cardiovascular, where it gave valuable results (see later).

In table 58 is presented the proportions of neurosyphilis as found in the autopsy population. It will be seen that 13 (6.2 per cent) out of a total of 209, were diagnosed as having neurosyphilis. This compares with 6.5 per cent for the total study group «Known». In males 6 (8.0 per cent) out of a total of 75, and in females 7 (5.2 per cent) out of a total of 134, showed syphilitic lesions of the central nervous system. The corresponding figures for the total study group «Known» were 9.2 and 5.1 per cent in the two sexes respectively (see table 57). The ratio males to females was 1.5 to 1, as compared with 1.8 to 1 in the total study group «Known» (see table 59, p. 227). Thus, there was practically no difference in respect to the frequency of neurosyphilis between the autopsy population and the total study group from which the autopsied patients were originally drawn. This is in contrast to what we found in cardiovascular, where the autopsy population showed a marked excess over the total study group (see pp. 284—285). The proportions of cardiovascular, as found in the total study group «Known» and the autopsy population, was 10.4 and 26.3 per cent respectively — a ratio of 1 to 2.5; whereas the corresponding proportions of neurosyphilis were 6.5 and 6.2 per cent — a ratio of 1.05 to 1.

Usually an autopsy population is more or less heavily weighted with serious cases as compared with the hospital population from which the autopsied patients come, and this is also true of the hospital population as compared with the total reservoir from which the patients originally are drawn. Since the comparison between the autopsy population and the total study group «Known» in respect to the frequency of neurosyphilis in the present series, as shown above, resulted in findings that are not in accordance with what we would expect, we shall have to analyse further the circumstances that may have been responsible for this.

In the first place we are interested in determining to what extent neurosyphilitics came to autopsy. Actually there were in the present series altogether 19 patients with neurosyphilis who were submitted to post-mortem examinations, but, for reasons explained in connection with table 58, we chose to omit 6 of them, leaving us with a total of 13. If we include both dead and living patients, and make use of all the 62 patients with neurosyphilis as a denominator, the proportion autopsied becomes 21.0 per cent. If we use only the 44[1] dead patients as a denominator, the proportion becomes 29.5 per cent. The corresponding proportions in cardiovascular were 59.8 and 66.0 per cent respectively (see p. 276). Thus, a considerably smaller proportion of the patients with neurosyphilis came to autopsy than was the case among those who had developed cardiovascular. If we now turn to the total study group «Known», the proportion autopsied among the dead (a total of 694 patients, see annex table XX, p. XLIV) was approximately 30 per cent, in other words, about the same as that found among the dead patients with neurosyphilis.

From the comparisons made above, it follows that the proportions, as found

[1] For distribution of patients with neurosyphilis according to status (living or dead) at time of investigation, see table 62, p. 237.

Table 58.

Proportions Found to Have Developed Neurosyphilis in Autopsy Population, According to Form, by Sex.

(All ages*) (13 patients**)

Number of Patients Autopsied	Patients in whom no Neurosyphilis was Found		Patients in whom Neurosyphilis was Diagnosed					
			General paresis	Tabes dorsalis	Meningo-vascular	Gumma of brain	Subtotal	
	No.	Per cent	No.	No.	No.	No.	No.	Per cent
Males								
75 (100 %)	69	92.0	3	1	1	1	6	8.0
Females								
134 (100 %)	127	94.8	4	0	2	1	7	5.2
Total								
209 (100 %)	196	93.8	7	1	3	2	13	6.2

* Age at infection.

** Among those who had experienced neurosyphilis the total number of autopsied patients was 19. Six of these, who were known to have had neurosyphilis previously, were omitted from the table, because no neurosyphilis was diagnosed at post-mortem examination.

in the autopsy population, can not possibly be considered as representing a maximum, and thus we are in no position to establish a range within which the true frequency of neurosyphilis in our series actually lies.

There are several reasons why the autopsy population showed such relatively small proportions of neurosyphilis as compared with cardiovascular:

1. In the pre-malaria days, most patients with general paresis ended up in asylums for the insane. Even after malaria treatment was introduced, several of these patients — considered too advanced for treatment — were transferred to the asylums. The asylums in question were usually not directly connected with a pathologic-anatomical laboratory, and therefore the proportions autopsied among those who died in these hospitals, must be assumed to have been considerably smaller than was the case in general hospitals with pathologic-anatomical services.

   For this reason alone the proportion of autopsies among the paretics would tend to become smaller than the corresponding proportion of those with cardiovascular, since the latter group of patients were usually admitted to general hospitals.

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2. Generally speaking, the fact that tabes dorsalis and meningovascular seldom are the primary cause of death, also would work in the direction of minimizing the number of autopsies in patients that may have experienced such forms of neurosyphilis.
3. Even if an autopsy is performed, another important factor enters the picture, namely the frequency with which the brain and/or the spinal cord are examined. This undoubtedly varies from one laboratory to another, and from one period of time to another, according to the interests of the clinicians and the pathologists in question. In most laboratories, and this also holds true for the laboratories we are dealing with here, the brain and/or spinal cord are not examined routinely, but only if the cause of death is obscure, or if the clinical signs definitely point toward some lesion of the central nervous system. Therefore we shall have to reckon with the possibility that some cases of neurosyphilis were overlooked in the present autopsy population, simply because the central nervous system was not examined. This is in contrast to what we usually find in respect to cardiovascular syphilis. Since the heart and the aorta are examined during autopsies in close to 100 per cent of instances, the chances are that practically no case of cardiovascular syphilis was overlooked in this autopsy population.
4. Even in those instances where the brain and the spinal cord are examined, some cases of neurosyphilis may be overlooked, either because the pathologists do not search specifically for such lesions, or because the process may be intermingled with others caused by non-syphilitic conditions. This is particularly true if the history, and the clinical examination, including laboratory tests, do not indicate the possibility of syphilitic lesions of the central nervous system. This factor also must be assumed to have minimized the number of cases with neurosyphilis in the present autopsy population.

From what has been said in the foregoing, it follows that an analysis of the autopsy population, has not brought us any closer to the true frequencies of neurosyphilis in the present series, and also, this population was found to be heavily weighted in the direction of cardiovascular as compared with neurosyphilis. This latter point was brought out in Rosahn's (1947) Yale material as well, and so far these investigations exemplify that neither an autopsy population per se nor an autopsy population that forms part of a broader study group, lends itself very well for the study of the quantitative aspects of neurosyphilis.

Table 59.

Ratio Males — Females in Neurosyphilis According to Form.

Forms of neurosyphilis	Males	Females	Ratio Males — Females
	Percentage*	Percentage	
Meningovascular plus vascular	3.3	1.7	1.9 — 1
General paresis	3.0	1.7	1.8 — 1
Tabes dorsalis	2.6	1.5	1.7 — 1
Gumma of brain	0.3	0.2	1.5 — 1
Total	9.2	5.1	1.8 — 1

* The percentages used are taken from table 57.

Sex Distribution.

In table 59 are given the ratios males to females as based on the proportions shown in table 57. It will be seen that neurosyphilis as a whole occurred more frequently in males than in females, the proportions being 9.2 versus 5.1 per cent, a ratio of 1.8 to 1. The same is true for each of the forms listed in the table, as follows: meningovascular 3.3 versus 1.7 per cent — ratio 1.9 to 1; general paresis 3.0 versus 1.7 per cent — ratio 1.8 to 1; tabes dorsalis 2.6 versus 1.5 per cent — ratio 1.7 to 1; and gumma of brain 0.3 versus 0.2 per cent — ratio 1.5 to 1. In principle this excess of males over females in neurosyphilis is in accordance with general experience, except perhaps in regard to gumma of the brain. This is a comparatively rare form of neurosyphilis. In the present series there were only two cases (one male and one female), so we can obviously make no statement as to the representativeness of the ratio found. In view of the fact that gumma of brain is pathologic-anatomically akin to the «benign» tertiary forms, which, as far as we know, are more common in women, it would seem more reasonable to believe this form of neurosyphilis as well to occur more frequently among women. But, because of the small numbers involved, it plays a minor role whether this ratio is representative or not.

In connection with the representativeness of the calculated ratios it is worth while to emphasize the following points:

1. The proportion of spinal fluid examinations was about the same in the two sexes (22.0 per cent and 22.1 per cent respectively). Also, in both sexes and in the majority of instances, the punctures were found to have been performed after 1940 (61.6 per cent in males and 65.6 per cent in females), and at durations from 30 years and upwards (82.2 per cent in males and 79.6 per cent in females). (For details on spinal fluid examinations we refer to Annex IV.)

2. The proportion autopsied among those with neurosyphilis was about the same in the two sexes (see table 58, p. 225).
3. The analysis of the quality of the diagnoses at time of final observation showed no appreciable differences between males and females. (See Annex VIII, p. XLIII).

Since no important differences between the management of male and female patients were disclosed through the use of the above indices (and others not mentioned here), we are inclined to believe that the ratio of males to females in neurosyphilis presented in table 59, gives a true picture of these relationships in the present series.

Why females develop proportionately less neurosyphilis than males is not definitely known, but it is commonly held that it has to do with the possible protective hormonal effects of pregnancies. As will be recalled, one of the questions that might be asked of the present material was the following: Do pregnancies protect against serious late complications? (See p. 73.) During the planning of this investigation, it was decided to collect as much information as possible on childbirths as well as abortions and stillbirths, and to determine, if possible, the time relationships of these phenomena as measured on the basis of onset of infection. If sufficient data could be provided, and these data were reliable, there was the possibilty that we might attempt comparisons as to the occurrence of serious late manifestations of syphilis between nulliparae on the one hand, and those who had experienced one or more abortions, and/or stillbirths, and/or ordinary childbirths, on the other.

It will be recalled that the majority of the women in the study group «Known» were dead at time of investigation (435 out of a total of 622 — 69.9 per cent).[1] For information on pregnancies in these individuals we had to rely on the numerous records from hospitals, clinics, and other sources (particularly the Bureaus of the Indigents), that were collected during the course of the present investigation. When it comes to those found to be alive at time of investigation (187 out of a total of 622 — 30.1 per cent)[1] we could base our search, partly on the history as given by the patients themselves, partly on records similar in nature to those mentioned for the dead.

After having attempted to collect information on pregnancies for quite some time, in both dead and living patients, it became evident that it was impossible to provide sufficiently reliable data to allow for the above mentioned comparisons. First, the various sources of information, medical as well as non-medical, showed considerable discrepancies as to number of abortions, stillbirths, and ordinary births. And besides, time relationships were either recorded with little accuracy, or not at all. These discrepancies became particularly striking

[1] Se annex table XIX (p. XLI).

when we compared the information as given by the patients themselves when examined by us, with that found in records stemming from previous admissions to hospitals or clinics, or from non-medical sources such as the Bureaus of the Indigents. As regards the living, the explanation must be sought partly in reduced ability to remember events dating back several decades, and also, as was our impression, extreme reluctance on the part of these women to give information on this point. Another important factor which aggravated the difficulties of getting reliable data in these matters, was revealed through the records of the Bureaus of the Indigents: a substantial number of these patients were found to have given birth to children out of wedlock. It is not at all surprising, therefore, that they later on tried to conceal data of this kind from doctors and others seeking information on their past.

From what has been said above, it is clear that on the basis of the history alone we could not determine with any degree of certainty whether we were dealing with nulliparae or not. And even in those known to have been pregnant, it was practically impossible to find out how many abortions, stillbirths and/or ordinary births they had experienced, and still more difficult to piece together any exact picture of the sequence of events as measured from onset of infection. This was true for both living and dead, although, of course, it was considerably more pronounced in the latter of the two groups. Since the great majority of the women in our series were dead at the time of investigation, it was considered futile to proceed with an analysis of this problem, and the question of how pregnancies may affect the outcome as to serious late lesions in syphilitics left untreated during the early phases of infection, had to be left unanswered.

Another of the questions which was asked of the present material is: What is the result on subsequent pregnancies (when secondary syphilis is left untreated or highly inadequately treated)? This question also had to be left unanswered for very much the same reasons as discussed in the foregoing. But there were also ethical reasons for omitting this question: By attempting to call in the still living «children»[1] of these women, and subject them to examinations for syphilis, we undoubtedly would run the risk of disclosing to them the fact that their mothers had had syphilis, in many instances a well-kept secret, as we learned from interviews with the patients who were examined by us at the Rikshospital. Here, of course, consideration of the families was more important than the possible scientific results we might have obtained.

Time Relationships and Age.

Since these phenomena are closely interrelated, both will be discussed in this section. There are, however, certain basic epidemiologic factors bearing on time

[1] All, or practically all, of these individuals must be assumed to have reached adult age at time of investigation.

relationships and age, that must be taken into account whenever an evaluation of the numerical results are attempted. These factors, being more or less general in character, are of particular importance for comparisons with other series, and therefore they will be considered before we proceed to a detailed description of the findings.

First, there is age at onset of infection. In respect to general paresis, it was shown, among others by Meggendorfer (1921) and Lomholt (1936), that the younger the patients at onset of infection, the longer the «period of incubation». Whether this is true also of the other forms of neurosyphilis is not known, but it would not seem unreasonable to believe it to be so.Thus, in any given series, the distribution of the patients according to age at onset of infection may be of importance for the numerical results as regards time relationships and age (at time of recognition).

As mentioned previously (p. 117) we omitted from our time-relationship tables patients aged under 15 and over 39 at onset of infection. This was done, partly to ensure uniformity, partly because it was felt that the averages might be unduly weighted if cases from these extreme age-groups were included. This principle was adhered to also for neurosyphilis, and thus we have omitted from the tables in this section 4 cases (3 male and 1 female) aged under 15 at onset of infection, and 2 (both female) aged over 39 (see table 56, p. 207). The number of cases falling within each one of these extreme age-groups were so small, that in the present series it mattered little whether we included them or not. On the other hand, it can not be excluded that the proportion of such cases may vary from one series to another, and from a comparative standpoint, therefore, they should, in our opinion, always be taken into account.

Second, since the various forms of neurosyphilis show differing «periods of incubation» — meningovascular, general paresis, and tabes dorsalis usually occurring in that order of sequence — time relationships and age must be considered for each form separately. Furthermore, there is in this connection a necessity for distinguishing between active and inactive forms of tabes and meningovascular, because cases of tabes dorsalis forme fruste and of sequelae of meningovascular can be expected on a average to be recognized considerably later during the course of the infection than are the same conditions when in an active stage.

Third, it must be taken into account under which circumstances the central nervous system lesions are recognized, in both dead and living patients. In some instances the time of recognition is dependent upon when the patients seek medical advice of their own accord, in others recognition may be the result of a planned follow-up examination and thus be dependent on when during the course of the infection the investigator has chosen to carry out his examinations. Since, in the present material, there is quite a number of patients who were examined by Bruusgaard (1929a) during his 1925—27 follow-up study, we would have to reckon with the possibility that some cases of neurosyphilis were discovered at that time solely because they were called-in for examination by him. A careful study of the records, however, revealed that among the 62 cases of neurosyphilis in the present series, there were only 3 (all male) that were recognized at that time because they were called-in for examinations by Bruusgaard. Two of these patients suffered from tabes dorsalis in an advanced stage and were admitted to other hospitals shortly after Bruusgaard had closed his investigations. The third was diagnosed as sequelae of meningovascular. Thus, the fact that some of the patients included in our material had been examined during a previous follow-up study obviously influenced the results as to time relationships and age very little. It is reasonable to believe that the limited use of spinal punctures is to be held partly responsible for the relatively small number of cases with neurosyphilis discovered as a result of Bruusgaard's own examinations. During the present investigation (1949—1951) not one case of active neurosyphilis was discovered that had not already been recognized elsewhere. This is not surprising when we consider the average duration of infection, which in these patients was about 50 years. There were, on the other hand, 7 cases of tabes dorsalis forme fruste (3 male and 4 female) and 2 of sequelae of meningovascular (both male), that were diagnosed for the first time, only because the patients in question were called-in for examinations by us. In these instances the time relationships and age at discovery were wholly dependent upon the time we chose to carry out our investigation. Also there were some cases of inactive neurosyphilis diagnosed only because the patients had been admitted to hospitals or clinics for some other disease, the time of recognition of the syphilitic central nervous system lesion then being dependent upon when the other ailment brought these individuals under medical observation.

Fourth, the frequency with which spinal punctures are used in diagnosis is a factor which must be considered. The fact that only a relatively small proportion of the patients in the present material were subjected to spinal fluid examinations, would probably work in the direction of increasing the average duration of infection and the average age at time of recognition. We have, however, no way of determining to what extent this factor may have influenced our findings.

We have here mentioned some of the basic epidemiologic factors that may influence the findings in respect to time relationships and age in neurosyphilis. These factors should, if possible, be accounted for in the description and analysis of the results in any series, but since they may vary considerably from one series to another, they are of particular importance when comparisons are attempted. It follows that comparisons are difficult, and in order therefore, to avoid misleading results, conclusions must be drawn with caution.

Table 60.

Duration of Infection at Recognition of Neurosyphilis, According to Form.

(Ages 15 — 39*)
(28 patients)

Part I. Males

Duration of infection at recognition in years	Forms of Neurosyphilis**							
	Meningo-vascular plus vascular Active	General paresis	Tabes dorsalis Active	Gumma of brain	Subtotal Active Forms	Tabes dorsalis Forme Fruste	Meningo-vascular Inactive	Total
	No.	No.	No.	No.	No.	No.	No.	No.
0 — 4	0	0	0	0	0	0	0	0
5 — 9	3	0	0	1	4	0	0	4
10 — 14	1	0	0	0	1	0	0	1
15 — 19	2	2	1	0	5	0	0	5
20 — 24	0	4	0	0	4	0	0	4
25 — 29	0	1	0	0	1	0	0	1
30 — 34	0	0	1	0	1	1	0	2
35 — 39	1	1	1	0	3	0	0	3
40 — 44	0	1	0	0	1	1	0	2
45 — 49	0	0	0	0	0	1	2	3
50 over	0	0	0	0	0	2	1	3
Total	7	9	3	1	20	5	3	28
Mean duration of infection among those aged 15—39 at onset of infection	15.1	25.6	29.2	—	21.8	46.7	48.0	29.1

Duration of infection and age at recognition. In tables 60 and 61 the duration of infection and age *at recognition* of the central nervous system lesions are presented. As in the chapter on cardiovascular syphilis, the time of recognition is defined as the date of first diagnosis, inside or outside a hospital. We know that many of the patients had shown symptoms of their disease for a shorter or longer period prior to the time of recognition, but the information given by the patients on this point usually is not sufficiently reliable to allow for calculations of this kind. Therefore it was felt that uniformity could best be achieved by the use of the above definition. Even this method has its definite shortcomings since the time of recognition will then be dependent upon the

Part II. Females

(28 patients)

Duration of infection at recognition in years	Forms of Neurosyphilis**							Total
	Meningo-vascular plus vascular Active	General paresis	Tabes dorsalis Active	Gumma of brain	Subtotal Active Forms	Tabes dorsalis Forme Fruste	Meningo-vascular Inactive	
	No.	No.	No.	No.	No.	No.	No.	No.
0 — 4	1	0	0	0	1	0	0	1
5 — 9	0	0	0	1	1	0	0	1
10 — 14	1	3	1	0	5	0	0	5
15 — 19	2	2	0	0	4	0	0	4
20 — 24	2	2	0	0	4	0	0	4
25 — 29	2	1	0	0	3	0	0	3
30 — 34	0	1	0	0	1	1	1	3
35 — 39	0	0	1	0	1	0	0	1
40 — 44	0	0	1	0	1	1	1	3
45 — 49	0	0	0	0	0	2	0	2
50 over	0	0	0	0	0	1	0	1
Total	8	9	3	1	21	5	2	28
Mean duration of infection among those aged 15—39 at onset of infection	18.8	19.7	30.8	—	20.4	44.8	37.5	25.9

* Age at infection.

** Categories not mutually exclusive. For principles employed in classification we refer to table 55, p. 204.

patient's habit in seeking medical advice, the availability of medical facilities, etc. etc.

In tables 60 and 61 the cases are sub-divided according to form of neurosyphilis, according to whether the conditions were recognized in an active stage or not, and according to sex. In our opinion, such a sub-grouping is a sine qua non for analyses of this kind, and particularly for purposes of comparisons. However, the tables readily reveal that this fine sub-grouping resulted in such small numbers within the various categories, that significant comparisons and definite conclusions could hardly be made. When we nevertheless chose to present our findings according to the above indices, it was not only because we

Table 61.

Age at Recognition of Neurosyphilis, According to Form.

(Ages 15 — 39*)

Part I. Males (28 patients)

Age at recognition	Forms of neurosyphilis**							Total
	Meningo-vascular plus vascular Active	General paresis	Tabes dorsalis Active	Gumma of brain	Active Subtotal Forms	Tabes dorsalis Forme Fruste	Meningo vascular Inactive	
	No.	No.	No.	No.	No.	No.	No.	No.
20 — 29	2	0	0	0	2	0	0	2
30 — 34	1	0	0	1	2	0	0	2
35 — 39	2	0	0	0	2	0	0	2
40 — 44	0	4	0	0	4	0	0	4
45 — 49	1	0	0	0	1	0	0	1
50 — 54	0	0	1	0	1	0	0	1
55 — 59	1	2	0	0	3	1	0	4
60 — 64	0	3	1	0	4	0	0	4
65 — 69	0	0	1	0	1	2	1	4
70 — 74	0	0	0	0	0	0	2	2
75 — 79	0	0	0	0	0	2	0	2
80 over	0	0	0	0	0	0	0	0
Total	7	9	3	1	20	5	3	28
Mean age at recognition among those aged 15—39 at onset of infection	37.5	52.5	60.8	—	47.5	69.5	70.8	53.9

wished to demonstrate the necessity of the sub-grouping mentioned, but also because there was the possibility that certain important trends might be brought out in spite of the small numbers involved.

In table 60, Parts I and II, are presented the cases of neurosyphilis according to duration of infection at recognition. Considering first the total column, it will be seen that the mean durations were 29.1 and 25.9 years in males and females respectively. These averages compare with the following, taken from the subtotal column (active forms only): 21.8 years in males and 20.4 years in females. In other words, the shorter durations are to be found among those patients who had had their central nervous system lesions diagnosed in an active stage of

Part II. Females (28 patients)

Age at recognition	Forms of neurosyphilis**							Total
	Meningo-vascular plus vascular Active	General paresis	Tabes dorsalis Active	Gumma of brain	Subtotal Active Forms	Tabes dorsalis Forme Fruste	Meningo-vascular Inactive	
	No.	No.	No.	No.	No.	No.	No.	No.
20 — 29	2	0	0	0	2	0	0	2
30 — 34	0	0	1	1	2	0	0	2
35 — 39	3	4	0	0	7	0	0	7
40 — 44	0	2	0	0	2	0	0	2
45 — 49	2	2	0	0	4	0	0	4
50 — 54	0	1	1	0	2	0	0	2
55 — 59	0	0	0	0	0	1	1	2
60 — 64	1	0	0	0	1	0	0	1
65 — 69	0	0	1	0	1	1	1	3
70 — 74	0	0	0	0	0	3	0	3
75 — 79	0	0	0	0	0	0	0	0
80 over	0	0	0	0	0	0	0	0
Total	8	9	3	1	21	5	2	28
Mean age at recognition among those aged 15—39 at onset of infection	40.0	42.5	50.8	—	42.3	68.3	60.0	48.4

* Age at infection.

** Categories not mutually exclusive. For principles employed in classfication we refer to table 55, p. 204.

the disease. The chief reason for the difference is to be sought in the fact that the totals also comprise cases diagnosed as tabes dorsalis forme fruste, and sequelae of meningovascular, which naturally were recognized considerably later during the course of the infection than were the active forms. Thus, as would be expected, the inclusion of the inactive forms, tended to increase the averages for the group as a whole. In spite of the small numbers involved, the findings nevertheless demonstrate the necessity of distinguishing between patients who had had their central nervous system lesions recognized in an active stage of the disease, and those who were diagnosed after the process had been stayed. Since cases of tabes dorsalis forme fruste, and of sequelae of meningovascular are usually recognized because the patients are called-in for examinations, or because they are admitted to hospital or clinic for some other disease, the duration of infection in these instances is totally dependent upon when during the course of the infection the above events take place. And, this will undoubtedly vary considerably from one series to another, and therefore, when it comes to comparisons, the inactive forms of neurosyphilis should be omitted from the material.

Next, if we turn to the various forms that make up the subtotal (active forms), the mean durations came out as follows: meningovascular — males 15.1 and females 18.8 years; general paresis — males 25.6 and females 19.7 years; tabes dorsalis — males 29.2 and females 30.8 years. The numbers involved are obviously too small to allow for significant comparisons, not only between the various categories, but also between the two sexes. The trend, however, would indicate meningovascular, general paresis, and tabes dorsalis to have occurred in that order, which in principle is in accordance with ordinary experience. There are only 2 cases of gumma of brain (1 male and 1 female), both recognized at durations from 5 to 9 years. This in itself seems reasonable in view of the fact that gumma per se usually manifests itself within the first decade and a half after onset of infection.

In table 61, Parts I and II (constructed like table 60), are to be found the distributions of the cases with neurosyphilis according to *age at recognition*. Since age at recognition is a product of age at onset of infection and duration of infection at recognition, the findings must in principle correspond to those already described in the foregoing section. First, the average ages for the group as a whole were 53.9 and 48.4 years for males and females respectively. This compares with the following averages taken from the subtotal column (active cases only): 47.5 years in males and 42.3 years in females. In other words, the inclusion of inactive forms like tabes dorsalis forme fruste and sequelae of meningovascular worked in the direction of increasing the averages for the group as a whole. Next, when considering the various active forms that make up the subtotal, it will be seen that the average ages were as follows: meningovascular — males 37.5 and females 40.0 years; general paresis — males 52.5 and females 42.5 years; tabes dorsalis — males 60.8 and females 50.8 years.

Thus, meningovascular, general paresis and tabes dorsalis seem to have occurred at different ages, in that order of sequence, which in principle is in accordance with what we would expect. This is about as far as we can go with the data available. The numbers involved are too small for comparisons between males and females, and also, for the same reason, there can be no question of proceeding to detailed comparisons between the various forms.

In summing up, we wish to stress the following points:

1. The sub-grouping described in the foregoing is absolutely necessary in our judgement, for an analysis of time relationships and age in neurosyphilis.

Table 62.

Distribution of Patients with Neurosyphilis According to Status (Living or Dead) at Time of Investigation, by Form and Sex.

(All ages*) (62 patients)

Status at Time of Investigation	Forms of Neurosyphilis**												Subtotal Males		Subtotal Females		Total	
	Meningo-vascular		Vascular		General paresis		Tabes dorsalis Active		Tabes dorsalis Forme Fruste		Gumma of brain							
	M	F	M	F	M	F	M	F	M	F	M	F						
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	Per cent	No.	Per cent	No.	Per cent
Dead	8	6	1	3	9	10	2	2	1	0	1	1	22	71.0	22	71.0	44	71.0
Living	3	2	0	0	1	0	1	2	4	5	0	0	9	29.0	9	29.0	18	29.0
Total	11	8	1	3	10	10	3	4	5	5	1	1	31	100.0	31	100.0	62	100.0

* Age at infection.

** Categories not mutually exclusive. For principles employed in classification we refer to table 55.

2. The present material is definitely too small to permit such a fine sub-grouping, and consequently the question of time relationships and age in neurosyphilis can not be answered authoritatively on the basis of the data available.
3. These are the reasons why we have chosen not to proceed any further with the analysis of these phenomena (see cardiovascular).

Neurosyphilis as a Cause of Death.

In table 62 is presented the distribution of the cases of neurosyphilis according to status (dead and living) at time of the investigation. From the total column it will be seen that 44 out of 62 (71.0 per cent) were dead, and 18 (29.0 per cent) were living. The subtotal columns reveal that there was no difference between the sexes in this respect.

In table 63 the 44 dead are grouped according to whether neurosyphilis was considered to be the primary cause of death or not. From the total column it will be seen that 28 out of 44 (63.6 per cent) died primarily as a result of their central nervous system lesions, whereas in the remaining 16 (36.4 per cent) these lesions were assumed to be non-related to the cause of death. Moreover, the proportions found to have died *of* neurosyphilis were the same in males and females (63.6 per cent in both sexes). Neurosyphilis is more frequently encountered in males, but it is natural to believe that once these lesions have developed, the outcome is just as serious in females. In spite of the small numbers involved, therefore, we are inclined to believe that our findings give a true picture of these relationships.

Next, the cases listed in the table are sub-divided according to form. This sub-grouping, necessary though it is, results in very small numbers within each one of the categories, so small, in fact, that significant comparisons were practically impossible. It should be noted, nevertheless, that the cases of general paresis constituted the majority of those in which neurosyphilis was considered to be the primary cause of death (19 out of 28). As to the remaining 9 of these 28 cases, meningovascular was held to be the primary cause of death in 4 instances; vascular in 2; tabes dorsalis in 1; and gumma of brain in 2. This is about as far as we can bring the analysis with the data available. In principle, however, the findings are in keeping with general experience, in so far as they show general paresis to be far more important as a primary cause of death than meningovascular or tabes dorsalis.

Table 63.

Distribution of Patients with Neurosyphilis According to Cause of Death, by Form and Sex.

(All ages*) (44 patients)

Cause of death	Forms of Neurosyphilis**										Subtotal Males		Subtotal Females		Total	
	Meningo-vascular		Vascular		General paresis		Tabes dorsalis		Gumma of brain							
	M	F	M	F	M	F	M	F	M	F						
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	Per cent	No.	Per cent	No.	Per cent
Primary	3	1	0	2	9	10	1	0	1	1	14	63.6	14	63.6	28	63.6
Contributory	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Non-related	5	5	1	1	0	0	2	2	0	0	8	36.4	8	36.4	16	36.4
Total	8	6	1	3	9	10	3	2	1	1	22	100.0	22	100.0	44	100.0

* Age at infection.

** Categories not mutually exclusive. For principles employed in classification we refer to table 55.

III. Discussion.

Occurrence.

Since we are here dealing with a group of syphilitics left untreated during the early phases of the infection, or at least highly inadequately treated, it can be anticipated that the proportions of neurosyphilis, as found in the present series, will be used for comparisons with other series. Before proceeding with such comparisons, however, it would be necessary to consider carefully the epidemiologic methods employed in establishing the materials in question. This is a sine qua non in all analyses of quantitative data, and it may seem superfluous to stress again the importance of it. However, the many examples from the literature of indiscriminate use of Bruusgaard's figures clearly demonstrate the necessity of caution in interpretations. Only too often comparisons are made without it being taken into account how basic differences as to methods of approach in themselves may have influenced the numerical results.

We have already discussed (see pp. 188—189) the two principal methods of providing figures on the frequency of neurosyphilis: 1. through the study of hospital and/or clinic populations, and 2. through follow-up studies. True enough, both methods have their definite shortcomings, but in this connection it is essential to bear in mind that figures arrived at through such basically different methods of approach usually are not comparable. This point can perhaps best be illustrated by considering the proportions of neurosyphilis in Moore's (1944) untreated white patients (table 53, p. 192), which is close to 40 per cent in males and over 20 per cent in females. The corresponding figures in the present series were 9.2 and 5.1 per cent, in the two sexes respectively. There can be no doubt that we would not have been confronted with differences of such a magnitude unless the materials in question originally were established on the basis of totally different principles: Moore's figures stem from a study of a *hospital and/or clinic population*, whereas ours are arrived at through a *follow-up study*.

As a matter of principle it has been maintained that an *autopsy population* is usually more or less heavily weighted with serious cases as compared with the hospital population from which it is drawn, and even more so if compared with the original «universe». In the present series it is exemplified in cardiovascular syphilis, where the autopsy population showed considerably greater proportions than the study group as a whole (see pp. 284—285). Depending on the circumstances, however, there are exceptions to the above mentioned rule. An autopsy population may, as demonstrated through Rosahn's (1947) Yale material, comprise a relatively small proportion of serious syphilitic central nervous system lesions, simply because the hospital in question did not admit such cases during the period chosen for study (see p. 32). Our own findings form another example, in so far as the autopsy population showed no greater proportions of neurosyphilis than the study group as a whole. Here too, we found that several cases of serious neurosyphilis, particularly of general paresis, had been admitted to hospitals other than those directly connected with a pathologic laboratory, and mostly then to asylums for the insane.

There are also other factors that may influence the numerical findings in respect to neurosyphilis in a given autopsy material. First, the frequency with which the brain and the spinal cord are opened undoubtedly varies from one laboratory to another, and from one period of time to another. Also, if the central nervous system is examined, there will be variations as to the thoroughness with which the examiners search for syphilitic lesions. Next, we must bear in mind that such forms of neurosyphilis as meningovascular and tabes dorsalis are relatively seldom the primary cause of death, something that in itself would tend to work in the direction of less complete autopsies. This is especially true of cases where the active manifestations of these complications date back some time, and the patients die of some other disease with only sequelae of their central nervous system lesions. Thus, an evaluation of the figures on neurosyphilis in autopsy populations obviously poses problems that make comparisons difficult. This being so, it must be considered as even more difficult to avoid misleading evaluations when comparisons are attempted between quantitative data arrived at through different methods of approach, such as are represented by autopsy studies on the one hand and follow-up studies on the other.

These are some of the reasons why we feel justified in emphasizing the necessity of doing a thorough analysis of the basic epidemiologic methods employed in establishing the materials, before even contemplating a comparison of the numerical results. In our opinion, it is actually a prerequisite for comparisons that the data stem from the same type of study, and as a consequence of this standpoint, we have chosen to limit the following discussion to findings from the various follow-up studies only.

Since the present study rests on the same material as that used by Bruusgaard (1929a) during his 1925—27 follow-up investigation, the first question to be answered is whether the re-analysis has confirmed his findings on the frequency of neurosyphilis. Considering the totals, Bruusgaard found 30 cases of neurosyphilis among his 473 patients (6.3 per cent), whereas we found 62 cases among our 953 patients (6.5 per cent). Turning to the various forms of neurosyphilis, the respective proportions (in per cent of the total number of patients in each series), as observed in the Bruusgaard series and the present one, came out as follows: meningovascular neurosyphilis 2.3 versus 2.3 per cent; general paresis 2.7 versus 2.1 per cent; tabes dorsalis 1.3 versus 1.9 per cent; and gumma of brain 0.0 versus 0.2 per cent. As the figures stand there are no marked differences between the frequencies, and this holds true both for the totals and the various sub-groups. At first glance, therefore, it would seem that the re-examination actually has confirmed the Bruusgaard findings. Before accepting this similarity as real, we shall have to consider whether or not the proportions of neurosyphilis are directly comparable. The necessity of analysing comparability is exemplified in cardiovascular syphilis, where the proportions also turned out about the same in the two series, but where an analysis of the methods employed in diagnosis and classification revealed dissimilarities that actually made the end results noncomparable (see pp. 314—316).

We have already pointed out the difficulties in evaluating Bruusgaard's figures on neurosyphilis, the main reason being the lack of information on the epidemiologic methods employed in tracing and identification of the patients, and in the collection of clinical data. When it comes to classification and diagnosis, it must be added that there is no detailed description of each single case, something that further aggravates the difficulties of evaluating the basis on which rest the numerical findings. Thus, with the information available, we have been unable directly to demonstrate any obvious dissimilarities between the two series as far as the basic data are concerned, and up to this point, therefore, we are in no position to determine whether the figures are comparable or not. But, an analysis of Bruusgaard's findings on a sex-specific basis brought out that there contrary to ordinary experience, was practically no difference between males and females in respect to the frequency of neurosyphilis; the proportions for the total were 6.1 per cent in males and 6.5 per cent in females. The corresponding figures in the present series were 9.2 and 5.2 per cent in the two sexes respectively. A further breakdown of Bruusgaard's figures according to form of neurosyphilis, showed males to have developed proportionately less general paresis (2.7 versus 3.1 per cent), and less meningovascular (1.9 versus 2.7 per cent), than females. Only in tabes dorsalis did males show an excess over females (1.9 versus 0.8 per cent). In the present series greater proportions of all forms of neurosyphilis were found in males than in females, as follows: general paresis 3.0 versus 1.7 per cent; meningovascular 3.3 versus 1.7 per cent; and tabes dorsalis 2.6 versus 1.5 per cent. Although we are fully aware of the relatively small numbers involved, the lack of sex difference in the Bruusgaard material, in our opinion, strongly indicates that an unconscious bias must somehow have been introduced. In other words, the sex and type analysis revealed a most important dissimilarity between the two series, so important in fact, that we feel justified in stating that the end results in respect to frequency of neurosyphilis actually are not comparable. Thus we can not directly determine whether the re-analysis has confirmed the Bruusgaard findings or not, and the question must be left open.

