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ORIGINAL ARTICLES

LUPUS ERYTHEMATOSUS - AN AUTO-IMMUNE DISEASE

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INTRODUCTION

Rayer in 1827 gave a more or less clear description of the skin diseases known as lupus erythematosus (L. E.). This name, meaning the red form of lupus, was first employed by Cazenave in 1828.

Lupus (wolf) was a term originally used to denote rodent skin diseases; doubtless, both carcinomata and such inflammatory processes as lupus vulgaris (a form of skin tuberculosis) and tertiary syphilis were grouped under this heading. In view of the fact that at that time the diagnosis had to be based on morphological criteria alone, it is not surprising that it was impossible to establish precisely the boundaries of this pathological condition.

The process was regarded as a disease confined to the skin, but as early as 1872, the dermatologist Kaposi called attention to the occurrence of internal complications, among them heart disease. It was only after the publication of the classic paper by Libman and Sacks that this pathological condition became reasonably familiar to physicians; these authors described four patients with endocarditis verrucosa, two of whom were also suffering from L. E. of the skin.

Nowadays, the consensus of opinion is that L. E. (both in its chronic and acute forms) is a manifestation of a generalized pathological process, a disease having no connection with tuberculosis (lupus) but resulting from a disorder of the production of antibodies by the reticulo-endothelial system (R. E. S.).

L. E. IS AN AUTO-IMMUNE DISEASE

One of the functions of the R. E. S. is the production of antibodies, including those to bacterial, viral and harmful chemical agents which obtain entry to the body. This defence may be cellular in nature (antibodies bound to lymphocytes) and/or humoral (y-globulins produced by plasma cells).

The rejection of a homeograft, i. e., of tissue originating from another organism of the same species, is similarly an immunological process; in this case,

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both humoral and cellular antibodies against foreign tissue components are produced.

Numerous investigations have made it clear that in the embryo the R. E. S. does not produce antibodies against its own tissues, which at this time are still differentiating, nor against hemografts, provided the grafting is not performed too late in the foetal period+).

In general, immunological defence only develops after birth, under the influence of the thymus. By that time, the R. E. S. can indeed distinguish between the components of the body's own tissues and those of foreign tissue.

Lupus erythematosus is an auto-immune disease, in other words, a disease in which the R. E. S. produces antibodies (y-globulins) directed against the components of the body's own cells and tissues.

These antibodies may be directed to the thrombocytes (thrombocytopenia), the erythrocytes (anaemia), the leukocytes (e. g, to components of the cytoplasm) (leukopenia), and further renal, cutaneous, vascular or other tissue.

In many cases it is still not possible to discover against which fraction of the attacked organs or tissues the antibodies are directed. In any one patient, several such antibodies may be circulating at the same time.

One of the very characteristics of normal antibodies is their specificity of action, each combining only with its specific antigen; however, in acute L. E. one may sometimes find a type of y-globulin circulating which attacks not only the nucleoprotein of the organism itself, but also that of other individuals and even that of other mammals and even of fishes.

It is as if the antibodies, which normally fit their corresponding antigens as specifically as a key fits a lock, have been changed into some sort of skeleton keys, which will fit any lock.

There is some evidence that this abnormality of the R. E. S. may on occasion be hereditary. It is to be expected that as a result of further investigations, the genetic basis of this process will be further elucidated.

The following classification of L. E. is sometimes used:

L. E. (chronicus (a. discoides; b. erythema perstans) / acutus (systematicus, visceralis etc.))

CHRONIC L. E.

Clinical characteristics

a. *Discoid L. E.* is localized mainly in exposed skin areas, viz. the face (fig. 1), the throat and neck, the upper chest wall and the backs of the hands (fig. 2). A typical feature is the butterfly pattern of eruption on the face.

+) In certain animal species, transplantation of homeografts can be carried out with permanent good results even for a short period after birth.

The margins of the eruption are red with an adjoining zone showing wide follicles and follicular hyperkeratosis, and an atrophic central area (fig. 3). In many cases, pigmentation, depigmentation and telengiectasia are also observed.

Often the eruption appears or is aggravated in the summer; when exposed to the sun, the affected areas may give sensations of heat, burning, or pain.

A typical symptom, which, however, is not always clearly present, is pain induced by pressure on the lesions.

The oral mucosa, the lips (fig. 4) and the conjunctiva, as well as the scalp are sometimes also affected by the process.

On occasion, the eruption may undergo acute dissemination over larger areas of skin (fig. 5), sometimes even in the absence of internal symptoms. However, in many cases one or more internal symptoms are demonstrable even in discoid L. E. There may for instance be mild asthenia or a subfebrile temperature, there may be transient articular pain or some perimalleolar oedema. In some cases there is a degree of anaemia or leukopenia, an increased γ-globulin concentration, an increased BSK and sometimes also other symptoms which actually belong to the clinical picture of acute L. E. (see table I).

A rare complication of chronic L. E. is malignant degeneration of the skin or the oral mucosa (planocellular carcinoma).

b. *Erythema perstans* gives rise to more complex diagnostic problems. Even its name is a contradiction in terms, since erythema is by definition only a *transient* redness. Persistent redness is seen in L. E. (fig. 6) and inter alia, in Boeck's disease, in tertiary syphilis, in toxicoderma (the classic example is antipyrine) in leprosy, in eosinophil (facial) granuloma and at many other points in the intricate embroidery of dermatological disgnosis. Often, valuable diagnostic information can in these cases be obtained by microscopic examination.

