Studies on the Pathogenesis of Morphea, Vitiligo and Acrodermatitis Atrophicans by Means of Transplantation Experiments.

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In the following an account will be given of some experiments aimed to investigate the pathogenesis of certain skin affections appearing on isolated well-defined areas by means of a special technique namely: transplantation experiments. The present studies deal in particular with vitiligo, circumscribed scleroderma (morphea) and acrodermatitis atrophicans. As is well known, the etiology of these affections is still obscure, but the hypotheses advanced in this respect emphasize especially the following possibilities:

1. Local infection of the skin with an unknown infectious agent.
2. Special, entirely local, changes in the cells of the skin.
3. So-called trophic disturbances, *i.e.*, changes involving especially the vegetative nervous system in its relation to certain skin regions.
4. Endocrine disturbances, possibly interacting with 2) and 3).

The method has been to transplant a piece of skin from a pathologically altered skin area to normal skin and vice versa. Such a double transplantation may easily be performed in one seance, simply by exchanging the place of the two flaps.

The technique here employed has been af follows: Under local anesthesia a Thiersch skin graft, about 2 sq. cm in size is taken from the area affected — most often from the center — by means of a razor blade fixed in a special holder. Then a graft of the same size is taken from an area of normal skin. After careful hemostasis the normal skin graft is placed where the pathological graft has been taken, and vice versa. Both grafts are covered with a small piece of sterile linen and then a piece of hydrophobic cotton that exerts a suitable pressure on the grafts after the bandage is fixed with strips of elastoplast. This bandage is removed after 6 days. In all the experiments but one the grafts healed well.

Each of the etiological possibilities mentioned above may be assumed to influence the grafts in its own particular way. 1) If the skin lesion is due to an infectious agent with local action, we would expect a pathological skin graft on transplantation in normal skin to preserve its pathological properties, which possibly might spread from the graft to the surroundings. We would likewise expect that a normal skin graft in a pathological area gradually would undergo pathological transformation, more likely commencing at its margin. 2) If the affection is due to particular properties of the cells of the skin, we would expect the pathological graft in normal surroundings to preserve its properties, whereas their extension beyond the border of the graft would not seem likely. Likewise we would expect the normal skin transplanted to a pathological area to preserve its normal character. 3) If the affection is due to trophic disturbances we would expect the pathological skin graft in normal surroundings gradually to lose its pathological character, and conversely we would expect the normal graft under the »trophic» influence to undergo pathological changes. 4) If endocrine disturbance is the decisive factor, and if this is independent of the nervous system, we would expect the pathological graft to preserve its particular properties, and we would expect a normal graft to remain normal. If, on the other hand, the endocrine factor exerts its influence by way of the nervous system, we would expect the same outcome as under 3).

A condition without which no conclusion may be drawn from the transplantation experiments of course, is that the grafts really

take solid hold and that the cells in these pieces of skin keep on living in the new surroundings, not being substituted gradually by other cells from the surroundings. No quite positive proof of this may be given, but several features indicate that such healing really takes place.

Thus histological examination of normal and pathological grafts in a case of morphea and a case of acrodermatitis atrophicans has shown the healing of the grafts to be solid, while the border between the grafts and the surrounding skin was sharply defined, without any sign of »invading» transformation from the margin. The transformation of the grafts that actually takes place, and which will be described later on, appears to take place simultaneously throughout the grafts. Also the clinical observation shows that in no instance was there any gradual »substitution» of the grafts from the margin.

Most likely, then, the healing of these grafts is permanent, and it will be justified therefore to draw conclusions from the changes they are undergoing in the course of time, and which will now be described. Largely I have limited myself to direct macroscopic observation. Histological examination of each graft would really have been desirable. But this would involve the risk that the scar formation which unavoidably accompanies the biopsy might blur the clinical features; besides, it could not be excluded that this little operation might disturb the natural course of the processes concerned. In the three diseases dealt with here, moreover, the changes are so characteristic and easy to estimate on ordinary direct inspection, that biopsy was refrained from except in the two cases mentioned (morphea and acrodermatitis) in which the purpose of biopsy primarily was to ascertain the healing, as a priori there might be some doubt about the solidity of this healing — especially in sclerodermic or atrophic skin.

It may be stated at once that in all the three diseases studied the outcome on the transplantation experiments mentioned was fundamentally uniform.

Experimental Results.

(In the following records the pathological grafts is designated as P., the normal as N.)