When it comes to other follow-up studies, those made by the Danish investigators Lomholt (1936) and Nielsen (1950), in our opinion, must be considered as having given the most reliable results hitherto available on the frequency of neurosyphilis in inadequately treated patients. The chief reason for this, as pointed out in other chapters, is to be found in the unique possibilities for follow-up studies of syphilitics in Denmark after the establishment of the Syphilis Registration Office at the State Serum Institute in Copenhagen. For details on the system we refer to pp. 148—150 and pp. 266—268. Before proceeding with the discussion of the findings, as compared with those of the present study, the following facts are worth recalling: Nielsen's study group comprised altogether 467 patients, all male, who had received 2—3 injections of salvarsan and some 50 inunctions of mercury. The period of observation ranged from 29 to 36 years. The total number of patients in Lomholt's study group was 538, all male. It is interesting to note that Nielsen's material is practically identical with that chosen by Lomholt, except that Nielsen omitted 71 patients in whom treatment was initiated with mercury instead of salvarsan. Also it should be noted that Lomholt's investigation was made with special reference to the frequency of general paresis, whereas Nielsen set out to determine the frequency of all forms of neurosyphilis. Finally, the period of observation in Lomholt's material was somewhat shorter, 14—23 years as compared with 29—36 years in Nielsen's. Both investigators made use of the Registration Office as a starting-point for their tracing efforts.

We have already stressed the importance of the Registration Office for the tracing and identification of syphilitics in Denmark, but in this connection it might also be added that the medical services of that country, as a whole, must be considered among the most highly developed in the world. Therefore it is reasonable to assume that the great majority of the patients in question who had developed general paresis, disabling tabes dorsalis, and the more serious forms of meningovascular, sooner or later ended up in hospitals and/or clinics, and thus were submitted to serologic tests for syphilis, which again would mean that all or nearly all of the cases were recorded by the Registration Office. The only exception to this rule would be those patients who may have developed syphilitic central nervous system lesions prior to the establishment in 1920 of the Registration Office. Since the patients in question had had their early syphilis between 1911 and 1920, the number of cases in whom neurosyphilis developed before 1920 is probably small. Also there is the possibility that some of the patients may have left the country before their central nervous system lesions gave rise to symptoms and signs. According to Lomholt, however, this group apparently played no role numerically. Finally it can not be excluded that some cases of meningovascular with uncharacteristic symptoms, and some cases of tabes dorsalis (forme fruste), may have gone undiagnosed, and thus may not have been recorded by the Registration Office.

In summarizing, we are inclined to believe that both Lomholt (who was concerned with this form of symptomatic neurosyphilis only) and Nielsen found all or practically all of the patients who had developed general paresis. Moreover, it is reasonable to believe that Nielsen found the great majority of those who had developed disabling tabes dorsalis and the more serious forms of meningovascular. There is, of course, a possibility that some cases of meningovascular, and tabes dorsalis, may have escaped the search of the latter investigator, but seen from a prognostic point of view, these cases probably represent the less serious manifestations of these diseases.

Among Nielsen's 467 patients (all male) 40 were classified as neurosyphilis (8.6 per cent), which compares with 31 among the 331 males in the present series (9.2 per cent). In other words, the proportions of neurosyphilis as found in the two series are practically the same. It should be noted that Nielsen's figure of 8.6 would have become somewhat higher — probably around 9 to 10 per cent (see p. 195) — if he had used the same methods of classification as adopted by ourselves. Since the difference this factor makes is so small, however, and we have no way of adjusting it for our purposes, we have chosen to use the 8.6 per cent for comparisons.

The proportions of the various forms of neurosyphilis (in per cent of total number observed) in Nielsen's series and in the males of our own series were as follows: general paresis 4.3 versus 3.0 per cent; meningovascular 3.2 versus 3.3 per cent; and tabes dorsalis 1.1 versus 1.3 per cent. Thus, by and large, the proportions lie within the same order of magnitude.

When it comes to general paresis the close proximity between the frequencies found by Lomholt (3.3 per cent) and Nielsen (4.3 per cent) is noteworthy. This is particularly important when we take into account the considerably longer period of observation in Nielsen's series (29—36 versus 14—23 years). In fact, that the proportions of neurosyphilis in Lomholt's and Nielsen's series of presumably inadequately treated cases, were not markedly different from those found in the present series of untreated cases, in our opinion suggests that the treatment in question was not sufficiently adequate to stop the natural course of the infection as far as the development of central nervous system lesions are concerned. Also, there is nothing in the figures presented to indicate that the types and amounts of treatment in question caused an increase in the frequency of neurosyphilis. Although definite conclusions on this latter point can not be drawn on the basis of these comparisons alone, the results are in accordance with the concept held by Moore (1944), that inadequate treatment is *not* a factor working in the direction of creating more neurosyphilis.

In this connection it is also interesting to note that the very same treatment that did not seem to prevent the development of neurosyphilis in Nielsen's patients evidently gave considerable protection against cardiovascular (see p. 319). Suffice it to mention here that the proportion of complicated aortitis in our series of untreated patients was about 19 times as high as the corresponding proportion in Nielsen's series of presumably inadequately treated patients. This too, fortifies a concept held by Moore (1944), namely that it takes less treatment to protect against cardiovascular than it takes to protect against neurosyphilis.

Finally, it is of interest to compare the proportions of neurosyphilis as found by Mattauschek and Pilcz (1912 and 1913) among their mercury treated Austrian Army officers with those arrived at in the present material of untreated patients. These were the percentages for the various forms of central nervous system involvement in the two series respectively: general paresis 4.7 versus 3.0 per cent; meningovascular 3.2 versus 3.3 per cent; and tabes dorsalis 2.7 versus 1.3 per cent. Total 10.7 versus 9.2 per cent. In other words, the findings of Mattauschek and Pilcz are not markedly different from our own, and neither do they differ much from those arrived at by Lomholt and Nielsen. This, in our opinion, is in keeping with what we would expect when we consider that our series comprised patients left untreated during the early stages of the disease, whereas Mattauschek and Pilcz' patients received highly inadequate treatment in the form of mercury inunctions, and Lomholt and Nielsen's patients were given relatively small amounts of salvarsan in addition to mercury inunctions.

Mattauschek and Pilcz' figures were, however, heavily criticized by Aebly (1920) particularly as regards general paresis (see pp. 196—197). Aebly undoubtedly was right in calling attention to the great difference between the proportions of general paresis among those of Mattauschek and Pilcz' patients who had been followed for an average of 29 years (9.72 per cent), and those who had been followed for an average of no more than 14 years (3.25 per cent). Also we are in agreement with Aebly when he stated that he could not accept the explanation given by the authors to the effect that better treatment in the latter of the two groups must be held responsible for the decrease in the proportions of general paresis.

Aebly argued that among the individuals with an average period of observation of 14 years, the authors must have missed quite a number of paretics, simply because the patients had not had time to develop the symptoms and signs of the disease. On a theoretical basis he then figured that the true frequency of general paresis among them probably was about 10 per cent, rather than about 3 per cent as found by Mattauschek and Pilcz (see p. 197). By including the above group of patients in the denominator, therefore, the authors had, according to Aebly's reasoning, presented a weighted average (4.7 per cent) that could not possibly be representative of the entire series. This seems the more reasonable when we take into account that the proportion of general paresis among those of the patients who had an average period of observation of 29 years, was 9.7 per cent.

As mentioned previously, Aebly reasoned as follows: according to general experience the average «period of incubation» in general paresis can be estimated to lie around 18—20 years, with a range from 2 to 30 years, and with a spread around the mean that must be assumed to form a fairly symmetrical curve. With Aebly we are inclined to believe that the 3 per cent general paresis found by Mattauschek and Pilcs in this particular group of patients represents a minimum. However, whether his estimates as to the frequency of general paresis among them, hold true in respect to order of magnitude is a different question. One of the unknown factors is the spread around the mean «period of incubation», and here we must also take into consideration that specific treatment seems to shorten the length of time it takes before general paresis develops, although we have no exact information as to how the various types and amounts affect the outcome in this respect. Since Mattauschek and Pilcs, as far as we know, did not continue their follow-up studies, we have no direct data showing how an increase of the period of observation might have influenced the end results in this special series of patients.

But, there does exist another experiment that at least may bring some information on this point. We refer to the two Danish follow-up studies mentioned previously, that of Lomholt (1936), where the period of observation was from 14 to 23 years, and that of Nielsen (1950), which by and large comprised the same patients, with a period of observation ranging from 29 to 36 years. Lomholt found 3.3 per cent general paresis. The author was also of the opinion that the period of observation was too short, and the proportion found therefore too low. By applying Aebly's reasoning on his own material Lomholt (1939) estimated that the true frequency of general paresis in his series probably was closer to 10 per cent. With a considerably longer period of observation, however, Nielsen found no more than 4.3 per cent general paresis in fact only a comparatively slight increase. The above findings do by no means prove that Aebly was wrong, but they do indicate that, through his theoretical considerations, he may have arrived at too high proportions of general paresis among those of Mattauschek and Pilcz' patients with the shorter period of observation. The next question that arises is the following: what about the 9.72 per cent general paresis among those of Mattauschek and Pilcz' patients who had an average period of observation of 29 years? With the data available, we are unable to determine whether this frequency is actually representative or not, but we are inclined to believe that some unconscious bias must have been introduced, leading to a proportion of general paresis that seems remarkably high compared with the corresponding proportions in Lomholt's, Nielsen's, and our own series. By and large, therefore, there is reason to exercise caution when figures from Mattauschek and Pilcz' material are used for comparisons, and this is true whether we accept their own figures or prefer to use Aebly's estimates.

Sex, and Age at Infection.

Sex. As mentioned previously, we have found an excess of males over females in all forms of neurosyphilis, and in principle this is in accordance with general experience. The proportions for the total were 9.2 and 5.1 per cent in males and females respectively, a ratio of 1.8 to 1. The ratios found in the literature vary somewhat from one author to the other. In Moore's (1944) white patients for instance, it was 1.8 to 1, whereas Stokes et al. (1944) state that neurosyphilis, irrespective of form, is three times as frequent in males as in females. If we consider a special form of neurosyphilis, like general paresis, the proportions in the present series were 3.0 and 1.7 per cent in males and females respectively, also giving a ratio of 1.8 to 1. In the literature it is commonly maintained that general paresis is about 4 to 5 times more frequent among males than among females. But these ratios are often based on mortality statistics, that is, the *number* of male and female cases in whom general paresis is found to have been the primary cause of death.

In our opinion it is dubious whether we can compare the ratios as found through the study of hospital and/or clinic populations with those arrived at in follow-up studies. The reason for this is to be found in the following: in the first instance the calculation of the proportions of neurosyphilis usually is based on a denominator, the representativeness of which can not be evaluated, because the size of the reservoir from which the patients were drawn, is unknown. In the second instance on the other hand, the calculation of the proportions rests on a well-defined denominator.

Similarly, in general paresis, these are considerable difficulties in comparing ratios from follow-up studies with those calculated on the basis of mortality statistics. This is exemplified in the following.

It will be recalled that Harrison (see pp. 24—26) based much of his criticism of Bruusgaard's figures on an analysis of the sex distribution in general paresis, demonstrating that Bruusgaard, contrary to ordinary experience, had found practically no difference between males and females in respect to frequency of this complication. We are fully in agreement with Harrison when he maintained that this in itself showed that selection must somehow have taken place. In order further to prove his point, Harrison quoted figures from official mortality statistics on the number of deaths from general paresis during the period 1914—1928 in Norway. Altogether there were 472 males and 105 females recorded as having died primarily of general paresis, which gives a ratio of males to females of a little more than 4 to 1. On the basis of these figures Harrison indicated that the frequency of general paresis in Norway was much lower among syphilitic females than among syphilitic males. Roughly speaking, this is what the figures show, but whether the order of magnitude of this ratio is generally representative or not is another question. It must be remembered that we are here dealing with *numbers*, not with *proportions*. Harrison was fully aware of that, and in order to illuminate the problem, he went on to quote the number of notified cases of syphilis as reported for the City of Oslo during the period 1900—1925, and found the ratio of males to females to be 2.3 to 1. Also he pointed to the widely accepted concept that a lower proportion of the syphilis in females is brought to light than in males, so that the ratio 2.3 to 1 was probably higher than it would be if every case of syphilis in females was detected and reported. If the ratio males to females in early syphilis was 2 to 1, then the actual ratio in general paresis would also be about 2 to 1, rather than the 4 to 1 demonstrated through the figures from mortality statistics. However, by indicating that the ratio in early syphilis is probably closer to 1 to 1 than 2 to 1, Harrison simultaneously indicated that he believed the 4 to 1 ratio in general paresis to give a true picture of these relationships.

So far Harrison's reasoning seems convincing. It should, however, be remembered that both Bruusgaard's and our own patients for the most part were drawn from the City of Oslo, and one is inclined, therefore, to ask the following question: Does the ratio males to females of 4 to 1, as demonstrated through the official figures on deaths from general paresis for the entire country, necessarily have to be representative also of the City of Oslo or parts thereof? In order to answer that question we have in table 64 presented the number of male and female deaths from general paresis as reported for the City of Oslo — and for the western and eastern parishes of that city — during the period 1900—1929.

First it will be noted that the ratio males to females varies from one period of time to another, and this holds true whether we consider the city as a whole or the special geographical areas within it. Next it will be seen that the ratios for the entire period 1910—1929 (which approximately corresponds to the period chosen by Harrison: 1914—1928) (see bottom of table) were 1.9 to 1 for the parishes located East, 5 to 1 for those located West, and 2.4 to 1 for the City total. In other words, only in the western partes of the city was the ratio of about the same order of magnitude (or somewhat higher) as that presented by Harrison for the country as a whole, whereas those found for the City total and the eastern parts of it, were considerably lower. This exemplifies that the ratios males to females in general paresis, as based on mortality statistics, may not only vary from one period of time to another, but also from one geographical area to another, and from one socio-economic group to another. In our opinion, the differences found in all probability reflect differences as to the ratios male to female infections within the various periods of time and the various geographical areas. Thus, the findings clearly demonstrate the difficulties connected with using numbers instead of proportions when it comes to an evaluation of these relationships.

Age at Infection. It is conceivable that such a factor as age at infection might influence the frequency of syphilitic central nervous system lesions, and also

Table 64.

Deaths from General Paresis as Reported in the City of Oslo from 1900—1929, by Sex.

Period of Time	Parishes Located West*			Parishes Located East*			Total		
	M	F	Ratio M/F	M	F	Ratio M/F	M	F	Ratio M/F
	No.	No.		No.	No.		No.	No.	
1900 — 1909	12	2	6.0 — 1	22	7	3.1 — 1	34	9	3.8 — 1
1910 — 1919	22	6	3.7 — 1	31	27	1.1 — 1	53	33	1.6 — 1
1920 — 1929	18	2	9.0 — 1	33	8	4.1 — 1	51	10	5.1 — 1
Total	52	10	5.2 — 1	86	42	2.0 — 1	138	52	2.7 — 1
Total 1910 — 1929	40	8	5.0 — 1	64	33	1.9 — 1	104	44	2.4 — 1

* For principles employed in sub-dividing the City of Oslo according to geographical areas, see pp. 50—51.

Adapted from Gjestland, T., Moen, E., and Trier, G.: A Regional Investigation of the Mortality in the City of Oslo During the Period 1890—1940. (To be printed.)

that it might influene the «period of incubation» in the various forms of these complications. As far as we know, there exist no reliable data as to how the frequencies may vary according to age at infection. There is, however, some evidence that age at infection may influence the «period of incubation». In respect to general paresis, it was indicated, among others by Meggendorfer (1921) and Lomholt (1936), that the later in life the patients were infected the shorter the «period of incubation».

Our own data permitted no definite statements on any of these points. The reason for this is that even with our 953 patients the numbers involved are too small for the fine sub-grouping necessary to illuminate the above problems. Since a group of untreated syphilitics larger than ours in all probability never will become available for study, the chances are that the influence of age at infection on the outcome in respect to neurosyphilis in untreated cases, is never going to be known.

There is, however, one finding that is worth mentioning. Among the 66 patients found to have been infected in childhood (mostly between the ages of 0—4), we found 4 cases of neurosyphilis (1 male and 3 female), whereas in the same group we did not find one single case of cardiovascular (see later). It is, of course, impossible to draw any definite conclusions on the basis of these small numbers, but our findings seem to indicate a certain similarity in respect to serious late complications between those infected in utero and those infected during early childhood. In both instances cardiovascular evidently is of rare occurrence, whereas neurosyphilis is not infrequently seen. If this hypothesis should be correct, it would mean that the acquired syphilis takes a course in patients infected during early childhood which is different from that usually seen in individuals infected as adults.

It is doubtful, however, whether the above hypothesis ever can be tested, because the chances are very small that anybody will ever be able to follow a sufficiently large group of children with untreated acquired syphilis for a sufficiently long period of time. Some information on this point might possibly be obtained through a study of the prevalence of cardiovascular and neurosyphilis among young adults in the areas of «endemic syphilis» in Yugoslavia (see Grin, 1953), where untreated fresh syphilis among children was prevalent up to recently. If the relationships as to frequency of cardiovascular and neurosyphilis turned out to be the same as those found in the present series, that might fortify this hypothesis. It can probably be anticipated that such a study would be connected with considerable difficulties, especially when it comes to determing whether the patients in question were infected as children or as adults. This would be especially true if the concept is correct that the earlier in life the patient is infected, the longer the «period of incubation».

Time Relationships and Age.

The various forms of neurosyphilis differ not only from a diagnostic and prognostic point of view, but also in respect to duration of infection and age at time of recognition. It is generally accepted that meningovascular, general paresis, and tabes dorsalis occur in that order during the course of the infection. Therefore, an analysis of the time relationships and age necessitates a subgrouping according to form. In addition there is an equally necessary distinction between cases of meningovascular and tabes dorsalis diagnosed in an active stage of the disease, and sequelae of meningovascular and tabes dorsalis forme fruste, since the latter forms are apt to be recognized considerably later during the course of the infection than the former. With a total of only 62 cases of neurosyphilis (31 males and 31 females) the above mentioned fine subgrouping naturally resulted in figures that were too small to permit definite conclusions. It follows, therefore, that our figures as to duration of infection and age at recognition in neurosyphilis, do not lend themselves well for comparisons either. Furthermore, our findings mean that a study group of 953 patients (our study group «Known») is too small for an analysis of this kind, provided the proportions of the various forms of neurosyphilis found, can be considered as approximately representative of the true frequencies in our series. This is the reason why we have abstained from comparisons with figures arrived at in other studies. For further details on the problems, we refer to pp. 232—238.

Summary and Conclusions.

1. The study group comprised 953 patients (study group «Known»), 331 males and 622 females, all followed to an «end point».
2. The method employed in classification was described.
3. The forms of neurosyphilis encountered among the 62 cases in the present series were distributed as follows: meningovascular plus vascular neurosyphilis, 37.1 per cent; general paresis, 32.3 per cent; tabes dorsalis, 27.4 per cent; and gumma of brain, 3.2 per cent.

   It could not be determined with the data available whether this distribution reflected the natural course of the infection.

   It is noteworthy that no case of asymptomatic neurosyphilis was found to have been diagnosed in the present series. The reasons for this were discussed.
4. The quality of the diagnoses in these 62 patients was analysed.

   It is felt that the diagnoses in the majority of instances rested on solid ground.
5. A total of 6.5 per cent of the patients observed were found to have developed neurosyphilis in one form or another.
6. Because of the relatively small number of cases involved, the influence of age at infection on the frequency of neurosyphilis, could not be determined. However, central nervous system lesions occurred in all age-groups listed.

   Among the patients aged under 15 at infection there were 4 cases of neurosyphilis.

   Definite conclusions on this point can not be drawn with the data available, but it seems as if there is a certain similarity in respect to serious late complications between those infected in utero and those infected during early childhood; cardiovascular syphilis evidently is of rare occurrence, while neurosyphilis is not infrequently seen.
7. It is emphasized that the various forms of neurosyphilis differ considerably, particularly from a prognostic point of view. Therefore, the proportions of each form, as calculated on the basis of the total number of patients observed, were presented: meningovascular plus vascular neurosyphilis 2.3 per cent; general paresis 2.1 per cent; tabes dorsalis 1.9 per cent; and gumma of brain 0.2 per cent.
8. The representativeness of the figures on neurosyphilis was analysed.

   The possibility could not be excluded that we had missed a certain number of cases with syphilitic central nervous system lesions, and the 6.5 per cent found in the study group «Known» was considered minimum, although it could not be determined to what extent. It is felt, however, that the cases missed for the most part must have been those that, from a prognostic point of view, were the least serious.

9. In order to elucidate the problem of representativeness further, the autopsy population too was analysed in respect to occurrence of syphilitic central nervous system lesions.

10. Of the total of 209 autopsied patients 6.2 per cent was diagnosed as having neurosyphilis. Thus, there was practically no difference in respect to frequency between the autopsy population and the total study group from which the autopsied patients were drawn.

    It is concluded that the proportion, as found in the autopsy population, could not represent a maximum, and therefore it was not possible to establish a range within which the true frequency of neurosyphilis in the present series could be assumed to lie.

11. As a whole neurosyphilis occurred more frequently in males than in females (9.2 versus 5.1 per cent — a ratio of 1.8 to 1). There was an excess of males over females in all forms listed, the proportions and the corresponding ratios being as follows:

meningovascular	3.3	versus	1.7	per cent —	ratio 1.9	to 1;
general paresis	3.0	«	1.7	—«—	1.8	« 1;
tabes dorsalis	2.6	«	1.5	—«—	1.7	« 1;
gumma of brain	0.3	«	0.2	—«—	1.5	« 1.

The representativeness of the ratios were discussed.

It is felt that the findings probably give a true picture of these relationships in the present series.

12. Since it is commonly held that the milder course of the syphilitic infection in women has to do with the protective effects of pregnancies, the possibility of analysing this question was considered.

    The conclusion is that the question had to be left open because the data available were not sufficiently reliable for an evaluation of this kind. For very much the same reason the question of the effects of the untreated infection on subsequent pregnancies had to be left open also.

13. Some of the *basic* epidemiologic factors that may influence the findings in respect to time relationships and age, was discussed.

14. For an analysis of time relationships and age in neurosyphilis sub-grouping according to form is essential. Also it is considered important to distinguish between cases recognized in an active stage of the disease, and those recognized as for example tabes dorsalis forme fruste, or sequelae of meningovascular.

15. The mean durations of infection for the various forms of syphilitic central nervous system lesions (exclusive of conditions recognized in an inactive stage) were: meningovascular neurosyphilis — males, 15.1, and females, 18.8 years; general paresis — males, 25.6, and females, 19.7 years; tabes dorsalis — males, 29.2, and females, 30.8 years.

    The mean ages at recognition were: meningovascular neurosyphilis — males, 37.5, and females, 40.0 years; general paresis — males, 52.5, and females, 42.5 years; tabes dorsalis — males, 60.8, and females, 50.8 years.

    Except for a trend showing that meningovascular, general paresis, and tabes dorsalis occurred at different durations and at different ages, the numbers involved were too small to permit detailed comparisons between males and females, and/or between the various forms.

    It is maintained that a study group of 953 patients (our study group «Known») is too small to provide answers to the questions of time relationships and age in neurosyphilis, provided the proportions of the various forms found are approximately representative of the true frequencies in the series.

16. The dead known to have developed neurosyphilis were grouped according to cause of death. It was found that these complications were the primary cause of death in 63.6 per cent of the instances, and the proportions were the same in both sexes. In the remaining 36.4 per cent of the cases, neurosyphilis was assumed to be non-related to the cause of death.

    The numbers within the various categories of central nervous system involvement are too small for significant comparisons, but it is noted that the cases of general paresis constitute the majority of those in which neurosyphilis was considered to be the primary cause of death (a little more than two-thirds of the total).

17. The circumstances under which comparisons can be made were discussed, and the importance of analysing carefully the basic epidemiologic methods employed in establishing the materials, was stressed.

    It is concluded that it is a prerequisite for comparisons that the data stem from the same *type* of study.

18. Since the present investigation was based on the same material as that used by Bruusgaard in his 1925—1927 follow-up study, a comparison was made between the frequencies of neurosyphilis in the two series, in order to determine whether the re-analysis had confirmed the Bruusgaard findings.

    Considering the totals there was practically no difference. Neither did sub-grouping according to form reveal any marked differences. The *sex* and *type* analysis, however, showed a most important dissimilarity between the two series: in Bruusgaard's material there was a slight excess of females over males in the total, and also there was more general paresis and more meningovascular among females than among males. In the present series there was an excess of males over females in the total and in all forms listed.

It is maintained that this dissimilarity actually makes the end results in respect to frequencies of neurosyphilis non-comparable, and thus we are in no position to determine whether the re-analysis confirmed the Bruusgaard findings.

19. Comparisons also were made between untreated and inadequately treated patients in respect to frequencies of neurosyphilis.

    It is felt that definite conclusions could not be made on these data alone, but the indication is that inadequate treatment is not a factor working in the direction of creating more neurosyphilis, and, moreover, it seems as if it takes considerably less treatment to protect against cardiovascular syphilis than it takes to protect against neurosyphilis.

Chapter IX

CARDIOVASCULAR SYPHILIS

I. Excerpts from and Comments on the Literature.

Definition.

If we wish to define cardiovascular syphilis in the broadest sense, it may be classified under the following three categories (Nicol, 1950):

1. Syphilis of the heart.
2. Syphilis of the medium-sized arteries.
3. Syphilis of the great vessels.

In most modern textbooks of syphilology, however, cardiovascular syphilis is limited to the following six forms (Thomas, 1949):

1. Uncomplicated aortitis.
2. Aortic insufficiency.
3. Saccular aneurysm.
4. Coronary ostial stenosis.
5. Gumma of the myocardium.
6. Diffuse syphilitic myocarditis.

As the last mentioned form is questionable (Thomas, 1949), and gumma of the myocardium very seldom diagnosed, what we mean by the term cardiovascular syphilis is usually disease of the aorta with secondary changes in the heart due to complications of the aortic disease (Kampmeier, 1943). The designation uncomplicated aortitis usually means that the aortitis is not complicated by aortic insufficiency, saccular aneurysm, or coronary ostial stenosis. The three latter entities are relatively clear-cut clinically, something which is not true of uncomplicated aortitis. It is noteworthy that most authors do not sub-group uncomplicated aortitis according to degree of pathologic involvement of the aorta, thus reflecting the difficulties in clinical diagnosis. However, as pointed out by Moore (1944), we find within this type of cardiovascular syphilis various clinical pictures depending on the stage of development of the lesions. He speaks first of a form where the involvement is so slight as to produce no symptoms and signs. Next he mentions a more advanced stage characterized by a diffuse and primarily supravalvular involvement that results in the production of uncomplicated aortitis *with* or *without* diffuse dilatation. When it comes to this form some observers, as stated by Moore, have suggested the term fusiform aneurysm, but he does not agree with this, mainly because he feels that such terminology would tend «. . . to identify this condition with one of more serious prognostic import.» (ibid. p. 281).

Diagnosis.

Uncomplicated aortitis. The question of diagnosis in cardiovascular syphilis has mostly revolved around the problem of the possibility of diagnosing uncomplicated aortitis clinically, and this has commanded the interest of cardiologists and syphilologists all over the world for a number of years. From clinical experience it was obvious that most patients with cardiovascular syphilis who came under observation, had already experienced irreparable damage, and that very little could be done by specific treatment, other than interference with the disease process. Autopsy studies, on the other hand, had shown that a good many syphilitics died with an uncomplicated aortitis which had caused the patient little or no inconvenience. It was only natural, therefore, that the clinicians were anxious to find methods by means of which a diagnosis could be made during the uncomplicated stage of cardiovascular syphilis, in order to be able to intercept the development early enough to stop the process before fatal complications occurred.

In a study by Moore, Danglade and Reisinger (1932) covering the period 1910—1930, it was shown that the clinical diagnosis of uncomplicated aortitis had been correctly made in only 6.2 per cent in a group of medical patients, as verified by necropsy. By comparing clinical and necropsy observations the authors listed seven criteria, and felt that the presence of any three of them was to be considered strong evidence of uncomplicated aortitis. Later it was found necessary to revise these criteria, and in 1944 Moore listed the following, which he thought would permit the diagnosis to be made with greater accuracy:

1. Demonstration of dilatation of the first portion of the aorta.
2. Heart failure or lowered cardiac reserve in the absence of hypertension or valvular disease.
3. Localized substernal pain.
4. Characteristic changes in the second aortic sound.

In the meantime a re-study of the problem at the Johns Hopkins Hospital (covering the period 1931—1940) showed that the percentage of correct clinical diagnoses had risen to 26.2 after the physicians had started to pay attention to the criteria set up by Moore and collaborators. In Norway, Müller (1935), in a study of 244 cases of cardiovascular syphilis autopsied at the Municipal Hospital of Oslo[1] during the period 1920—1931, found that correct clinical diagnosis had been made in 6 per cent of the patients with uncomplicated aortitis. Müller carefully examined the records of these patients and stated that a correct clinical diagnosis could have been made in 27 per cent with the data already available.

Besides observers who, as Moore and Müller, thought it was possible to diagnose uncomplicated aortitis clinically in a fair number of the patients, there were also a good many experts who disagreed with these opinions, an example being Kampmeier (1943). After having discussed the problem he came to the following conclusion (ibid. p. 312): «. . . Certainly, as the result of observing much of both syphilitic and nonsyphilitic cardiovascular disease among colored as well as white patients in the past decade, I must admit that it is impossible for me to make the clinical diagnosis of uncomplicated aortitis». In 1944 Stokes et al. summed up the situation by asking two questions: «a) Can aortitis be definitively diagnosed before *complications*[2] appear? b) Can aortitis when recognized be diagnosed by direct evidence (distinctive symptoms and signs) as syphilitic aortitis?» He answers these with the following statement: «The weight of opinion, broadly speaking, answers both questions with a *qualified*[2] no. Uncomplicated syphilitic aortitis may be suspected rather than diagnosed» (p. 908, fig. 681). They follow this statement with a list of authoritative pros and cons, nine publications supporting an answer of *yes* to the first question and seven publications with an equally emphatic *no*. Despite their own opinion they pay tribute to Moore and his collaborators for having placed a well-defined symptomatology of uncomplicated aortitis at the disposal of the physician and emphasize that «. . . there do not exist absolute criteria for diagnosis, but rather suspicion-arousers . . .» (ibid. p. 905).

Moore (1949a), in a review on cardiovascular syphilis, again calls attention to the possibilities for clinical diagnosis of uncomplicated aortitis, and in the section on this problem he draws the following conclusion: «The available evidence indicates that in the hands of an experienced and duly suspicious observer, the clinical diagnosis of uncomplicated aortitis can be made successfully and accurately, as demonstrated by subsequent necropsy findings, in a fair proportion of patients with this condition, but that the diagnosis rests on a combined evaluation of relatively insignificant symptoms, physical signs, and highly expert radiologic study». It must be stressed, however, that the symptoms and signs and radiologic findings referred to by Moore (they are in principle the same as those listed in 1944) relate to patients «. . . with known late syphilis (i.e., of more than four years' duration) and in the absence of hypertension, extensive arteriosclerosis, or rheumatic mitral heart disease . . .» (ibid.).

[1] Probably drawn from all wards of the hospital.

[2] Italicized by Stokes.

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It is to be noted that Moore thinks it possible to diagnose uncomplicated aortitis, even under the best possible conditions, only in a fair proportion of the cases with this condition, and also that he makes rather strong reservations relative to absence or presence of diseases which are by no means infrequent. Furthermore, the proof offered for the reliability of the clinical diagnosis rests with the subsequent finding of an uncomplicated aortitis at autopsy. It is dubious, however, whether the autopsy findings as proof of the accuracy of the clinical diagnosis can be accepted in view of the fact that we do not know the actual frequency of uncomplicated aortitis in untreated syphilis, the time it takes to develop, and the period that it remains uncomplicated. Thus the higher the actual frequency, the higher the proportion of correct pre-mortem diagnoses as based on autopsy verification. Therefore, as we stand today, it is probably safe to say that the question of the diagnosis of uncomplicated aortitis is still unsettled, although it is reasonable to believe, with Moore, that the diagnosis can be made in a certain number of cases. However, this is not proven quantitatively at the present time and it is doubtful whether it can ever be proven. Stokes' statement of 1944, that no conclusive criteria for the diagnosis exist, but that there are only suspicion-arousers, is as true today as it was then.

Complicated aortitis — aortic insufficiency, aneurysm and ostial stenosis. Whether the diagnosis of ostial stenosis can be made with any degree of reliability ante mortem is questionable, because the symptoms and signs are in the main identical with those in coronary sclerosis (Thomas, 1949). However, in comparison with the problem of the clinical diagnosis of uncomplicated aortitis this definitely is a minor problem, ostial stenosis, as far as we know, being a relatively rare complication.

As for aortic regurgitation and aneurysm, these conditions also pose problems of diagnosis, but it is generally held that it can be made correctly in most cases on a clinical basis. The error of diagnosis in aortic regurgitation has been estimated at less than 10 per cent (Nicol, 1950) as shown by autopsy, whereas the error in aneurysm is somewhat higher according to the same author. This will probably vary somewhat with the availability of diagnostic facilities. Among Müller's 244 patients (see p. 257) 160 were classified as complicated, and among these patients the ante-mortem diagnoses had been made correctly in 51.3 per cent. Specific figures for the various complications are not given, but the majority of the cases showed aortic insufficiency, which constituted 45.6 per cent of the total 244. Müller also estimated that the diagnoses could have been made correctly in 80.6 per cent of the cases with the data already available in the clinical records. Under all circumstances, the possibilities for incorrect diagnoses of the complicated forms of cardiovascular syphilis are far less than for uncomplicated aortitis, but should nevertheless be borne in mind when it comes to the question of frequency in various series.

It will be noted that we have here limited ourselves to matters of principle when it comes to the review of the literature in connection with the diagnosis of cardiovascular syphilis. No attempt has been made to go into details, the reasons for this being that in the present publication we are concerned first and foremost with the quantitative aspects of these complications. Only in so far as the diagnostic problems are of importance for the numerical evaluation of such things as frequency have they been considered.

Sex and Age.

Sex. There is general agreement that cardiovascular syphilis is more common among males than among females. However, most authors lump all forms of cardiovascular syphilis together when giving figures on the ratio males to females, and this does not seem logical when we take into account the uncertainty connected with the clinical diagnosis of uncomplicated aortitis, and even less reasonable if we accept that the prognosis of the latter form is much better than in the serious forms of aortic insufficiency and aneurysm. The possibility that the difference between the sexes increases as we go from the uncomplicated aortitis to the complicated types, is in the present author's opinion worthwhile considering. If this holds true, it would fit in very well with the concept that hard physical labour is responsible at least in part for the higher frequency of complicated aortitis in the male. Furthermore, the proportion of males to females varies quite considerably from one series to another as shown by the examples below. There are probably many reasons for this, and the above mentioned factor may be one of them. In White and Jones' series of 95 patients (White, 1944) the ratio was 5 : 1, distribution of forms not being mentioned. Kampmeier (1943) found a ratio of 3.4 : 1 in aortic insufficiency (27 males and 8 females, white patients), and in aneurysm 7 : 1 (131 males and 18 females, white patients). Müller (1935) found 3 : 1, all forms included, but two-thirds of the 244 cases were classified as complicated aortitis. Turner (1930) in a material from the Johns Hopkins Hospital (a statistical survey of 6,420 patients with untreated syphilis) found 13.9 per cent of the males and 6.7 per cent of the females to be suffering from cardiovascular syphilis, or a ratio of about 2 : 1. The distribution among the forms (males and females combined) was as follows: uncomplicated aortitis 5.3 per cent; aortic insufficiency 2.7 per cent; aneurysm 1.2 per cent; and other diagnoses 0.7 per cent. In Frazier and Li's (1948) series (white patients) the ratio was 3.7 : 1 (130 males and 35 females); aortic insufficiency[1] 3.5 : 1 (116 males and 33 females); and aneurysm 7 : 1 (14 males and 2 females). Broch (1947) found a ratio of 3.8 : 1 (all forms).

[1] All cases of uncomplicated aortitis and aortic valvular disease were here classified together, and the group given the descriptive title of Aortic Insufficiency.

The explanations offered for the difference between the sexes are: the protective influence of pregnancy and menstruation against serious late manifestations of the disease (Stokes et al., 1944); the factor of greater physical activity in the male (White, 1944); and the possible greater male exposure to syphilis (White, ibid.). The sex difference in cardiovascular syphilis probably must be considered an established fact, but the order of magnitude of this difference will certainly vary with a great many factors, and the explanations suggested are hypotheses which have not been proven as yet. As to the figures quoted here, it must be emphasized that they are all based on hospital populations, and whether these are truly representative of the average «syphilis universe» in this respect is questionable. As mentioned above, the variations in the ratio of males to females in the different series certainly reflect variations in the selections of the materials studied, whatever the reasons may be. Broch's (1947) study may serve to illustrate one possibility.

