

ANALYSIS OF ETIOLOGICAL FACTORS OF SQUAMOUS CELL SKIN CANCER OF DIFFERENT LOCATIONS

I. The lower limbs

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Introduction

Squamous cell skin cancer is generally regarded as one of the undesired effects of extensive exposure to sunlight (2, 11). Other etiological factors are mechanical, chemical or thermal trauma of the skin (1, 2, 8). Squamous cell cancer has also been found in association with skin diseases such as lupus vulgaris, psoriasis, chronic leg ulcers, leprosy and several others (6, 7, 9). Also dermatological therapy has been implicated as causative factor in the development of skin cancer. Arsenic treatment has a particularly bad reputation, but also tar treatment has in several cases been suspected of giving rise to squamous cell cancer (4, 12, 13). Tar was the first agent used in experimental chemical carcinogenesis (15). Ditranol, which has been used against psoriasis for about 50 years, interacts with deoxyribonucleic acid DNA (14) and gives rise to mutations in yeast (5). Ditranol, has been found to be a potent co-carcinogen in mice (3). X-ray therapy has since long also been known to have a carcinogenic effect (2, 6).

The physician who has to choose between different therapeutic agents must have some knowledge about the carcinogenic hazards of different treatments, and the scientist developing new principles of treatment must know, whether or not there is a correlation between laboratory data, for instance mutagenicity, and clinical effects such as carcinogenicity.

From experiments with microorganisms or laboratory animals precise and reliable information may be obtained. Such information is, however, not always applicable to humans. Experiments on humans to study carcinogenicity can not generally be undertaken. Retrospective studies are often the only possible approach to these problems. Data on the patients medical history, either taken directly from the patient or obtained through his medical records may be incomplete or to some extent erroneous. Although it is difficult to evaluate the validity of such data, retrospective studies may give important information (10).

We have wished to evaluate the importance of different etiological factors in the genesis of squamous cell cancer. We have chosen to study certain body regions separately since different body regions are affected differently by skin diseases or trauma. In the first study we have investigated squamous cell cancer on the lower limb.

Material and Methods

The Cancer Registry of The Swedish National Board of Health was started on Jan. 1st, 1958. All cases of cancer in Sweden are reported to this organisation. When the present investigation started, The Cancer Registry (C. R.) was complete up to and including 1963, but also a certain number of reports from the years 1964-65 were

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available. During the period 1959-1963 about 500 cases of squamous cell cancer of the skin were on the average reported to the C. R. per year.

When this investigation started, a complete list of all recorded cases of squamous cell cancer of the skin was obtained from the C. R. The list comprised 548 patients for the period 1958-1965. The material did not include cases of skin cancer of the head.

From the report of the C. R. it was possible to identify the hospital and the clinic where the patients diagnosis had been established. Copies of the patients medical records were requested in all cases except for 6 patients, where information on the name of the reporting hospital was missing. In total, records of 475 patients were obtained, that is 86.7% of the entire number of records requested. In the remaining 13.3% the patients records could not be obtained.

The present investigation deals with squamous cell carcinoma of the lower limb. There was a total of 157 patient records in this group. Fourteen patients were omitted from the investigation because they had other forms of cancer which did not belong to the squamous cell cancer type as determined by histological examination. These cases had been incorrectly reported as squamous cell cancer to the C. R. or some error had occurred in the registration process.

The information on the medical history of the patients was fairly good in the hospital records. Concerning patients from outpatients department, the history was sometimes abbreviated and concerned only the actual disease. Sometimes there was uncertain information about the exact localisation of the tumor. It also seems possible that some patients with previous history of skin disease may not have remembered to mention the latter if they saw a doctor just to have a small tumor or ulceration treated. In order to get an idea of how often this error could be expected to happen, we made a more thorough investigation of 16 cases in the group where no possible etiological or associated factors to ulcers could

be obtained, such as skin disease etc. By letter interviews we asked these patients about history of earlier skin disease (e.g. psoriasis). We also inquired about earlier dermatological treatment (e.g. tar, arsenic drugs). In order not to upset the patients we did not ask about their cancer history. To check the diagnoses all pathological specimens from the patients in the group "unspecified ulcer" localized to the legs were requested and scrutinized by an experienced pathologist. We are greatly indebted to Professor J. Pontén, Uppsala, who made that work. In only 4 out of 55 cases diagnosis was not evident in the histologic examination. It is, however, possible that this may be due to receiving slides from a wrong part of the excised skin specimen.