I. *Circumscribed scleroderma (morphea).* 5 cases.

1) Male, aged 12. Typical morphea on abdomen. 1/4/43: Transplantation. 3/5/43: N. appears quite unchanged, with solid healing in the center of morphea, which has spread a little marginally. P. detached. 22/9/44: N. now undergone complete sclerodermic transformation, uniform throughout. The border line between the graft and surroundings can barely be made out.

2) Male, aged 43. Typical morphea on abdomen. 5/5/43: Transplantation. 11/6 43: Solid healing of P. and N., both preserving their original characters. 16/8/43: P. undergoing transformation to normal skin; N. to sclerodermic. These changes are uniform throughout the respective grafts. On repeated subsequent examinations the transformation is seen to progress gradually. 12/7/44: P. Now completely transformed to normal skin, N. into scleroderma.

3) Female, aged 20. Morphea on back, marginally as white-spot disease. 15/4/46: Transplantation. 14/8/46: P. and N. still presenting their original characters. 21/9/46: P. begins to transform to normal skin. N. showing no distinct changes yet. 25/10: Same as on preceding examination. 16/11: Now N. begins to transform too, being slightly sclerodermic. 21/2/47: P. completely transformed to normal skin, N. to scleroderma. Change in the character of morphea, which has become somewhat smoother and less infiltrated. In its appearance, N. corresponds to this later phase of the disease.

4) Female, aged 19. Morphea on back. 25/2/46: Transplantation. 13/5/46: P. and N. still preserving their original appearance.

15/7/46: Beginning transformation of P. to normal skin, of N. to scleroderma.

5) Female, aged 31. Morphea on forearm. 8/11/46: Transplantation. 3/1/47: P. and N. still preserving their original characters. 1/4/47: P. completely transformed to normal skin, N. to scleroderma.

Histological examination was performed in Case 2), 49 days after the transplantation. At that time P. showed normal epithelium. The papillæ of the corium were flattened; the corium in general somewhat edematous. No distinct hyalinization in relation to the surrounding tissue. No conspicuous changes in the elastic tissue. The border is sharply defined, made up of loose connective tissue, rich in cells, with numerous small vessels and some infiltration with lymphocytes and histiocytes. N. showed higher epithelium than

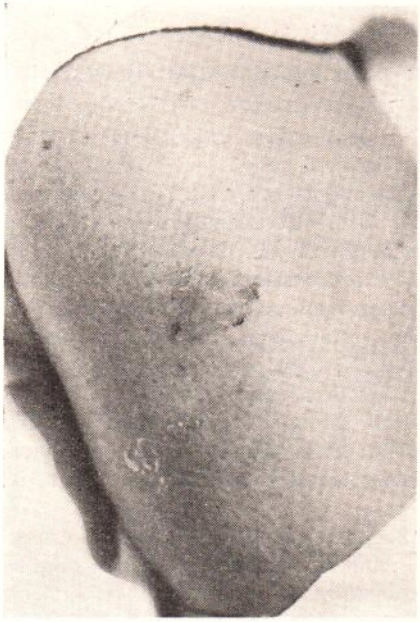

Fig. 1 a. Scleroderma. N., 8 days after transplantation.

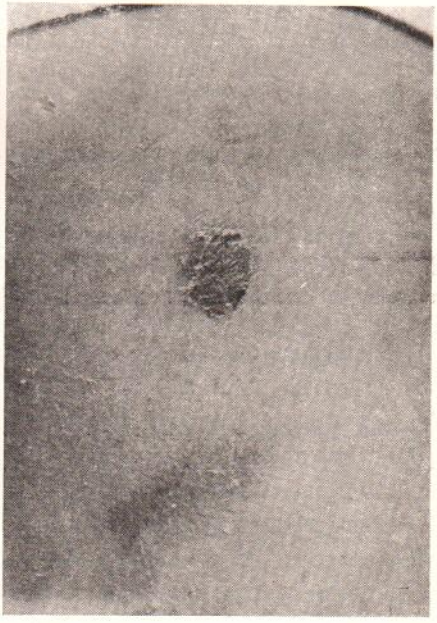

Fig. 1 b. Scleroderma. P., 8 days after transplantation.