It is now commonly held that the ratio of males to females with fresh syphilis is close to 1 : 1 (although this fact is usually not reflected in the figures given for notified cases, where the ratio more often is about 2 : 1). However, this ratio of 1 : 1 need not necessarily be found in all population groups in all places or at all times in the past. It is conceivable that the incidence of early syphilis is higher among males in certain areas, and if so, we must expect the number of complications to become correspondingly higher in the males of a hospital population drawn from that reservoir. Broch's findings are based on a study of all forms of syphilis in a Norwegian County Hospital covering the period 1938—1946. The series comprises 75 cases of cardiovascular syphilis, 59 male and 16 female, or, as mentioned, a ratio of 3.8 : 1. A careful examination of the records showed that 47 per cent of the male patients in this series either had been employed, or were at the present employed, as seamen or whalers. And according to the author, this figure represents a minimum, because not all the male patients had been asked directly about their occupation, present or past. Furthermore, Broch states that in 1930, 16.3 per cent of the total male population over 18 years of age in that county were classified as seamen or whalers according to information gathered from the Central Bureau of Statistics. Finally, the author quotes the Danish investigator Reymann as having found that 11.8 per cent of the personnel in the Danish Merchant Marine had had syphilis, and that seamen were responsible for 95 per cent of the «imported» syphilis. Taking all these things into account, it is reasonable to believe that the reservoir from which Broch's patients were drawn represents one where the incidence of syphilis among males is probably greater than that reflected by a 2 : 1 ratio, and this in itself would under otherwise identical conditions eventually lead to a greater number of cases of cardiovascular syphilis among the males in the hospital population studied. Broch's study, therefore, exemplifies that the magnitude of the ratio of males to females in for instance cardiovascular syphilis may depend in part on factors in a community which lead to increased exposure to syphilis among certain groups. This also shows the necessity for caution in interpretation of data based on hospital populations.

Age. Syphilitic involvement of the cardiovascular system has been found to occur practically within all age-groups from birth to old age, but actually we have no reliable figures on frequency relative to age at infection. A study of the age at the time cardiovascular phenomena are recognized, however, may give us an approximate picture of the situation.

We know that its occurrence in congenital syphilis is not common. McCulloch (1930), in a study of 939 children with congenital syphilis, found only 5 cases with cardiovascular disease among the 498 who were over 2 years of age, and in all instances the heart disease was of rheumatic origin. In the 441 under 2 years 32 died, and in 3 of these there was demonstrated syphilitic heart disease, while the 409 others showed no symptoms or signs of cardiovascular involvement. In a monograph on the subject Hinrichsen (1943) stated that myocardial lesions may be present in infantile congenital syphilis, but that valvular syphilitic manifestations had never been demonstrated in late congenital syphilis. In a study of 82 children with congenital syphilis treated with salvarsan (and in some cases combined with mercury or Bismuth) during the period 1918—1924 and re-examined in 1942—1944, Aggerbeck (1949) found only one case with definite cardiovascular disease. The diagnosis was aneurysm of the ascending aorta and hemiplegia (vascular syphilis of the brain?). Duration of infection was estimated at about 21 years.

Then we have the possibility of cardiovascular syphilis occurring at an early age following acquired infection during childhood. It is usually held that such cases are rare, but no figures on frequency exist, and the reason for this is obvious: No-one has ever been able to follow a group of children with acquired syphilis for a sufficient length of time. It is probable, however, that cardiovascular syphilis in young adults was more common some decades ago when acquired syphilis in children was more frequently seen as a result of poor hygienic conditions in the homes. And one might expect to find cardiovascular syphilis in younger age-groups in areas where acquired (non-venereal) syphilis in children has been prevalent (for example in Yugoslavia, Grin, 1953). Schamberg (1946) states that a number of cases with cardiovascular syphilis in young adults have been reported in the literature, and the author describes 5 cases who had shown serious cardiovascular lesions at an early age. In only 2 of the 5 was the duration of infection definitely known. In White and Jones' series of 95 cases of cardiovascular syphilis, there was one patient under 10 years of age, and four between 20 and 30 years (White, 1944). In Müller's series of 244 cases 1.2 per cent falls within the age-group 20—30 (Müller, 1935). None of the last mentioned authors give any information as to duration of infection in these cases.

A further analysis of these data shows that cardiovascular syphilis has been most commonly diagnosed in middle life: White and Jones found eleven of their 95 cases between 30 and 40 years, twentyfive between 40 and 50, thirty-three between 50 and 60, twenty between 60 and 70, and one over 70 years. Müller's series (autopsy material) revealed the following age distribution: 31 to 40 years — 7.4 per cent; 41 to 50 — 22.1 per cent; 51 to 60 — 33.0 per cent; 61 to 70 — 24.0 per cent; 71 to 80 — 11.1 per cent; and 81 to 90 — 1.2 per cent (mean age: 56.7 years). Frazier and Li (1948) found the mean age at recognition of cardiovascular phenomena to be 47.6 years in white males, and 39.7 years in white females.

Duration of Infection.

Figures on duration of infection in cardiovascular syphilis practically always relate to the time when the involvement is first recognized, which often coincides with the time the patient seeks medical advice of his own accord. In orderly conducted follow-up studies on the other hand, a certain proportion of the cases may be diagnosed for the first time during the period of investigation, while others are found to have been previously recognized elsewhere. As far as we know there exist no reliable figures relative to duration of infection at the time the involvement actually becomes clinically recognizable. An important contribution to our knowledge on this point was made by McDermott, Tompsett and Webster (1942) and Reader et al. (1947), who presented data which indicated that both syphilitic aortic insufficiency and aneurysm may be clinically recognizable for years before symptoms develop, and thus during this phase of the development are only discovered by routine physical examinations or examinations in connection with some other disease. Depending on how the study group is chosen, therefore, the time relationships of cardiovascular syphilis may vary considerably from one series to another. It is evident, for instance, that it will be different in a group of patients seeking medical advice for their cardiac symptoms and a group of patients where the cardiovascular syphilis is discovered during an examination for some other disease. And also, it may differ to no small extent in the various follow-up studies, according to the duration of infection at time of investigation, and according to the thoroughness with which the investigator collects clinical information for the years which have elapsed before he undertakes his own examinations. The attitude of the investigator towards the question of the possibility of diagnosing uncomplicated aortitis clinically also bears on the time relationships. If the investigator is convinced he can diagnose that condition early, and a great many of his patients are classified in this category, it is obvious that the duration of infection in his series is apt to be much shorter than would be the case in a series where the investigator feels that this diagnosis can only be made at autopsy.

The factors discussed above should of course, always be taken into account, but they are of particular importance when we attempt to compare time relationships in various series. And here again it must be emphasized that lumping all forms of cardiovascular syphilis together should be avoided because of the uncertainty connected with the diagnosis of uncomplicated aortitis, and the corresponding lack of information as to the period in the infection during which this condition manifests itself. The figures from the literature quoted here should be judged with the reservations made necessary by the above considerations. Stokes et al. (1944) writes that cardiovascular syphilis is seldom recognized during the first decade of infection; 45 per cent is diagnosed in the second decade; and 30 per cent in the third. In the white patients of Frazier and Li (1948) the mean duration of infection in cardiovascular syphilis — calculated as the difference between mean ages at time of clinical phenomena and onset of infection — was 18.1 years for males, and 14.1 years for females.

Occupation.

There seems to be evidence that heavy labour plays an important role in the development of the complications of syphilitic aortitis. Although it is practically impossible to separate the factors of race and physical stress, many observers have taken the greater frequency of cardiovascular syphilis in Negroes as an indication of the effect on the cardiovascular system of the hard physical work usually done by the members of this race. It has furthermore been indicated (White, 1944) that the excess morbidity from these conditions among males as compared with females, is caused, at least in part, by the greater incidence of hard labour among the former. Kampmeier (1938) in a study complication to heavy labour. Kemp and Cochems (1937), in a study of 747 of 633 cases with saccular aneurysm, found a definite relationship of this patients with syphilis, divided the cases of cardiovascular syphilis into two groups according to occupational stress and arrived at the following figures: heavy or moderate labour — 14.1 per cent cardiovascular syphilis; sedentary work — 8.7 per cent cardiovascular syphilis. Also, it was found that the complicated forms were more common in the first group, while uncomplicated aortitis was more frequently diagnosed in the other.

Occurrence.

Generally, figures on the frequency of cardiovascular syphilis have been found through either of two methods:

1. By determining the prevalence in syphilitics belonging to hospital populations,
   a) in still living patients,
   b) in autopsied patients,
   c) in both groups combined.

2. By doing follow-up studies of patients who have received either no treatment or various kinds and amounts of treatment for their original infection, and after a certain duration of infection to determine what proportion has developed cardiovascular disease.

The results in studies of hospital populations will practically always be weighted on the side of greater frequency because disease brought the patient to the hospital, and the findings in autopsy investigations are apt to be still more biased in the same direction because the patients have been so ill that death has occurred during their stay in the hospital. Another definite shortcoming, which is almost invariably connected with studies of hospital populations, is the fact that duration of infection is usually unknown in a relatively great proportion of the patients. In view of the above considerations, it is fairly obvious that the second method of study is preferable as a matter of principle. We are then able to determine the duration of infection, and, what is very important, we have a more accurate denominator on which to base our proportional frequencies. But here too we are apt to encounter several difficulties, some of the most frequent ones being the lack of a sufficiently long period of observation and loss from observation. In fact, many observers believe that statistically valid results can only be had if the patients are followed until death, and preferably with verification of diagnosis by autopsy (Moore, 1949a). A search of the literature will readily show that no study completely fullfils these criteria.

Whatever method of study is used, the problem of the clinical diagnosis of uncomplicated aortitis enters the picture, the only exemption being the autopsy investigations. The inaccuracy of the diagnosis of uncomplicated aortitis will necessarily influence the frequency estimates to a great extent, and the greater the number of still living and non-autopsied dead in the series, the more pronounced this error will be. Not only will the number of such cases vary with the general attitude the investigator in question takes towards the possibility of diagnosing this condition ante mortem, but great variations may also be expected depending on whether the diagnoses have been made prior to or after the time Moore and his collaborators established the so-called «suspicion-arousers». Finally, even if it is possible to examine living patients after what is considered a sufficiently long post infection period, a great proportion of these individuals will then have developed diseases such as arteriosclerosis and hypertension, which make the diagnosis of uncomplicated aortitis still more dubious.

According to Kampmeier (1943) there exist actually no figures on the frequency of uncomplicated aortitis that are worth while, and he adds that one of the most common faults with statistics on cardiovascular syphilis is that all forms of aortitis are lumped together. The latter point is, of course, particularly important if we attempt to make comparisons between the findings in various series. Kampmeier has not reported on the frequency of uncomplicated aortitis at all, but limited himself to those forms (aortic insufficiency and saccular aneurysm) where the diagnoses rest on relatively firm ground. This seems to be very logical in view of the present position of the problem of diagnosis of uncomplicated aortitis. Whatever the attitude taken, however, evaluation of the frequency of cardiovascular syphilis should always be done with this viewpoint in mind, and sub-grouping according to form must be considered a *sine qua non*.

The figures from the literature quoted below, should also be looked upon with the necessary reservations which have been touched upon in the foregoing. Turner's (1930) study from the Johns Hopkins Hospital is based, as mentioned previously, on the admission diagnoses of 6,420 patients with untreated late syphilis. He found that 10 per cent was suffering from cardiovascular syphilis, with the following distribution according to type of lesion: uncomplicated aortitis 5.3 per cent; aortic insufficiency 2.7 per cent; aneurysm 1.2 per cent; and other diagnoses 0.7 per cent. It is noteworthy that a little more than one-half of the patients with cardiovascular syphilis falls within the category uncomplicated aortitis, and that the diagnoses were made clinically without verification by autopsy. In 6,253 patients with late or latent syphilis in the Cooperative Clinical Group Study (1936), 619 patients (9.9 per cent) showed cardiovascular syphilis, and the various types were represented as follows: uncomplicated aortitis 4.8 per cent; aortic insufficiency 4.1 per cent; saccular aneurysm 1.2 per cent; and syphilitic myocarditis 0.8 per cent. Kampmeier (1943), among 2,961 cases of late syphilis in the Vanderbilt University Hospital Syphilis Clinic, found 90 cases of aortic insufficiency, or 3.0 per cent. McDermott, Tompsett and Webster (1942) found a frequency of 3.4 per cent aortic insufficiency among 2,718 syphilitic patients.

Among the follow-up studies that of Bruusgaard (1929a) is the only one dealing with patients left untreated or highly inadequately treated during the early stages of the infection. As already mentioned in Chapter I (Introduction), we know very little about the fundamental epidemiologic methods employed in his study. When it comes to cardiovascular syphilis the following points seem worth while emphasizing: Bruusgaard does not define cardiovascular syphilis. When summing up his findings he writes that 67 patients out of 473 (14.2 per cent) had been found to suffer from cardiovascular disease («vessel disease»). It is noteworthy that he does not use the expression cardiovascular syphilis, although he does indicate in the text that the majority of the conditions classified in the group «vessel disease» in his opinion was of syphilitic etiology. A study of the tables presented (see annex tables I—VI) reveals that vascular lesions of the brain have been included in his group «vessel disease». Furthermore, it will be noted that the majority of the cases listed among his 309 living patients as suffering from «vessel disease» falls within the group called «dilatation of the heart and the aorta» (13 out of 21). A careful examination of the records very strongly suggests that these diagnoses were x-ray diagnoses and in many instances the x-ray diagnosis of cardiovascular disease was merely suggestive. In other words, these represent cases which today in all probability would be classified clinically as uncomplicated aortitis. In addition to the 13 cases of «uncomplicated aortitis», we find one case of aortic insufficiency, 6 cases of aneurysm, and one case of apoplexia. Among the 164 dead patients there were 46 cases of «vessel disease», of which 7 cases were diagnosed as uncomplicated aortitis (verified at autopsy), 2 as aortic insufficiency, and 3 as aneurysm, making a total of 12 where the diagnosis of syphilitic heart disease was definitely established, and 34 classified otherwise. In the total material of living and dead, there are, consequently, only 19 cases out of 67, where there is reason to believe that the diagnosis of syphilitic heart disease rests on relatively firm ground. Furthermore, the distribution according to type among these 19 cases (9 aneurysms, 3 aortic insufficiencies, and 7 with uncomplicated aortitis) indicates the possibility of bias inasmuch as Bruusgaard found three times as many with aneurysm as with aortic insufficiency, which is contrary to ordinary experience. Under these circumstances it must be considered extremely difficult to evaluate Bruusgaard's figures on cardiovascular syphilis, and the facts mentioned above strongly suggest that the figures must be used with the utmost caution.

The general aspects of Nielsen's study (1950) was described in more detail in the chapter on «benign» tertiary syphilis (pp. 148—150), but the following facts are worth repeating in this connection: The series comprises males only. The patients received highly inadequate treatment for their original infection (2—3 injections of salvarsan plus some 50 inunctions of mercury). The period of observation was 29—36 years.

The author found that 17 (3.6 per cent) out of 467 patients developed cardiovascular syphilis. Thirteen or more than three-fourths of the 17, were diagnosed as aortitis (meaning uncomplicated aortitis), 3 as aortic insufficiency, and 1 as aneurysm. He does not elaborate on how the diagnoses were made and in what proportion they were verified by autopsy. He does mention, however, that he omitted from the material some cases of uncomplicated aortitis where the diagnosis was not made until autopsy had been performed. The reason for this omission is not stated, but it may indicate that all the cases retained in the material had their diagnoses of cardiovascular syphilis made during life. It is notable that of the 3.6 per cent cardiovascular syphilis found, the cases with uncomplicated aortitis constitute 2.8 per cent and the serious complications (aortic insufficiency and aneurysm) not more than 0.8 per cent of the total number of patients in the series. Provided the diagnoses in the cases classified as uncomplicated aortitis are based on clinical observations only, the figures presented for this form of cardiovascular syphilis must be considered with the reservations made necessary by the possible inaccuracy of that diagnosis, and for this reason alone an evaluation of the order of magnitude for comparative purposes seems practically impossible. As to the more serious forms, aortic insufficiency and aneurysm, the diagnosis generally rests on relatively safe ground, and therefore, the frequency of these complications can be evaluated with less difficulty. Taken at its face value, the figure 0.8 per cent for complicated aortitis, or less than one in a hundred, seems remarkably low, when we take into account the apparently inadequate treatment these patients received during the early phase of the infection, and therefore the completeness of follow-up comes into the picture.

The author states that thanks to the Syphilis Registry of the Serum Institute in Copenhagen, the original group of patients selected for study automatically was under observation all through the period prior to his analysis. «Being under observation» in this respect obviously means that any one of these syphilitics on whom a blood test or a spinal fluid examination for syphilis was made, would necessarily be registered, because all such samples are sent to this one institute. The only exceptions to this rule, as mentioned by the author, were those patients who had already developed late lesions and had had tests made prior to the establishment of the registry in 1920.

The present author understands the registry to have operated according to the following main principles: If a test turns out positive for syphilis, that individual will be registered under all circumstances. If it shows negative results, and the patient in question has been registered previously or has a history of syphilis, the findings will also be entered. However, if the patient has not been registered previously, shows negative tests, and has no history of syphilis, the findings will not be recorded. And finally, it is self evident that patients on whom no tests for syphilis are made, will not be found in the archives of the Syphilis Registry.

The figures presented for the serious forms of cardiovascular syphilis (and other late manifestations for that matter), must be evaluated on the basis of the principles of registration inasmuch as the completeness of follow-up is wholly dependent on the completeness of registration at the Serum Institute. In this connection it would then be natural to ask the following questions:

1. Can it be assumed with reasonable certainty that all or the majority of the patients who developed symptoms and signs of aortic insufficiency or aneurysm have at one time or another sought medical advice and thus submitted themselves to examination?
2. If examined, what proportion was hospitalized and where, and what proportion was seen by practitioners?
3. To which extent were serologic tests for syphilis employed by the hospitals and the practitioners respectively during the period of time through which the patients in question lived?

4. How many of the patients died of other causes with these syphilitic complications remaining undiagnosed?
5. If any of these patients came to autopsy, were the findings of syphilis recorded also?

These questions can not be answered with the data available, but certain assumptions can nevertheless be made, and in fact they point in the direction that the frequency of serious cardiovascular syphilis found by Nielsen represents a minimum. It is reasonable to believe that most of the patients who survived for some time after symptoms and signs of complicated aortitis developed, sooner or later ended up either in a hospital or with a private practitioner. Thus the majority of these latter patients in all probability have been examined, but it is dubious whether serologic tests for syphilis — at least during the earlier years of the existence of the Serum Institute — were employed by hospitals and practitioners in the various parts of Denmark to the extent that the patients in question all were registered by the above institution. The present author is inclined to believe that a certain proportion of these individuals was not registered by the Serum Institute simply because blood tests were not taken. Also, in view of our present knowledge, there will always be some patients with complicated aortitis who die of other causes and in whom the syphilitic heart conditions are not diagnosed ante mortem. Examples of this are sudden death from ostial stenosis and symptomless cases of aortic insufficiency and aneurysm. Unless autopsy is made and the findings reported to the Serum Institute, these cases can not possibly have been registered there. In view of the above, therefore, the present author feels that the 0.8 per cent complicated aortitis reported by Nielsen is a minimum, but with the data available there is no way of determining to what extent the factors discussed above may have influenced the findings.

The third follow-up investigation to be discussed here is the second part of Aggerbeck's study (1949). The study group consists of 555 patients, 377 males (67.9 per cent) and 178 females (32.1 per cent). The cases were chosen from three different policlinics in Copenhagen, Denmark, and were treated during the years 1918—1924. Only patients treated during the primary stage were included (primary seronegative 461 (83 per cent), primary seropositive 94 (17 per cent)). A study of the treatment given at the three policlinics as outlined by the author, readily reveals that the material is by no means uniform in this respect. The treatment varied considerably from one policlinic to the other, and it became more intensive as time passed from 1918 to 1924. It is furthermore to be noted that according to some schedules the patients received two courses, and according to others presumably only one. In commenting on this question the author himself points out that in some instances the patients continued treatment in other policlinics or with private practitioners. It is, however, not indicated what proportion of the patients had two courses, nor how many were subsequently treated elsewhere. Under these circumstances it is difficult to evaluate the adequacy of the original treatment in this series, but by and large one would be inclined to agree with the author when he states that it was inadequate as measured by accepted modern standards. During a discussion on the tracing methods, however, the author maintains that most of his patients never showed positive seroreactions subsequently. What this indicates as to the adequacy of treatment is not clear, and it is not clarified what is meant by «most of the patients», as no figures are presented. The majority of the patients (83 per cent) were treated during the seronegative stage, and if we accept the above statement, this means that the types and amounts of treatment employed were sufficiently adequate to prevent serologic relapse in most of these cases. According to common experience with substandard dosages of antisyphilitic remedies, this seems highly improbable, and in the present author's opinion it would be much more reasonable to expect a fair proportion of these patients to show positive seroreactions at some time. As the author has not presented the evidence on which the above statement on the serologic status is based, we are in no position to assess its validity, and are obliged, therefore, to stick to the first assumption, that treatment was substandard according to modern concepts of what constitutes adequacy.

The author only briefly touches upon the question of possible treatment in the interim period between the termination of the early stage and the final observation. He says it was impossible to get complete information on this point in spite of the fact that an attempt was made during the period of investigation (1942—1946) to find out where and to what extent the patients might have received treatment during the intervening years. The only explanation offered is a general statement to the effect that the patients' own information was not very reliable after so many years (about 20), and there is no mention of the number of patients found to have received such treatment, if any. It must be assumed that a certain proportion of these patients was hospitalized or saw private practitioners for syphilitic or non-syphilitic diseases during the many years elapsing between the original discharge and the final observation, and, they lived through a period of time in which it became more and more common to submit hospital patients and others to routine serologic tests for syphilis. Under these circumstances it would be reasonable to believe that a certain number of these patients were diagnosed as having latent or late syphilis and subsequently received treatment. The almost complete lack of information relative to treatment in the interim period, therefore, might suggest that the search for clinical data was incomplete, and this further aggravates the difficulties in evaluating the influence of treatment on the end results in Aggerbeck's series.

There is only a very brief description of the tracing process and practically no details as to methods employed. According to the author the main principles were as follows: with original name, date of birth, and address as a starting-point a search for the patients was made through various sources such as the Population Register, the Salvation Army Investigation Office, and others, in order to establish the address of the individuals as of the time of the investigation (1942—1946). Neither is there any information as to the methods of proving identity, but as the majority of the patients evidently was found and eventually showed up for examination (see later), it was presumably a relatively easy matter to determine to which extent identification was successful or not. Incidentally, there is no mention of possible incorrect identifications. As mentioned previously (see pp. 148—150 and 266—268) the natural starting-point for any follow-up study of syphilitics in Denmark is the Syphilis Registry of the Serum Institute in Copenhagen. The author seems to have considered this possibility at the beginning of his investigation, but states that due to difficulties in identification it was possible only in some instances to follow a patient from the early stage up to the point when cardiovascular syphilis had developed. Also, he emphasizes that in some instances where his patients appeared to be identical with those found in the Syphilis Registry, a search of the records of the hospitals or of the practitioners who had forwarded the blood tests, showed that identity had actually *not* been established. On the basis of these experiences the author maintains that the Syphilis Registry could not be utilized as a basis for his follow-up study. This is not in accordance with the experience of other Danish investigators (Lomholt, 1936, and Nielsen, 1950), and therefore, it would have been desirable if Aggerbeck had given more exact evidence for his opinions. If a representative sample of the total material had been chosen and the patients in it submitted to a rigid search through the leads given by the archives of the Syphilis Registry, it might have been possible to express quantitatively whether the registry is suited as a basis for follow-up studies of syphilitics. However, the author does not mention how many of his original 555 patients were actually searched for through the Syphilis Registry and what the findings were. The only explanation offered for the seemingly meagre results obtained from the registry, which necessitated other tracing methods, is the statement that most of the patients in this series had never shown positive seroreactions. If this explanation is accepted, however, it means, as mentioned previously, that the treatment given these patients must have been sufficiently adequate to prevent serologic relapse in practically all cases, and also that it has prevented the majority of the patients from developing clinically recognizable late manifestations of «benign» tertiary, cardiovascular, and neurosyphilis. This, in the present author's opinion, is highly improbable, in view of the original type and amount of treatment given these patients, and we certainly would have expected a fair number of them to have been recorded by the registry at one time or another. Also, if the statement is correct, that identification was not possible on the basis of the data found on the cards in the Syphilis Registry, it would mean that the registry does not fulfil one of its original purposes, namely to form a starting-point for follow-up studies of syphilitics in Denmark. However, this is contradicted by the findings of various other investigators, and therefore his statement must be proven before it can be accepted.

This investigation was performed during the years 1942—1946 — 18 to 26 years after infection — and the author succeeded in locating 483 (87 per cent) of the original 555; 426 were living, while 57 were dead. The sex distribution among those followed is practically identical with that in the original material: 325 males (67.3 per cent) and 158 females (32.7 per cent), as compared with 377 males (67.9 per cent) and 178 females (32.1 per cent). The mean duration of infection was 22 years. Among the 483 patients 29 (6 per cent) showed evidence of cardiovascular syphilis according to the criteria set forth by the author. The 29 were again sub-divided as follows: definite cardiovascular syphilis 5 (1 per cent); probable 14 (2.9 per cent); and possible 10 (2.1 per cent).

Before proceeding with an appraisal of these figures the following point should be borne in mind, that the analysis was not done on a sex-specific basis. Although no specific definition of cardiovascular syphilis was given, he included in this category syphilis both of the heart and the great vessels, and syphilis of the medium-sized and small vessels. The analysis was carried out according to type of lesions, but there are no tables showing the distribution according to type *and* sex.

In table 65 the findings, as adapted from Aggerbeck's figures, are presented on a sex-specific basis and according to type of lesion. Two cases of syphilis of the medium-sized or small arteries, both male, (one diagnosed as syphilitic endarteritis of the brain, and one as syphilitic endarteritis of the lower extremity), have been omitted from the material in order to bring the definition in accordance with our own, and thus allow for eventual comparisons. A study of the sex distribution (including all other forms) shows no appreciable difference between males and females (5.5 versus 5.7 per cent). This is contradictory to usual experience, there being practically unanimous agreement that cardiovascular syphilis is more commonly found among males. The number of cases in each sex-group is admittedly small, but in the present author's opinion this finding nevertheless points in the direction of possible bias. An analysis of the various forms, however, reveals that uncomplicated aortitis constitutes 81.5 per cent of the total (22 of 27); of the males 77.8 per cent (14 of 18); and of the females 88.9 per cent (8 of 9). Thus, the series is heavily weighted with cases classified as uncomplicated aortitis (about four-fifths), and comprises only a relatively small number of cases with complicated aortitis (about one-fifth). It might be added that the diagnosis of uncomplicated aortitis was made clinically in 19 of the 22 so classified, and only in 3 cases was it verified by autopsy.

Table 65.
Distribution of Cases of Cardiovascular Syphilis According to Form and Sex.

Number Observed	Aneurysm		Aortic insufficiency		Uncomplicated aortis		Subtotal	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Males								
325 (100 %)	2	0.6	2	0.6	14	4.3	18	5.5
Females								
158 (100 %)	1	0.6	0	—	8	5.1	9	5.7
Total								
483 (100 %)	3	0.6	2	0.4	22	4.6	27	5.6

Adapted from Aggerbeck, I.: «Cardio-vascular lues og dens tidlige prophylaxe. En klinisk og katamnestisk Studie», Rosenkilde og Baggers Forlag, København, 1949.
(Constructed on the basis of Aggerbeck's figures).

Under these circumstances, it does not seem justified to lump all forms together and express the percentage of cardiovascular syphilis in the series on that basis. If this is done, an analysis of the sex distribution, as shown in the foregoing, will lead to the surprising result that there is no difference between males and females as to frequency of cardiovascular syphilis. If we sub-group the cases by type and analyse the sex distribution in the group with uncomplicated aortitis, it will be noted that the percentage is about the same in the two sexes (4.3 per cent in males and 5.1 in females), and since these cases constitute the great majority, this obviously is the explanation why there is no sex difference in the total. The reason why the author found *no* sex difference in cardiovascular syphilis is difficult to decide, but two explanations may be offered: first, it may have to do with the small number of patients involved. And, second, there is the possibility that the sex difference is less pronounced in uncomplicated aortitis than in the more serious forms of aortic insufficiency and aneurysm. However, the findings can hardly be interpreted to mean this in view of the fact that most of the diagnoses rest on clinical observations only, and thus are not accurate enough to permit conclusions which are contradictory to ordinary experience. If the diagnoses, on the other hand, had been verified by autopsy, this possibility might have been considered. In the present author's opinion, the most reasonable explanation is that some unconscious bias has been introduced, leading to findings where no sex difference in cardiovascular syphilis seems to exist. It is dubious, therefore, that the figures presented in this series on frequency of cardiovascular syphilis can be used for comparisons. At any rate, if this is done, sub-grouping according to sex and form should be made, and due attention paid to the factors discussed in the foregoing.

Other types of investigations found in the literature are usually purely retrospective and start with a clinic or hospital population in all late stages of syphilis observed for varying periods of time, and attempt to relate outcome to treatment received in the past. For the most part, those lost from observation are not taken into account. Nevertheless, practically all such investigations show a definite trend, pointing in the direction that the more adequate the treatment given during the early phases the less cardiovascular involvement. «Adequate» treatment appears to prevent entirely the development of cardiovascular syphilis, while so-called substandard treatment seems to cause a considerable decrease in frequency as compared with no treatment. It is obvious, however, that the order of magnitude in respect to the occurrence of cardiovascular syphilis in a given series will not depend on treatment alone, but also on a number of other factors such as for example length of period of observation, sex, race, proportion of clinically diagnosed uncomplicated aortitis included, etc.

It is noteworthy that the examples given below are widely quoted without any detailed description of these important factors. The period of observation has been given as «10—20 years» or as «more than 10 years» and so on. The proportion of cases diagnosed clinically as uncomplicated aortitis usually is not mentioned, and there is no breakdown as to sex and race. Without breaking down the figures in this way, it is almost impossible to explain the rather great variations in frequency found in the various series. Therefore we shall have to limit ourselves to an evaluation of the trends demonstrated rather than try to assess the actual order of magnitude of the percentages presented. The Cooperative Clinical Group (1936) results have been summarized by Stokes et al. (1944) as follows: (observation period 10—20 years), of 328 patients receiving no treatment for early syphilis 3.4 per cent were found to have cardiovascular involvement; of 191 with «substandard» treatment 5.8 per cent; and of 61 with «standard» treatment none had cardiovascular. Kemp and Cochems' (1937) findings, as quoted by Moore (1949a) were considerably different: (observation period more than 10 years), little or no treatment 27.6 per cent with cardiovascular; «inadequate» treatment 13.6 per cent; and with «adequate» treatment as in the previous report no cases of cardiovascular developed. Rosahn (1937), quoted by Aggerbeck (1949), provides another set of data: (observation period 10 years), «very little» treatment 12.0 per cent cardiovascular; «little» treatment 11.2 per cent; and seemingly «adequate» treatment 7.2 per cent. The latter percentage is higher than Stokes' group with no treatment. Such differences can be explained only through careful analysis of the data and the method of investigation.

There are also numerous reports in the literature on the amounts of treatment originally given patients admitted with cardiovascular syphilis, and here we

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find a similar trend in that the great majority of these cases was found to have received either no treatment or highly inadequate treatment during the early phases of the infection.

Prognosis.

Quantitative prognostication in cardiovascular syphilis is extremely difficult, and it is particularly complicated when we attempt to compare the outcome in one series with that of another. The important factors to take into account are:

1. Race and sex.
2. Occupation, both during part of the period preceding the development of cardiovascular disease, and after the diagnosis has been established.
3. Age at infection and at time of recognition of clinical phenomena, and the length of period of observation.
4. Form of cardiovascular syphilis and stage of decompensation at time of diagnosis.
5. Treatment, both antisyphilitic and general, herein included the possibilities that the patients can follow the regimen recommended.

Finally, the actual assessment of the outcome must depend on an analysis of the cause of death, and here another important factor complicates the picture, namely the rate at which the syphilitic patients succumb to other diseases before cardiovascular syphilis itself causes death. This again depends on the period of time in question, the geographical area, and type of population group involved.

In view of the many difficulties involved in the determination of the prognosis, it is not surprising that reliable quantitative data for comparisons are almost non-existent. In general, it is held that aortitis as long as it remains uncomplicated has a very good prognosis, and this concept is based on the fact that this condition is the primary cause of death in only a relatively small proportion of instances. Moore (1944) reports on 105 cases of uncomplicated aortitis diagnosed at autopsy, and in 10 of these patients was the aortitis considered to be the primary cause of death. When it comes to the more serious manifestations, aortic insufficiency and aneurysm, it is generally felt that the outlook is gloomy once the diagnosis is established. In all probability the reason for this is that prognostication in most of the cases is based on hospital patients with varying degrees of failure. The previously mentioned investigation by Reader et al. (1947), however, revealed that prognosis even in such cases was far better than generally believed, and especially if proper treatment was carried out. According to these authors patients may maintain compensation even after symptoms have developed and live for several years (2—14 years, average 5—6).

II. Present Investigation.

Introductory Remarks.

1. For the study of cardiovascular syphilis we have chosen *all* patients in the group «Known» (see table 21, p. 93), 331 male and 622 female, or a total of 953. This means that we have included only those patients who were followed to an «end point» (that is, patients on whom date of death was definitely established, and patients who were found alive within the investigation period (1949—1951)). There are some patients in the group «Partially Known» who also might have been included, but it is difficult to determine for how long they ought to have been followed in order to justify such inclusion, and it was therefore felt that uniformity was best achieved by limiting the study of these conditions to the group «Known». Incidentally no case of cardiovascular syphilis was discovered among the patients in the «Partially Known» group, indicating that the periods of observation for these individuals in general were too short.
2. *All* patients in the category «Known» were included irrespective of stage during which they were originally seen by Boeck, and irrespective of specific treatment they might have received prior to, during, or shortly after discharge from Boeck's department. In other words — unlike the procedure adopted for the analysis of clinical secondary relapse — we have not excluded those patients seen originally by Boeck in secondary recurrence. Neither have we omitted those who received specific treatment (mercury) during this early phase of the infection. As will be recalled, the number of patients hospitalized by Boeck with secondary recurrence was comparatively small (see table 18, p. 59) and played a minor role numerically. And the specific treatment given was considered highly inadequate. Under these circumstances, it was felt that inclusion of these patients would not appreciably influence the end results as to later serious complications.
3. Relative to the specific treatment given some of the patients for secondary relapse experienced after discharge from Boeck's department, and to those patients who developed «benign» tertiary syphilis, we refer to discussions on pp. 120—121 and 168—169 respectively. These patients were not excluded from the analysis of cardiovascular syphilis either.
4. General factors relative to time relationships and age are discussed in considerable detail on pp. 289—292. As to the intervals in the various time-relationship and age computations, they relate to the period between the termination of the original secondary syphilis and the beginning of the event in question. This goes for the vast majority of the patients, the only exception being those seen originally by Boeck in secondary recurrence, in whom the starting-point coincides with the termination of the latter phase of the infection. (See also point 2.)

Definition.

Cardiovascular syphilis is here taken to mean the disease of the aorta with the secondary changes in the heart due to complications, and the following forms are included:

uncomplicated aortitis,
aortic insufficiency,
saccular aneurysm,
and coronary ostial stenosis.

Forms of Cardiovascular Syphilis and the Quality of the Diagnoses.

In table 66 is presented the percentage distribution of the forms of cardiovascular syphilis encountered in this series. Among the total of 92 patients, uncomplicated aortitis was diagnosed in 25 cases (27.2 per cent); aortic insufficiency in 41 (44.6 per cent) — by far the most common form —; saccular aneurysm in 16 (17.4 per cent); and ostial stenosis in only 2 cases (2.2 per cent); the combined forms accounted for 6 cases (6.5 per cent). It will furthermore be noted that two cases are classified separately as «uncomplicated» aortitis with sudden death. It was felt that they could not very well be placed in the category uncomplicated aortitis, and due to the fact that no autopsy was made, it was impossible to determine whether they were suffering from ostial stenosis or an ordinary coronary sclerosis plus uncomplicated aortitis, to mention two of the existing diagnostic possibilities.

In table 67 the 92 cases of cardiovascular syphilis are grouped according to form and in relation to the basis on which the diagnosis was made. First, it will be seen that in 55 instances (59.8 per cent) the diagnoses were verified by autopsy. Second, it will be noted that the diagnosis of uncomplicated aortitis was made at autopsy in 22 of 25 instances, and in none of these 22 was the diagnosis made ante mortem. Also, in the 4 cases where ostial stenosis was demonstrated (alone or in combinations), diagnosis was verified by autopsy. Thus, most of the instances where the diagnosis was based on clinical examinations alone, relate to cases with aortic insufficiency and aneurysm. In other words, it can safely be said that the diagnoses in this series, when made, rest on relatively safe ground, inasmuch as most of the cases where a clinical diagnosis is either questionable or impossible, the diagnosis was made at autopsy, while the majority of the patients who were diagnosed on clinical examinations alone suffered from aortic insufficiency or aneurysm, where the diagnosis can be made with considerable accuracy without autopsy.