Results

In medical records of 143 patients with squamous cell skin cancer of the lower limbs (in the following abbreviated to SCLL) have been investigated. Fig. 1 gives the age distribution of the material. 122 of the patients had developed cancer in an ulceration or had an ulcerated cancer. Only 21 patients had non-ulcerating tumor. In the latter instance the tumors were almost equally distributed to the thigh, leg and foot. In one instance the tumor developed in a scar from previous burns. In the other instances no possible causative or associated factors were mentioned in the records. In the 122 patients with squamous cell cancer in ulcerations or with ulcerated cancer more interesting information could be obtained. The distribution of these tumors with respect to localization and sex is given in table 1. The most common localization, the leg, and possibly also the knee are more frequently affected in females than in males.

Usually the medical records indicated whether or not the tumor had arisen in skin abnormalities like scar after burn injury, mechanically injured or diseased skin. Hypostatic ulcers could not with certainty be separated out as a group and have been included in "unspecified ulcers". Table 2 shows the distribution of the material (non-

ulcerating tumors not included) with respect to sex, localization, causative or associated factors. The dominating group in table 2 is unspecified leg ulcers especially in women. The rare disease acrodermatitis chronica atrophicans Herxheimer contributes a surprising number of patients. Psoriasis, eczema and other skin diseases contributes relatively few cases. Malignant growth in burn scars appears mainly to occur on the thigh while mechanical trauma seems mostly to affect the legs and feet. Of the 5 psoriatic patients 3 had arsenic treatment 10-20 years before the cancer was diagnosed. Among the eczema cases one patient had arsenic treatment and one x-ray treatment several years earlier. In the group "other skin disease" there were 2 cases of lichen ruber, one scleroderma and 3 poorly defined cases.

The largest and most interesting group is

Table 1. Distribution of the ulcerated squamous cell cancers by localization and sex

Localization	Male	Female	Total
Thigh	6	7	13
Knee	1	3	4
Leg	36	53	89
Foot	7	9	16
Total	50	72	122

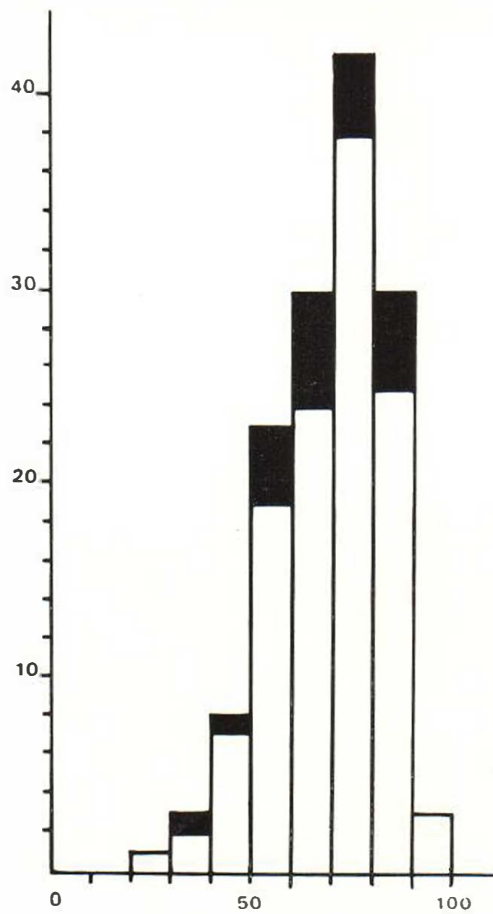


Fig. 1. Age distribution of the study material. Black areas represent non-ulcerating cancers.