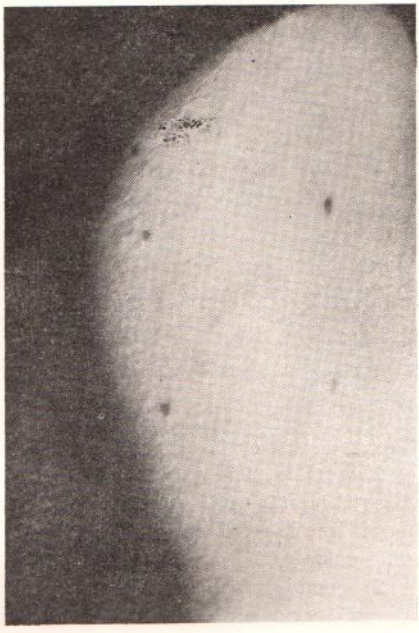

Fig. 1 c. Scleroderma. N., 16 weeks after transplantation. N. is now completely transformed to sclerodermic tissue.

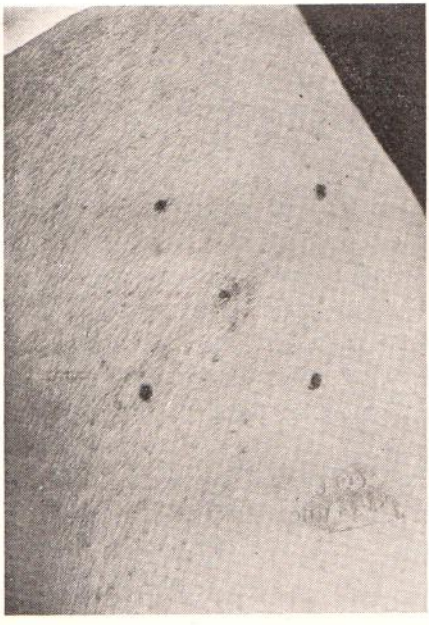

Fig. 1 d. Scleroderma. P., 16 weeks after transplantation; now almost transformed to normal skin.

the surroundings and higher papillæ. Corium somewhat edematous. Collagenic tissue dense, partly hyalinized. No conspicuous changes in the elastic tissue. Blood vessels scanty. Merely insignificant infiltration with lymphocytes and histiocytes.

In these cases of morphea the results show that normal skin transplanted to the center of a sclerodermic area within some months is transformed to sclerodermal skin. This transformation appears to take place uniformly throughout the graft — not from the margin inwards. Sclerodermic skin transplanted to a normal skin area gradually loses its sclerodermic character.

II. *Vitiligo.* 4 cases.

1) Female, aged 19. 22/8/43: Transplantation. 15/9/43: P. and N. still remaining quite unchanged. 30/8/44: N. now entirely bleached; its border line barely discernable. P. has become pigmented and is now of the same color as its surroundings.

2) Female, aged 21. 4/3/46: Transplantation. 7/5/46: P. and N. still apparently unchanged. 3/12/46: N. completely bleached and hardly distinguishable from the surrounding vitiligo. P. has become somewhat pigmented, though considerably less than the surrounding skin.

3) Female, aged 12. 23/8/46: Transplantation. 23/9/46: P. and N. still appearing quite unchanged. 1/11/46: N. shows beginning bleaching; P. unchanged. 16/6/47: N. completely bleached; P. apparently quite unpigmented yet. γ 4) Female, aged 37. 16/4/47: Transplantation. 22/5/47: P. and N. still unchanged.

So the results obtained in these cases of vitiligo are of similar character as in scleroderma. In the three cases who have been under observation sufficiently long the normal skin transplanted to an area of vitiligo gradually lost its pigment; conversely, vitiligo skin transplanted to an area of normal skin became pigmented again in two cases — completely in Case 1), partly in Case 2) — whereas it remained free from pigment in Case 3).

I contrast to these findings in vitiligo, it will be appropriate to mention a case of circumscribed congenital hyperpigmentation (lentigo), in wich the grafts remained unchanged even after about one year.

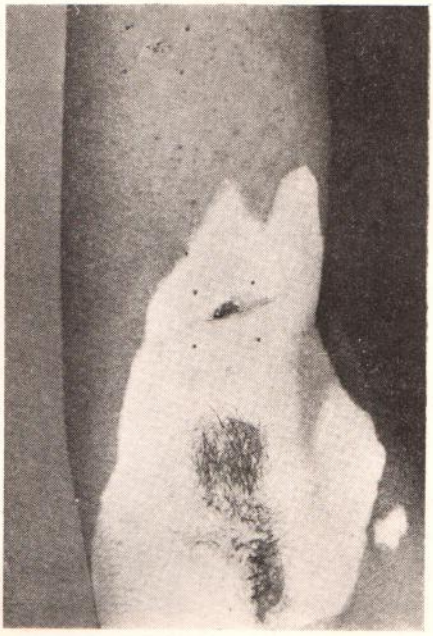

Fig. 2 a. Vitilig, 8 days after transplantation.