Age at Infection.

In table 68 will be found the distribution of cases with cardiovascular syphilis according to age at infection. First it is to be noted that not one single case was

Table 66.

Distribution of the Forms of Cardiovascular Syphilis, by Sex.

(Ages 15 — 40 over*) (92 patients)

Forms of cardiovascular syphilis**	Males		Females		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Uncomplicated aortitis	8	17.8	17	36.2	25	27.2
«Uncomplicated aortitis with sudden death	2	4.4	0	—	2	2.2
Aortic insufficiency	22	48.9	19	40.4	41	44.6
Saccular aneurysm	8	17.8	8	17.0	16	17.4
Ostial stenosis	1	2.2	1	2.1	2	2.2
Aortic insufficiency plus saccular aneurysm	3	6.7	1	2.1	4	4.3
Aortic insufficiency plus ostial stenosis	1	2.2	1	2.1	2	2.2
Subtotal Complicated forms	37	82.2	30	63.8	67	72.8
Total	45	100.0	47	100.0	92	100.0

* Age at infection.
** Categories mutually exclusive.

found among the 66 patients whose age at infection was under 15 years. The number of patients of these age-groups is relatively low, but even so the fact that none of them was found to have experienced cardiovascular syphilis, points in the direction that this condition was rare among the persons whose infection dated back to childhood. Second, this finding is in sharp contrast to the 12.3 per cent cardiovascular involvement which occurred in the 73 patients with age at infection of 40 and over, showing that such lesions were by no means infrequent in those age-groups, in spite of the comparatively shorter period of time during which these patients could possibly develop cardiovascular syphilis before they succumbed to some other disease.

In addition to the phenomena just described for the extreme age-groups, a study of the total seems to reveal a slight trend towards increasing frequency of cardiovascular involvement the later in life syphilis was acquired, up to the 40 and over group, something that was also indicated for «benign» tertiary syphilis. The differences, however, are no greater than could be expected by chance and this distribution therefore permits of no definite conclusions. The decrease at ages 40 and over is actually more in keeping with what one would expect when we take into account the relatively long «period of incubation» for cardiovascular syphilis, and the short span of life left for these patients compared with those of younger ages at infection.

Table 67.

Distribution of Cases of Cardiovascular Syphilis According to Form and Quality of Diagnosis at last Observation, in Dead and Living Patients, by Sex.*

(Ages 15 — 40 over**) (92 patients)

Forms of cardiovascular syphilis***	Males					Females					Total				
	Dead			Living		Dead			Living		Dead			Living	
	Autopsy only	Clinical exam. plus autopsy	Clinical exam. only	Clinical exam.	Subtotal	Autopsy only	Clinical exam. plus autopsy	Clinical exam. only	Clinical exam.	Subtotal	Autopsy	Clinical exam. plus autopsy	Clinical exam. only	Clinical exam.	Grand total
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
Uncomplicated aortitis	7	0	0	1	8	15	0	2	0	17	22	0	2	1	25
«Uncomplicated» aortitis with sudden death	0	0	2	0	2	0	0	0	0	0	0	0	2	0	2
Aortic insufficiency	1	10	10	1	22	2	6	9	2	19	3	16	19	3	41
Saccular aneurysm	2	2	2	2	8	1	2	2	3	8	3	4	4	5	16
Ostial stenosis	1	0	0	0	1	1	0	0	0	1	2	0	0	0	2
Aortic insufficiency plus saccular aneurysm	0	2	1	0	3	0	1	0	0	1	0	3	1	0	4
Aortic insufficiency plus ostial stenosis	0	1	0	0	1	0	1	0	0	1	0	2	0	0	2
Total	11	15	15	4	45	19	10	13	5	47	30	25	28	9	92
	26 — 57.8 %		19 — 42.2 %			29 — 61.7 %		18 — 38.3 %			55 — 59.8 %		37 — 40.2 %		

* At time of investigation (1949 — 1951).
** Age at infection.
*** Categories mutually exclusive.

Explanation of Terms:

Autopsy only: No clinical diagnosis of cardiovascular syphilis made.
Clinical Examination + Autopsy: Diagnosis of cardiovascular syphilis made clinically and verified by autopsy.
Clinical Examination only: Diagnosis not verified by autopsy.

Table 68.

Proportions Developing Cardiovascular Syphilis, by Sex and Age at Infection.

(92 patients)

Age at infection	Males			Females			Total		
	Number of patients observed	Patients developing cardiovascular syphilis		Number of patients observed	Patients developing cardiovascular syphilis		Number of patients observed	Patients developing cardiovascular syphilis	
		No.	Per cent		No.	Per cent		No.	Per cent
0 — 14	28	0	—	38	0	—	66	0	—
15 — 19	43	7	16.3	131	7	5.3	174	14	8.0
20 — 29	180	24	13.3	330	26	7.9	510	50	9.8
30 — 39	52	10	19.2	78	9	11.5	130	19	14.6
40 over	28	4	14.3	45	5	11.1	73	9	12.3
Total	331	45	13.6	622	47	7.6	953	92	9.7
Ages 15 — 39	275	41	14.9	539	42	7.8	814	83	10.2
Ages 15 — 40 over	303	45	14.9	584	47	8.0	887	92	10.4

The influence of age at infection as far as the extreme age-groups are concerned, is demonstrated at the bottom of table 68. First, if we omit the patients whose age at infection was under 15 and over 39, limiting ourselves to the 15—39 age-groups, the proportion of cardiovascular syphilis becomes very slightly higher (10.2 per cent versus 9.7 per cent). If the 40 and over age-group is retained in the material it will mean practically no change in the proportions (10.4 versus 10.2 per cent). In view of the fact that cardiovascular syphilis among the patients whose age at infection was under 15 evidently is rare (no case in our series), and also because most other series will probably include very few, if any, such patients, it is felt that this group should be omitted for comparative purposes, whereas the group over 40 can be used since all series will no doubt include such ages.

Occurrence.

A. *Occurrence in the total study group «Known».*[1] From table 68 it will be seen that a total of 9.7 per cent of the patients studied was found to have developed cardiovascular syphilis in one form or another. However, if we subtract from the denominator those patients whose age at infection was under 15, as discussed in the section on the influence of age at infection, the proportion will be 10.4 per cent. The difference is small, but for comparative purposes we have chosen to use the latter figure.

As mentioned in the section on literature, figures on cardiovascular syphilis do not give a true picture of its occurrence when all forms are lumped together. Table 69, therefore, was constructed in order to give the proportions of each form based on the numbers observed. It will be seen that uncomplicated aortitis was found in 2.8 per cent of the total persons observed; aortic insufficiency in 4.7 per cent; saccular aneurysm in 2.1 per cent; ostial stenosis in 0.5 per cent; and finally «uncomplicated» aortitis with sudden death in 0.2 per cent. Uncomplicated aortitis was diagnosed in 2.8 per cent as compared with a total of 7.6 per cent for the complicated forms. Thus, 10.4 per cent of our patients were found to have developed cardiovascular syphilis irrespective of form, a proportion which definitely represents a minimum, as will be shown in the following.

The representativeness of the figures given for any of the serious late complications will to no small extent depend on the quality of the final diagnosis, the general aspects of which are discussed in Annex VIII, p. XL. Here we shall consider some of the points which are particularly important for the evaluation of the frequency of cardiovascular syphilis. First, the 2.8 per cent uncomplicated aortitis obviously does not represent the true frequency of this condition in our series. It should be remembered, as mentioned previously, that most of the cases with uncomplicated aortitis were diagnosed at autopsy, and

[1] See p. 275 Introductory Remarks, point 1.

Table 69.

Proportions Developing Cardiovascular Syphilis According to Form, by Sex.

(Ages 15 — 40 over*) (92 patients)

Total number observed	Forms of cardiovascular syphilis**	No.	Per cent
Males			
303 (100 %)	Uncomplicated aortitis	8	2.6
	Aortic insufficiency	22	7.3
	Saccular aneurysm	11	3.6
	Ostial stenosis	2	0.7
	«Uncomplicated» aortitis with sudden death	2	0.7
	Subtotal Complicated forms	37	12.2
	Total	45	14.9
Females			
584 (100 %)	Uncomplicated aortitis	17	2.9
	Aortic insufficiency	19	3.3
	Saccular aneurysm	9	1.5
	Ostial stenosis	2	0.3
	«Uncomplicated» aortitis with sudden death	0	—
	Subtotal Complicated forms	30	5.1
	Total	47	8.0
Total			
887 (100 %)	Uncomplicated aortitis	25	2.8
	Aortic insufficiency	41	4.6
	Saccular aneurysm	20	2.3
	Ostial stenosis	4	0.5
	«Uncomplicated» aortitis with sudden death	2	0.2
	Subtotal Complicated forms	67	7.6
	Total	92	10.4

* Age at infection.

** Categories not mutually exclusive. Combinations of aortic insufficiency and aneurysm have been classified arbitrarily under aneurysm (3 males and 1 female), and combinations of aortic insufficiency and ostial stenosis similarly classified under ostial stenosis (1 male and 1 female) (see table 66).

at autopsy only. The explanation is probably to be found in the fact that the majority of our patients who were seen alive were either examined during a period of time when the so-called «suspicion-arousers» for the clinical diagnosis of uncomplicated aortitis were not yet established, or, when it comes to those examined later (that is after 1932), the latter had already reached an age where complicating diseases, particularly arteriosclerosis, had developed to an extent so as to make the clinical diagnosis of the former condition extremely difficult, if not to say impossible, in most of them. Among our dead, who constitute the majority of the patients studied (694 out of a total of 953 — 72.8 per cent) the proportion autopsied was about 30 per cent (see annex table XX, p. XLIV). Under the circumstances this group formed the only one in the material where an *accurate* diagnosis of uncomplicated aortitis was made. Therefore, we can by no means exclude the possibility that a fair number of the non-autopsied patients and some of the living, may have suffered from undiagnosed uncomplicated aortitis. Our figure of 2.8 per cent consequently is too small, and the fact that this figure *per se* represents a minimum, necessarily bears on the total of 10.4 per cent cardiovascular syphilis, which must also be a minimum for that same reason.

When it comes to the complicated forms, there can be little doubt that we have come much closer to the true frequency than is the case in uncomplicated aortitis, mainly because of the greater accuracy with which the clinical diagnoses are made in the former conditions. But even so, it is felt that the 7.6 per cent complicated aortitis in all probability also represents a minimum, for reasons to be discussed below. We again refer to annex table XX. Among the total of 694 dead patients, 209 (30.1 per cent) were autopsied, and within this group there is good reason to assume that practically no case of complicated aortitis was overlooked. The two next groups of patients in the table are those where the final diagnosis was based on clinical examinations in a hospital just prior to death (200 — 28.8 per cent), and those where it was based on examinations in a hospital a relatively short time before death plus the information found on the death certificate (100 patients — 14.4 per cent). Here too we believe that only few clinically recognizable cases were overlooked, particularly when we take into account the relatively long duration of infection at time of death, namely on an average 28.6 and 30.4 years for males, and 25.3 and 33.6 years for females in the two groups respectively, (see annex table XXI, p. XLV). We must, on the other hand, reckon with a certain number of cases with complicated aortitis in which the clinical diagnoses were either very difficult, or impossible, and some of these may well have been overlooked among the patients belonging to these two groups, tending to minimize somewhat the number of such cases in our series. Incidentally, among the 92 patients with cardiovascular syphilis in our material (see table 67) there were 8 cases of complicated aortitis in whom the condition was not diagnosed at clinical examination but found at autopsy, namely 3 cases with aortic insufficiency, 3 with saccular aneurysm, and 2 with ostial stenosis.

Then follows the third group of patients in annex table XX, p. XLIV, namely those who were found not to have been hospitalized within a reasonably short period of time prior to death, and where the final diagnosis, therefore, rests to a large extent on the information found on the death certificate (146 patients — 21.0 per cent). In this connection it is worth emphasizing, however, that in spite of the most exhaustive search through the many sources available to us, we were not able to provide clinical data for the period preceding death, a fact which indicates that many of these patients would seem to have been well up to the time when the fatal disease, or accident, occurred. But there is reason to assume that some cases of complicated aortitis were missed in this group. First, on filling out death certificates, many physicians prefer to avoid the use of the word «syphilitic» or «luetic» in order to keep this information from relatives of the patient; instead they often limit themselves to such general terms as «heart disease» or «heart failure», even if the patient in question is known to have died of *syphilitic* heart disease. Second, we have the patients who died *of* some other disease, but *with* undiagnosed complicated aortitis. And finally, there will always be some cases of sudden death, where specific clinical diagnosis actually is impossible, ostial stenosis being an example of the latter possibility.

The fourth group among the dead includes those patients where the fact of death was established, but without any additional clinical information being available (39 patients — 5.6 per cent), an evaluation of the diagnoses thus being out of the question. This group, however, is of minor importance, and whatever these patients may have died of the findings would not substantially influence the end results as to complicated aortitis in our series.

When it comes to the diagnoses among those patients who were found to be alive at the time of our investigation (1949—1951) we refer to annex pp. XLVI —LII for general considerations. The following features are particularly important in this connection: these patients had had their infection for an average of about 50 years and had reached an age of close to 70 years (see annex tables XXIV and XXV, p. XLIX). Under these circumstances there is little reason to assume that any important number of cases with complicated aortitis were overlooked among these 216 examined patients (83.4 per cent of those alive), (annex table XXIII, p. XLVIII), although a few cases of clinically unrecognizable complicated aortitis might exist among them. In the alive although not examined group (43 patients — 16.6 per cent) the information gathered showed that the vast majority of them were well, but there is a slight possibility that some of them were suffering from symptomless complicated aortitis. However, the number of cases with complicated aortitis missed in these two groups was in all probability so small as to mean very little for the end results.

On the basis of the considerations made in the foregoing it is reasonable to believe that our figure for complicated aortitis also is a minimum, although it is probably more representative of the true frequency in the series than is the case in uncomplicated aortitis. Therefore the proportion of 10.4 per cent found to have experienced cardiovascular syphilis in the total study group «Known» is definitely too small, but with the data hitherto available we are not in a position to determine to what extent this is so. In order to elucidate that problem further, we have chosen to analyse the occurrence of cardiovascular lesions in the autopsy population as well.

B. *Occurrence in the autopsy population.* For general information on the autopsy population we refer to annex VIII. It is worth recalling that the proportions autopsied were about the same in males and females, and the findings as to mean age and mean duration of infection at time of death not markedly different from those found for the remainder of the dead. As far as comparisons according to these indices go, the autopsy population can be considered as being representative of the dead patients in the series. Generally speaking, however, the autopsy population is usually weighted in the direction of more serious cases, and thus not representative of the hospital population from which it is originally drawn, and even less representative of the total «universe» particularly if the latter contains both dead and living patients. In this connection it is interesting to note that the proportion autopsied among the total number of dead patients in the present series was about 30 per cent as contrasted with about 66 per cent of those among the dead found to have experienced cardiovascular syphilis[1] (see annex table XX, p. XLIV, and table 67, p. 278 respectively). According to the above considerations we would expect the proportions of cardiovascular involvement in the autopsy population to represent a maximum. Thus, by giving minimum figures as based on the findings in the total study group «Known» on the one hand, and maximum figures from the autopsy population on the other, we should be able to demonstrate a range within which probably lies the true frequency of cardiovascular lesions in the present series.

In table 70 is presented the frequency of cardiovascular lesions in the autopsy population, by sex and according to forms. The total column reveals that cardiovascular syphilis in one form or another was diagnosed in a little more than one-fourth of the patients (55 out of a total of 209 — 62.3 per cent). Of these, 22 (10.5 per cent[2]) showed uncomplicated aortitis, while 33 (15.8 per cent[2]) were found to suffer from complicated aortitis. Due to the fact that the vast majority of our patients with uncomplicated aortitis was diagnosed at autopsy

[1] In table 67, p. 278, the proportion autopsied (about 60 per cent) is figured out on the basis of both dead and living patients. If figured out on the basis of dead patients alone, the percentage would be about 66.

[2] Per cent of total 209.

Table 70.

Proportions Found to Have Developed Cardiovascular Syphilis in Autopsy Population, According to Form, by Sex.

(All ages*) (55 patients)

Number of patients autopsied	Patients in whom no cardiovascular was found		Patients in whom cardiovascular was diagnosed					
			Uncomplicated aortitis		Complicated aortitis		Subtotal	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Males								
75 (100 %)	49	65.3	7	9.3	19	25.4	26	34.7
Females								
134 (100 %)	105	78.4	15	11.2	14	10.4	29	21.6
Total								
209 (100 %)	154	73.7	22	10.5	33	15.8	55	26.3

* Age at infection.

and at autopsy alone, it is obvious that the use of the total study group «Known» as a denominator necessarily resulted in too small figures. Under these circumstances it is not surprising that this condition was 3.8 times as frequent in the autopsy population (10.5 per cent in the latter as contrasted with 2.8 per cent in the former). Whether the 10.5 per cent is representative of the total syphilis population studied is difficult to determine, but it is probably safe to state that it comes much closer to the true frequency in the series than does 2.8 per cent. The 15.8 per cent complicated forms represents a frequency which is 2.1 times as great as that found for the study group «Known» as a whole (7.6 per cent). This is in accordance with what we would expect in so far as an autopsy population practically always contains a greater number of patients with serious complications than does the hospital population from which it is drawn, and the latter again a greater number of such patients than the total «syphilis universe». The proportion complicated aortitis (15.8 per cent) found among the autopsied patients must consequently be considered to be too high and not representative of the total syphilitic population studied. And, if the proportion of 7.6 per cent found in the total study group represents a minimum, the true frequency of these complications lies within a range of 7.6 to 15.8 per cent. Although we are not in a position to determine the exact proportion with the data available, we are inclined to believe that the former figure comes somewhat closer to representativeness than does the latter.

Table 71.

Ratio Males — Females in Cardiovascular Syphilis According to Form.

Forms of cardiovascular syphilis	Males	Females	Ratio
	Percentage*	Percentage	Males — Females
Uncomplicated aortitis	2.6	2.9	1. — 1.1
Aortic insufficiency	7.3	3.3	2.2 — 1.
Saccular aneurysm	3.6	1.5	2.4 — 1.
Ostial stenosis	0.7	0.3	2.3 — 1.
«Uncomplicated» aortitis with sudden death	0.7	0	—
Subtotal Complicated forms	12.2	5.1	2.4 — 1.
Total	14.9	8.0	1.9 — 1.

* The percentages used are taken from table 69.

Sex Distribution.

A. *Sex distribution in the total study group «Known».* The importance of not lumping all *forms* together when giving figures on the occurrence of cardiovascular syphilis was stressed in the foregoing. As will be shown below, it is of no less importance to keep the sexes separate. In table 71 are given the ratios of males to females according to proportions found for the total and for the various forms of cardiovascular involvement. It will be seen that these conditions as a whole occurred more frequently among males than among females (a total of 14.9 per cent versus 8 per cent respectively — a ratio of 1.9 to 1). Next, it will be noted that uncomplicated aortitis was found in about the same proportions in the two sexes (2.6 per cent versus 2.9 per cent — a ratio of 1 to 1.1), whereas complicated forms were diagnosed in 12.2 per cent of the males as compared with 5.1 per cent of the females, or a ratio of 2.4 to 1.

When considering the various sub-groups within the category complicated forms, the proportions, and the corresponding ratios of males to females, came out as follows: aortic insufficiency 7.3 per cent versus 3.4 per cent — a ratio of 2.2 to 1; saccular aneurysm 3.6 per cent versus 1.4 per cent — a ratio of 2.6 to 1; and ostial stenosis 0.7 per cent versus 0.3 per cent — a ratio of 2.3 to 1. The numbers in the various sub-groups are small, but it is nevertheless noteworthy that practically no sex difference was found in uncomplicated aortitis, while all complicated forms showed an excess of males over females.

Table 72.

Ratio Males — Females in Autopsied Patients with Cardiovascular Syphilis According to Form.

Forms of cardiovascular syphilis	Males	Females	Ratio Males — Females
	Percentage*	Percentage	
Uncomplicated aortitis	9.3	11.2	1. — 1.2
Complicated aortitis	25.3	10.4	2.4 — 1.
Total	34.7	21.6	1.6 — 1.

* Percentages used are taken from table 70.

The sex difference is also reflected in the percentage distribution of the forms of cardiovascular syphilis (table 66), where it will be seen that uncomplicated aortitis constitutes 36.2 per cent of all forms in the females as contrasted with 17.8 per cent in the males, while complicated aortitis comprises 63.8 and 82.2 per cent respectively in the two sexes. This is what would be expected in view of the ratios of table 71 and indicates that there was relatively more uncomplicated aortitis among females than among males.

In connection with these problems it should be remembered that the diagnoses of cardiovascular lesions by and large rest on very much the same basis in the two sexes: the proportion autopsied was 57.8 per cent among the males as compared with 61.7 per cent among the females, and in 7 out of 8 male and 15 out of 17 female cases the ordinarily difficult diagnosis of uncomplicated aortitis was made at autopsy and at autopsy only (see table 67). Another important point is that the analysis of the quality of the final diagnosis in the total number of dead and living patients studied, showed no appreciable differences between males and females (for details we refer to the foregoing section on occurrence and to annex VIII, p. XL). The findings as regards the ratio between the sexes in uncomplicated aortitis, therefore, seem to give a true picture of this relationship in our series in spite of the relatively small figures. Further evidence pointing in the same direction is found in the following section.

B. *Sex distribution in the autopsy population.* In the foregoing section on occurrence, the discussion of the minimum proportions in the total study group «Known» and the maximum proportions in the autopsy population was based on the totals in each group, but the assumptions made were general in character and applied to males as well as females. When it comes to order of magnitude on the other hand, the obvious necessity of analysis on a sex-specific basis will be shown in the following. We refer to tables 70 and 72. First it will be seen that cardiovascular lesions, irrespective of form, were diagnosed in a little more than one-third of the males (34.7 per cent) as compared with a little more than one-fifth of the females (21.6 per cent), which gives a ratio of males to females of 1.6 to 1. This ratio is not markedly different from that found in the total study group «Known» (1.9 to 1, see table 71). The proportion of uncomplicated aortitis was slightly higher among the females (11.2 per cent versus 9.3 per cent — a ratio of males to females of 1 to 1.2), whereas the proportion of complicated aortitis was 25.3 per cent among the males as compared with 10.4 per cent among the females — a ratio of 2.4 to 1. These latter ratios are about the same as those found in the total study group «Known», which were 1 to 1.1 and 2.4 to 1 for the two groups respectively (see table 71). In respect to the relationships between the sexes the findings in the autopsy population seem to corroborate those already described for the total study group «Known» and lend further evidence to the representativeness of the latter.

As mentioned above, the proportions of uncomplicated aortitis in the autopsy population were approximately the same in males and females (9.3 per cent and 11.2 per cent respectively), and in our opinion these figures are definitely closer to the true frequencies in the series than those found in the total study group «Known» (2.6 and 2.9 per cent respectively), for reasons already discussed in the section on occurrence. Furthermore, males in the autopsy population showed 25.3 per cent and females 10.4 per cent complicated aortitis compared with 12.2 and 5.1 per cent respectively in the total study group «Known», the proportions in the former group thus being a little more than twice as high in both sexes. The range within which lie the true frequencies of complicated aortitis in the present series, therefore, is 12.2 per cent to 25.3 per cent for males, and 5.1 per cent to 10.4 per cent for females, as demonstrated through minimum and maximum figures.

Occupation.

An analysis of the effect of physical labour on the occurrence of cardiovascular involvement in our patients was not possible, and the reasons for this are discussed in the following.

The occupational status of the patients in the study group at time of infection was described on pp. 47—50, and it was shown that the vast majority of them were working-class people. The information on type of work, however, was not considered complete enough to justify sub-grouping as to extent of physical labour, but it can safely be assumed that in general these people had to work nard in order to make a living, and it should be remembered that working hours were long and working conditions poor at the turn of the century. But this is only the beginning of the story, and in order to evaluate the effect of physical stress on the development of cardiovascular syphilis with its comparatively long «period of incubation», it would in the present author's opinion, be necessary to have a nearly complete occupational history from the onset of infection up to the «end point». True enough, whether physical stress in the early phases has a part in the later development of cardiovascular disease in those patients whose aorta is invaded by spirochetes during the general spread of the infection, we do not know, but the possibility can hardly be excluded. As for the time when a symptomless uncomplicated aortitis already is present, it would seem reasonable to assume that hard physical work may contribute to the further development of the condition as well as to a certain extent determine the period of time it takes before symptoms of cardiac involvement occur. As soon as the latter stage is reached it is fairly apparent that hard physical labour can only worsen the patient's condition and shorten his life. On the basis of these considerations, it is felt that in an attempt to evaluate the influence of physical stress on the occurrence of cardiovascular syphilis, one should not only take into account the occupational history of the patient just prior to or at the time he seeks medical advice for his cardiac condition — important though that may be — but also the type or types of work he has had all through the presumably many years before the development reached that far.

As mentioned previously, we have only incomplete information as to type of work for the early periods of the infection. And when it comes to the intervening years up to the «end point» the data are even less complete, because, the majority of our patients were dead at the time the investigation took place, a fact that necessarily prevented the establishment of a good occupational history through personal interviews, and because the information on occupational history usually was very scarce in the ordinary hospital records collected; and finally it was our impression that it was very difficult even among the still living patients to obtain satisfactory data on this point, the main reason probably being the many years (an average of fifty) that had elapsed between onset of infection and the time of investigation. Under the circumstances it was felt that a reliable analysis of the effect of physical stress on the occurrence of cardiovascular syphilis could not be made with the data available.

Time Relationships and Age.

Because these phenomena to a great extent are interrelated, time relationships and age will both be discussed in this section. There are, however, certain basic epidemiologic factors which must be taken into account in the analysis of the findings in any series, and which are even more important when it comes to *comparisons.* These factors are more or less general in character and may bear on some or all of the time-relationship and age estimates; therefore, a discussion of them is going to be given as an introduction to the detailed description of our findings.

First, age at onset of infection must be considered. As mentioned previously, patients who were under 15 or over 39 years of age at onset of infection have usually been omitted from our time-relationship tables in order to ensure uniformity (see p. 117). In principle this method of procedure has also been adhered to for cardiovascular syphilis. As contrasted with clinical secondary relapse and «benign» tertiary syphilis, however, not one single case of cardiovascular syphilis was found to have occurred among the patients who acquired their infection during childhood. That group, therefore, posed no problem in this connection. When it comes to the patients who were infected after the age of 39 on the other hand, cardiovascular syphilis was discovered in a fairly high proportion of the patients, and for descriptive and comparative purposes, it seems to be worth while to demonstrate how inclusion of such individuals might influence the findings. Due to the comparatively short period of time left for these persons in which to develop cardiovascular lesions, the duration of infection at time of recognition and at final observation would tend to be shorter and age higher because age at infection was so much higher than that of the average syphilitic patient. Of course, the number of patients whose age at infection is 40 and over will be small in any series, but it may vary considerably from one series to another and therefore should always be taken into account in description and analysis. In our series 4 male and 5 female patients, or 9 out of a total of 92 (close to 10 per cent), fell within this age-group (see table 68).

Second, we must consider the number of patients with cardiovascular syphilis found to be alive at the time of the investigation. Relative to these individuals two questions may be asked when it comes to time relationships and age: 1) At what time during the course of the infection did the investigation take place? 2) How many of the living patients had their cardiovascular lesions recognized for the first time, because they were called-in for examinations? In our series there were 4 male and 5 female patients alive at the time of the investigation, or 9 out of a total of 92 (close to 10 per cent) (see table 67). They had all had their infection for more than 40 years (average 52 years), and the average age was about 75 years. Four, 2 males and 2 females, had had their cardiac condition diagnosed elsewhere prior to our examinations, because they had sought medical advice for their ailment. The remaining 5, 2 males and 3 females, had their cardiovascular lesions recognized for the first time on examinations by us. In this latter group time relationships and age thus depended on the period of time during the course of infection which we chose to carry out our investigation. Because of the many years that had elapsed between onset of infection and time of investigation, the number of patients in this category in the present series necessarily became relatively small. But in others where the period of observation may be comparatively much shorter, the number of such patients may be correspondingly greater and thus influence time-relationship and age estimates to a considerable degree.

Third, we must consider under what circumstances the cardiovascular syphilis was recognized in patients — living or dead — whose condition was diagnosed prior to our own examinations. In many of these instances time relationships and age will depend on when the patients sought medical advice for their cardiac ailment. In others the first recognition of the condition may be the result of a planned follow-up study, and thus dependent upon when the investigator in question made his examinations. A certain number of our patients were known to have been examined during the previous follow-up study made by Bruusgaard (1929a) in 1925—27, hence we had to reckon with the possibility of some cases of cardiovascular syphilis being discovered at that time only because the patients were called-in to the hospital. A careful study of the records, however, revealed that this pertained to no more than 2 of our patients (1 male and 1 female), both cases of symptomless complicated aortitis at time of recognition. The reason for the small number of such patients in our series lies first and foremost in the fact that cases examined by Bruusgaard and diagnosed as «dilatation of the heart and aorta» were not accepted by us as representing cardiovascular syphilis (see pp. 265—266) because of the great uncertainties connected with the diagnoses. And, except for the two above mentioned cases, the remaining patients with cardiovascular syphilis found by Bruusgaard and included in our series, had either been diagnosed also prior to Bruusgaard's investigation, or had been hospitalized and recognized elsewhere a relatively short time after his examinations were closed. In these instances, therefore, time relationships and age were not markedly influenced by the time chosen by Bruusgaard for his follow-up study. But it is conceivable that it may prove to be of considerable more importance in recent years because of greater emphasis on follow-up studies. Therefore, when it comes to comparisons of time relationships and age in various series, the circumstances under which the cardiovascular involvement was diagnosed should always be described in as much detail as possible.

Finally it is essential for the evaluation of time relationships and age not to lump all forms of cardiovascular syphilis together. If we consider uncomplicated aortitis the forerunner of the complicated forms, both from a pathologic-anatomical point of view and relative to time, it is obvious that the number of patients with uncomplicated aortitis in any given series may substantially influence the findings. The greater the number, the shorter the duration of infection, and the lower the age at time of recognition for the group as a whole, just to mention an example. Furthermore, the basis on which rests the diagnosis of uncomplicated aortitis must be taken into account. In one series the majority may have been recognized at autopsy only, while in others the diagnoses may have been based exclusively on clinical examinations. In the first instance time relationships and age depend on the time during the course of the syphilitic infection when the fatal disease struck, whereas in the second instance these

Table 73.

Duration of Infection at Recognition of Cardiovascular Syphilis, According to Form.

(Ages 15 — 39*)

Part 1. Males (41 patients — 37 dead — 4 living**)

Duration of infection at recognition, in years	Forms of cardiovascular syphilis***					Subtotal compli-cated forms	Total
	Uncompli-cated aortitis	Aortic insuffi-ciency	Saccular aneurysm	Ostial stenosis	«Uncompli-cated» aortitis with sudden death		
	No.	No.	No.	No.	No.	No.	No.
0 — 9	0	0	0	0	0	0	0
10 — 14	0	3	1 (1)	0	0	4 (1)	4 (1)
15 — 19	2	0	0	1	1	2	4
20 — 24	1 (1)	1	0 (1)	1	1	3 (1)	4 (2)
25 — 29	1	5 (1)	2	0	0	7 (1)	8 (1)
30 — 34	0	3	1	0	0	4	4
35 — 39	1	4	2	0	0	6	7
40 — 44	2	4	0	0	0	4	6
45 — 49	0	0	1	0	0	1	1
50 over	0	1	2	0	0	3	3
Total	7 (1)	21 (1)	9 (2)	2	2	34 (3)	41 (4)
Mean duration of infection among those aged 15—39 at onset of infection	29.6 (7 pts.)	31.7 (21 pts.)	37.3 (9 pts.)	—	—	31.8 (34 pts.)	31.4 (41 pts.)
Mean duration of infection among those aged 15—40 over at onset of infection	28.8 (8 pts.)	31.5 (22 pts.)	31.7 (11 pts.)	—	—	30.9 (37 pts.)	30.1 (45 pts.)

factors may be totally dependent on the duration of infection at the time the clinical examinations took place. In the present series the majority of the cases with uncomplicated aortitis fell within the former category, as shown in table 67.

We have here discussed some of the epidemiologic factors which are considered important for the evaluation of time relationships and age in cardiovascular syphilis. It is obvious that these factors may vary considerably from one series to another, making comparisons a fairly complicated matter and necessitating caution in drawing conclusions.

Duration of infection and age at recognition. Tables 73 and 74 were

Part II. Females (42 patients — 37 dead — 5 living**)

Duration of infection at recognition, in years	Forms of cardivascular syphilis***					Subtotal complicated forms	Total
	Uncomplicated aortitis	Aortic insufficiency	Saccular aneurysm	Ostial stenosis	«Uncomplicated» aortitis with sudden death		
	No.	No.	No.	No.	No.	No.	No.
0 — 9	1 (1)	0	0	0 (1)	0	0 (1)	1 (2)
10 — 14	2 (2)	0	1	0	0	1	3 (2)
15 — 19	2	2	1	0	0	3	5
20 — 24	3	3	0	0	0	3	6
25 — 29	1	2	1	0	0	3	4
30 — 34	0 (1)	4	0	1	0	5	5 (1)
35 — 39	1	3	0	0	0	3	4
40 — 44	0	2	3	0	0	5	5
45 — 49	3	3	2	0	0	5	8
50 over	0	0	1	0	0	1	1
Total	13 (4)	19	9	1 (1)	—	29 (1)	42 (5)
Mean duration of infection among those aged 15—39 at onset of infection	26.2 (13 pts.)	33.0 (19 pts.)	36.7 (9 pts.)	—	—	34.1 (29 pts.)	31.7 (42 pts.)
Mean duration of infection among those aged 15—40 over at onset of infection	23.7 (17 pts.)	33.0 (19 pts.)	36,7 (9 pts.)	—	—	33.2 (30 pts.)	29.8 (47 pts.)

* Age at infection.
** Dead or living at time of investigation (1949—1951).
*** Categories not mutually exclusive. Combinations of aortic insufficiency and aneurysm have been arbitrarily classified under aneurysm, and combinations of aortic insufficiency and ostial stenosis similarly classified under ostial stenosis (see table 69).

Note: in the part of the table above the small seperation, the numbers in parenthesis denote patients whose age at infection was 40 and over.

constructed in order to demonstrate the duration of infection at the time cardiovascular syphilis was first *recognized.* Time of recognition is here defined as the date the patient first had his syphilitic heart disease diagnosed by a physician, in or outside a hospital. We know that some of the patients had had symptoms for a longer or shorter period of time before they sought medical advice, while others fell victim to rather acute attacks of heart failure, and still others died a sudden death. Under these circumstances and because the patient's own information as to the beginning of the symptoms usually was not sufficiently reliable for estimates of this kind, it was felt that the above definition was the only one through which we could achieve a certain extent of uniformity.

Considering table 73, Parts I and II, it will be seen in the total column, ages 15—39, that the average duration of infection at time of recognition of cardiovascular syphilis, irrespective of form, was about the same in males as in females (31.4 and 31.7 years respectively). As mentioned in the foregoing, sub-grouping according to form is considered essential for the analysis of the phenomena of cardiovascular syphilis, and time relationships form no exception to this rule. It should be noted, however, that the fine sub-grouping has resulted in small figures, so small in fact, that definite conclusions can not be drawn. It is felt, nevertheless, that this method of procedure does make it possible to demonstrate certain important trends. First, it is noticeable that the average duration of infection in uncomplicated aortitis was somewhat shorter than that found for cardiovascular total in both males and females (29.6 versus 31.4 years in males and 26.2 versus 31.7 years in females). Second, a comparison between the total and the sub-group «complicated forms» reveals that the longer duration of infection is to be found in the latter (average 31.8 versus 31.4 years in males, and 34.1 versus 31.7 years in females). In other words, the inclusion of the cases with uncomplicated aortitis tended to lower the average of the duration of infection for the group as a whole. And this is actually what we would expect inasmuch as uncomplicated aortitis, also relative to time, must be considered as constituting the first step in the development of the complicated forms. The differences found were somewhat more pronounced in females, probably because of the proportionately greater number of cases with uncomplicated aortitis among them.