Table 2. Distribution of the ulcerated squamous cell cancers by localization, sex, etiological or associated factors

	Thigh		Knee		Leg		Foot		Total
	M	F	M	F	M	F	M	F	
Burn scar	2	2	1	-	1	-	-	-	6
Mechanical injury	2	-	-	-	7	1	2	1	13
Acrodermatitis chronica atrophicans Herxheimer	-	-	-	-	1	5	-	1	7
Psoriasis	-	-	-	-	3	-	1	1	5
Eczema	-	-	-	1	2	1	1	1	6
Other skin disease	-	-	-	1	1	3	-	1	6
Osteomyelitis	-	1	-	-	6	-	1	-	8
Unspecified ulcers	2	4	-	1	15	40	2	4	68
Incomplete records	-	-	-	-	-	3	-	-	3

Table 3. *Distribution of the ulcerated squamous cell cancers by sex and regions of the leg*

	Ventral		Lateral		Dorsal		Medial		Not specified	
	M	F	M	F	M	F	M	F	M	F
Proximal	—	1	—	—	—	1	—	—	—	—
Middle	2	3	1	1	—	1	—	—	—	—
Distal	3	1	2	12	—	1	2	8	—	4
Not specified	1	1	1	2	—	—	1	—	2	4

Table 4. *Latency period between ulceration and diagnosis of squamous cell cancers in different localization of the leg*

	Latency period in years						
	Less than 1 year	1—4	5—9	10—19	More than 20 years	Many years	Not specified
Ventral	2	1	2	3	3	1	—
Medial	1	—	—	4	4	2	—
Lateral	—	7	4	4	3	—	1
Dorsal	1	—	1	—	1	—	—
Not specified	—	1	1	—	5	1	2

the "unspecified ulcers" on the leg. To obtain more information about this group the distribution of the ulcers with respect to proximal, middle, distal, lateral, dorsal, medial and ventral localization was investigated. The findings are given in table 3. The distal lateral part is most frequently affected followed by the distal medial part. Hypostatic ulcers are most frequently localized to the distal medial part of the leg. Some of the ulcerations on the lateral side might therefore be primary cancers which had ulcerated and not hypostatic ulceration which developed squamous cell cancer. In table 4 the time between appearance of the ulceration and the diagnosis of the cancer has been given with respect to localization. Although the numbers in the different groups are small most of the ulcerations on the lateral side of the leg had been present for less than ten years before diagnosis of malignancy while on the medial side practically all ulcerations had been present for more than ten years before malignancy was diagnosed.

In fig. 2 the age distribution of the eight first groups in table 2 plus the arsenic treated cases have been given. The malignancies seem to occur at earlier age after burn injury, mechanical trauma, psoriasis,

eczema and "other skin disease" than in connection with acrodermatitis chronica atrophicans Herxheimer and the "unspecified ulcer" group. The latency period between burn injury and diagnosis of squamous cell cancer in our material was over 20 years for 5 patients and between 10 and 20 years for one patient. Following mechanical trauma the latency period was over 20 years for 6 patients and between 10 and 20 years for 3 patients. For 5 patients the latency period was less than 4 years but the medical records of these patients were inadequate for conclusions to be drawn. In three of these patients other factors could also have been involved in the carcinogenesis. In no instance could mechanical trauma with certainty be implicated within two years in connection with squamous cell cancer. Two of the seven patients with acrodermatitis chronica atrophicans Herxheimer had the disease for more than 20 years, one between 10 and 20 years and 4 between 5 and 9 years before the skin cancer was diagnosed. The five psoriatic cases had their condition for more than 20 years before the diagnosis of skin cancer was made. In the eczema and "other skin disease" groups all had their disease for more than 10 years and about half of them