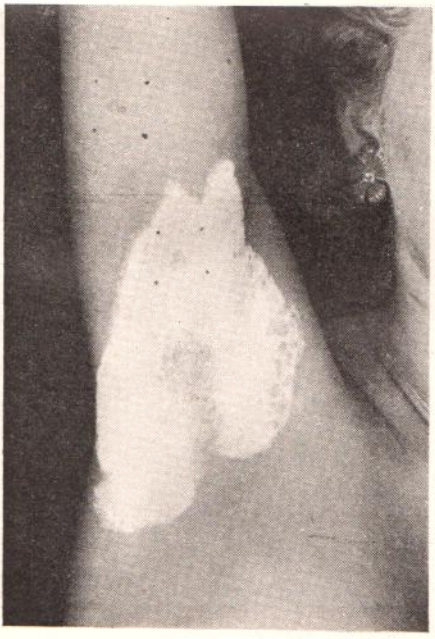

Fig. 2 b. Vitiligo, ca. 1 year after transplantation. N. is now completely bleached, while P. has become pigmented.

Fig. 3 a. Lentigo, 10 days after transplantation.

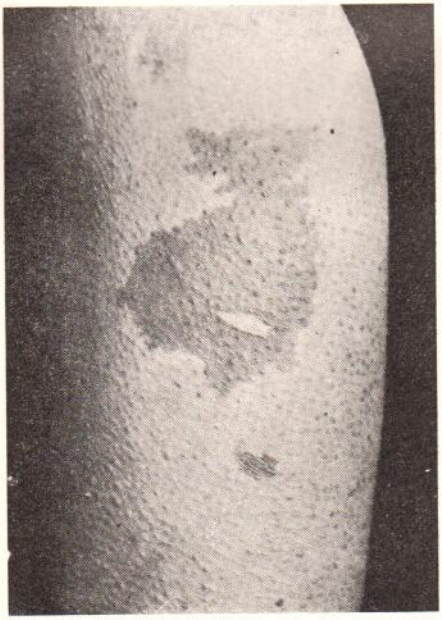

Fig. 3 b. Lentigo, ca. 1 year after transplantation. Both transplants have preserved their original character.

III. *Acrodermatitis atrophicans.* 4 cases.

1) Female, aged 55. 31/3/43: Transplantation. 11/5/43: P. still unchanged; N. shows commencing atrophy. 7/11 44: P. completely transformed to normal skin; N. to atrophic skin.

2) Female, aged 60. 5/1/46: Transplantation. 3/5: P. and N. still apparently unchanged. 21/9: P. still distinctly atrophic. N. has become quite atrophic, of the same character as the surroundings. 7/2/47: P. is now transformed to normal skin. N. entirely atrophic.

3) Female, aged 49. 28/11/46: Transplantation. 17/4/47: P. is beginning to transform into normal skin. N. almost transformed into atrophic skin. 21/6/47: P. still markedly atrophic, N. now almost like its surroundings.

4) Female, aged 52. 19/11/44: Transplantation. 12/12/44. P. unchanged. N. shows beginning atrophy. 26/9/46: P. completely transformed to normal skin, N. completely atrophic.

Histological examination was performed in Case 1), 51 days after the transplantation. At this time P. still showed the atrophic changes characteristic of the disease, although the epidermis here was considerably thicker than the epidermis in the pathological skin outside N., with beginning papilla formation. Also the elastic tissue was better developed, and besides fragments of elastic fibers, fairly well developed, wavy fibers are seen in several places; scanty lymphocytic infiltration, especially at the margin, N. showed commencing atrophy with flattening of the epidermis. No distinct changes in the connective tissue, but beginning deterioration of the elastic tissue; scanty lymphocytic infiltration. So, both in P. and N. the histological picture showed commencing transformation to the structures of the area of transplantation.