It is also noteworthy that aortic insufficiency seems to have been recognized earlier than saccular aneurysm in both sexes (31.7 versus 37.3 years in males, and 33.0 versus 36.7 years in females for the two forms respectively). Again it must be emphasized that we are fully aware of the small numbers involved, and obviously nothing definite can be said on this point with the data available. The above possibility is nevertheless worth while keeping in mind, and in the present author's opinion it would not be unreasonable to believe that aortic insufficiency gives rise to symptoms from the cardiovascular system earlier than does saccular aneurysm, bringing the patients with the former condition under medical observation at an earlier date, provided the patients are left to decide for themselves when they are going to seek medical advice for their ailment. Of course, it would be an entirely different matter if the patients were subjected to follow-up examinations, or examinations in hospitals for some other disease than their cardiovascular syphilis. Then the time of recognition would depend on the thoroughness of the x-ray examinations among other things, and it might very well be that no difference in time would be found between the two forms. Even if our figures are too small for significant comparisons, on the basis of these findings we feel justified in stressing the importance of sub-

Table 74.

Percentage Distribution of Patients with Cardiovascular Syphilis According to Duration of Infection at Recognition, by Decades and According to Complicated and All Forms, by Sex.

(Ages 15 — 39*) (83 patients — 74 dead — 9 living**)

Duration of infection at recognition by decades	Males				Females				Total			
	Complicated forms		All forms		Complicated forms		All forms		Complicated forms		All forms	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
First	0	—	0	—	0	—	1	2.4	0	—	1	1.2
Second	6	17.6	8	19.5	4	13.8	8	19.0	10	15.9	16	19.3
Third	10	29.4	12	29.3	6	20.7	10	23.8	16	25.4	22	26.5
Fourth	10	29.4	11	26.8	8	27.6	9	21.4	18	28.6	20	24.1
Fifth	5	14.7	7	17.1	10	34.5	13	31.0	15	23.8	20	24.1
Sixth	3	8.8	3	7.3	1	3.4	1	2.4	4	6.3	4	4.8
Total	34	100.0	41	100.0	29	100.0	42	100.0	63	100.0	83	100.0

* Age at infection.
** Dead or living at time of investigation (1949 — 1951).

Table 75.

Age at Recognition of Cardiovascular Syphilis, According to Form.
(Ages 15 — 39*)

Part 1. Males (41 patients — 37 dead — 4 living**)

Age at recognition	Forms of cardiovascular syphilis***					Subtotal Compli-cated forms	Total
	Uncom-plicated aortitis	Aortic insuffi-ciency	Saccular aneurysm	Ostial stenosis	«Uncompli-cated» aortitis with sudden death		
	No.	No.	No.	No.	No.	No.	No.
20 — 29	0	0	0	0	0	0	0
30 — 34	0	1	0	0	0	1	1
35 — 39	0	1	0	0	0	1	1
40 — 44	3	3	0	0	0	3	6
45 — 49	0	1	1	2	1	5	5
50 — 54	1	2	1	0	1	4	5
55 — 59	0	4	2	0	0	6	6
60 — 64	2	3	2 (1)	0	0	5 (1)	7 (1)
65 — 69	0	4	1	0	0	5	5
70 — 74	1 (1)	2 (1)	0	0	0	2 (1)	3 (2)
75 — 79	0	0	1	0	0	1	1
80 over	0	0	1 (1)	0	0	1 (1)	1 (1)
Total	7 (1)	21 (1)	9 (2)	2	2	34 (3)	41 (4)
Mean age at recognition among those aged 15—39 at onset of infection	53.9 (7 pts.)	56.3 (21 pts.)	62.9 (9 pts.)	—	—	57.2 (34 pts.)	56.6 (41 pts.)
Mean age at recognition among those aged 15—40 over at onset of infection	56.3 (8 pts.)	57.0 (22pts.)	64.6 (11 pts.)	—	—	58.4 (37 pts.)	58.0 (45 pts.)

grouping according to form when it comes to analysis of cardiovascular phenomena.

At the bottom of table 73, Parts I and II, we have demonstrated how inclusion of patients whose ages at onset of infection were over 40 influences the averages of duration of infection. The theoretical considerations on this point made in the foregoing, were confirmed in so far as the inclusion of these patients showed a trend, although slight, working in the direction of lowering these averages.

Part II. Females (42 patients — 37 dead — 5 living**)

Age at recognition	Forms of cardiovascular syphilis***					Subtotal	Total
	Uncomplicated aortitis	Aortic insufficiency	Saccular aneurysm	Ostial stenosis	«Uncomplicated» aortitis with sudden death	Complicated forms	
	No.	No.	No.	No.	No.	No.	No.
20 — 29	1	0	0	0	0	0	1
30 — 34	1	0	0	0	0	0	1
35 — 39	1	0	0	0	0	0	1
40 — 44	3	5	0	0	0	5	8
45 — 49	1	1	3	1	0	5	6
50 — 54	0 (2)	1 (1)	0	0	0	1 (1)	1 (3)
55 — 59	1 (1)	6	1	0	0	7	8 (1)
60 — 64	2	2	1	0	0	3	5
65 — 69	1	1	2	0	0	3	4
70 — 74	1	1	1	0	0	2	3
75 — 79	0	1	1	0	0	2	2
80 over	1 (1)	1	0	0	0	1	2 (1)
Total	13 (4)	19 (1)	9	1	0	29 (1)	42 (5)
Mean age at recognition among those aged 15—39 at onset of infection	51.9 (13 pts.)	56.8 (19 pts.)	60.8 (9 pts.)	—	—	57.8 (29 pts.)	55.3 (42 pts.)
Mean age at recognition among those aged 15—40 over at onset of infection	53.9 (17 pts.)	56.6 (20 pts.)	60.8 (9 pts.)	—	—	57.6 (30 pts.)	55.7 (47 pts.)

* Age at infection.

** Dead or living at time of investigation (1949 — 1951).

*** Categories not mutually exclusive. Combinations of aortic insufficiency and aneurysm have been arbitrarily classified under aneurysm, and combinations of aortic insufficiency and ostial stenosis similarly classified under ostial stenosis (see table 69).

Note: In the part of the table above the narrow separation the numbers in parenthesis denote patients whose age at infection was 40 and over.

If there had been greater differences this effect would have to be taken into account for comparative purposes.

In table 74 is presented the percentage distribution by ten-year duration periods of cases of cardiovascular syphilis (complicated and all forms) according to duration of infection at time of recognition. For reasons discussed previously, we hold that figures given for complicated forms are more representative than those given for the total, where uncomplicated aortitis is included. Turning then to the total column, complicated forms, and considering the extreme durations first, it will be noted that no such case was found to have been recognized during the first decade, whereas 4 (6.3 per cent) were diagnosed as late as the sixth. Next it will be seen that 10 patients (15.9 per cent) fell within the second decade. Thus the great majority had their cardiovascular involvement discovered during the third, fourth and fifth decades, the proportions being fairly evenly distributed in the respective decades, (16 (25.4 per cent), 18 (28.6 per cent), and 15 (23.8 per cent), totalling 49 (77.8 per cent)). Further, it will be seen that including uncomplicated aortitis did not substantially influence the figures (total column, all forms), but 1 case (a female) was found to have been diagnosed during the first decade. When it comes to the sex distribution the picture remains very much the same as that described for the total. It can not be excluded, however, that symptomatic cardiovascular involvement actually occurred somewhat later in females than in males, a trend in this direction being demonstrated by the fact that a greater proportion of females among those with complicated forms was found during the fifth and sixth decades (37.9 per cent for females as compared with 23.5 per cent for males). The figures in the present series, however, are too small for significant comparisons, but this possibility should also be kept in mind.

In table 75, Parts I and II, is presented the age at recognition of cardiovascular syphilis according to form. If we consider the total column (for those infected at ages 15—39) including all forms, it will be seen that the average age at time of first recognition was 56.6 years for males and 55.3 years for females. The average age for the complicated forms was somewhat higher (57.2 and 57.8 years for the two sexes respectively). The reason for this again is to be found in the fact that the patients who had their cardiovascular lesions diagnosed as uncomplicated aortitis on an average were younger (53.9 and 51.9 years in the two sex-groups). Thus, as would be expected, inclusion of these latter cases tended to lower the averages. It is noteworthy also that the average age at time of recognition is not markedly different in the two sexes. The fact that recognition seems to take place after longer durations in females than males (table 74) may mean that females contract syphilis at an earlier age than males. This is generally thought to be true and in this material also there is indication that this is true, despite small differences (see table 23, p. 94). The inclusion of patients whose age at infection was 40 and over only slightly influenced the figures in the present series, as demonstrated by the averages given at the bottom of table 75.

In table 76 is presented the percentage distribution of cardiovascular syphilis according to age at time of recognition, and according to complicated and all forms, by sex. If we first turn to the total column, «complicated forms»,

Table 76.

Percentage Distribution of Patients with Cardivascular Syphilis According to Age at Recognition and According to Complicated and All Forms, by Sex.

(Ages 15 — 39*)
(83 patients — 74 dead — 9 living**)

Age at recognition	Males				Females				Total			
	Complicated forms		All forms		Complicated forms		All forms		Complicated forms		All forms	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
20 — 39	2	5.9	2	4.9	0	—	3	7.1	2	3.2	5	6.0
40 — 49	8	23.5	11	26.8	10	34.5	14	33.3	18	28.6	25	30.1
50 — 59	10	29.4	11	26.8	8	27.6	9	21.4	18	28.6	20	24.1
60 — 69	10	29.4	12	29.3	6	20.7	9	21.4	16	25.4	21	25.3
70 over	4	11.8	5	12.2	5	17.2	7	16.7	9	14.3	12	14.5
Total	34	100.0	41	100.0	29	100.0	42	100.0	63	100.0	83	100.0

* Age at infection.
** Dead or living at time of investigation (1949 — 1951).

it will be seen that such conditions were only rarely diagnosed before the age of 40 (2 cases — 3.2 per cent), whereas the number recognized at the age of 70 and over was greater (9 cases — 14.3 per cent). Thus the great majority was found between 40 and 70 (52 cases — 82.5 per cent), with the following distribution: 40—49, 28.6 per cent; 50—59, 28.6 per cent; and 60—69, 25.4 per cent. The even distribution within the above mentioned three 10-year age periods and also the relatively high percentage found at the age of 70 and over, is noteworthy, and what it actually means is this: if the patients are left to seek medical advice of their own accord — as was usually the case in our series — the cardiac symptoms seem to develop, not chiefly during the early part of middle life but all through the period from 40 and up to old age, with a natural falling tendency after the age of 70.

In principle the picture just described for the total (complicated forms) remains very much the same when we sub-group according to sex, although there seems to be certain differences between males and females in some of the ages in the table. The figures are too small, however, for significant comparisons.

Duration of illness between time of recognition and final observation. As one of the indices for the prognosis of cardiovascular syphilis, the duration of illness between time of recognition and final observation is of considerable importance, but the evaluation of the factors which influence this interval in any given series is a very complicated matter due to the many variables which enter the picture. It appeared to us, therefore, that a description of the findings in the present series could only be of limited value from a comparative point of view. This is true also of duration of infection and age at time of final observation because the values found are determined by the duration of illness after recognition, and are thus influenced by the same factors. When we nevertheless have chosen to present our results (see annex VI, pp. XXVIII—XXX), this has been done not only for completeness sake, but also because a discussion of the difficulties involved in analysis might prove useful in itself and serve as a warning against possible comparisons with the findings in other series.

Cardiovascular Syphilis as a Cause of Death.

Table 77 was constructed in order to demonstrate the frequency with which patients died *of* their cardiovascular syphilis, or primarily of some other disease but *with* cardiovascular syphilis. First, if we consider the total column (that is, cardiovascular syphilis irrespective of form), it will be seen that this condition was considered the primary cause of death in 25 of 41 males (61.0 per cent), and in 20 of 42 females (47.6 per cent). It was a contributory cause of death in 6 males (14.6 per cent) and 6 females (14.3 per cent), and finally the males showed 10 cases (24.4 per cent) where the cardiovascular syphilis was non-related to the cause of death, as compared with 16 cases in females (38.1 per

Table 77.

Distribution of Patients with Cardiovascular Syphilis According to Cause of Death, by Form and Sex.

(All ages*) (83 patients**)

Cause of death	Forms of cardiovascular syphilis***							Subtotal Complicated forms		Total	
	Uncomplicated aortitis	Aortic insufficiency	Saccular aneurysm	Ostial stenosis	Aortic insufficiency plus ostial stenosis	Aortic insufficiency plus aneurysm	«Uncomplicated» aortitis with sudden death				
	No.	No.	No.	No.	No.	No.	No.	No.	Per cent	No.	Per cent
Males.											
Primary	0	14	4	1	1	3	2	25	73.5	25	61.0
Contributory	0	4	2	0	0	0	0	6	17.6	6	14.6
Non-related	7	3	0	0	0	0	0	3	8.8	10	24.4
Total	7	21	6	1	1	3	2	34	100.0	41	100.0
Females.											
Primary	0	15	2	1	1	1	0	20	80.0	20	47.6
Contributory	3	1	2	0	0	0	0	3	12.0	6	14.3
Non-related	14	1	1	0	0	0	0	2	8.0	16	38.1
Total	17	17	5	1	1	1	0	25	100.0	42	100.0

* Age at infection.
** Refers to the 83 patients, out of the total of 92, who were found to be dead at time of investigation (1949 — 1951).
*** Categories mutually exclusive.

cent). Second, by studying the various forms, we find that in no instance was uncomplicated aortitis found to be the primary cause of death. In 7 out of 7 males and 14 out of 17 females this condition was non-related, whereas in the remaining 3 females it was considered to be contributory. In this connection it should be recalled (see p. 276) that the vast majority of our cases with uncomplicated aortitis was diagnosed at autopsy only and thus in all probability represented the early stages of the pathologic-anatomical development of this condition *per se*. When it comes to the complicated forms (see subtotal column) it will be seen that these conditions proved fatal in the majority of instances (25 out of 34 males — 73.5 per cent, and 20 out of 25 females — 80.0 per cent). Further, they were held to be the contributory cause of death in 6 males (17.6 per cent) and 3 females (12.0 per cent) and in only 3 males (8.8 per cent) and 2 females (8.0 per cent) were they considered to be non-related.

In the present series the seriousness of these complications is clearly demonstrated by the fact that about three-fourths to four-fifths of the patients, who had developed complicated aortitis, died primarily *of* their cardiovascular syphilis, while only close to one-tenth of them died of some other disease *with* their cardiovascular syphilis non-related to the cause of death. It does not subtract much from the seriousness that in a certain proportion of the cases complicated aortitis was held to be «only» a contributory cause of death (17.6 and 12.0 per cent respectively for males and females).

A comparison between males and females shows certain trends which are important and in spite of the small figures involved are in keeping with what we would expect. The most striking difference is the greater proportion of males dying *of* their cardiovascular syphilis (61.0 per cent compared with 47.6 per cent in females), and the correspondingly greater proportion of females dying *with* their cardiovascular syphilis (38.1 per cent compared with 24.4 per cent in males). The main reason for this lies in the greater proportion of cases with uncomplicated aortitis among the females, and the fact that this condition was in no instance found to be the primary cause of death. As soon as complicated aortitis had developed, however, the outcome was very similar in the two sexes, as demonstrated by the finding that the majority of these cases ended fatally in both (73.5 per cent in males and 80.0 per cent in females). Quantitatively the above described findings are the most important features revealed by this table, and so far the results seem logical. The figures obviously are too small to justify further comparisons within the various sub-groups.

III. Discussion.

Age at Infection.

It can probably be considered an established fact that cardiovascular involvement in late congenital syphilis is a rare event. Aggerbeck (1949) for example, found only one case among his 88 patients (see p. 261). In this connection it is of interest to note that no case of cardiovascular syphilis was found among the 66 persons in our series who acquired their disease before the age of 15 (see table 68, p. 279). It must be emphasized that the majority of them were infected at ages 0—4. With the relatively small number observed, we are in no position to state that cardiovascular syphilis does not occur in such patients, but our findings suggest that these complications are rare. Thus, using cardiovascular involvement as an index, it seems that in those infected in utero and in those infected during early childhood, the syphilitic infection takes a considerably milder course than would be expected.

Our findings are in keeping with the fact that cardiovascular syphilis among young adults is only seldom reported in the literature. However, when it comes to cases of cardiovascular syphilis among young adults described from hospitals and elsewhere, we must take into account that the size of the syphilis reservoir from which these patients are drawn is usually unknown; we are dealing with numbers of cases and not with proportions. If the reservoir is small, the number of cases with cardiovascular lesions must necessarily also be small, even if patients infected during early childhood developed these complications in the same proportions as do those infected in adult life. Although varying from country to country and from area to area, the number of persons infected during early childhood in all probability has been relatively small in most countries, particularly during the past 20—50 years. An example being our own series where patients aged under 15 at infection constitute no more than 6—7 per cent of the total study group, in spite of the fact that our patients were drawn from the lower socio-economic strata of the population at the turn of the century when the possibility of non-venereal spread of the infection to children was much greater than later on, because of the poor hygienic conditions then prevailing in many of the homes. When it comes to areas of endemic syphilis, however, infection of children is a common occurrence, as shown by Grin (1953) in his investigations in Yugoslavia, and this has probably been so for many decades preceding the recent surveys. In other words, if acquired non-venereal syphilis in children (untreated) resulted in the same proportions of cardiovascular lesions as does the untreated infection in the adult, and there were no marked differences between the two groups as to «incubation period» of these complications, we would expect cardiovascular syphilis among young adults to be no rarity at all in those areas of Yugoslavia. On the other hand, if our hypothesis is correct, namely that the syphilitic infection takes a milder course in patients infected during childhood, as measured by the frequency of subsequent cardiovascular lesions, we would expect cardiovascular syphilis among young adults to be rare also in the Yugoslav areas of endemic syphilis. Therefore, a study of the prevalence of cardiovascular involvement among young adults in the above mentioned areas may give further evidence either for or against our hypothesis. Incidentally, Grin (1953) writes that cardiovascular lesions are well known in endemic syphilis areas, but there is no statement as to its occurrence among young adults.

For the age-groups 15—19, 20—29, and 30—39 we found a tendency towards increasing frequency of cardiovascular involvement the later in life syphilis was acquired (8.0 per cent, 9.8 per cent, and 14.6 per cent in the three groups respectively, see table 68, the total column, p. 279). The differences, however, were not statistically significant, and thus we are not in a position to determine whether our findings represent a true picture of these phenomena or not. But seen in connection with the fact that there was only a slight decrease at ages 40 and over (12.3 per cent cardiovascular involvement), it is safe to state that even in patients infected rather late in life, the risk of developing cardiovascular lesions still seems to be considerable compared with those infected at younger ages.

Although we are fully aware of the fact that definite conclusions can not be drawn with the data available, the trend demonstrated could nevertheless form the basis for the following hypothesis: using the frequency of cardiovascular involvement as an index, the later in life that syphilis is acquired, the more potentially serious the outcome. In the present author's opinion the hypothesis definitely deserves further testing as shown by the considerations made below.

We know that females do not develop serious late complications to the same extent as do males, and one of the theories advanced to explain this phenomenon has to do with a protective mechanism of certain hormonal effects of pregnancies and menstruation. If females are really protected through these hormonal effects, then one might be inclined to believe that the longer the latter have a chance to exert their influence, the smaller the proportions of serious complications. In other words, after sexual maturity is reached, the earlier in life syphilis is acquired the more protection. If so, we would expect an increasing frequency of cardiovascular involvement the later a woman is infected. Among the females in our series the proportions developing cardiovascular lesions were as follows: age at infection 15—19, 5.3 per cent; 20—29, 7.9 per cent; 30—39, 11.5 per cent; and 40 and over, 11.1 per cent. Provided the differences are not a product of chance, the findings would fit in with the above mentioned hypothesis. A possible decrease at ages 40 and over could be explained by the shorter span of life left for these patients in which to develop cardiovascular lesions. However, further testing of this part of the hypothesis necessitates a comparison between males and females. If a trend similar to that described for the females, is also demonstrated for the males, it is obvious that the increasing frequencies of cardiovascular involvement the later in life a woman is infected can not possibly be explained on the basis of the hormonal effects of pregnancies and menstruation alone. Then the factor or factors responsible for this distribution must be common to both sexes. On the other hand, if the proportions among the males showed no such trend, that would be more in keeping with what we would expect as to the effects of pregnancies and menstruation according to the hypothesis advanced. In the present series the proportions among the males came out as follows: age at infection 15—19, 16.3 per cent; 20—29, 13.3 per cent; 30—39, 19.2 per cent; and 40 and over, 14.3 per cent. Here too there is a suggestion of a trend towards increasing frequency the later in lifte syphilis is acquired up to the 40 and over group (except ages 20—29), but the differences are small, and we are in no position to draw conclusions on the basis of a comparison between males and females in this respect. Thus, our findings actually leave the entire question open.

Sex.

It is generally accepted that the outcome of the syphilitic infection as to serious late lesions to a great extent is influenced by sex. Here we are dealing with a series of patients untreated or highly inadequately treated for their early lesions, and when it comes to the sex difference our findings are in principle in accordance with what would be expeceted. The proportions developing cardiovascular lesions, irrespective of form, are about twice as high in males (14.9 per cent versus 8.0 per cent in males and females respectively, or a ratio of 1.9 to 1, (see table 71, p. 286). When sub-grouping according to complicated and uncomplicated aortitis, we find a more pronounced sex difference in the former group (12.1 per cent versus 5.1 per cent in males and females respectively, or a ratio of 2.4 to 1), as contrasted with almost equal proportions in the latter (2.6 per cent versus 2.9 per cent respectively, or a ratio of 1 to 1.1). In this connection it is worth recalling that an analysis of the autopsy population with its probable maximum proportions of cardiovascular involvement, shows about the same ratios for males and females as those found in the study group «Known» as a whole (uncomplicated aortitis: 9.3 versus 11.2 per cent for males and females respectively, or a ratio of 1 to 1.2; complicated aortitis 25.3 versus 10.4 per cent respectively, or a ratio of 2.4 to 1, (see table 72, p. 287). As regards the sex difference in cardiovascular syphilis, the findings in the present series thus seem to represent the end results of a process of development which has left us with almost equal proportions of uncomplicated aortitis on the one hand, and with a marked excess of males over females in complicated aortitis on the other. It these relationships between males and females relative to the outcome of cardiovascular syphilis are accepted as being representative of the natural course of the disease, how can we explain what has actually happened?

When and in what proportions spirochetal invasion of the aorta takes place during the early phases of infection is not known. It is usually held, however, that the central nervous system is invaded to the same extent in males and females, as judged from the fact that no sex difference seems to exist in asymptomatic neurosyphilis. Also the external manifestations of the general spread of the infection during the period of secondary syphilis and secondary relapse are by and large identical in the sexes, both qualitatively and quantitatively. Thus, there is indirect evidence pointing in the direction of the aorta being invaded in equal proportions too. Next, we do not know how many of the patients whose aorta has been invaded originally, subsequently develop recognizable uncomplicated aortitis. It is obvious on the other hand, that all those who end up with complicated forms of cardiovascular involvement pass through an uncomplicated stage before the former conditions develop.

In order to explain the end results in the present series in respect to the ratios males to females during the various stages of cardiovascular involvement, we must assume the following to have taken place (see fig. 9). (It should be noted that the diagram has been constructed only for the purpose of demonstrating the *ratios* males to females. The *number* of cases used have been chosen arbitrarily and do *not* correspond to the actual findings in our series). First, in accordance with the considerations made in the foregoing, we have reckoned with spirochetal ivasion of the aorta in equal proportions (starting-point 100 males and 100 females — ratio 1 to 1). Next, males must have developed clinically and/or macroscopically recognizable uncomplicated aortitis to a greater extent than females did (40 out of 100 males, and 25 out of 100 females — ratio 1.6 to 1), whereafter males among these patients with uncomplicated aortitis went on to develop complicated forms in a comparatively still greater proportion (25 out of 40 males as compared with 10 out of 25 females — ratio 2.5 to 1). Thus, as a result of this development, we are left with 15 males and 15 females in the category uncomplicated aortitis, a ratio of 1 to 1.

If the hypothetical considerations made above should be correct, it would mean that the mechanism which to a certain extent protects females against cardiovascular complications — whatever that mechanism may be — exerts its influence from the time that aortitis is in the process of developing, something which would not seem unreasonable. Due to the unknown factors involved, however, we are not in a position to draw definite conclusions on this point, but we do feel that the theory advanced is a plausible one.

The next question one might ask in this connection is the following: How do the assumptions made on the basis of the findings in our series, fit in with the hypothesis advanced to explain the sex difference in cardiovascular syphilis?

It is a well known fact that physical activity affects the cardiovascular system in general, and there is considerable evidence that it is of importance for the development of cardiovascular lesions in syphilis. A definite relationship between physical stress and cardiovascular complications has been established by several

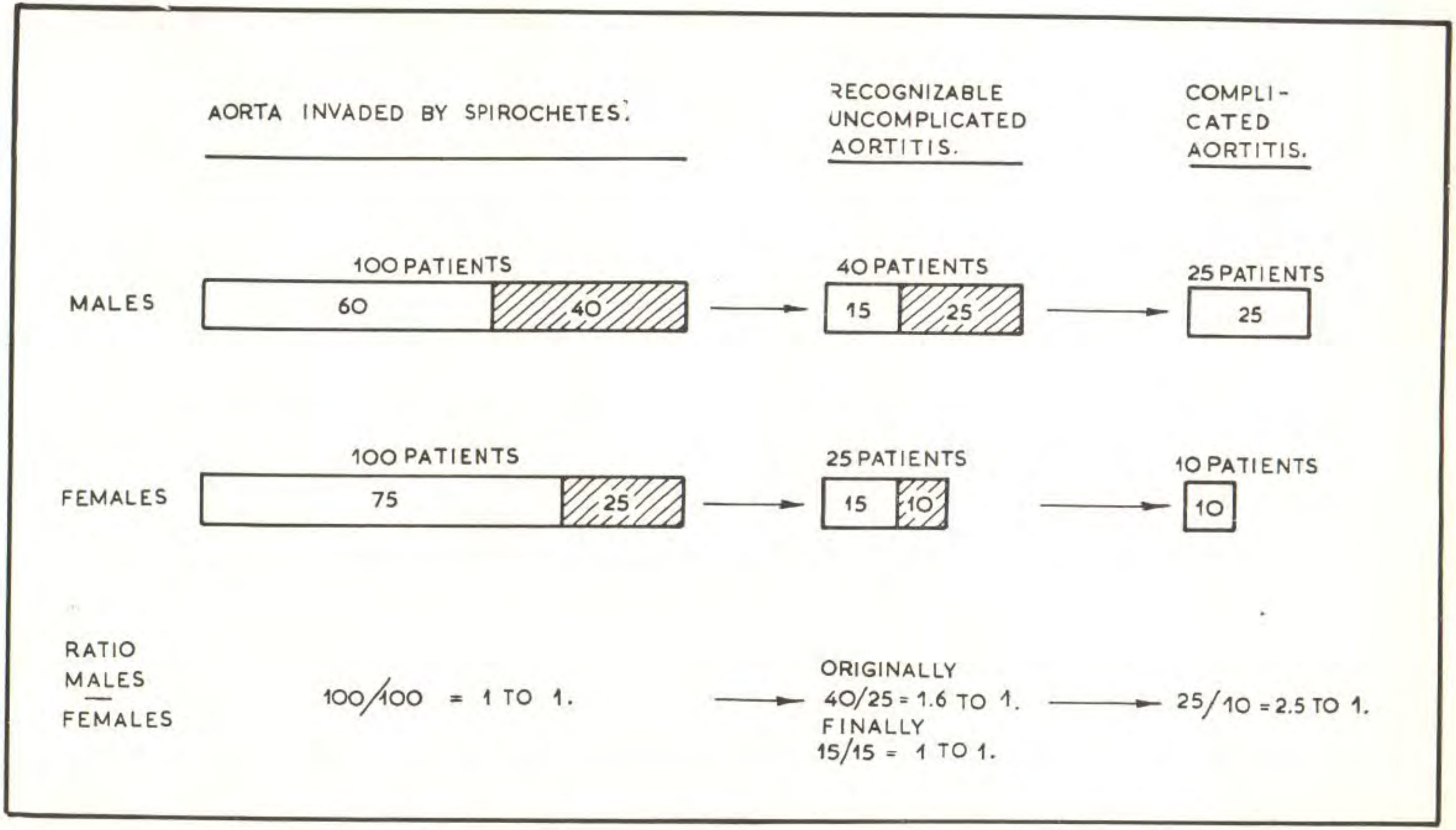


FIG. 9.

The Possible Development of the Ratios Males to Females Through the Various Stages of Cardiovascular Involvement.

authors, Kemp and Cochems (1937) and Kampmeier (1943). It would thus be natural to believe, as suggested among others by White (1944), that greater physical activity is also responsible for the greater frequency of cardiovascular involvement among males as compared with females. If we accept this explanation, then — according to our theory — one must assume the factor of physical stress to be working during the period between the spirochetal invasion of the aortic wall and the development of recognizable uncomplicated aortitis, thus leading to a greater proportion of males with that condition. Thereafter the factor continues to exert its influence among those with uncomplicated aortitis, resulting in a still greater proportion of males with complicated forms. This appears to us to be a logical sequence of events, and so far our findings seem to be in keeping with the hypothesis that physical labour may be responsible for the excess of males over females in cardiovascular syphilis.

Occurrence.

The many factors influencing the end results in any given series in respect to frequency of cardiovascular syphilis were discussed at considerable length in the section on literature, and in the description of our own findings. We were left with the impression that — even under favorable conditions — it was close to impossible to account for *all* these factors. As a consequence, therefore, conclusions based on comparisons between various series as to occurrence of cardiovascular involvement must be drawn with caution in order to avoid misinterpretations.

It is essential first of all, to consider carefully and analyse critically *the basic epidemiologic methods* used in establishing the study groups in question, which, of course, is a prerequisite for any evaluation of data.

It is obvious, for instance, that figures arrived at through the study of autopsy populations are not comparable with those found in ordinary follow-up studies. Any autopsy population will necessarily be more or less heavily weighted with serious cases as compared with the hospital population from which it is drawn, and even more so as compared with the original «syphilis universe». This phenomenon was clearly demonstrated in our series, where the autopsied patients showed a considerably higher frequency of cardiovascular lesions than the study group as a whole. Moreover, if we consider the dead, the fact that about 66 per cent of those with cardiovascular involvement was found to have been autopsied, as compared with about 30 per cent of the total, shows that persons who had developed such complications ended up in hospital *and* were submitted to autopsies to a far greater extent than did the others (see p. 284). When it comes to hospital populations including a varying number of dead and living patients, materials selected from such groups also tend to become biased in the direction of more serious cases, because disease brought the patient to the hospital, and thus figures arrived at in studies of this nature can not be directly compared with those arrived at in follow-up studies. Finally, this is probably true as well of figures found in the studies of patients picked from hospitals *and* clinics (or out-patient departments), although not quite to the same degree as in the first two instances mentioned.

Since the present investigation has all the characteristics of a follow-up study, it is hardly advisable to compare our quantitative data in respect to cardiovascular syphilis, with those arrived at through the various other methods of approach just mentioned. As a matter of principle, therefore, we are inclined to consider it a prerequisite for such comparisons that the figures in question stem from a similar type of study. But this in itself is not a sufficient guarantee for comparability since methods of tracing, identification and collection of clinical data may vary from one follow-up study to another according to geographical area, population groups involved, the investigator's attitude towards the problems, and other factors, all of which may have a considerable bearing on the end results. A critical evaluation of these factors and how they may have influenced the findings, undoubtedly forms another requirement for eventual comparisons. The point is exemplified in our discussion of Aggerbeck's (1949) and Nielsen's (1950) Danish studies (pp. 266—273) as well as in the analysis of our own data. Thus, only after having evaluated the basic epidemiologic methods employed in establishing the materials in question, is it in our opinion, worthwhile to proceed to a discussion of the many other factors involved, the most important of which are going to be considered in the following.

1. *Sex.* Practically all investigators have found an excess of males over females in cardiovascular syphilis. The findings in the present series show that this is also true of patients who have received little or no treatment for their early manifestations and highly inadequate treatment subsequently. There is, therefore, good reason to consider this a characteristic feature of the natural course of the syphilitic infection. That being so, it is self-evident that the analysis always must be done on a sex-specific basis, and when it comes to *comparisons* it is a sine qua non. Only too often do we find quotations in the literature where the figures are those based on the totals in the respective series. Figures presented in such a manner leave an impression which may be misleading seen from a prognostic point of view, in the sense that they usually tend to give a too favorable picture of the outcome for males and too serious a picture of the outcome for females. This is exemplified in the present series where the proportions of cardiovascular syphilis irrespective of form, were 10.4 per cent for the total, as compared with 14.9 per cent for males and 8 per cent for females. The phenomenon is even more strikingly demonstrated if we limit ourselves to the complicated forms, where the percentages were as follows: 7.6 per cent for the total, 12.2 and 5.1 per cent for males and females respectively.

2. *Length of period of observation.* The length of the period of observation probably is one of the most decisive and at the same time one of the most difficult

factors to account for, when it comes to comparisons between proportions of cardiovascular syphilis in the various studies. We must bear in mind that we are dealing with a type of complication which is characterized by its pronounced chronicity on the one hand, and by its various stages of pathologic development on the other. In order to compare like with like it is not only a question of demanding that the patients in the respective series are followed for about the *same* length of time, but it is also a matter of deciding what constitutes a *sufficiently long period of observation.* The latter problem is not an easy one, because of the many gaps in our knowledge of the natural course of the infection. First, we do not know when and to what extent uncomplicated aortitis develops, neither for how long it remains uncomplicated. Second, there is no reliable data showing when and to what extent we can expect to encounter symptomless complicated aortitis, and finally, we have only an approximate idea as to when the complicated forms give rise to symptoms which force the patients to seek medical advice. In the past it was usually assumed that cardiovascular lesions had an «incubation period» of about 20 years. In this connection cardiovascular lesions probably for the most part meant complicated forms as seen in hospitals and/or clinics. Twenty years, therefore, was considered by many observers to be a sufficiently long period of observation, and quite a number of investigations were carried out on the basis of that concept. A follow-up of patients 10—20 years after infection is in itself by no means without value inasmuch as it may serve to detect cases suspicious of uncomplicated aortitis and early cases of complicated aortitis (with or without symptoms), but it is definitely too short an observation period when we think in terms of an all-over evaluation of the outcome for comparative purposes. This standpoint is based on the findings as to complicated forms in our series, where the average duration of infection at time of recognition is somewhat more than 30 years (31.8 years and 34.1 years for males and females respectively, (see table 73,[1] p. 292), and where only about one-sixth (15.9 per cent) of the cases had been recognized at the end of the second decade (see table 74,[1] p 295). The latter table further reveals that the proportions recognized through the third, fourth and fifth decades of infection are 25.4 per cent, 28.6 per cent and 23.8 per cent respectively, with a natural decrease in the sixth (6.3 per cent). This, we believe, is an important point implying that we may expect the majority of such complications to give rise to symptoms *after* twenty years with the proportions relatively evenly distributed over the third, fourth and fifth decades of infection. In view of the many factors playing a part in the development of these conditions, the above seems to be a logical sequence of events, probably reflecting — at least in principle — the natural course of infection. If our findings are accepted as representative in that respect, it follows that an *average* observation period of at least thirty years is necessary *for comparative purposes*. What an average

[1] The figures refer to complicated forms.

observation period of thirty years means is illustrated by the fact that we have followed the majority of our patients until death and the remainder for a period averaging about 50 years.

3. *Forms of cardiovascular involvement.* We are fully in agreement with Kampmeier (1943) when he states that one of the most common faults with statistics on cardiovascular syphilis is that all forms are lumped together. The reason why this should be avoided is the great uncertainty connected with diagnosing uncomplicated aortitis clinically, and in our opinion, Kampmeier is also right when he says that there are no figures on the frequency of this condition that are worth while — and we might add, there probably never will be. Even if we accept Moore's (1949) concept that uncomplicated aortitis under certain specified conditions can be diagnosed ante mortem in a fair number of instanes, figures arrived at in any given series can at best never be but approximate and thus do not lend themselves well for comparisons. The only way to avoid the dilemma and secure uniformity would be to follow all, or the vast majority of the patients until death with verification of the diagnoses through autopsy, a requirement which no investigation up to the present time has met. The «Alabama» study (see p. 28) may form an exception; the preliminary reports indicate unusually high proportions of autopsies. That study, however, suffers from a most significant shortcoming inasmuch as the duration of disease actually is unknown.

At any rate, before proceeding to comparisons, sub-grouping according to form is essential, as is also a careful consideration of the methods employed in diagnosing. However, since uncomplicated aortitis represents the earliest manifestation of cardiovascular involvement on the one hand, and on the other may or may not remain uncomplicated, the frequency with which it can be expected to occur is highly dependent on when during the course of the infection the examinations take place. Consequently the length of the observation period must be taken into account as well. Finally, sub-dividing according to uncomplicated and complicated aortitis takes on added importance in view of the great prognostic differences between the two groups of lesions.