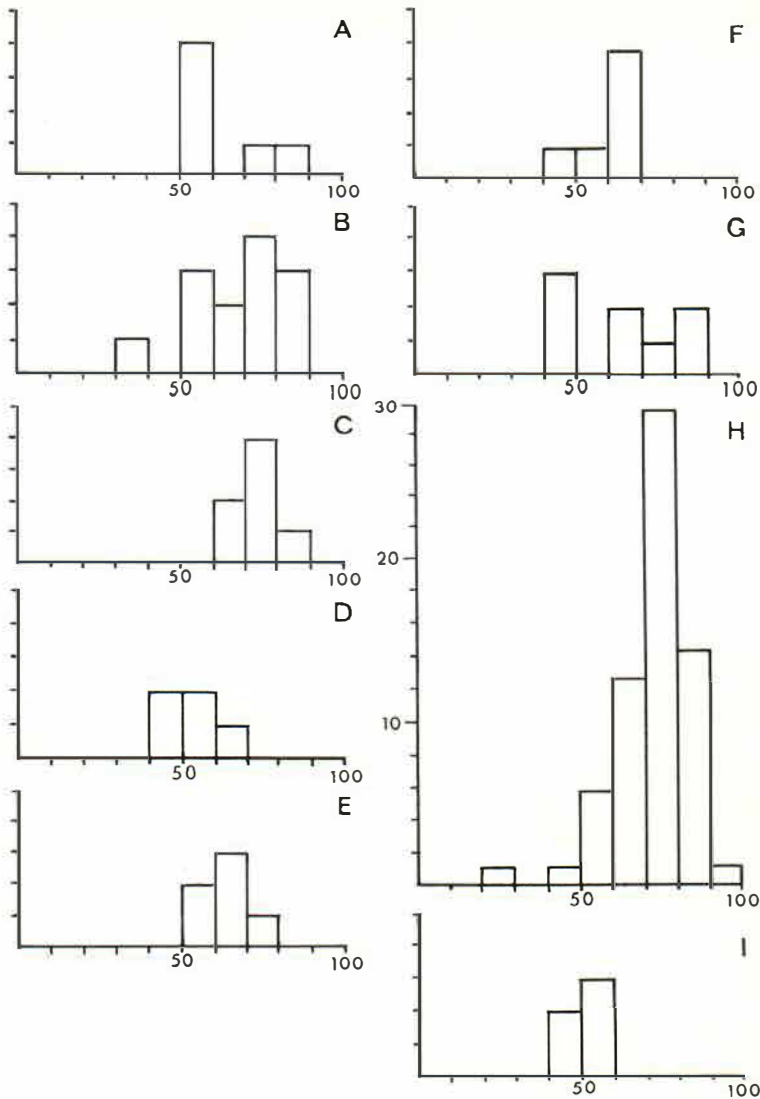


Fig. 2. Age distributions of the different groups of table 2. A Burn scar. B Mechanical trauma. C Acrodermatitis chronica atrophicans Herxheimer. D Psoriasis. E Eczema. F Other skin diseases. G Osteomyelitis. H Unspecified ulcers. I Arsenic treated patients.

for more than 20 years before the skin malignancy was found. In the osteomyelitis group 6 had a perforating osteomyelitis for more than 20 years, 2 between one and four years and one less than one year before the diagnosis of squamous cell cancer was made. The data concerning the main part of the "unspecified ulcer" group are given in table 4.

Fig. 1 shows that squamous cell cancer of the lower limb is a disease which mainly occurs in people fifty years of age and

older. On the basis of the 1963 population statistics of Sweden and the data in fig. 1 we have estimated the number of squamous cell cancer cases localized to the lower limb per 100,000 individuals of different age groups. The data are given in fig. 3 (logarithmic scale) and shows that the incidence of this particular type of cancer increases exponentially with age. The frequency is doubled approximately in eight years.

In the group of 21 patients with non-

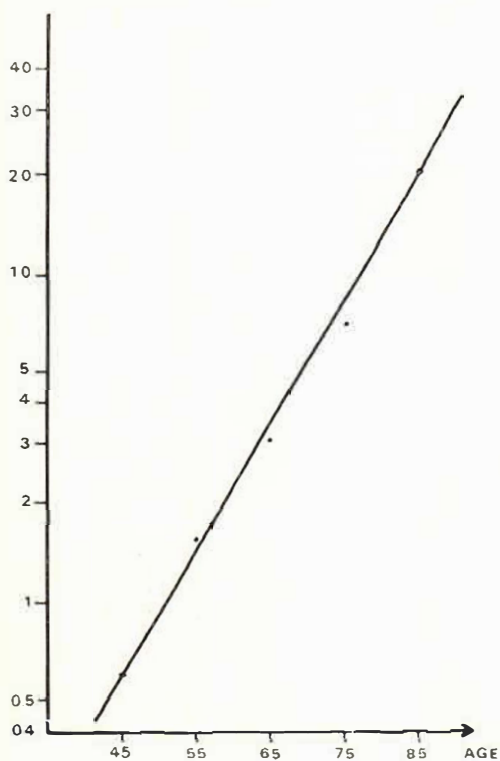


Fig. 3. Number of squamous cell cancer cases with tumors on the lower limbs per 100 000 people in different age groups. Logarithmic scale on the ordinate.