In acrodermatitis atrophicans thus quite similar conditions are met with as in scleroderma and vitiligo: After transplantation to a normal skin area the abnormal skin graft is gradually transformed into normal skin, while normal skin grafts in atrophic milieu gradually undergo atrophy of the same character as that of the surrounding skin. The latter process appears to proceed more rapidly than the former, but in both cases the transformation takes several months. Under the transformation of the normal skin to atrophic, in no instance was an infiltrative stage observed corresponding to what often is seen during the spontaneous development of the

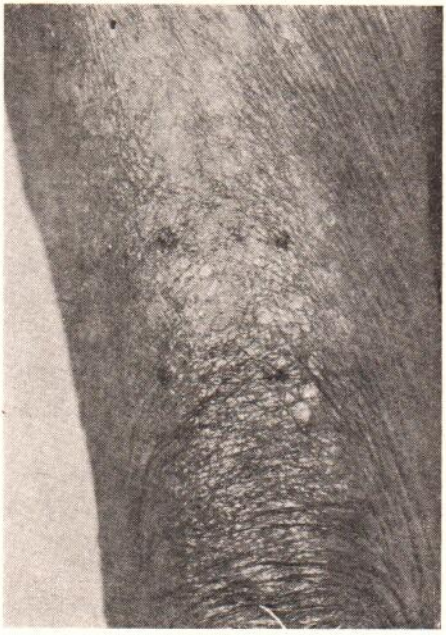

Fig. 4 a. Acrodermatitis atrophicans. N., 3 weeks after transplantation.

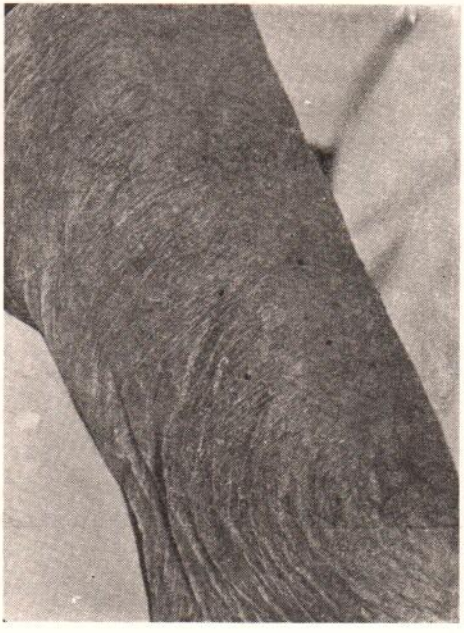

Fig. 4 b. Acrodermatitis atrophicans. N., ca. 1 ½ years after transplantation, now completely transformed to atrophic skin.

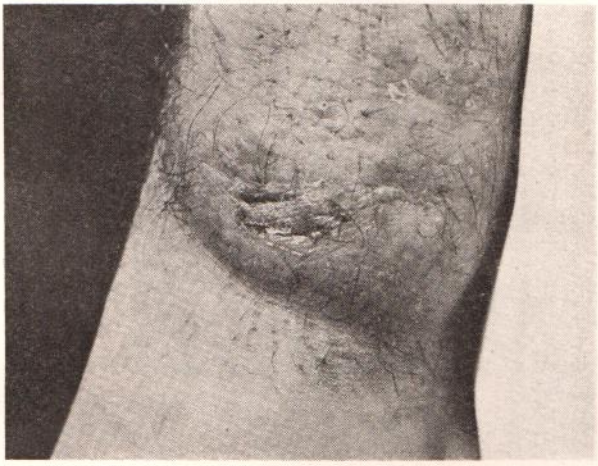

Fig. 5 a. Myxoedema circumscriptum. N., 14 days after transplantation.

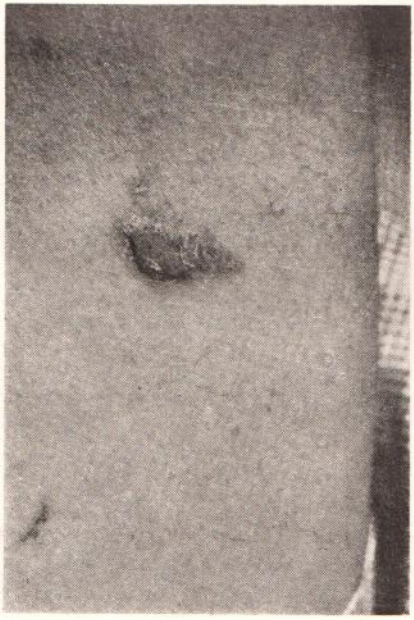

Fig..5 b. Myxoedema circumscriptum. P., 14 days after transplantation.