4. *Patient's socio-economis status, period of time during which infection takes place, and mortality from diseases other than syphilis.* Since cardiovascular syphilis has a relatively long «incubation period» the rate at which the patients succumb to other diseases before the cardiovascular lesions have had a chance to develop, may have a considerable bearing on the frequency of the latter complications. It is generally accepted that syphilis is a social disease and, therefore, whenever we pick a large sample of syphilitics, we are apt to get a group of patients, which in addition to the syphilitic infection is exposed to a host of other diseases more commonly found in the lower socio-economic strata of the population. In this connection the most important diseases are those striking with high case fatality rates during the earlier years of the syphilitic infection.

Tuberculosis is a typical example. Thus, the death rates from tuberculosis, and other diseases, in any given series of syphilitics, will to no small extent determine how many of the original patients are going to survive long enough to experience cardiovascular syphilis, particularly the complicated forms. And again, those death rates are not only dependent on the socio-economic status of the patients in question, but they are apt to vary considerably from one period of time to another, and according to geographical areas concerned.

In respect to our own patients it is worth recalling that most of them were drawn from the lower socio-economic classes and were infected with syphilis around the turn of the century, when mortality from many diseases — and tuberculosis in particular — was greatly different from what it is today.[1] In the present series, therefore, the relatively high death rates from diseases other than syphilis would work in the direction of minimizing somewhat the proportions developing cardiovascular lesions. In principle this will practically always be true of any large sample of syphilitics, because it is difficult to conceive of such a group *not* being exposed to the many other diseases connected with poverty, ignorance and neglect. As mentioned above, however, the rate at which the patients in question succumb to other diseases before cardiovascular syphilis has had time to develop, may nevertheless *vary* from one series to another, and for purposes of comparisons that must be taken into account.

5. *Occupation.* As mentioned previously, there seems to be a definite relationship between physical activity and the frequency of cardiovascular lesions, particularly the complicated forms. It has furthermore been suggested that the excess of cardiovascular syphilis among Negroes as compared with whites, is due to the greater amount of hard labour usually done by members of the former race, and finally it has been indicated, among others by ourselves, that physical stress may be responsible for the excess of males over females. Evidence thus points in the direction of occupation as representing another of the environmental factors which may play an important part in determining to what extent cardiovascular complications are going to develop among the patients in any given series. And also, there is reason to believe that the ratio males to females may vary according to the degree that the members of the two sexes in a group of syphilitics are exposed to occupational stress. In comparisons, therefore, this factor should always be taken into consideration, if possible. However, we have already opined that it is not only a matter of physical activity during the period just prior to the emergence of symptoms and signs of cardiac disease, but as much a question of the type and/or types of work the patients may have been doing all through the many years before the pathologic process reached that far. Under those circumstances there can be no doubt that an analysis of the

[1] The death rate from tuberculosis (all forms) in Norway reached a maximum of 31 per 10,000 in the five-years period 1896—1900, whereafter it dropped steadily until 1942 when it was 7.3 per 10,000, a decrease of about 77 per cent (Schiøtz, 1948).

effects of physical activity on the frequency of cardiovascular lesions, in itself poses problems of a very complex nature. And when we have to deal with more than one series of patients for comparative purposes, the difficulties are correspondingly aggravated, in so far as the extent to which the patients are exposed to occupational stress may vary considerably from one series to another, according to such indices as geographical area, ethnic or population groups involved, and working conditions prevailing during the period of time from onset of infection and up to the point when cardiovascular lesions manifest themselves.

Due to lack of pertinent information we had to abstain from a detailed analysis of the occupational factor (see p. 289). But we are inclined to believe that our patients, coming as they did from the lower socio-economic strata of the population, and being infected with syphilis at about the turn of the century, were exposed to a considerable amount of physical stress, because, in order to make a living, they were obliged to work long hours under conditions which were definitely much poorer than we find them today. Although our own material thus illustrates the difficulties involved in evaluating the effects of occupation on the occurrence of cardiovascular lesions in a long-term follow-up study, we are nevertheless of the opinion that comparisons are too often made without even attempting to account for this factor.

6. *Treatment.* It can be considered an established fact that antisyphilitic treatment during the early stages of the infection plays a decisive role in the outcome as regards serious late lesions, and the frequency of cardiovascular involvement naturally forms one of the most important indices through which can be measured the efficacy of such treatment. On the one hand evaluation may be based on comparisons between treated and untreated patients, and on the other on comparisons between patients having received various types and amounts of treatment. In many of the retrospective follow-up studies, it evidently has been a fairly simple matter for the investigator to determine what the patients were given in the form of treatment for their very first manifestations of the disease, but as soon as we get into the problem of collecting information on proportions having been re-treated because of serologic or clinical relapse, or having continued treatment outside the original hospital or clinic, it seems as if considerable difficulties have been encountered as judged from the lack of data on this point which characterizes several of the investigations. There can be no doubt that a thorough analysis of types and amounts of treatment administered all through *the early period of infection* is essential for comparative purposes, but also it is of importance to find out when and to what extent the patients in question may have received treatment *in the interim*, i.e. between the termination of the early stages and the time when cardiovascular complications can be expected to manifest themselves. The problem of treatment in the interim period is not an easy one in these times of almost universal treatment

of all forms of syphilis, latent syphilis included, and the fact that so many investigators have had to disregard it, in part or completely, is not at all surprising. True enough, we have only a limited knowledge of the protective effects on the cardiovascular system of antisyphilitic therapy administered for «benign» tertiary, neuro or latent syphilis, but there is good reason to believe that such treatment, if adequate, may prevent the development of serious cardiovascular complications in a fair number of instances. Therefore, it is not a satisfactory method of procedure to limit our study to those found to have experienced cardiovascular syphilis; it is necessary to find out, if possible, whether the remainder did not escape these complications because of antisyphilitic treatment given in the interim period. This is admittedly difficult, but there can be no denying that the factor may influence to no small degree the end results as to cardiovascular syphilis in any given group of patients, and thus, from a comparative viewpoint, forms another of the many variables that must be considered in order to avoid misinterpretations.

In respect to our own series, it has been credibly established that the majority of the patients was left untreated during the period of hospitalization in Boeck's department, and that only a negligible number subsequently received specific treatment (usually highly inadequate) for relapses. Furthermore, although some of the patients were given specific treatment during the interim period, it has been shown through a chain of inferences that it was probably administered in such types and amounts, so as to have affected the natural course of the infection less than in any other group of syphilitics studied up to the present.

In this discussion we have stressed the importance of paying attention to the many factors which may play a part in the end results as to the frequency of cardiovascular lesions in any given series, while we have constantly kept in mind the possibility of our own figures being used as a natural base-line for eventual comparisons between untreated or highly inadequately treated patients and patients having received varying amounts and types of treatment. And we feel justified in pointing to the complexity of these matters and to the necessity of exercising caution in drawing conclusions based on such comparisons.

The fact that the present investigation is based on a material which by and large is the same as that utilized by Bruusgaard (1929a) some twenty-five years ago, offers an opportunity to further elaborate on some of the problems of comparability. And at the same time to test the validity of the findings in the previous follow-up study, one of the principal aims of our re-analysis.

The proportion found by Bruusgaard to have developed cardiovascular syphilis (or probable cardiovascular syphilis) was 14.2 per cent, as compared with 10.4 per cent in the present study. In other words, as the figures stand, it seems that the conclusion reached by Sowder (1940), namely that Bruusgaard's findings tended to exaggerate the seriousness of the infection, is confirmed by the re-analysis. However, these figures are *not* comparable and the chief reason for this is to be found in the differing concepts held by Bruusgaard and the present investigator as to which cases should be classified under cardiovascular syphilis. Bruusgaard came to a proportion of 14.2 per cent by using a total of 67 cases as a numerator and 473 patients observed, directly or indirectly, as a denominator. As mentioned previously (p. 21) we are inclined to accept Bruusgaard's use of the 473 investigated cases as a denominator, rather than basing the calculations on the original 2,181 patients in the material, as suggested among others by Sowder. So, from a comparative standpoint, the problem actually revolves around the principles of definition employed in establishing the numerator. And, before proceding to comparisons of proportions, we shall have to consider that numerator in view of our own definitions, and determine the order of magnitude accordingly. This method of procedure first necessitates the elimination of the 34 patients among Bruusgaard's dead (see p. 266) diagnosed as suffering from such vessel diseases as paralysis of the heart, arteriosclerosis, apoplexy of the brain, etc. Bruusgaard included these 34 cases in the numerator, assuming that the majority of the diseases in question were of syphilitic etiology (see p. 14), as judged from the data presented, however, without much qualification. Next, it is necessary to omit one case of apoplexy among the living (see p. 266), thus making a total of 35 which, according to our definitions, shall have to be subtracted from the original numerator of 67, in order to make the proportions in the two series comparable up to this point. That leaves us with 32 cases altogether, and if we apply this numerator on the investigated 473 patients it gives a percentage of 6.8 as contrasted with Bruusgaard's original 14.2, and ours of 10.4. So far, by comparing the totals in each series it seems as if Bruusgaard's *actual* findings tended to minimize rather than exaggerate the seriousness of the infection. However, as emphasized on several earlier occasions, comparisons based on the totals in the respective series do not give a true picture of the relationships in question, the reason being that all cases of cardiovascular syphilis are included in the numerator irrespective of form. Sub-grouping according to form thus constitutes the next step in this discussion of comparability.

First, among the 32 cases in Bruusgaard's series, for comparative purposes now used as a numerator, there were 12 cases of complicated aortitis (2.5 per cent of the total of 473). The 2.5 per cent compares with the 7.6 per cent complicated aortitis in the present series, meaning that we have found proportionately three times as many cases with serious complications as did Bruusgaard. Second, according to present-day definitions, the majority of the above mentioned 32 cases, namely 20 (4.2 per cent of the total of 473), falls in the category uncomplicated aortitis. The diagnosis was verified at autopsy in only 7 instances, whereas the remaining 13 were examined by Bruusgaard and classified as «dilatation of the heart and aorta», evidently on the basis of x-ray findings or merely x-ray suggestions. Furthermore, 12 of the 13 again, were submitted to examinations from 20 to 40 years after infection (see annex tables I, II and III), indicating that most of them probably were 40 and over at time of diagnosis. In view of the great uncertainties connected with the clinical diagnosis of uncomplicated aortitis, particularly in patients aged 40 and over, it is dubious — at least from a comparative standpoint — whether these 13 can be accepted as representing cases of cardiovascular syphilis. At any rate, Bruusgaard's proportion of uncomplicated aortitis, 4.2 per cent (20 cases), is made up of 1.5 per cent (7 cases) where the diagnosis was definitely established, and 2.7 per cent (13 cases) where it was questionable. This compares with our proportion of 2.8 per cent (25 cases), which consists of 2.5 per cent (22 cases) where the diagnosis was made at autopsy, and 0.3 per cent (3 cases) where it was made clinically. It follows that the proportions of uncomplicated aortitis in the two series are incomparable as they stand, and in our opinion the only way of creating uniformity is to eliminate 13 cases from Bruusgaard's numerator and 3 from our own. The proportions then become 1.5 per cent and 2.5 per cent respectively. So, after having brought the definitions in accordance with our own, cardiovascular syphilis in Bruusgaard's series constitutes 4.0 per cent (2.5 per cent complicated and 1.5 per cent uncomplicated aortitis) as compared with 10.1 per cent (7.6 per cent compliated and 2.5 per cent uncomplicated aortitis) in ours. As a result of sub-grouping according to form, we are thus able to demonstrate essential quantitative and qualitative differences in the two series, differences which would not have been brought out if we had limited ourselves to an evaluation of the proportions based on the totals.

We are fully aware of the fact that there exist several other dissimilarities between the two investigations which might bear on the end results as to frequency of cardiovascular syphilis, but in our opinion, the above considerations suffice to justify the following conclusions: 1) The proportions of cardiovascular syphilis in the present series are not comparable with those *originally* presented by Bruusgaard. 2) *Adjustment* of Bruusgaard's figures through application of our own definitions so reduced the proportions that they can hardly be considered as representative. 3) As a consequence of the statements made under points 1) and 2), it is felt that we are not in a position to determine whether the re-analysis confirmed the findings in the previous follow-up study or not, and the reason for this is simply lack of comparability.

Nielsen's (1950) follow-up study is the only one known to us that was carried out after a sufficiently long period of observation, namely 29—36 years. The series consisted of males only, and the patients had received highly inadequate treatment (2 to 3 salvarsan injections and some 50 inunctions of mercury), at least according to modern accepted standards (for details on Nielsen's study see pp. 266—268). The proportion found to have developed cardiovascular syphilis was 3.6 per cent (2.8 per cent uncomplicated aortitis and 0.8 per cent complicated forms), as compared with 14.9 per cent (2.6 per cent uncomplicated and 12.2 per cent complicated aortitis) among the *males* in the present series. Taken at their face value these figures seem to indicate practically no difference as to frequency of uncomplicated aortitis, while we found proportionately about nineteen times more cases with complicated forms in our series. When it comes to the proportions of uncomplicated aortitis, however, the basis on which the diagnoses in the two series rest is totally different, and therefore the figures can hardly be considered comparable. Nielsen did not state how the diagnoses were made in his cases, but as far as we have been able to judge from the data available, they were apparently based for the most part on clinical and/or x-ray observations. Consequently, an evaluation of the order of magnitude in respect to frequency in his series is not possible because of the great uncertainties connected with the clinical diagnosis of uncomplicated aortitis. It is, nevertheless, reasonable to believe that Nielsen's 2.8 per cent represents a minimum, but the important point is that we can not determine — even approximately — to what extent this is true. In our own series, on the other hand, the majority of the diagnoses were made at autopsy and so far rest on firm ground. But, due to the relatively small proportion of autopsied patients in the material, it is felt that our proportion of 2.6 per cent uncomplicated aortitis represents a minimum as well. This is further borne out by the analysis of the autopsy population (see table 70, p. 285), which shows a percentage of 9.3, indicating that the true frequency of these conditions lies somewhere between 2.6 per cent and 9.3 per cent, these figures representing minimum and probable maximum proportions respectively. Under these circumstances, there can be no question of comparing the proportions of uncomplicated aortitis in the two series. Again we have an example of the complexity of evaluating figures on cardiovascular syphilis when the diagnostic problems of uncomplicated aortitis are involved. And again we feel justified in stressing the importance of sub-grouping according to form.

Whatever the attitude taken towards the possibility of establishing representative figures on uncomplicated aortitis, there can be no doubt, from a prognostic point of view, that the complicated forms constitute a more reliable and a more important index for the evaluation of the final outcome of the infection. In the discussion of Nielsen's findings it was indicated that his proportion of complicated aortitis (0.8 per cent) in all probability represents a minimum, but this is also true of the 12.2 per cent in our own series, and by and large we are inclined to believe that Nielsen's tracing methods resulted in a smaller number of patients missed, in that special category, than did ours. Therefore, the marked difference between the two series in respect to complicated forms of cardiovascular syphilis indicates that even highly inadequate treatment during the early phases of the infection is sufficient to prevent serious cardiovascular involvement in a considerable number of instances. In other words, the amounts and types of treatment employed for fresh syphilis in Nielsen's patients may not have been as inadequate as one would expect. It will be noted that we have chosen to express ourselves with caution in these matters, the reason being that it can not be definitely established with the data at hand whether this particular treament *alone* can be held responsible for the seemingly favorable results reflected through the above comparison. First, it is not quite clear how many of Nielsen's 467 patients, if any, received additional treatment after the orginal discharge but within the early periods of infection. In our opinion we must reckon with the possibility that some of these patients continued treatment elsewhere, whereas others again may have been submitted to re-treatment because of clinical or serologic relapses, thus bringing the total amount of treatment in those instances closer to adequacy than would otherwise have been the case. The data presented by Lomholt (1936) (see p. 108) show that clinical and serologic relapses were not uncommon during the early days of the salvarsan era, and there is reason to believe that the majority of these cases, when recognized, were re-treated. Aggerbeck (1949) found that many of his patients had continued treatment outside the hospital or clinic to which they first had been admitted. Second, Nielsen's analysis was limited to those among his original 467 patients who were found to have experienced clinical (or x-ray) manifestations of late syphilis, while there is no mention of what might have happened to the remaining. In other words, we do not know how many of the patients who escaped late lesions had received specific treatment in the interim, that is between the termination of the secondary syphilis (or the clinical or serologic relapse) and the «end point». It should be remembered that all of Nielsen's patients were infected after salvarsan and serologic tests had been added to our therapeutic and diagnostic armamentarium. And they lived through a period of time characterized by an ever increasing usage of antisyphilitic remedies, not only in cases with symptoms and signs, but also in cases of latent syphilis. It is conceivable, therefore, that a certain proportion of Nielsen's patients may have been diagnosed as suffering from latent syphilis and submitted to treatment, which in turn may have protected these individuals from developing serious late lesions. In view of the long «period of incubation» in cardiovascular syphilis it is admittedly no easy matter to account for treatment given the patients in the interim, whether it be in the early or later stages of the infection, but on the other hand there can be no denying that this factor is of the greatest importance when it comes to a comparative evaluation of the effects of the *original* treatment on the outcome. In addition to the factor of treatment in the interim, there are also others which may have influenced the end results in Nielsen's series, examples being mortality from other causes than syphilis, and socio-economic and occupational status of the patients. Since we have no information on either of these points, we can not possibly determine in what direction they may have worked, and the results of the comparisons must be judged with the reservations made necessary by that fact. In our opinion, however, the pronounced difference in respect to frequency of complicated aortitis in Nielsen's and our own series, nevertheless suggests that even relatively small amounts of specific treatment given during the early phases of the infection have a protective effect on the cardiovascular system, and definitely contradicts the theory of no treatment being more beneficial to the patients than inadequate treatment.

Time Relationships and Age.

Points which, from a comparative standpoint, may be of importance for an evaluation of figures on time relationships and age in cardiovascular syphilis, were dealt with at considerable length on pp. 261—263 and pp. 289—292 to which we refer in order to avoid repetitions. Furthermore, though the discussion in the foregoing section primarily was devoted to problems of comparability as related to *occurrence*, it goes without saying that all or most of the factors mentioned therein may also have bearing on *time relationships* and *age*. It follows as a consequence of considerations made previously, that comparisons between data arrived at through various types of investigations are connected with numerous possibilities for misinterpretations, and as far as we can judge, there actually exist no figures that are directly comparable with our own. We shall thus have to abstain from detailed comparisons and limit our discussion of these phenomena to broad principles.

When it comes to *duration of infection* at recognition, we subgrouped our cases according to sex, form, and age at infection, and found the following averages (see bottom of table 73, Parts I and II, p. 292): *Age at infection 15—39:* all forms, males — 31.4 years, and females — 31.7 years; complicated forms, males — 31.8 years, and females — 34.1 years. *Age at infection 15—40 over:* all forms, males — 30.1 years, and females 29.8 years; complicated forms, males —30.9 years, and females 33.2 years. As to the effects of such factors as sex, form, and age at infection, our material did not permit definite conclusions because of the small numbers involved; nevertheless we felt justified in pointing out certain trends, which, it seemed to us, were in keeping with what we would expect. These were: the inclusion of cases of uncomplicated aortitis tended to lower the average duration of infection for the total, and so did the inclusion of patients whose age at infection was 40 and over. And finally, it seemed as if females had their cardiovascular lesions recognized somewhat later than did males. Be that as it may, in this connection the most important finding lies in the fact that the mean duration of infection was about 30 years, or a little more, in both males and females, and irrespective of whether we sub-grouped according to form and age at infection or not.

Our mean of about 30 years compares with these average durations in Frazier and Li's (1948) white patients: 18.1 and 14.1 years in males and females respectively. In other words, the cases in the latter series were observed much earlier during the course of the infection than were ours, roughly about 12 years earlier in males and 16 in females. The reasons for this marked difference in respect to the average length of the «incubation period» in cardiovascular syphilis are not easy to explain, but among others the following possibilities might be considered:

1. Frazier and Li's series might contain a greater proportion of cases with uncomplicated aortitis, something which would probably work in the direction of lowering the averages for the total. Since the authors did not sub-group their cases according to uncomplicated and complicated forms (see footnote p. 259) we have no way of determining how this factor may have affected the end results.

2. Among their patients who were found to have developed cardiovascular lesions, there might be a greater proportion whose age at infection were 40 and over, or at least beyond average age, at onset of infection, something which would also tend to lower the averages for the total. But the authors themselves state that sub-grouping of these patients according to age at onset of infection was not possible with the available information, and thus we are in no position to evaluate to what extent this factor may have influenced the findings.

3. Frazier and Li's white patients were selected through the record files of the syphilis clinic of the Johns Hopkins Hospital in Baltimore, and according to the authors in all likelihood represented the general hospital population of whites in that city. This probably means that disease brought the patients under observation, and the material must be assumed to be weighted in the direction of more serious cases, a phenomenon that characterizes all hospital populations as compared with the «universe» from which the patients are drawn. For the same reason it is conceivable that such a sample would also contain a comparatively greater number of cases in whom symptoms and signs had developed relatively early during the course of the infection, which again would result in lower durations. The authors, however, give no detailed description of the circumstances under which these patients were admitted to the clinic, and we can therefore only indicate the above factor as being one possibly responsible for the differences in question.

4. At least in part the differences may have to do with the method used by Frazier and Li in calculating the means in question. Duration of infection in cardiovascular syphilis was estimated as the difference between mean age at time of clinical phenomenon (cardiovascular) and mean age at onset of infection. But, there was evidently no information on age at onset of infection in those patients who constitute the cardiovascular group, and due to lack of such information the authors used the mean ages for the patients who had been admitted to the clinic of the Johns Hopkins Hospital with fresh syphilis during the same period of time. In other words, in this instance the average duration of infection was found by subtracting mean age at onset of infection in one

group of patients (with fresh syphilis) from the mean age at recognition of another group of patients with cardiovascular. This method of procedure was evidently adopted under the assumption that the average age at onset of infection in the above group of patients with fresh syphilis (about 30 years for males and 26 years for females) was representative of the «universe». This is reflected in the following, quoted from Frazier and Li (ibid. p. 32): «. . . for, contrary to the commonly held opinion, syphilis is not a disease of youth but rather it is one of sexual maturity . . .». This may be true, but we cannot escape the impression that the average ages found were rather high; at any rate, we do not feel convinced that age at onset of infection necessarily has to be constant under all circumstances and at varying periods of time. This is exemplified by our own findings which showed the following average ages at infection: 25.6 years in males and 24.3 years in females. Thus, there is the possibility that the methods of calculation used by Frazier and Li may have resulted in too short an average duration of infection at recognition of cardiovascular involvement. But even if we were to assume that Frazier and Li's patients with cardiovascular syphilis, like ours, had contracted syphilis on the average at 24—25 years of age, and we subtracted mean age at onset of infection from mean age at recognition of clinical phenomena (cardiovascular), the result would still be considerably shorter average durations in Frazier and Li's investigation than in the present one, so under no circumstances can the above mentioned method of calculation be held more than partly responsible for the differences found. Finally, it will be noted that Frazier and Li found a trend pointing in the direction of a shorter duration of infection at recognition in females than in males (averagely 14.1 years versus 18.1 years, difference not statistically significant) and this was not confirmed by the findings in the present investigation, where the trend — if any — rather pointed in the direction of women having their cardiovascular lesions observed somewhat later during the course of infection than males. In view of the fact that the infection usually takes a *milder* course in females, it would not be unreasonable if the complications also gave rise to symptoms and signs *later* than in males, and though our figures were too small for significant comparisons on that point, we are of the opinion that our findings are more in keeping with what we would expect than are Frazier and Li's. Although we are unable with the available data, to give definite reasons for the differences with respect to duration of infection at recognition in the two series, we are by and large inclined to believe our figures to be the more representative of the natural course of the infection.

In order further to elucidate these problems, we also presented the percentage distribution of the patients with cardiovascular syphilis according to duration of infection at recognition by decades, and according to complicated and all forms, by sex. It was fairly obvious, however, that sub-grouping in this manner resulted in figures too small for significant comparisons, so that we could only indicate certain trends which were mentioned in the foregoing. A search of the literature showed that figures on duration of infection in cardiovascular syphilis usually are presented without sub-grouping according to form, and often without sub-grouping by sex, and as far as we know there exists no study where the sub-divisions used in the present investigation were employed. For these and other reasons previously discussed, there can be no question of detailed comparisons; we shall again have to limit ourselves to matters of principle. These were the findings in our series (see table 74, p. 295): During the first decade after infection 1.2 per cent of the cases was recognized; during the second 19.3 per cent; the third 26.5 per cent; the fourth 24.1 per cent; the fifth 24.1 per cent, and the sixth 4.8 per cent. This distribution compares with the following data taken from Stokes et al. (1944): cardiovascular involvement seldom recognized during the first decade after infection, with 45 per cent in the second, and 30 per cent in the third. It is not quite clear on which material or materials the latter figures are based, but in all probability it includes both men and women, and cases of uncomplicated as well as complicated aortitis. The above figures from our own investigation refer to those found in the total column, all forms, in table 74. First, it will be seen that our findings are in accordance with the concept, also held by Stokes et al., that cardiovascular syphilis is seldom recognized during the first decade after infection. Next, the comparison indicates that as a whole their cases were observed considerably earlier during the course of the infection than were ours, inasmuch as 75 per cent were found to have been recognized at the end of the third decade as contrasted with 47 per cent in the present study. But the question of what factors may be responsible for the difference found can not be answered directly since we have no detailed information concerning the material to which the above distribution, taken from Stokes et al., refers. However, their figures reveal one feature which was also typical of Frazier and Li's material as compared with ours, namely that observation took place earlier during the course of infection, and the chances are that here too we are dealing with findings based on cases picked from among clinic or hospital populations. If so, one might be inclined to consider this another example of such materials possibly being biased in the direction of cases observed relatively early, and thus not representative of the natural course of the infection, as already indicated in the discussion of Frazier and Li's figures.

Now for *age* at recognition of cardiovascular involvement. Age at recognition is a product of age at onset of infection and duration of infection between onset and observation. And for comparative purposes both factors must be taken into account. It is usually held that cardiovascular syphilis is most commonly diagnosed in middle life, but it is not always clear what is meant by that expression, perhaps between 40 and 50 years of age. In the present study the findings in respect to age at time of recognition were as follows: (see bottom of table 75, Parts I and II, p. 296). *Age at infection 15—39:* all forms, males —

56.6 years, females — 55.3 years; complicated forms, males — 57.2 years, females — 57.8 years. *Age at infection 15—40 over:* all forms, males — 58.0 years, females — 55.7 years; complicated forms, males — 58.4 years, females — 57.6 years. Here too the figures involved were too small for significant comparisons, but suggested certain trends: inclusion of uncomplicated aortitis appeared to lower the average age at recognition a bit, whereas inclusion of patients whose ages at infection were 40 and over rather tended to increase the averages somewhat. Finally, it appeared as if women by and large had their cardiovascular lesions observed at about the same or at a somewhat younger age than did males, even though the former tended to show longer average durations of infection at time of recognition. This seemingly controversial finding can, however, be explained by the fact that women, according to general experience, usually contract syphilis earlier in life than males. Among the patients in the present study group, women were found to have been infected averagely about a year earlier than men (about 24 versus about 25 years), and in Frazier and Li's patients with fresh syphilis males were averagely about 3 years older than females at onset of infection.

Whatever such factors as sex, age at infection and form may have meant for the end results in the present study, the most important finding is reflected in the fact that the average age at recognition in cardiovascular syphilis was somewhere around 55—58 years, which compares with these averages found by Frazier and Li (1948): males 47.6 years and females 39.6 years. Again there is a rather marked difference between the two series and particularly pronounced in females. Since age at recognition is a product of age at onset of infection and duration of infection at observation (of cardiovasular), both the latter factors might be responsible for the relatively low averages found by Frazier and Li. If their patients with cardiovascular had contracted syphilis earlier than ours had, and the duration of infection in the two series was the same, their patients necessarily would have been recognized at a younger age. This, in our opinion, is a rather remote possibility, but not knowing the age at onset of infection in Frazier and Li's cases of cardiovascular syphilis, it can not be completely excluded. Next, their cases may have been observed after a shorter duration of infection, and if age at onset of infection was about the same in the two series, again their patients would have been diagnosed at a younger age than ours. As mentioned previously (pp. 320—321), however, the way the average duration of infection was calculated, leaves some doubt as to the validity of their findings on this point. But the fact still remains that their cases really *were* observed at considerably younger ages than were ours, especially as regards women. Now, if Frazier and Li's cardiovascular group contained a greater proportion of cases with uncomplicated aortitis, that might tend to lower the average age at recognition for the group as a whole. Inclusion of patients of 40 and over, or at least beyond average age at onset of infection, might on the other hand have worked in the opposite direction. Due to lack of information on these factors we have no way of determining their weight. Finally, the difference may have to do with the fact that Frazier and Li's patients were selected from a clinic or hospital population, as already indicated under point 3 in the foregoing discussion on duration of infection, to which we refer. But this in itself offers no explanation for the great differences between the sexes in Frazier and Li's material, where females were about 11 years younger at time of recognition than males, a phenomenon which was not confirmed by the findings in the present study. Even if we take into account that women usually contract syphilis at a younger age than males, and we assume that duration of infection in the two sexes is approximately the same, there can be no question of a difference which amounts to about 11 years in age at recognition. The only possibility, therefore, is that these females sought medical advice, and were admitted to clinic or hospital, earlier than the males under otherwise identical conditions. Or, some unconscious bias may have been introduced.

In conclusion it is fairly safe to state that comparisons between the findings in various series in respect to time relationships and age in cardiovascular syphilis is an extremely complicated matter, as exemplified through the above discussion. By using Frazier and Li's figures as a background, we have merely *attempted* to demonstrate *some* of the possible sources of error connected with such comparisons. Other examples might certainly have brought out other possibilities, but this, in our opinion, will suffice to stress the difficulties one is apt to encounter, and the necessity of exercising caution in drawing conclusions. We do feel, however, that our own figures are more representative of the natural course of the infection than any based exclusively on the study of clinic or hospital populations, Frazier and Li's included.

Summary and Conclusions.

1. The study group comprised 953 patients (study group «Known»), 331 males and 622 females, all followed to an «end point».
2. Cardiovascular syphilis was defined to mean the disease of the aorta with the secondary changes in the heart due to complications.
3. The forms of cardiovascular syphilis as encountered among the 92 cases in the present series, were distributed as follows: uncomplicated aortitis 27.2 per cent; «uncomplicated» aortitis with sudden death 2.2 per cent; aortic insufficiency 44.6 per cent; saccular aneurysm 17.4 per cent; and ostial stenosis 2.2 per cent.
4. The diagnosis was verified by autopsy in close to 60 per cent of the instances. In uncomplicated aortitis 22 out of 25 were discovered by

autopsy. Most of the instances where the diagnosis was based on clinical examination only, related to aortic insufficiency and aneurysm.

It is concluded that the diagnoses in the present series, when made, rested on relatively safe ground.

5. Among the patients aged 15—39 (at infection) the data available permitted no conclusions as to the influence of age at infection on the frequency of cardiovascular.

   It was noteworthy that among those whose age at infection was under 15, not one single case of cardiovascular was found. The indication is that cardiovascular syphilis is rare among patients whose infection dates back to childhood. And it is pointed out that, using cardiovascular involvement as an index, the syphilitic infection seems to take a milder course than expected, both in those infected in utero and in those infected during early childhood.

   In those aged 40 and over at infection, the frequency of cardiovascular syphilis did not differ markedly from that found among those infected at younger ages (15—39), suggesting that even in patients infected rather late in life, the risk of developing cardiovascular still is considerable.

6. A total of 10.4 per cent of the patients studied was found to have developed cardiovascular syphilis in one form or another.

7. It is emphasized that figures on cardiovascular do not give a true picture of its occurrence when all forms are lumped together. Therefore, the proportions of each form, as calculated on the basis of the total number of patients observed, were presented as follows: uncomplicated aortitis 2.8 per cent; aortic insufficiency 4.6 per cent; saccular aneurysm 2.3 per cent; ostial stenosis 0.5 per cent; and «uncomplicated» aortitis with sudden death 0.2 per cent.

   Uncomplicated aortitis thus was diagnosed in 2.8 per cent as compared with 7.6 per cent for the complicated forms.

8. The representativeness of the figures was discussed.

   It is concluded that the proportion of 10.4 per cent found to have developed cardiovascular in the total study group is minimum, but to what extent could not be determined exactly.

9. In order to elucidate the problem of representativeness further, it was decided to analyse the occurrence of cardiovascular lesions in the autopsy-population as well.

10. Of the total of 209 autopsied patients, cardiovascular syphilis in one form or another was diagnosed in a little more than one-fourth of the cases (26.3 per cent).

    Uncomplicated aortitis was found in 10.5 per cent, and complicated aortitis in 15.8 per cent (of the total 209). Thus uncomplicated aortitis was

3.8 times as frequent in the autopsy population as in the total study group, whereas the complicated forms were 2.1 times as frequent.

Whether the 10.5 per cent uncomplicated aortitis as diagnosed in the autopsy population is representative of the total syphilis population studied, is considered difficult to determine, but it is maintained that it comes much closer to the true frequency in the series than does the 2.8 per cent in the total study group «Known».

The proportion of complicated aortitis in the autopsy population is considered to be too high, but since the 7.6 per cent found in the total study group represents a minimum, the true frequency of these complications is thought to lie within a range of 7.6 and 15.8 per cent, and in all probability the former figure comes somewhat closer to representativeness than does the latter.

11. Cardiovascular lesions as a whole were diagnosed more frequently among males than among females (14.9 versus 8.0 per cent — a ratio of 1.9 to 1).

    Uncomplicated aortitis was found in about the *same* proportions in the twa sexes (2.6 versus 2.9 per cent — a ratio of 1 to 1.1), whereas complicated forms were diagnosed in 12.2 per cent of the males as compared with 5.1 per cent of the females (a ratio of 2.4 to 1).

    All complicated forms showed an excess of males over females.

    The representativeness of the ratios were discussed and it is concluded that the findings, in spite of the relatively small numbers involved, probably give a true picture of these relationships in the present series.

12. The occurrence of cardiovascular syphilis in the autopsy population also was analysed on a sex-specific basis. The results seem to corroborate those described for the total study group «Known», and lend further evidence to the representativeness of the latter.

13. The findings in the present series as regards the ratio males to females seemed to represent the end results of a process of development which left us with almost equal proportions of uncomplicated aortitis on the one hand, and with a marked excess of males over females in complicated aortitis on the other.

    A hypothesis explaining this phenomenon is set forth, and it is pointed out that the theory advanced appears logical, although no definite conclusions can be drawn. The hypothesis also is thought to fit in with the concept that physical labour may be responsible for the excess of males over females in cardiovascular syphilis.

14. The relationship between physical activity and the frequency of cardiovascular lesions was discussed.

    It is emphasized that occupation is one of the environmental factors that may play an important part in determining to what extent these complications are going to develop in any given series. And also, it is indicated that the ratio males to females may vary acording to the degree the members of the two sexes in a group of syphilitics are exposed to occupational stress.

It is maintained that an analysis of the effects of physical activity on the frequency of cardiovascular lesions, poses problems of a very complex nature, but nevertheless, it is urged that this important environmental factor, if possible, be taken into account in comparisons.

Due to lack of pertinent information, however, we have abstained from a detailed analysis of the influence of the occupational factor on the frequency of cardiovascular manifestations in the present series.

15. Some of the basic epidemiologic factors considered important for the evaluation of time relationships and age at recognition were discussed.

16. In patients aged 15—39 at infection the average duration of infection at time of recognition of cardiovascular syphilis, irrespective of form, was 31.4 and 31.7 years in males and females respectively.

In uncomplicated aortitis the average duration of infection was 29.6 years in males and 26.2 years in females, whereas in complicated aortitis the averages were 31.8 and 34.1 years in the two sexes respectively.

Thus uncomplicated aortitis seemed to have been recognized earlier than the complicated forms, and the inclusion of the cases of uncomplicated aortitis tended to lower the averages for the group as a whole.

Aortic insufficiency apparently was recognized earlier than saccular aneurysm in both sexes (31.7 versus 37.3 years in males, and 33.0 versus 36.7 years in females for the two forms respectively).

Sub-grouping according to form is held to be essential for analysis of the time relationships in cardiovascular syphilis. It is emphasized, that the fine sub-grouping necessary led to so small figures within each of the sub-groups, that *significant* comparisons could not be made. It is felt, however, that the *trends* demonstrated, are sufficiently important to justify the sub-grouping made.

17. The percentage distribution of the cases of complicated aortitis by 10-year duration periods, gave these results: no such case was recognized during the first decade, whereas 15.9 per cent fell within the second. The great majority had had their cardiovascular involvement discovered during the third, fourth, and fifth decades, the proportions being fairly evenly distributed in the respective 10-year periods (25.4, 28.6, and 23.8 per cent, totalling 77.8 per cent); 6.3 per cent was diagnosed as late as the sixth decade.