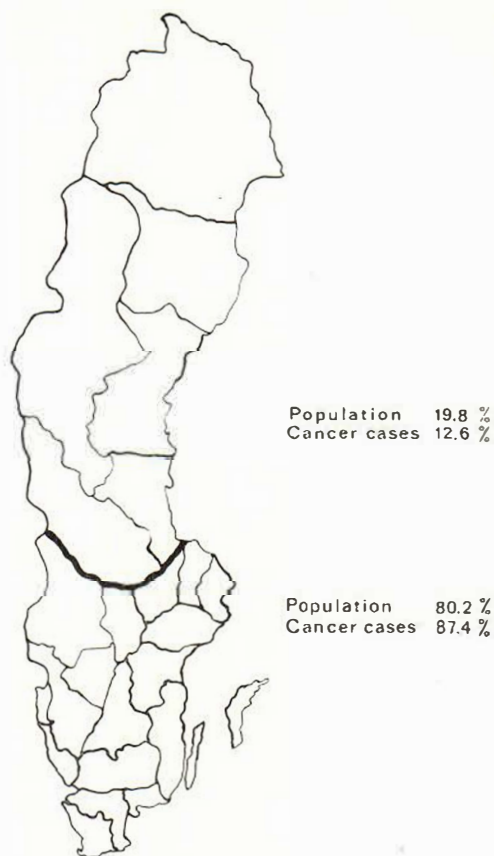


Fig. 4. Map showing the counties of Sweden. The thick line indicates the northern and southern part of Sweden according to our division.

Table 5. *Metastatic frequency with respect to suspected etiological or associated factors*

	Number of cases with metastases	
	Only to lymph nodes	To other organs
Burn scar	—	I
Mechanical trauma	I	I
Acrodermatitis chronica atrophicans Herxheimer	I	—
Psoriasis	2	I
Eczema	3	—
Other skin disease	2	—
Osteomyelitis	—	—
Unspecified ulcers	6	2

ulcerating cancer there were 3 with metastases to regional lymphnodes only and 3 with metastases to other organs, e.g. lungs and liver. Of the 122 patients with squamous cell cancer and ulcerations 15 had metastases in regional lymphnodes only while 5 had metastases also in other organs. The distribution in the latter group of the metastatic cases with respect to etiological or associated factors is given in table 5. The total number of patients in the different groups is found in the last column of table 2.

If Sweden is divided in a northern and southern part according to fig. 4, 19.8 percent of the population lived in 1963 in the northern part. 12.6 percent of all cancer cases in our material came from this area. The southern part thus had 80.2 percent of the population and 87.4 percent of the cancer cases. Of all cases with metastases 11.5 percent came from the northern part and 88.5 percent from the southern part. According to the above figures there are thus 1.74 times more squamous cell cancer cases of the lower limbs in the southern part than in the northern part per one million inhabitants. From the figures of all types of cancer reported to the Swedish Cancer Registry in 1963 one can calculate that there are 1.25 times more cancer in the southern part per one million people. The differences between the two regions is thus higher for squamous cell cancer of the lower limbs than for all other types of neoplasms taken together.

The interview group was selected from the "unspecified ulcer" group with cancer localization to the leg. Of the 16 patients selected 4 patients were dead, one could not be reached. Of the 11 which answered our interviewing form one reported that he had psoriasis previously, 3 had skin disease and had been treated with tar ointment, but no one with arsenic.

Discussion

All diagnosed squamous cell cancers of the lower limbs reported in Sweden during a certain period have been investigated. A

selection of certain types of cancers which may be seen at particular clinics is thus avoided. It is probable that the information on skin diseases or other associated or etiological factors reported in this paper is incomplete due to negligence of the patient or the physician when the medical history is reported. We endeavoured to check the medical history of the patients with "unspecified ulcer" of the leg by using a special interview letter. The patients in our material are old and several of them were dead when the interview study started. Of the 11 patients who answered the interview letter 7 never had a skin disease and had not been treated with either arsenic or tar ointment. One patient had had psoriasis and 3 other skin disease. It is not known if these 3 patients meant their squamous cell cancer since we did not wish to refer to cancer in our interviewing letter. We are of the opinion that there is no significant overrepresentation of psoriatic patients in the material, certainly not if the 3 arsenic treated cases are excluded. In the literature there are only a few cases reported where squamous cell cancer has developed in a psoriatic lesion. If precancerous lesions had been included in our study the number of arsenic treated cases might have been much higher. The number of eczema cases and cases with other skin diseases do not seem to be higher in our material than in a normal population. An exception is acrodermatitis chronica atrophicans Herxheimer which—in spite of its rarity—contributes with more cancer cases than psoriasis. Of these cases all had their skin disease for more than five years and several considerably longer before the cancer was diagnosed.