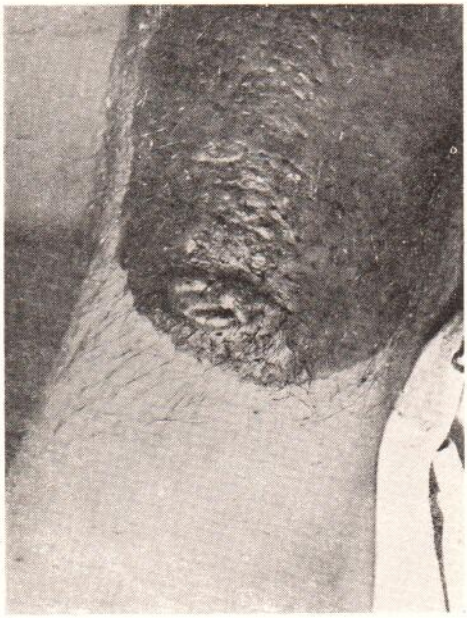

Fig. 5 c. Myxoedema circumscriptum. N., ca. 2 months after transplantation.

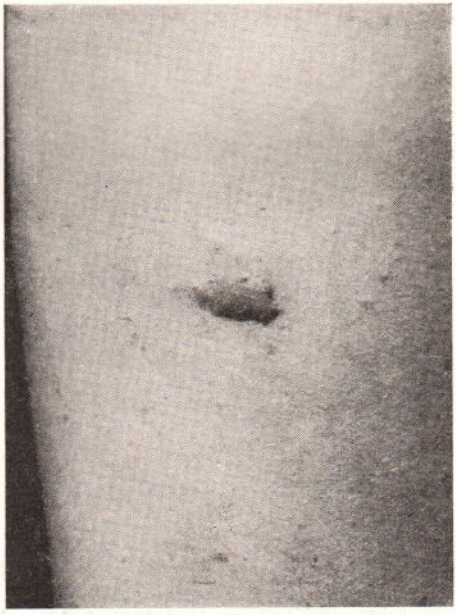

Fig. 5 d. Myxoedema circumscriptum. P., ca. 2 months after transplantation. N. has now undergone myxedematoid transformation while P. has preserved its myxedematous character.

lesion in fresh efflorescences or at the margin of the atrophic areas. The transformation appears not to proceed from the margin but take place evenly throughout the graft.

Discussion.

From these transplantation experiments in cases of scleroderma, vitiligo and HERXHEIMER's acrodermatitis it is evident that the course of the resulting changes in the grafts fundamentally has been of the same character in all three diseases. In all the cases with a sufficiently long observation period, after healing in a normal skin area, the pathological graft has gradually lost its pathological character, being transformed into apparently normal skin. In one case of vitiligo, only, there was no sign of such transformation yet about 10 months after the transplantation. On the other hand, after healing in the pathologic skin area, the normal graft has gradually been transformed into pathological tissue of the same character as that of the surroundings. In several cases the transformation of the normal graft to pathologic skin is seen to proceed more rapidly than the reverse process. In no instance has the transformation proceeded from the margin of the graft, but this process has been going on equally throughout the transplant.

From the results obtained it would seen unreasonable to assume that the abnormal changes in the three diseases mentioned are due to some particular characters of the skin itself or to other factors with an entirely local effect — as, for instance, some infectious agent. For, if so, we would expect the pathological, transplant after healing to preserve its pathologic character (cf. the experiment in the case of lentigo), or that the morbid character of the graft possibly extended to the surroundings. The circumstance that the pathological graft gradually is transformed into normal skin shows that the etiologically decisive factor no longer exerts its effect when the graft is placed in an area of normal skin. It really is surprising that such pronounced pathological changes as those which characterize scleroderma and acrodermatitis are capable of regression, whereas this is less striking in the slighter changes

characteristic of vitiligo. The fact that normal skin transplanted to a morbid area gradually takes on the pathological character of the latter shows the presence of active factors in this limited area capable of transforming normal skin into the skin lesion concerned.