There were no marked differences between males and females, but it is indicated that symptomatic cardiovascular involvement may actually occur somewhat later in females than in males, a trend in this direction being demonstrated by the fact that a greater proportion of females with complicated forms was found in the fifth and sixth decades (37.9 per cent versus 23.5 per cent).

18. In patients aged 15—39 (at infection) the average age at recognition was 56.6 years in males, and 55.3 years in females. The average age of those who had developed complicated forms was somewhat higher (57.2 and 57.8 years in the two sexes respectively), whereas those who had had their cardiovascular lesions diagnosed as uncomplicated aortitis on an average were younger (53.9 and 51.9 years in the two sex-groups). Inclusion of the cases of uncomplicated aortitis thus tended to lower the averages for the group as a whole.

    The average *age* at recognition was not markedly different in the two sexes, even though females tended to show longer average *durations* at time of recognition. This seemingly controversial finding is thought to be due partly to the fact that women usually contract syphilis earlier in life than men, something that is also true in this material.

19. The percentage distribution of the cases of complicated aortitis according to age at recognition gave these results: such conditions were only rarely recognized before the age of 40 (3.2 per cent), whereas the number diagnosed at the age of 70 and over was greater (14.3 per cent). The great majority (82.5 per cent) was found between 40 and 70, with the following distribution: 40—49, 28.6 per cent; 50—59, 28.6 per cent; and 60—69, 25.4 per cent.

    The even distribution within the above mentioned three 10-year periods, and also the relatively high percentage found at 70 and over, is noteworthy, and it is indicated that the cardiac symptoms do not seem to develop chiefly during the early part of middle life, but all through the period from 40 and up to old age, with a natural falling tendency after the age of 70.

20. The frequency with which patients died *of* their cardiovascular syphilis, or primarily *of* some other disease, but *with* their cardiovascular syphilis was considered.

    Irrespective of form, these complications were held to be the primary cause of death in 61.0 per cent of the male cases, and in 47.6 per cent of the female cases. They were held to be the contributory cause of death in 14.6 and 14.3 per cent in the two sexes respectively, and finally, they were considered to be non-related to the cause of death in 24.4 per cent of the male cases, and in 38.1 per cent of the female cases.

    Complicated aortitis proved fatal in 73.5 per cent of the male cases, and in 80.0 per cent of the female cases. It was held to be the contributory cause of death in 17.6 and 12.0 per cent in males and females respectively, while it was thought to be non-related to the cause of death in 8.8 per cent of the male cases, and in 8.0 per cent of the female.

In no instance was *uncomplicated aortitis* found to be the primary cause of death.

The seriousness of these complications is emphasized by pointing to the fact that about three-fourths to four-fifths of the patients who had developed complicated aortitis died primarily *of* their cardiovascular syphilis, while only close to one-tenth died of some other disease but *with* their cardiovascular syphilis non-related to the cause of death.

The most striking difference between males and females was the greater proportion of males dying *of* their cardiovascular syphilis (61.0 versus 47.6 per cent), and the correspondingly greater proportion of females dying *with* their cardiovascular syphilis (38.1 versus 24.4 per cent).

The main reason for this is thought to lie in the greater proportion of cases with uncomplicated aortitis among the females, and in the fact that this condition was in no instance the primary cause of death.

It is stressed that once complicated aortitis had developed, the outcome was very similar in the two sexes.

21. The circumstances under which comparisons can be made between various series in respect to frequencies of cardiovascular syphilis, were disussed. It was constantly kept in mind that our own data might be used as a base-line for comparisons between untreated or highly inadequately treated patients, and patients having received varying amounts and types of treatment.

It is concluded that it is a prerequisite for such comparisons that the data in question stem from studies similar in *type*.

It is furthermore maintained that a critical evaluation of the following basic epidemiologic factors forms another requirement for comparisons: methods of tracing, identification, and collection of clinical data; geographical areas, and population groups involved; and the investigators' attitude towards the problem.

Finally, from a comparative point of view, it is held essential to pay attention to such epidemiologic factors as: sex, length of period of observation, and forms of cardiovascular involvement included; patients' socio-economic status; period of time during which the infection originally took place; and mortality from other causes than syphilis; occupation; and treatment.

22. An attempt was made to determine whether the re-analysis had confirmed the findings on the frequency of cardiovascular syphilis in the previous follow-up study made by Bruusgaard. It is concluded that, due to lack of comparability between the two series, we are in no position to answer the question.

23. Comparisons with the frequencies found in series of treated patients suggest that even relatively small amounts of specific treatment given during the early phases of the infection, have a protective effect on the cardiovascular system.
24. Time relationships and age at recognition were discussed on a comparative basis.

    It is emphasized that all or most of the factors mentioned under point 21 in this summary, may also have a bearing on time relationships and age. It is further maintained that there actually exist no figures that are directly comparable with our own, and therefore it was necessary to abstain from detailed comparisons and limit the discussion of these phonomena to broad principles.

Chapter X.

OTHER LATE SYPHILIS

We have previously defined «benign» tertiary syphilis, cardiovascular syphilis and neurosyphilis. By other late syphilis is here meant all late manifestations not included in any of the three above mentioned categories.

In the present series only 2 out of the total 953 patients (0.2 per cent) in the study group «Known» were classified as other late syphilis. Both cases were gumma of the liver and both were observed in females. The duration of infection at recognition was 35 and 47 years. In both instances the manifestation was considered to be the primary cause of death.

In the one instance the diagnosis was verified by autopsy, whereas in the other the diagnosis rested on clinical examinations. Thus in the total autopsy population of 209 patients other late syphilis was diagnosed in 1 case (0.5 per cent).

In view of the above a discussion of the representativeness of these findings must be considered futile. However, the fact that even in the autopsy population there was observed only 1 case (0.5 per cent), would indicate that these lesions must have been comparatively rare in the present series. This is about as far as we can go with the data available.

In our opinion, the figures given in the literature on the occurrence of the manifestations that — according to our definition — fall in the category «other late syphilis», are extremely difficult to evaluate. This and the fact that our own figures obviously do not lend themselves for comparisons, are the reasons why we have abstained from further discussion of the quantitative aspects of this problem.

Chapter XI.

THE PROGNOSTIC SIGNIFICANCE OF CLINICAL SECONDARY RELAPSE AND «BENIGN» TERTIARY SYPHILIS

A. The Prognostic Significance of Clinical Secondary Relapse.

It is commonly held that clinical secondary relapse does not occur in untreated secondary syphilis, but is caused by inadequate and/or irregular treatment. And furthermore it is usually held that this manifestation is of grave prognostic importance, in so far as relapsers (provided they are not detected and re-treated) show a considerably greater frequency of serious late complications than non-relapsers. In other words, inadequate treatment in itself is not only held responsible for the occurrence of clinical secondary relapse, but also for the subsequent development of late complications (see pp. 115—116).

We have already tested the first part of the above hypothesis, and shown that clinical secondary relapse is not necessarily *caused* by inadequate treatment, but that it occurs in untreated secondary syphilis as well (in about 25 per cent of the cases), and thus must be considered as being a result of the natural course of the disease during the early years of the infection. In order to test the second part of the hypothesis, one must attempt to answer the following questions:

a) What is the frequency of serious late complications among the relapsers as compared with the non-relapsers in untreated secondary syphilis?
b) What are the frequencies of these late manifestations in patients observed to have relapsed after inadequate and/or irregular treatment as compared with the corresponding frequencies in patients found to have experienced relapse following untreated secondary syphilis?

In table 78 we have presented the proportions of late manifestations in the present series as found in relapsers on the one hand, and in non-relapsers on the other. Before proceeding to a description of the findings it is necessary to clarify certain points:

1. Since this was a question of determining frequencies of late manifestations, it was a prerequisite that all the patients were followed to an «end point». Therefore we have used for analysis the study group «Known» comprising

Table 78.

Comparison of Final Outcome in 169 Untreated Patients Who Relapsed and 692 Untreated Patients Who Were Not Observed to Relapse, by Sex.

(All ages*)

Males

	Total number of patients	Patients found to have developed:							
		«Benign» tertiary syphilis		Cardiovascular (Complicated forms**)		Cardiovascular (All forms**)		Neurosyphilis (All forms***)	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Clinical secondary relapse not observed	239	37	15.5	26	10.9	31	13.0	22	9.2
Clinical secondary relapse observed	57	8	14.0	4	7.0	6	10.5	6	10.5
Subtotal males	296	45	15.2	30	10.1	37	12.5	28	9.5

Females

Clinical secondary relapse not observed	453	74	16.3	20	4.4	33	7.3	20	4.4
Clinical secondary relapse observed	112	27	24.1	6	5.4	7	6.3	9	8.0
Subtotal females	565	101	17.9	26	4.6	40	7.1	29	5.1

Total

Clinical secondary relapse not observed	692	111	16.0	46	6.6	64	9.2	42	6.1
Clinical secondary relapse observed	169	35	20.7	10	5.9	13	7.7	15	8.9
Grand total	861	146	17.0	56	6.5	77	8.9	57	6.6

* Age at infection.

** For explanation of terms see table 66, p. 277.

*** Symptomatic forms; no case of asymptomatic neurosyphilis observed.

953 patients (622 female and 331 male). (For explanation of terms see table 21, p. 93.)

2. Because it was a question of determining the prognostic importance of clinical secondary relapses following *untreated secondary syphilis,* we found it necessary to remove from the material all patients in the study group «Known» who originally had been seen by Boeck in secondary recurrence, and in addition, all those who had received specific treatment, however inadequate, prior to, during, or immediately after hospitalization in Boeck's department (see also p. 116). This amounted to 92 patients (57 female and 35 male), and we were left with a total of 861 patients (565 female and 296 male).
3. Moreover, it should be noted that we have sub-grouped cardiovascular according to «complicated forms» and «all forms» (that is, uncomplicated plus complicated forms). Also it is worth emphasizing that no case of asymptomatic is included in our group «neurosyphilis». These points are important, particularly from a comparative standpoint, since uncomplicated aortitis and asymptomatic neurosyphilis differ considerably from the complicated forms of aortitis and the symptomatic forms of neurosyphilis respectively, both as to diagnosis and prognosis, and in respect to time relationships.

Considering first the total section at bottom of table 78, it will be seen that there were no marked differences between the relapsers and the non-relapsers in respect to proportions of the various late complications listed. If we sub-group by sex, the picture remains very much the same, particularly in males. In females there seems to be a certain tendency towards more «benign» tertiary syphilis and more neurosyphilis in the relapsers as compared with the non-relapsers. However, the differences found are *not* statistically significant.

Thus, with the data at hand, we can not authoritatively state that clinical secondary relapse following untreated secondary syphilis should or should not be considered a prognostically serious phenomenon. However, our findings *do* show that, not only does clinical secondary relapse occur in untreated secondary syphilis, but also it is followed by proportions of late complications that are at least as great as those found in non-relapsing secondary syphilis. Therefore, this development must be assumed to form part of the natural course of the infection, and is not necessarily *caused* by interference with the immune-mechanism through inadequate and/or irregular treatment of early syphilis.

In regard to the question of frequencies of the late complications in treated and untreated patients who have experienced clinical secondary relapse, there exists, as far as we know, only one investigation, the findings of which might perhaps form a basis for comparisons with those arrived at in the present series, and that is the study made by Padget (1940) (see p. 115 in the present monograph). There are, however, fundamental differences between the two series that actually make a direct comparison of the numerical findings practically impossible.

First, the period of observation is not the same. In Padget's series the mean period of observation for the material as a whole was 10.8 years, which compares with the following averages in the present series: dead patients, 26.8 and 26.0 years in males and females respectively; living patients, about 50 years in both sexes (see Annex tables XXI and XXIV, p. XLV and p. XLIX).

Second, the relapse problem was not analysed by Padget on a sex-specific basis.

Third, in respect to those among Padget's patients who were observed to have relapsed and later found to have developed cardiovascular, there is no distinction between uncomplicated and complicated aortitis. In the total study group 20 out of 24 cases with cardiovascular were listed under uncomplicated aortitis.

Fourth, when it comes to those among Padget's relapsers who were found later to have experienced central nervous system lesions, there is no distinction between asymptomatic and symptomatic neurosyphilis. In the total study group about one-half of the cases with central nervous system lesions were listed under asymptomatic neurosyphilis.

In our opinion it is difficult to evaluate the seriousness of the relapsing lesions in early syphilis, unless the factors mentioned above are accounted for. Therefore, in our own series the analysis was carried out on a sex-specific basis; we distinguished between «complicated forms» and «all forms» of cardiovascular; and finally, under neurosyphilis we listed only symptomatic cases (since no case af asymptomatic was found to have been diagnosed among our patients).

A comparison between Padget's and our own findings, i.e. a comparison between the final outcome in patients who were found to have relapsed after inadequate and/or irregular treatment on the one hand, and the outcome in those observed to have relapsed following untreated secondary syphilis on the other, can thus only be done with strong reservations as to how the above mentioned factors may have influenced the end results in the former of the two groups. In our opinion, however, the figures for the late complications as presented by Padget, seem remarkably high (except perhaps for «benign» tertiary syphilis), particularly when we take into account the relatively short period of observation. These are the proportions of the various forms of late manifestations among those 78 of Padget's patients who were observed to have relapsed: «benign» tertiary syphilis 12.8 per cent; cardiovascular 7.7 per cent; neurosyphilis 35.9 per cent; and multiple manifestations (types not given) 5.1 per cent (see table 34, p. 144 in the present monograph). The corresponding proportions as found in the present series (see total column of table 78) were as follows: «benign» tertiary syphilis 20.7 per cent; cardiovascular (all forms) 7.7 per cent; neurosyphilis (all forms except asymptomatic) 8.9 per cent.

If one were to accept the figures in both series as they stand, two explanations may be offered for the differences found:

a) relapse following inadequate and/or irregular treatment of early syphilis is of more ominous prognostic importance than is clinical secondary relapse following untreated secondary syphilis.
b) or, the figures presented by Padget are weighted in the direction of too many serious cases and therefore do not give a true picture of these relationships.

Although we can not answer definitely with the data available, which of the two explanations must be considered as the more credible one, there is, in our opinion, indirect evidence that Padget's material is considerably selected. The chief reason for it probably is to be found in the way Padget's material was established (ibid.): «In the basic selection of material there were reviewed the records of the approximately 6,000 patients with early syphilis who had been admitted to the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital. Selected for study were those *551 patients who had been completely re-examined five years or more after the termination of the original treatment for early syphilis . . .*»[1] There is no question of a systematic follow-up of a well-defined group of patients. Rather, one must question if patients, who, for one reason or another, have returned to the hospital and/or clinic for examinations, returned because of complaints directly connected with the syphilitic infection or not. As far as we can judge, therefore, it is highly probable that this method of choosing those to be studied has resulted in a material which, taken as a whole, is biased in the direction of too many serious cases. And, we are inclined to believe also that this is even more true of the relapsers than the non-relapsers, because in the first instance the patients as a result of the unfortunate course of the infection during the early stages, have been made acutely aware of their disease, and therefore these individuals are apt to submit themselves to examinations more often than the others.

Since we do believe Padget's material to be weighted in the direction of too many serious cases, we feel that the differences between the findings in the two series can not be interpreted as meaning that clinical secondary relapse following inadequate and/or irregular treatment of early syphilis is of more ominous prognostic importance than is clinical secondary relapse following *untreated* secondary syphilis. Therefore, until more evidence to the contrary is provided, our hypothesis is the following: Inadequate and/or irregular treatment does not necessarily *cause* clinical secondary relapse, but rather it can be said that this treatment has not been sufficiently adequate to prevent the natural course of the infection as demonstrated by the occurrence of a certain

[1] Italicized by the present author.

proportion of cases with clinical secondary relapse. And neither has the same treatment been sufficiently adequate to prevent the occurrence of the late manifestations that in a certain proportion of the cases may be expected to follow clinical secondary relapse, something which also reflects the natural course of the infection. To test this hypothesis we would need two basically similar series of patients, the one showing a certain proportion of cases with clinical secondary relapse after inadequate and/or irregular treatment, and the other showing a certain proportion of these manifestations following untreated secondary syphilis. And in order to deny the hypothesis we must by comparison find a significantly higher frequency of late complications in the former of the two groups. However, whether it will ever be possible to provide materials that will allow for such a comparison is very questionable.

B. The Prognostic Significance of «Benign» Tertiary Syphilis.

«Benign» tertiary syphilis not only is a less serious manifestation than the other late forms of the disease as seen from a prognostic point of view, but also it is commonly held to represent a pathologic process that in itself affords protection against lesions of the cardiovascular and central nervous systems. The latter concept is probably in the main based on the well-known fact that concurrent «benign» tertiary syphilis and cardiovascular syphilis and/or neurosyphilis, is relatively seldom noted. This is exemplified in Frazier and Li's (1948) investigation among others. The authors remark about these problems (ibid. p. — 79): «A noteworthy characteristic of extra-neural concomitance was the absence of cutaneous and skeletal lesions in patients with cardiovascular syphilis . . .», and «. . . As in the case of cardiovascular involvement, the skin was not a focus of disease when there was manifest neurosyphilis . . .» To measure the prognostic significance of «benign» tertiary lesions on the basis of the frequency with which we find concomitant manifestations of that complication and cardiovascular, and/or neurosyphilis, is, however, only one of three methods that might be utilized. The two others are the following: to determine to what extent lesions of the cardiovascular and the central nervous system are preceded by «benign» tertiary. Or, and this is probably the most reliable method, to follow a group of patients found to have experienced «benign» tertiary syphilis and to compare the final outcome as to frequencies of serious late complications, with the outcome in a corresponding group of patients that had *not* been observed to have developed «benign» tertiary. As far as we have been able to find, there exist no reliable figures on the prognostic significance of «benign» tertiary syphilis that are based on any of the two last mentioned methods. In order to illuminate the problem further, therefore, we have chosen to analyse our own material according to all the indices indicated above.

First we analysed our patients in respect to the frequency with which «benign» tertiary lesions were found in the presence of cardiovascular on the one hand, and symptomatic neurosyphilis on the other. Among the 45 males found to have developed cardiovascular, there were only 2 cases (one with uncomplicated and one with complicated aortitis) in whom there was found active «benign» tertiary lesions at the time of recognition of the cardiovascular manifestations. Among the 47 females with cardiovascular there was no such case. Moreover, among the 31 males observed to have experienced neurosyphilis, there were 3 who showed active «benign» tertiary syphilis simultaneously with the central nervous system lesions (one with tabes dorsalis forme fruste, one with general paresis, and one with meningovascular). The corresponding number among the 31 females with neurosyphilis was 2, both with meningovascular. In other words, «benign» tertiary lesions were found to have occurred simultaneously with cardiovascular in 2 out of a total of 92 cases, and simultaneously with symptomatic neurosyphilis in 5 out of a total of 62 cases. Thus our findings analysed in this manner lend confirmatory evidence to the generally accepted concept that lesions of the skin, the mucous membranes, and the bones are relatively seldom present in patients with cardiovascular, or symptomatic neurosyphilis. It is questionable, however, whether this phenomenon can be interpreted as meaning that «benign» tertiary in itself protects against the more serious late manifestations. It must be remembered that the «period of incubation» is different in the three types of complications, «benign» tertiary, symptomatic neurosyphilis, and complicated aortitis on an average occurring in that order of sequence as measured on the basis of duration of infection at time of recognition. In the present series for instance, the mean duration of infection at time of recognition was as follows in the three types of complications respectively: «benign» tertiary, males 12.8 and females 11.2 years (see table 50, p. 170); symptomatic neurosyphilis (active forms), males 21.8 and females 20.4 years (see table 60, p. 232); cardiovascular (complicated forms), males 31.8 and females 34.1 years (see table 73, p. 292). Furthermore, it will be recalled that 75.2 per cent of the cases found to have experienced «benign» tertiary were recognized within the first 15 years of infection (see p. 171). «Benign» tertiary, thus, is first and foremost a manifestation of the first decade and a half of infection, whereas the great majority of the cases of symptomatic neurosyphilis, and especially of complicated aortitis, by and large are recognized later during the course of the infection, that is, from the second decade on. Therefore it is actually in keeping with what we would expect that concomitant lesions of «benign» tertiary and the more serious late complications are only relatively seldom encountered. In our opinion, the differences in respect to time relationships offer a more reasonable explanation for this phenomenon than does the theory of the protective effects of the pathologic process in «benign» tertiary syphilis.

Table 79.

The Extent to Which Cases Observed to Have Developed Cardiovascular and Neurosyphilis Were Found to Have Been Preceded by «Benign» Tertiary, by Sex.

(All ages*)

(45 males and 47 females with cardiovascular, and 31 males and 31 females with neurosyphilis).

Males

	Forms of serious late complications									
	Cardiovascular syphilis				Neurosyphilis					
	Uncomplicated aortitis	Complicated aortitis	Subtotal Cardiovascular		General paresis	Tabes dorsalis	Meningo-vascular	Gumma of brain	Subtotal Neurosyphilis	
	No.	No.	No.	Per cent	No.	No.	No.	No.	No.	Per cent
Cases found to have been preceded by «Benign» tertiary	2	5	7	15.6	0	1	2	1	4	12.9
Cases not found to have been preceded by «Benign» tertiary	6	32	38	84.4	10	7	10	0	27	87.1
Total	8	37	45	100.0	10	8	12	1	31	100.0

Females

Cases found to have been preceded by «Benign» tertiary	6	4	10	21.3	1	2	3	0	6	19.4
Cases not found to have been preceded by «Benign» tertiary	11	26	37	78.7	9	7	8	1	25	80.6
Total	17	30	47	100.0	10	9	11	1	31	100.0

* Age at infection.

In series of treated patients, there is another factor that, at least in part, must be held responsible for the rare occurrence of concomitant lesions of «benign» tertiary and the more serious late complications. After the introduction of salvarsan there has been a steady decrease in the number of cases observed with «benign» tertiary, but it is reasonable to believe that the decrease, under otherwise identical conditions, has been comparatively more pronounced in this form of manifestation than in the others, because it evidently takes less adequate treatment during the early phases of the infection to protect against «benign» tertiary than it takes to protect against cardiovascular and neurosyphilis. So this factor too would work in the direction of minimizing the number of cases in whom active lesions of the skin, the mucous membranes, and the bones, are observed in the presence of cardiovascular and neurosyphilis.

Next, we have considered to what extent the cases of cardiovascular and neurosyphilis were found to have been preceded by «benign» tertiary (table 79). It will be seen that among the 45 males observed to have experienced cardiovascular, 7 (15.6 per cent) had previously had «benign» tertiary, and among the 31 males found to have developed neurosyphilis, the corresponding number was 4 (12.9 per cent). Among the 47 females observed to have experienced cardiovascular, 10 (21.3 per cent) had had «benign» tertiary lesions diagnosed previously, and the corresponding number among the 31 females found to have developed neurosyphilis, was 6 (19.4 per cent). The above proportions of «benign» tertiary may be compared with the occurrence of «benign» tertiary in the study group «Known» as a whole: Males 15.4 per cent and females 17.2 per cent (see table 43, p. 159). In other words, there are no marked differences between the proportions of «benign» tertiary found to have preceded the more serious late complications, and those found for the study group as a whole. We are fully aware of the small numbers involved, but as they stand, there is nothing in our findings suggesting that lesions of the skin, mucous membranes, and bones, when preceding the serious late complications, represent a protective mechanism against the development of the latter. If this were actually the case, we could have expected the proportions of «benign» tertiary that preceded the cardiovascular and the central nervous system lesions, to be smaller than the proportions in the study group as a whole.

Finally, we have compared the end results in those who were observed to have experienced «benign» tertiary, with those not found to have developed these manifestations (table 80). It should be noted that we are again using the total study group «Known», comprising a total of 953 patients (331 male and 622 female), (see table 21, p. 93 for explanation of terms). Furthermore, it will be seen that we have listed the serious late complications according to form. There can be no doubt that prognosis to a considerable extent is dependent on what form of cardiovascular syphilis, or neurosyphilis, is involved. The subgrouping, desirable as it is, resulted in such small numbers within each one of

Table 80.

Comparison of Final Outcome in 158 Patients Observed to Have Developed «Benign» Tertiary Syphilis, and 795 Patients Who Were Not Found to Have Experienced «Benign» Tertiary Syphilis, by Sex and Form of Serious Late Complication.

Males

(All ages*)

	Forms of serious late complications									
	Cardiovascular syphilis				Neurosyphilis					
	Uncompli-cated aortitis	Complicated aortitis	Subtotal Cardiovascular		General paresis	Tabes dorsalis	Meningo-vascular	Gumma of brain	Subtotal Neurosyphilis	
	No.	No.	No.	Per cent	No.	No.	No.	No.	No.	Per cent
Patients found to have developed «Benign» Tertiary 51 (100 %)	3	6	9	17.6	1	2	3	1	7	13.7
Pts. not found to have developed «Benign» Tertiary 280 (100 %)	5	31	36	12.9	9	6	9	0	24	8.6
Total 331 (100 %)	8	37	45	13.6	10	8	12	1	31	9.4

Females

Patients found to have developed «Benign» Tertiary 107 (100 %)	6	4	10	9.3	1	2	5	0	8	7.5
Pts. not found to have developed «Benign» Tertiary 515 (100 %)	11	26	37	7.2	9	7	6	1	23	4.5
Total 622 (100 %)	17	30	47	7.5	10	9	11	1	31	5.0

* Age at infection.

the categories that individual comparisons are practically impossible. Therefore we have chosen to calculate the proportions only for the subtotals in the two main groups of serious late manifestations. Considering these subtotals, the table reveals that in no instance was the outcome more favorable among those who were known to have had «benign» tertiary than among those not observed to have developed that special form of late complication. As the figures stand, therefore, and with the reservations made necessary by the small numbers involved, it is probably safe to state that the findings in the present series do not provide evidence for the concept that lesions of the skin, the mucous membranes, and the bones, in themselves exert a protective influence against serious late manifestations.

To conclude: as far as the findings in the present series are concerned, and irrespective of which index we utilize in order to analyse the prognostic significanse of «benign» tertiary syphilis, this particular form of late manifestation does not seem to protect against the development of the more serious lesions of the cardiovascular and the central nervous systems.

Chapter XII

MORTALITY

I. Introductory Remarks.

It is commonly accepted that untreated, or inadequately treated, syphilitics always show a higher mortality than the normal population, or other controls that may be chosen for comparison. The figures we have are for the most part based on actuarial studies, and according to Moore and Schamberg (1947) «. . . The data so obtained indicate that syphilis imposes an extra mortality hazard ranging from 138 to 188 per cent of expected mortality».[1]

Regarding the reliability of the figures available the above authors consider the studies on which they are based, as «. . . incomplete, inaccurate and unsuitable for the determination of a policy in regard to the insurability of syphilitic persons . . .» (ibid.), for the following reasons:

«1. The known syphilitic population is compared with a supposedly non-syphilitic population, the latter of which, however, contains an unknown proportion of persons with actuarially unrecognized syphilis.

2. The published mortality data (in a syphilitic population) consider as a group persons with all stages and types of syphilitic infection, ranging from recently acquired (primary and secondary) syphilis, to various grave forms of late syphilis (i.e. cardiovascular and neurosyphilis). In the early cases the life expectancy is high, partly because most such patients are young at the time of infection and partly because the mortality from syphilis is concentrated within the period twenty or more years after infection. In the late cases the life expectancy is low, partly because those manifestations occur in older age groups and partly because of the inherent and inevitable mortality from syphilis itself (as in aneurysm).

3. *The exact mortality due primarily or even secondarily to syphilis is not determinable from the causes of death provided on death certificates.*[2] There is reason to believe that in a syphilitic population the assigned cause of death

[1] «Expected mortality» is, in actuarial terms, 100 per cent. (Footnote by Moore and Schamberg.)

[2] Italicized by the present author

may be in error by as much as 50 per cent, partly through inadvertence (the physician's inability to recognize the extent to which syphilis contributes directly or indirectly to death) and partly through intent (deliberate omission of syphilis as a primary or secondary cause of death in order to protect the patient, even post mortem, from disclosure of a «social disgrace»).

4. *Consideration is not given to the weighting of syphilis mortality figures by the fact that syphilis is primarily a disease of those in lower socioeconomic groups, which are subject to increased mortality risk from many other diseases and conditions (such as acute infections, tuberculosis and industrial hazards) and which are therefore not directly comparable to the population as a whole.*[1]

5. Consideration is not given to the adequacy of present day treatment methods. Such actuarial data as are available with respect to treatment relate to the prearsenical era (prior to 1910) or to the early days of metal chemotherapy (1910 to 1925). Moreover, the data do not relate treatment to the stage of syphilitic infection for which it was given.»

Thus, there can be no doubt that the data we possess on the mortality of syphilis, as gained through actuarial methods, can only be accepted with great reservations. Notwithstanding the lack of reliability of the figures presented, however, there seems to be general agreement among experts that the excess mortality found in groups of syphilitics, untreated or poorly treated, ordinarily is greater than one would expect in view of the proportions dying primarily as a result of the infection. In order to explain this phenomenon two theories have been advanced:

1. Syphilis is a disease that practically always is associated with socio-economic status, or rather with various disturbances of the socio-economic equilibrium. Therefore, whenever we choose a relatively large population-group of syphilitics for study, we invariably end up with patients who by and large come from the lower socio-economic strata of society. These same patients, in addition to the risk imposed on them by the syphilitic infection *per se*, are naturally also exposed to the risk of a whole series of other diseases more commonly encountered in such population-groups, and naturally they would be expected to show a greater mortality from *all* causes than nonsyphilitics do. Syphilis, therefore, can only partly be held responsible for the excess mortality usually found.

2. Syphilis is a generalized systemic disease affecting to a variable degree most of the organ-systems of the body. True enough, in a certain proportion of those infected the disease causes death primarily, but it may also without causing death directly, produce changes in the host, presumably non-specific in character, that increase the morbidity and thereby the mortality from a considerable number of illnesses other than syphilis.

[1] Italicized by the present author.

Both theories have their adherents. Among those expressing belief in the first hypothesis is Willners (1939) who, on the basis of his findings in a follow-up study of syphilitics originally treated during the early salvarsan era (1912—1913) in Sweden, stated: «. . . that such a person is a bad risk not merely because he has contracted syphilis, but that he has acquired syphilis, among other reasons, because he is a bad risk». Schamberg leaves no doubt as to his standpoint in these matters. In his (1945) review of the prognosis of syphilis, he states: «There is no evidence that syphilis adversely influences life expectancy except through the known lethal effects of its serious late manifestations, in particular those of the central nervous system and cardiovascular system . . .» Moore and Schamberg in their previously quoted paper of (1947) write: «There is no sound evidence that the existence of acquired syphilitic infection predisposes to an increased death rate from other causes, such as cancer and tuberculosis».

The second hypothesis was particularly brought into the foreground through the «Alabama» study (see pp. 28—31), which indicated that not only did the syphilitics show an excess mortality of about 70 per cent over the controls, but also that the former showed evidence of an increased morbidity from other diseases than syphilis, specially as regards those of the cardiovascular system. Since, as mentioned previously, the controls apparently were chosen without bias, the findings certainly seem to lend weight to the second of the theories listed. Further evidence pointing in the same direction was provided by Rosahn in his (1952) experimental study of the mortality in mice infected by treponemes. There can be no doubt whatsoever that his results give favorable support to the hypothesis set forth on the basis of the Alabama Study, showing that «. . . syphilitic infection in mice, even though it produces no lesions of syphilis, in and of itself causes a reduction in longevity . . .». In summing up Rosahn says, among other things, «It is concluded that syphilitic infection in mice exerts a deleterious effect on longevity. Although the mechanism producing this effect is conjectural, it is suggested that syphilis depresses resistance to other mortal diseases. If the same mechanism is operative in man, and there is good reason to believe that it is, then syphilis by itself and exclusive of modifying socioeconomic factors exerts an adverse influence on the lifespan of the human host.»

II. Present Investigation.

a. *Causes of Death.*

In respect to the circumstances under which the final observation took place and the basis on which the determination of the cause of death rested, we refer to Annex VIII, where these problems are discussed in considerable detail. Suffice it to mention here that the determination of the cause of death was based on all the information available, including autopsy reports, hospital and other

Table 81.

Primary Cause of Death among 694 Patients in Study Group «Known» Arranged According to Order of Importance.

(All ages*)

Part I. Males.

Tuberculosis.	Deaths		Per cent	
Tuberculosis of the respiratory system	44	45		17.4
Tuberculosis of the intestines	0			
Tuberculosis of the genito-urinary system	1			
Syphilis.				
Cardiovascular syphilis	25	39	9.7	15.1
Neurosyphilis	14		5.4	
Other	0		—	
Cancer and Other Tumors.				
Cancer (all forms)	30	32		12.4
Non-malignant, or tumors of undetermined nature	2			
Diseases of the Circulatory System.				
(syphilitic heart disease excluded)		28		10.8
Diseases of the Respiratory System.				
(not specified as tuberculosis)		25		9.7
Diseases of the Urinary and Genital Systems.				
(not venereal)		16		6.2
Diseases of the Nervous System and Sense Organs. (neurosyphilis excluded)				
Cerebral hermorrhage	12	14		5.4
Other	2			
Accidental Deaths		11		4.2
Diseases of the Digestive System		7		2.7
Suicide		6		2.3
Infective and Parasitic Diseases. (tuberculosis and syphilis excluded)		6		2.3
Leucaemia		4		1.5
Senility — Old Age		3		1.2
Diabetes Mellitus		1		0.4
Pernicious Anaemia		1		0.4
Acute Alcoholism		1		0.4
Ill Defined Causes of Death.				
Sudden death	7	20		7.7
Other deaths from unknown or unspecified causes	13			
Total		259		100.0

Part II. Females.

	Deaths		Per cent	
Tuberculosis.				
Tuberculosis of the respiratory system	73	74		17.0
Tuberculosis of the intestines	1			
Tuberculosis of the genito-urinary system	0			
Diseases of the Circulatory System.				
(syphilitic heart disease excluded)		72		16.6
Cancer and Other Tumors.				
Cancer (all forms)	67	71		16.3
Non-malignant, or tumors of undetermined nature	4			
Diseases of the Respiratory System.				
(not specified as tuberculosis)		42		9.7
Syphilis.				
Cardiovascular syphilis	20	36	4.6	8.3
Neurosyphilis	14		3.2	
Other	2		0.5	
Diseases of the Nervous System and Sense Organs. (neurosyphilis excluded)				
Cerebral hermorrhage	26	34		7.8
Other	8			
Diseases of the Digestive System		24		5.5
Diseases of the Urinary and Genital Systems. (not venereal, or connected with pregnancy or the puerperium)		16		3.7
Infective and Parasitic Diseases. (tuberculosis and syphilis excluded)		13		3.0
Senility — Old Age		9		2.1
Accidental Deaths		9		2.1
Diseases of Pregnancy, Childbirth and puerperal state		8		1.8
Suicide		4		0.9
Diabetes Mellitus		2		0.5
Leucaemia		1		0.2
Acute Alcoholism		1		0.2
Diseases of the Joints and Other Organs of Movement		1		0.2
Ill Defined Causes of Death.				
Sudden death	4	18		4.1
Other deaths from unknown or unspecified causes	14			
Total		435		100.0

* Age at infection and age at death.

records, plus death certificates, and therefore the data presented are considered to be more reliable than those usually taken from mortality statistics, where ordinarily the death certificate is the only source of information. We feel justified also in emphasizing the importance of this from a comparative point of view.

In table 81 are to be found the primary causes of death among 694 patients, according to order of importance, and by sex. The deaths were coded according to the International List, 5th revision, as adopted for use in the United States. It will be noted that in the main we have confined ourselves to broad groups of causes. In syphilis, we have distinguished between cardiovascular, neurosyphilis, and other late syphilis (visceral). For details as to the extent to which the various forms were found to have caused death primarily, we refer to the foregoing chapters on cardiovascular, neurosyphilis, and other late syphilis.