Most skin diseases cover a relatively large part of the body surface and a coincidence of skin disease and squamous cell cancer without any etiological relationship can not be excluded. Burn scar and scar after mechanical trauma usually covers a small part of the body and therefore a coincidence of scar and squamous cell cancer suggest a more probable etiological relationship. Epidermal atrophy such as occurs in a scar or in acrodermatitis chronica atrophicans

Herxheimer thus seems to predispose to malignant growth.

The largest group in table 2 is the "unspecified ulcer" group. Further analysis of this group showed that most cancers were situated on the lateral side of the leg in contrast to hypostatic ulcers which most frequently occur on the medial side. There are also more women than men in the "unspecified ulcer" group. The latency period between appearance of the ulcer and diagnosis of the cancer was shorter for the lesions on the lateral side than for the medial side. The lateral side of the leg of females receives more sun radiation than the medial side and, because of differences in clothing habits, also more than the leg of males, and it is possible that sun light is an etiological factor in the "unspecified ulcer" group. It is also probable that several of the cases in this group had a primary cancer with subsequent ulceration and not ulcerations of other etiology which later developed malignant growth.

There were 1.74 times more SCLL per million people in the southern than in the northern part of Sweden. Many factors may be contributing to this difference. There are fewer physicians in the northern part per million people. This may be one of the possible explanations. However, the corresponding ratio for all types of malignancies was 1.25. A possible factor may also be the more extensive sun radiation, particularly in the ultra violet range, in the southern part as compared to the northern part of Sweden.

Most cancers were of the ulcerating type. Greither and Tritsch (6) regard the exophytic and the ulcerating type as two different clinical entities, while for instance Belisario (2) regarded them as different stages of one clinical entity. Of the 22 cases of exophytic cancer in our material 3 had metastasized to lymphnodes only and 3 had metastasized also to other organs. Of the 122 cases of ulcerating cancers 15 had metastasized to lymphnodes and 5 also to other organs. Thus the metastatic tendency does not seem to be greater for the ulcerat-

ing type than for the exophytic type. The latter seems generally to arise in a previously normal skin while the ulcerating type often arise in skin damaged or abnormal in any other sense. We are therefore of the opinion that the factor determining the type of squamous cell cancer is the condition of the skin at the site where the tumor arises.

SUMMARY

The present investigation was undertaken to evaluate the importance of etiological factors in squamous cell cancer of the skin with particular reference to those not concerning sunlight. The medical records of all cases with squamous cell cancer on the lower limbs reported to the Swedish Cancer Registry from 1958-1966 have been analysed. It was found that 21 patients had a non-ulcerating tumor and 122 patients had squamous cell cancer in an ulceration or had an ulcerated cancer. The frequency of metastases was similar in the two groups. Skin abnormalities at the site of the cancer were found in several cases. Six cases had developed cancer in old burn scars, 13 at sites of earlier mechanical injury, 7 in lesions of acrodermatitis chronica atrophicans Herxheimer. Five patients had had psoriasis at the site of the cancer, six patients had eczema, 6 other skin diseases, 8 perforating osteomyelitis and 68 unspecified ulcers. Data on the localization of the cancer in the different groups, age distribution, latency period between ulceration and diagnosis of cancer and frequency of metastases are given. A higher frequency of squamous cell cancer on the lower limbs was found per million people in the southern part of Sweden than in the northern part. If dermatological therapy (e.g. As, tar) has contributed to the number of squamous cell cancers on the lower limbs the contribution is insignificant. The only dermatosis which appears to predispose to squamous cell skin cancer in Sweden is acrodermatitis chronica atrophicans Herxheimer and possibly also hypostatic leg ulcers.

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