As to the nature of these factors, nothing may be said with certainty. Still, the results here reported point in a definite direction. It is highly improbably that they might be entirely local factors in the skin. For, if so, we would expect the normal graft to be transformed from the margin — just as we would expect the pathological graft to preserve its character. Nor may humoral factors — *e.g.*, of endocrine nature — alone explain the results, as they have to be assumed indeed to exert their action on the pathological graft too, so that we would expect this to preserve its properties after transplantation to normal skin.[1] It is not possible a priori to exclude local circulatory changes as the cause of these results. But, as is well known, no characteristic primary vascular changes have been demonstrated in the three diseases mentioned — nay, in vitiligo, I think, it may even be said that the condition of the vessels hardly deviates from those of normal skin.

It then remains as the most probable explanation of the characteristically limited effect of the morbid factors that they consist in changes in the innervation. In other words, it is the old theory about »trophic» disturbances — which, as a matter of fact, finds support in many clinical observations — that again turns up as an explanation, and at any rate it is quite in keeping with the findings here reported. Thus it explains the transformation of normal skin into abnormal after transplantation into an area where the trophic factors exert their influence; and it also explains the transformation of pathological skin to normal when the graft heals in an area outside the trophic influence. In all probability this influence is brought about through the vegetative nervous system;

[1] In a case of so-called »local myxedema» of the leg in a patient suffering from exophthalmic goiter a similar experiment was performed. Here N. was found to be transformed rapidly into pathological tissue, whereas P. not only preserved a pathological character, but it was even more pronounced after 2 months. Unfortunately this patient failed to return for further observation (see Fig. 5).

and from the localization of the skin affections the cause is presumably to be looked for in an affection of the more central part of this nervous system. It is obvious that the three skin diseases mentioned here involve different processes in the nervous system, just as presumably they may involve both irritative symptoms and signs of insufficiency. Finally, it is to be mentioned that endocrine factors possibly may be contributory to the appearance of the clinical features, though presumably only by way of the vegetative nervous system, not through direct influence on the skin.

Undoubtedly the transplantation method here described may be employed also in studies on the pathogenesis of skin diseases other than the three lesions dealt with in this paper. Thus I have used it in some cases of psoriasis where the results were found foundamentally to deviate from those here described. As a rule psoriasis transplanted to normal skin preserves its pathological character, and sometimes it extends from the graft into the surroundings. Normal skin transplanted to the center of a psoriasis plaque will usually be »infected» from the margin and gradually invaded throughout by psoriasis. In this usual course of the grafts, however, various irregularities are seen, and any conclusive estimation of the results therefore will have to wait till a larger material is available.

Summary.

Transplantation experiments are performed in cases of circumscribed scleroderma (morphea), vitiligo and acrodermatitis atrophicans with healing of pathological skin grafts in normal skin areas and with normal skin grafts in areas that have undergone pathological changes.

In all three diseases the normal grafts were found within some months gradually to undergo transformation to the special pathological picture respectively; conversely, the pathological grafts gradually turned into apparently normal skin.

The results lend support to the assumption based on many clinical observations: that the skin affections here concerned arise under local »trophic» influences presumably exerted through the vegetative nervous system.

Résumé.

Nous avons fait dans des cas de sclérodermie circonscripte (morphée), Vitiligo et Acrodermatitis atroficans quelques expériments de transplantation dans la manière suivante: Une greffe de l'affection en question est transplantée à une partie normale de la peau, et en même séance une greffe de peau normale est transplantée au centre de l'affection.

Dans toutes les trois maladies les greffes de peau normale ont eté transformées après quelques mois à l'affection spéciale; tandis que les greffes pathologiques ont été transformées a peau apparamment normale. Les resultats supportent la théorie basée sur plusieurs observations cliniques, que les affections en question sont dues a des troubles trophiques exercées par le système nerveux.

Zusammenfassung.

Bei Sclerodermia circumscripta (Morphæa), Vitiligo und Acrodermatitis atrophicans wurden Transplantationsversuche in der Weise vorgenommen, dass ein Läppchen der pathologisch veränderten Haut an eine normale Hautstelle und umgekehrt ein Läppchen normaler Haut an eine zentrale Stelle der krankhaften Veränderungen transplantiert wurden.

Bei allen drei Krankheiten wurden die normale Läppchen nach einigen Monaten zum speziellen pathologischen Gewebe transformiert, während die pathologischen Läppchen sich zu scheinbar normaler Haut umbildeten.

Diese Erfolge entsprechen die durch klinische Erfahrungen gestützte Auffassung, dass die erwähnten Krankheiten wahrscheinlich auf einer Störung der trophischen vegetative Innervation beruhen.