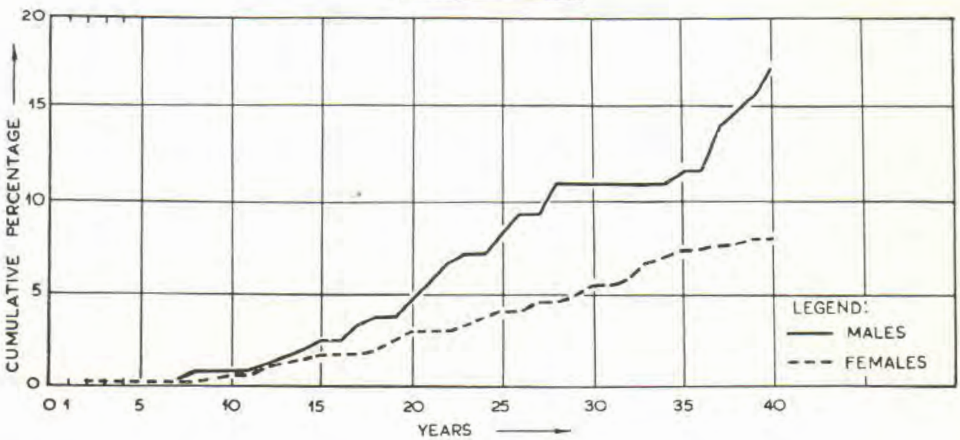
The table reveals that syphilis was found to have caused death primarily in 39 out of 259 males (15.1 per cent) and in 36 out of 435 females (8.3 per cent), giving a ratio of males to females of 1.8 to 1. In principle this is what we would expect since females are known to develop serious late manifestations to a lesser extent than males. Next it will be seen that cardiovascular was responsible for more deaths than neurosyphilis in both sexes: 25 cases (9.7 per cent) versus 14 cases (5.4 per cent) in males, and 20 cases (4.6 per cent) versus 14 cases (3.2 per cent) in females. The ratio cardiovascular to neurosyphilis in males was 1.7 to 1, and in females 1.4 to 1, indicating that cardiovascular syphilis was relatively more serious in males than in females. The sex difference furthermore is reflected by the fact that among males syphilis ranked second in the all-over picture of the causes of death, tuberculosis being the only disease that caused more deaths, whereas among females syphilis ranked fifth, tuberculosis, diseases of the circulatory system (syphilitic heart disease excluded), cancer, and diseases of the respiratory system, being responsible for more deaths. This difference between males and females is an extremely important feature particularly when we consider the order of magnitude of the excess mortality in the two sexes as found through comparison with the controls (see later).

Finally, the table readily reveals that syphilis, although an important cause of death, particularly in males, was actually not a great killer, even in this one-hundred per cent syphilitic population. The other causes, covering a wide range of diseases and organ-systems, far outweighed syphilis as a primary cause of death.

When it comes to the question of representativeness of the figures arrived at, we refer to the foregoing sections on occurrence of cardiovascular, neurosyphilis, and other late syphilis. In view of the methods used in tracing and in the collection of clinical data, and on the basis of direct and indirect evidence, we felt justified in assuming that we had probably come fairly close to the true

FIG. 10.

PROBABILITY OF DYING PRIMARILY AS A RESULT OF THE SYPHILITIC INFECTION.



frequencies in the present series as regards those of the patients in whom syphilis really was the *primary* cause of death. On the other hand, there can be no doubt that syphilis was a secondary cause of death in a certain proportion of instances, but with the data available we were in no position to evaluate even approximately to what extent that might have been the case.

The very complex matter of comparing the causes of death among the syphilitics with those among the controls, will be taken up in a later publication (Gjestland, Moen, and Trier, to be printed).

b. *The Probability of Dying Primarily as a Result of the Syphilitic Infection.*

The calculation of the probability of dying directly as a result of the syphilitic infection is presented in annex table XXVIII, p. LIII, and in fig. 10 the findings are presented diagrammatically. First it will be seen that the cumulative probability of dying primarily from syphilis by the end of 40 years was 17.1 per cent in males, and 8.0 per cent in females. We have chosen not to go beyond the 40-year duration period, because the denominator in males then drops off under the 100 mark. The development in the mortality from syphilis with the passage of time was characterized by the following main features: the disease was only to a very small extent lethal during the first decade of infection, the probability by the end of 10 years being less than one per cent in both sexes. Thereafter the probability increased relatively slowly during the second decade, to reach 4.8 per cent in males and 3.0 per cent in females by the end of 20 years. During the third decade the increase was somewhat greater in males, the probability reaching 11.0 per cent by the end of 30 years, as compared with 5.5 per cent in females. And the picture remained very much the same during the fourth decade, the probability in males increasing to 17.1 per cent, and in females to 8.0 per cent. The ratios males to females were as follows: by the end of 10 years, 1.3 to 1; by the end of 20 years, 1.6 to 1; by the end of 30 years, 2.0 to 1; and by the end of 40 years, 2.1 to 1.

In males the probability of dying directly as a result of the syphilitic infection was more than trebled during the third and fourth decades (from 4.8 to 17.1 per cent), and in females the probability increased a little more than two and one-half times during the same period (from 3.0 to 8.0 per cent). Thus the findings confirm the general impression that syphilis exerts its lethal effect first and foremost from the second decade of infection on.

c. *Excess Mortality among the Syphilitics as Compared with the Controls.*

For details regarding the establishment of controls, we refer to the section «Establishment of Controls», p. 88, and particularly to pp. 90 and 91.

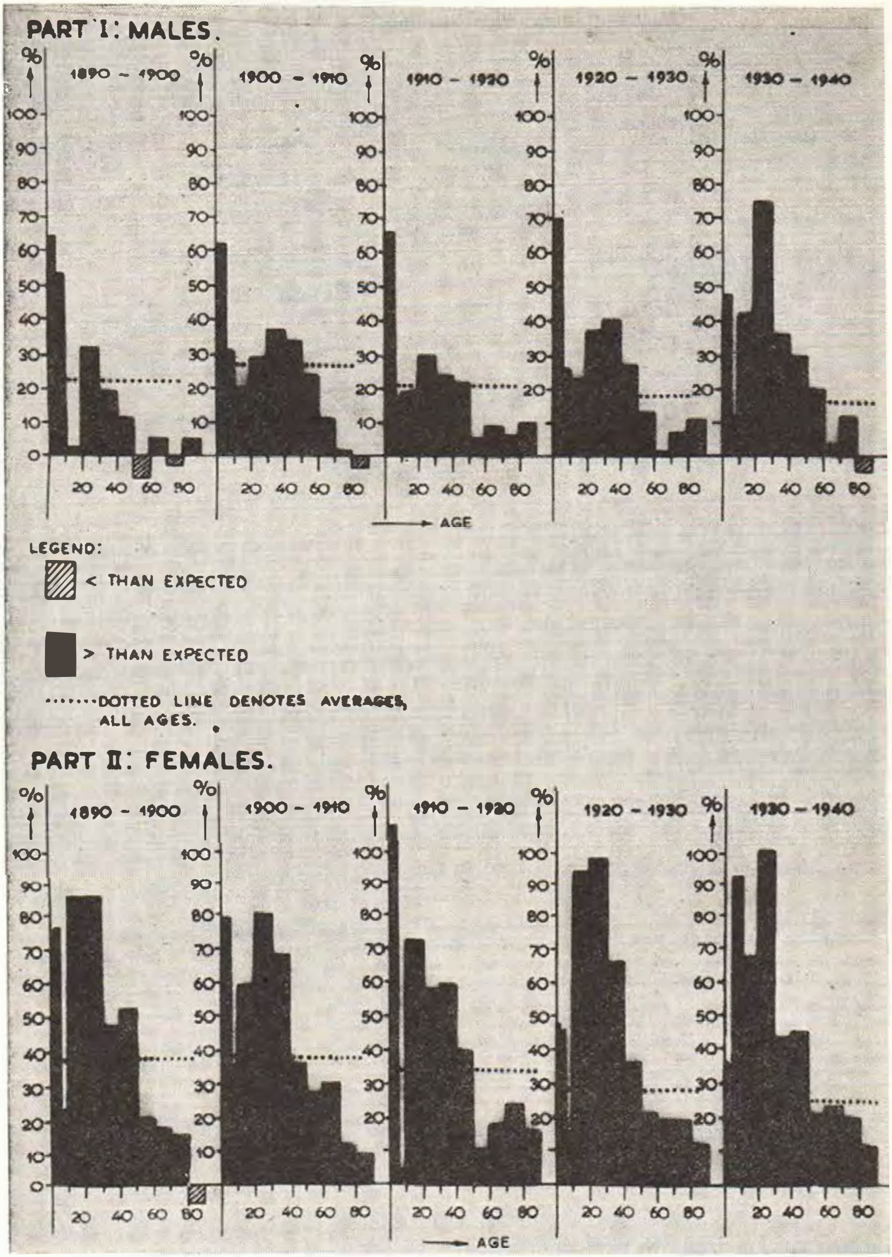
As will be recalled, «it was decided to do a regional study of the mortality of the City of Oslo by age, sex, cause and decade, comparing the western and eastern populations, and at the same time provide mortality data for appropriate study group and eastern population comparisons».

The most important results that came out of the comparison between the populations of East and West are to be found in fig. 11. The diagram is constructed on the basis of the figures in annex table XXIX, p. LV. It will be noted that we have confined ourselves to the period 1890—1940, in spite of the fact that the investigation of the patients was not closed until 1951. The reason we felt obliged to omit the last 10-year period, 1940—1950, from the study, had to do with the fact that the last war with the German occupation of Norway (1940—1945), created abnormal conditions which naturally also were reflected in population and mortality statistics, and in our opinion, the factors involved could not easily be accounted for in the interpretation of the data in question.

Briefly, the findings, as presented in fig. 11, can be summarized as follows: there was an excess mortality among the residents of the eastern parishes, in both sexes, in practically all age-groups, and in all the 10-year periods listed. The average excess mortality East (all ages) ranged between 16 and 27 per cent in males, and between 25 and 38 per cent in females. It was a noteworthy characteristic that females residing East showed a greater excess mortality than males, when compared with their respective western counterparts. Also the diagram clearly demonstrates that the excess mortality in the eastern population was considerably greater than the average in certain age-groups. When it comes to the illnesses responsible for the excess mortality East, the

Fig. 11.

Excess Mortality Among Residents of the City of Oslo in Parishes Located East, as Found on the Basis of a Comparison with Residents Living in Parishes Located West, by Age and Sex, According to 10-Year Periods 1890—1940.



Reproduced from Gjestland, T., Moen, E., and Trier, G.: «A Regional Investigation of the Mortality in the City of Oslo during the Period 1890—1940». (To be printed).

Fig. 12.

Excess Mortality of Patients in the Study Group «Known» as Found on the Basis of Comparisons between this Group and Residents of the City of Oslo in Parishes Located East, for the Total Period 1890—1940, by Age and Sex.

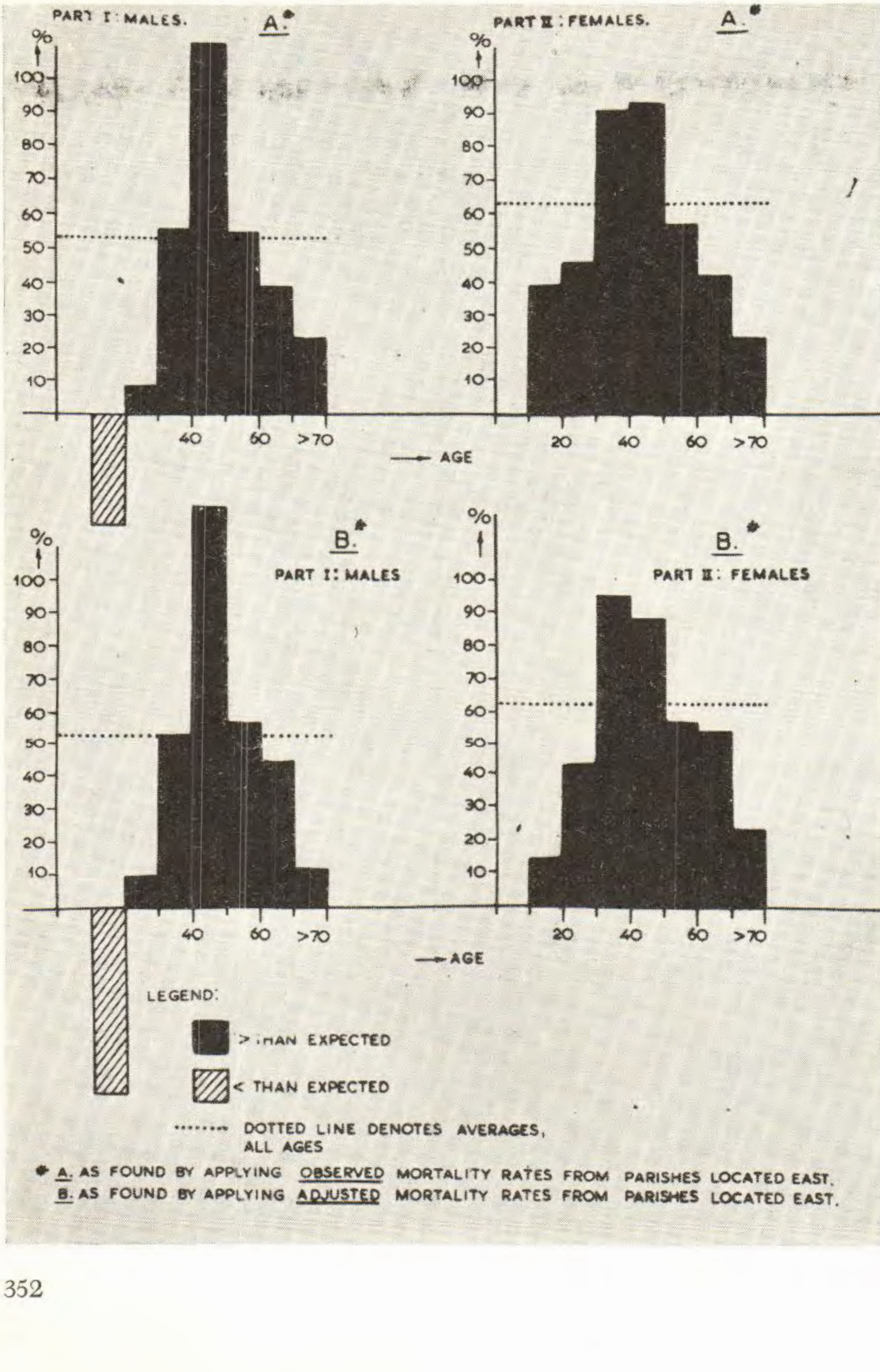


Table 82.

Excess Mortality of Patients in the Study Group «Known» as Found on the Basis of Comparisons Between this Group and Residents of the City of Oslo in Parishes Located East, for the Total Period 1890—1940, by Age and Sex.

Part I. Males.

Ages	Number of personyears (1)	Observed deaths (2)	Expected deaths* A (3)	Expected deaths* B (4)	(2)/(3) % (5)	(2)/(4) % (6)
10 — 19	348	1	1.5	2.3	67	43
20 — 29	1854	15	13.9	13.7	108	109
30 — 39	2595	33	21.2	21.5	156	153
40 — 49	2262	55	26.0	24.8	212	222
50 — 59	1704	48	30.9	30.5	155	157
60 — 69	798	41	29.6	28.4	139	144
70 over	187	21	17.1	18.9	123	111
All ages	9748	214	140.2	140.1	153	153

Part II. Females.

Ages	Number of personyears (1)	Observed deaths (2)	Expected deaths* A (3)	Expected deaths* B (4)	(2)/(3) % (5)	(2)/(4) % (6)
10 — 19	649	5	3.6	4.4	139	114
20 — 29	4142	42	28.7	29.4	146	143
30 — 39	5784	84	43.9	43.1	191	195
40 — 49	4341	69	35.8	36.8	193	188
50 — 59	3153	60	38.1	38.3	157	157
60 — 69	1092	41	28.8	26.6	142	154
70 over	350	31	25.2	25.3	123	123
All ages	19511	332	204.1	203.9	163	163

* A. As found by applying observed mortality rates from parishes located East.
B. As found by applying adjusted mortality rates from parishes located East.

data are not available yet, but preliminary analyses indicate that, with very few exceptions, all main groups of diseases were involved. Actually, this is in keeping with what we would expect when we take into consideration that an excess mortality was found in practically all age-groups.

To conclude, the hypothesis originally set forth in the section «Establishment of Controls» was confirmed by the regional study undertaken: the residents of the parishes located East showed a significantly higher mortality than those living in parishes located West. It seems fully justified, therefore, to use the eastern population for controls rather than the total population of the City of Oslo.

The results of the comparisons between the study group and the population East are to be found in table 82 and the corresponding diagram (fig. 12). It will be noted again that we have not carried the investigation beyond 1940, for reasons explained in the foregoing. The number observed deaths (214 male and 332 female) therefore is not identical with the number given in table 81, where all deaths observed through 1951 were included. However, the number of personyears (9,748 in males, and 19,511 in females) shows that we were left with a still fair-sized sample.

The excess mortality among the syphilitics, as compared with the eastern population from which they originally were drawn, was 53 per cent in males, and 63 per cent in females (all ages). Also, there was an excess mortality among the patients in all except one of the age-groups listed, namely males aged 10—19. In this age-group, however, we had only 1 observed death, so the result may very well be due to chance. Finally it is noteworthy that the excess mortality was more pronounced in certain age-groups than in others. This pertains to males between 30 and 60 and to females between 30 and 50.

Although the syphilitics showed a greater excess mortality as compared with the eastern population, than the latter did as compared with the western population, the two sets of comparisons nevertheless brought out certain common features, which obviously are of great importance when it comes to evaluating the influence of socio-economic factors on mortality. First, females, both in the eastern population, and among the syphilitics, showed a greater excess mortality than the males. And also, the excess mortality, both in the eastern population as compared with the western population, and among the syphilitics as compared with the eastern population, was greater than the average in certain age-groups.

III. Discussion.

The mortality among originally untreated or highly inadequately treated syphilitics, as demonstrated through the findings in the present series, is characterized by the following main points:

1. Even in a one hundred per cent syphilitic population syphilis was not a great killer, as shown by the fact that it was found to be the primary cause of death in only 15.1 per cent of the males and in 8.3 per cent of the females.
2. In spite of this the syphilitic population showed a considerable excess mortality as compared with the eastern population from which it came (53 per cent in males and 63 per cent in females, all ages). In principle,

at least, these findings are in accordance with ordinary experience, and again the question comes up: what is the reason for this excess mortality when the serious late manifestations can not be held responsible for death in more than a relatively small proportion of instances?

At first glance our findings seem to lend confirmatory evidence to the theory advanced by Rosahn, namely that syphilis in and of itself, without causing death directly, exerts a deleterious effect on longevity through a factor, the character of which is unknown. However, in order to explain the results arrived at in the present investigation on the basis of the possible effects of this unknown factor,

we must assume that it exerts its influence at all ages and at all durations, since an excess mortality among the syphilitics was found in all age-groups listed;

we must assume that it exerts its influence to a varying degree in the various age-groups, and at various durations, since the excess mortality among the syphilitics varied with age;

we must assume that it exerts its influence through a whole series of other diseases in various organ-systems, including those that are known never to be the site of syphilitic lesions, ranging from cancer over tuberculosis to the pneumonias and the leucaemias and many others.

In our opinion, it is difficult to conceive of a mechanism that could possibly work in this manner. Therefore, we are inclined to explain the excess mortality found among the syphilitics on the basis of the fact that they came from the lower socio-economic strata of the population, and thus, in addition to syphilis, were exposed to the risk of a host of other diseases that ordinarily take their toll among such individuals.

When we consider the similarity in pattern of the excess mortality as brought out through the comparisons between the western and eastern population on the one hand, and between the eastern population and the syphilitics on the other, it is reasonable to believe that when we go from a higher to a lower socio-economic group of the population, the excess mortality found is always due to a whole series of diseases, syphilis of course being one of them, but hardly a decisive one, even when the prevalence is high or very high.

To conclude, our findings seem to fit in well with the concept held by Schamberg, that syphilis does only kill through the lethal effects of its serious late manifestations.

Chapter XIII

SPONTANEOUS CURE

It is a general impression that a fairly large proportion of those who acquire syphilis go through life unharmed even if they are left untreated. Some are actually cured spontaneously, exhibiting no evidence whatever of their previous syphilitic infection; some have a positive serologic test with no clinical evidence; others have minor symptoms and signs which may or may not be attributed to this disease. Evidence pointing in this direction has been provided by various studies but particularly by Bruusgaard (1929a) through his follow-up study, and by Rosahn (1947) through his autopsy investigation.

In Moore's (1944) wording, Bruusgaard's findings were described as follows: «Taking the data at their face value, they indicate that of every 100 patients acquiring syphilis, 23 will develop a late lesion which will incapacitate or kill; 12 will develop a more benign late manifestation; and 64 will probably pass through life unharmed, so far as they themselves are concerned . . .»[1] The caution exercised by Moore in formulating this statement reveals that he accepted Bruusgaard's figures with the reservations suggested by Bruusgaard himself. In spite of this, the above figures have been widely quoted in the literature, often *without* reservations, the reason being that these findings were the only ones available that could give an approximate idea of the frequency of spontaneous cure. But, these figures have also been seriously criticized, particularly by Harrison, (see p. 26), who called attention to the possibility that those among Bruusgaard's patients who were regarded as «spontaneously» cured, might not have had syphilis at all, since the original diagnoses were non-proven according to modern standards (diagnosis is discussed on p. 65 and p. 67).

Rosahn's autopsy study gave these results: a little more than 2 out of 10 syphilitics died as a result of syphilis, while as many as 6 of 10 died with no evidence of syphilis at all, and a little less than 2 out of 10 died of unrelated causes but with syphilitic lesions present.

[1] See p. 18 of the present monograph.

at least, these findings are in accordance with ordinary experience, and again the question comes up: what is the reason for this excess mortality when the serious late manifestations can not be held responsible for death in more than a relatively small proportion of instances?

At first glance our findings seem to lend confirmatory evidence to the theory advanced by Rosahn, namely that syphilis in and of itself, without causing death directly, exerts a deleterious effect on longevity through a factor, the character of which is unknown. However, in order to explain the results arrived at in the present investigation on the basis of the possible effects of this unknown factor,

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When we consider the similarity in pattern of the excess mortality as brought out through the comparisons between the western and eastern population on the one hand, and between the eastern population and the syphilitics on the other, it is reasonable to believe that when we go from a higher to a lower socio-economic group of the population, the excess mortality found is always due to a whole series of diseases, syphilis of course being one of them, but hardly a decisive one, even when the prevalence is high or very high.

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[1] See p. 18 of the present monograph.

We have previously indicated the possible factors of selection in Rosahn's study and emphasized that his findings and those of Bruusgaard are not directly comparable. Nevertheless it is of importance to realize that as many as 61 per cent of Rosahn's untreated syphilitics showed no evidence of syphilitic anatomic lesions at autopsy (see pp. 31—34).

There is no doubt that the data available on the frequency of «spontaneous» cure have their definite shortcomings, but nevertheless they suggest that a fairly large proportion of untreated syphilitics has little or no inconvenience as a result of the disease, some are actually spontaneously cured.

Before attempting to go any further with our evaluation of the findings as presented by Bruusgaard and by Rosahn, and before comparing them with those of the present study, a definition of what constitutes spontaneous cure must be agreed upon. We have not been able to find a comprehensive definition in any of the leading textbooks of syphilology.

The following is one suggested by Moore (1949 b) and slightly modified by ourselves. To be classified as unquestionably spontaneously cured a patient would have to be an originally untreated syphilitic who:

a) had shown no symptoms of syphilis after the early outbreak;
b) had received no specific treatment for latent syphilis during the interim period;
c) had been examined before death with normal physical findings as far as syphilis was concerned, a negative serologic test and a negative spinal fluid;
d) had at autopsy shown no evidence of syphilis.

As pointed out by Moore, this is a much more rigid definition than usually employed by those interpreting the Bruusgaard data, and would automatically eliminate anybody not already dead. Nevertheless, for the definition to become fully satisfactory, further clarification on some of the points is needed. For example, it would be necessary to determine what type of examinations, clinical and others, would be required to declare a patient «normal» (as far as syphilis is concerned), and to decide on the requirements of a complete post-mortem examination. For our purposes, however, as will be shown in the following, the definition is sufficiently comprehensive as it stands.

It is evident that there are no existing series of patients which fulfils the above criteria. Bruusgaard's series comprised 473 patients, 309 living and 164 dead. Only 40 had been autopsied (8.5 per cent of the total of 473). Thus, according to this definition there were only 40 patients that might have been considered for an analysis of the problem of spantaneous cure, at least from a quantitative standpoint. And in our opinion, this fact alone is reason sufficient to state that the Bruusgaard material does not lend itself for an evaluation of this kind, irrespective of whether the other requirements are met.

Rosahn's series, on the other hand, comprises autopsied patients only. But, it is not stated how complete were the examinations for syphilis before death, nor specifically how many of the patients had had the brain and the spinal cord examined at autopsy. Moreover, there is no mention of the proportion of cases in whom «benign» tertiary had been diagnosed previously, it being noteworthy that no such lesions were listed among the autopsy findings. According to our own percentages of «benign» tertiary, in Rosahn's material we would have expected some 15 per cent to have had these manifestations, provided the average duration of infection in the two series was approximately the same. Finally, Rosahn's series is obviously weighted in the direction of too many cases of cardiovascular and, as pointed out by the author himself, by too few cases of neurosyphilis. By and large, therefore, it is difficult to evaluate the representativeness of Rosahn's figures, and this is particularly true if we use the rigid definition suggested above. Even so, there can be no doubt that Rosahn's findings represent the most valuable contribution hitherto made in respect to certain quantitative aspects of spontaneous cure.

The findings of the present series also have their limitations for this analysis. Only 209 of the group «Known» of 953 (30.1 per cent) were autopsied, and furthermore, our autopsy population is not representative of the reservoir from which it was originally drawn. It is weighted with too many cases of cardiovascular on the one hand, and contains a comparatively small number of cases with neurosyphilis on the other (see pp. 284—288 and 223—226 respectively). Also, the completeness with which the post-mortem examinations were done varied considerably from one patient to another, particularly in respect to the frequency with which the brain and the spinal cord were opened.

Next, there is the question of negative serologic tests at time of death. In this connection it must be emphasized that we are here dealing with a group of patients in whom the final observations took place over a period of 60 years, from 1891 to 1951. It follows that we should have to reckon with a certain number of patients in whom serologic tests could not possibly have been done, namely those who died prior to the introduction of the Wassermann (in Norway 1910). In the remaining patients, who died later, there was the possibility of serologic tests for syphilis having been performed, either shortly before death or at time of death, but the period 1910—1951 was characterized, among other things, by an ever-increasing sensitivity of the tests employed. Thus, we were confronted with the difficulty of determining whether seronegativity in 1910 meant the same as seronegativity in 1951, just to mention an extreme example. Obviously there is no way of making allowances for differences in laboratory technique over the years, and therefore it is practically impossible with any degree of accuracy, to distinguish between the patients who fulfil the requirement of negative serologic tests at time of death, and those who do not.

Table 83.

Outcomes among Living and Dead (953 Patients) in the Study Group «Known», According to Type of Progression, and Cause of Death among 694 of These Patients.

(All ages*) (Categories mutually exclusive)

	Males			Females			Total		
Total numbers	331			622			953		
Patients observed to have developed	No.		Per cent	No.		Per cent	No.		Per cent
«Benign» tertiary alone		36	10.9		89	14.3		125	13.1
Neurosyphilis preceded by «benign» tertiary	3	15	4.5	6	18	2.9	9	33	3.5
Neurosyphilis plus «benign» tertiary	2			2			4		
Cardiovascular syphilis preceded by «benign» tertiary	6			10			16		
Cardiovascular syphilis plus «benign» tertiary	2			0			2		
Neurosyphilis plus cardiovascular preceded by «benign» tertiary	1			0			1		
Cardiovascular plus neurosyphilis plus «benign» tertiary	1			0			1		
Cardiovascular plus neurosyphilis	7	7	2.1	2	3	0.5	9	10	1.0
Cardiovascular plus visceral syphilis	0			1			1		
Neurosyphilis alone		17	5.1		21	3.4		38	4.0
Cardiovascular syphilis alone		28	8.5		34	5.5		62	6.5
Visceral syphilis alone		0	—		1	0.2		1	0.1
Either cardiovascular, neurosyphilis, or both		67	20.2		77	12.4		144	15.1
Some type of late syphilis		103	31.1		166	26.7		269	28.2
Syphilis as a primary cause of death**		39	15.1		36	8.3		75	10.8

* Age at infection.
** Proportions calculated on the basis of the patients who were dead at time of investigation (1949—1951), 694 (259 male and 435 female) out of the total of 953.

Finally, there is the question of negative spinal fluids at time of death. The analysis of the quantitative aspects of the spinal fluid examinations in the present series (Annex IV, p. XV) clearly demonstrates that this question can not possibly be answered on the basis of our material. Suffice it to mention here that no more than 22.0 per cent of the total 953 patients were found to have had spinal fluid punctures done. And since the majority of them were performed on patients called-in for examinations by us, we shall have to reckon with a considerably smaller proportion of spinal fluid examinations among the autopsied patients than in the total study group.

In the foregoing we have mentioned merely a few of the most important requirements set forth in the definition of spontaneous cure. It should be clear from this brief analysis that our data do not provide answers to the question. It appears unlikely to us that any material will ever become available which upon analysis will provide satisfactory answers to the problem of spontaneous cure. In our opinion, therefore, spontaneous cure in syphilis must be considered a purely academic question, the quantitative aspects of which are practically impossible to illuminate with any degree of accuracy.

In view of what has been stated above it was felt we had to employ a considerably less rigid definition, and confine ourselves to the following question: to what extent does a group of untreated or highly inadequately treated syphilitics pass through life with little or no inconvenience as a result of the disease? The method to be used is simple, inasmuch as it includes nothing more than determining the proportions found to have developed some type of late lesion on the one hand, and the proportions *not* found to have experienced such manifestations on the other. Actually, this is exactly what Moore (p. 15) did in presenting his interpretations of the Bruusgaard data.

Two sets of tables have been constructed for the purpose of demonstrating our findings. In table 83 are to be found the outcomes among the patients in the study group «Known» according to mutually exclusive categories, where as in annex table XXX, p. LVI, which is otherwise similarly constructed, the categories are *not* mutually exclusive. The method employed in table 83 is preferable, since it gives a more reliable picture af these relationships, but for completeness' sake, and for possible comparisons we also are presenting in annex table XXX figures as calculated on the basis of *not* mutually exclusive categories. It will be recalled that no statement was made as to whether the categories were mutually exclusive in the table presented by Moore on the Bruusgaard findings (see table 1, p. 16).

These are the most important features as revealed by the total column of table 83: out of every 100 patients, 13 were found to have developed «benign» tertiary alone; 15 were found to have developed cardiovascular and/or neurosyphilis, either alone or in various combinations; i.e. a total of 28 were found to have developed some type of late manifestation. In other words, some 72 patients out of every 100 were found *not* to have developed any late lesion. In this connection it must be emphasized that our figures on the various complications were considered to be minimum although not too far from the true figures (see sections on occurrence in chapters on «benign» tertiary, neurosyphilis, and cardiovascular). Therefore, the above figure of 72 out of 100 patients is probably not truly representative. As mentioned previously, it was very difficult to estimate to what extent our figures for the various complications *were* minimum. But, if we *assume* that *somewhere between 60 and 70, and probably closer to 60 than 70, out of every 100 untreated syphilitics in the present series went through life with little or no inconvenience as a result of the disease, we are probably not too far from the truth.*

By considering the totals we only get part of the story; sub-grouping by sex is as essential here as in all other analyses of the natural course of the syphilitic infection. Among the males 10—11 out of every 100 were found to have developed «benign» tertiary syphilis alone; about 20 were found to have developed cardiovascular and/or neurosyphilis, alone or in various combinations; a total of about 30 were found to have developed some type of late lesion and 70 none. The corresponding figures for females were as follows: about 14 out of every 100 were found to have developed «benign» tertiary; 12—13 out of every 100 were found to have developed cardiovascular and/or neurosyphilis, alone or in combinations; a total of 26—27 were found to have developed some type of late lesion, and 73—74 no syphilitic lesions of any clinically detectable kind.

The proportions in whom syphilis was considered to have been the primary cause of death were 15 out of every 100 in males, and about 8 in every 100 in females. As would be expected, the males showed an excess over females in respect to the more serious late lesions, 20.2 per cent versus 12.4 per cent, or a ratio of males to females of 1.6 to 1; and also in respect to the extent to which the syphilitic infection caused death primarily, the proportions being 15.1 versus 8.3 per cent, giving a ratio of males to females of 1.8 to 1.

With the data available this is about as close as we can come in our attempt to illuminate the problem of «spontaneous» cure. We urge that in any subsequent use of, or interpretations of, our data, these limitations be borne in mind.

Since our study represents a re-analysis of the Bruusgaard material, the next question to arise is the following: do our findings conform with those of Bruusgaard? As the figures stand there is a striking similarity in so far as the estimates of the final outcomes in both series showed some 60—70 out of every 100 patients to have gone through life with little or no inconvenience as a result of the disease. One might, therefore, be inclined to answer the above question in the affirmative. However, under the previous discussion of the frequencies of the various late complications we have already pointed out that, due to differing methods of classification etc., the proportions as found by ourselves are not directly comparable with those presented by Bruusgaard. The above figures are not comparable either, but are fortuitously, not scientifically, similar. Thus the question must be left open. Neither are our numerical results directly comparable with those presented by Rosahn, and for very much the same reasons as given previously when we discussed Rosahn's use of the Bruusgaard figures (see pp. 33—34).

GENERAL SUMMARY AND CONCLUSIONS

By studying a large group of patients deliberately left untreated for their early manifestations during the period 1891—1910, an attempt has been made to fill the need for information on the natural course of the syphilitic infection. In the planning and execution of this investigation the epidemiologic method was adopted, and the study provides an illustration of the application of this method to field research.

The chief results of this follow-up study of some 900 to 1,100 untreated patients were as follows:

1. About 1 out of every 4 patients (23.6 per cent) with *untreated* secondary syphilis developed *clinical secondary relapse*, with no appreciable difference between the sexes.

   There is *no direct evidence* that clincal secondary relapse following untreated secondary syphilis was of ominous prognostic importance in respect to subsequent development of late lesions.
2. *«Benign» tertiary syphilis* occurred in about 1 out of every 6 patients (15.8 per cent). Indication is that «benign» tertiary syphilis was more frequent in females than males.

   These manifestations are found *not* to represent a pathologic process exerting a protective influence against serious late complications.
3. *Neurosyphilis* occurred in 6.5 per cent of the patients. The lesions of the central nervous system were about twice as frequent in males as females (9.2 versus 5.1 per cent).

   Among the dead known to have developed neurosyphilis, these manifestations were the primary cause of death in close to two-thirds of the instances.
4. *Cardiovascular syphilis* occurred in about 1 out of every 10 patients (10.4 per cent). These complications were about twice as frequent in males as females (14.9 versus 8.0 per cent).

   Among the dead known to have developed complicated aortitis these lesions were the primary cause of death in three-fourths to four-fifths of the instances.
5. *Other late syphilis*, in the form of gumma of the liver, occurred in 2

patients, both females. In both instances this manifestation was the primary cause of death.

6. Syphilis was the primary cause of death in about 1 out of every 10 patients (10.8 per cent).

   The disease caused death primarily about twice as frequently in males as in females (15.1 versus 8.3 per cent). Cardiovascular was responsible for more deaths than neurosyphilis in both sexes (9.7 versus 5.4 per cent in males and 4.6 versus 3.2 per cent in females). The ratio cardiovascular to neurosyphilis was 1.7 to 1 and 1.4 to 1 in the two sexes respectively, indicating that cardiovascular was relatively more serious in males than in females. The sex difference was furthermore reflected in the fact that syphilis ranked second in the all-over picture of the causes of death in males, whereas it ranked fifth among females.

   It is stated that syphilis, although an important cause of death, particularly in males, was actually not a great killer even in this 100 per cent syphilitic population. The other causes covering a wide range of diseases and organ-systems, far outweighed syphilis as a primary cause of death.

   The excess mortality among the syphilitics as compared with the controls was 53 per cent in males and 63 per cent in females (all ages). Also there was an excess mortality among the syphilitics in practically all age-groups, and probably from most of the important causes.

   It is concluded that the findings in the present series are best explained on the basis of the fact that the syphilitics were drawn from the lower socio-economic strata of the population, and thus in addition to syphilis, were exposed to the risk of a host of other diseases. Also it is maintained that the findings fit in well with the concept that syphilis does not kill except through the lethal effects of its serious late manifestations.

7. Our data did not provide answers to the question of *spontaneous cure*.

   It was found, however, that out of every 100 patients 13 had developed «benign» tertiary alone; 15 were found to have developed cardiovascular and/or neurosyphilis, either alone or in various combinations; that is, 28 were found to have developed some type of late lesion. Thus some 72 patients out of every 100 were found not to have developed any late lesions.

   The representativeness of these figures was discussed, and it is *assumed* that *somewhere between 60 and 70, and probably closer to 60 than 70, out of every 100 untreated syphilitics went through life with little or no inconvenience as a result of the disease.*

   The outcome of untreated syphilis as estimated from the follow-up of this material, adds evidence supporting the correctness of the principles set forth by professor Boeck, supports some of the conclusions of professor Bruusgaard, and fortifies the expressed ideas of modern experts in syphilology.

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