MICROSCOPIC FEATURES

In discoid L. E. we find a thin epidermis with follicular hyperkeratosis, hydropic degeneration of the basal layer, degeneration of the connective tissue, and wide vessels with slight lymphocytic infiltration, which, however, is mostly found near the adnexa of the skin. As a rule, the microscopic picture is only really typical in those cases in which the clinical picture is so clear that confirmation of the diagnosis is hardly necessary.

In erythema perstans, the modifications are in principle identical, but they are present in much milder degree. For this reason, an unequivocal diagnosis cannot as a rule be made on the basis of the microscopic findings alone.

FLUORESCENCE MICROSCOPY

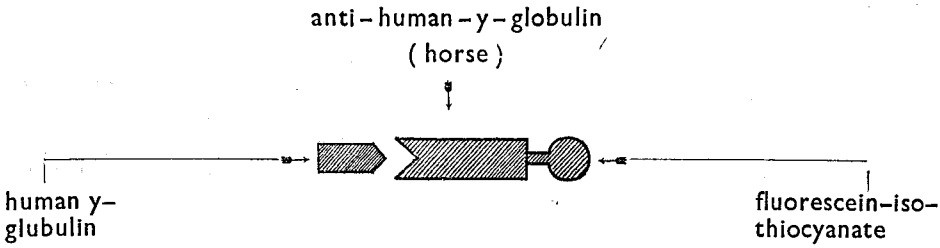
Since the work of Cormane and Kalsbeek and independantly by Burnham, Neblett and Fine, it has become possible to make the diagnosis of L. E. rapidly and

with certainty, even in cases where the skin changes are not specific, with the aid of immuno-fluorescent techniques.

Contrary to what was until recently believed, even chronic L. E. is an auto-immune process; in these patients circulating antibodies (y-globulins) are present, directed against components of the basal membrane.

The presence of these y-globulins in the basal membrane can easily be demonstrated. The principle of this technique is as follows.

Animals, for instance the horse, can be sensitized to human y-globulins ; the horse then produces antibodies (y-globulins) against human y-globulin. The y-globulins of the horse are then conjugated with a fluorescent compound e. g. fluorescein isothiocyanate. Microtome sections of a skin lesion are incubated with these conjugated anti-y-globulin-fluorescein isothiocyanate; where human y-globulins are present in the section, complexes are formed consisting of:



If these sections of chronic L. E. lesions are then examined with the fluorescence microscope, the yellow-green fluorescence of fluorescein isothyocyanate can be observed (fig. 7), indicating where the anti-human-y-globulins of the horse, and hence, the human y-globulins are localized in the tissue.

All doubt as to the immunological nature of this fixation of human globulin to the basal membrane has been removed since Cormone and Kalsbeek succeeded in demonstrating, with the aid of a similar technique, that complement is involved in this process.

As far is now known, this fluorescence is specific for L. E., and y-globulins fixed to the basal membrane are not present in other skin diseases.

However, future investigations will have to show whether or not this phenomenon may be present in other auto-immune diseases.

ACUTE L. E.

Witnin the scope of this brief communication, it is impossible to give a detailed and complete description of this pathological condition, because it may appear in so many different forms.

The disease occurs primarily in women; the patients often feel very ill and have high fever; commonly seen are renal involvement (generally in the form of a nephrosis), blood abnormalities (anaemia, thrombocytopenia and leukopenia occur in 30% or more of cases, and the y-globulin level is frequently increased), and articular disorders. Myositis, peri-and endocarditis, pleurisy, adenopathy and splenomegaly have been reported, and in addition, peripheral neurological (neuritis) and cerebral conditions (convulsions, mental changes). The skin lesions may sometimes be absent (see table). Discoid L. E. may occur and may precede the acute symptoms by some years. Certain cases may present a patchy redness (fig. 8), bullae, purpura, urticaria, erythema nodosum, erythema exsudativum multiforme and, in a high percentage of the patients, perniosis and Raynaud's disease.

THE L. E.-CELL.

It was precisely in severe cases of acute L. E. that the so-called L. E.-cells were discovered, viz. in 1948 by HARGRAVES, RICHMOND and MORTON.

These cells are usually polynuclear leukocytes (but other cells, such as monocytes, may be involved), in which there is a mildly eosionphilic amorphous inclusion in the protoplasm. This inclusion body represents nuclear material of disintegrated cells.

The L. E. phenomenon may be present in the blood of patients with acute L. E., but is not necessary to the diagnosis.

The blood of such patients may contain y-globulins (the L. E. factor), directed against nucleoprotein. This factor is powerless against intact cells; for this reason, most laboratory methods (not discussed here) for the demonstration of the L. E. factor involve purposely damaged white blood cells. The nuclear material that is liberated in this process is attacked by the anti-nucleoprotein factor (y-globulin). A normal nucleus is basophilic owing to the presence of DAN;* if the y-globulin directed against this DNA attaches itself to the molecule, the acid groups are covered, as a result of which the nucleus becomes mildly eosinophilic. The nucleus thereafter swells and becomes amorphous. These amorphous masses are surround by polynuclear leukocytes (rosette formation), which have entered the vicinity to discharge their function as scavengers. A leukocyte which has taken up an amorphous fragment of nucler material is termed an L. E. cell.

It should be realized that in L. E. these cells are demonstrable only if antibodies against nuclear material are present, which is not always the case.

A negative L. E. phenomenon does not exclude the possibility of acute L. E., nor is a positive L. E. phenomenon absolute proof of the existence of acute L. E.

L. E. cells are also present in cases of intoxication with hydralazine, penicillin, hydantoin, tetracycline, INH and chlorpromazine. As a rule, the number of L. E.

* Desoxgribonucleic acid.

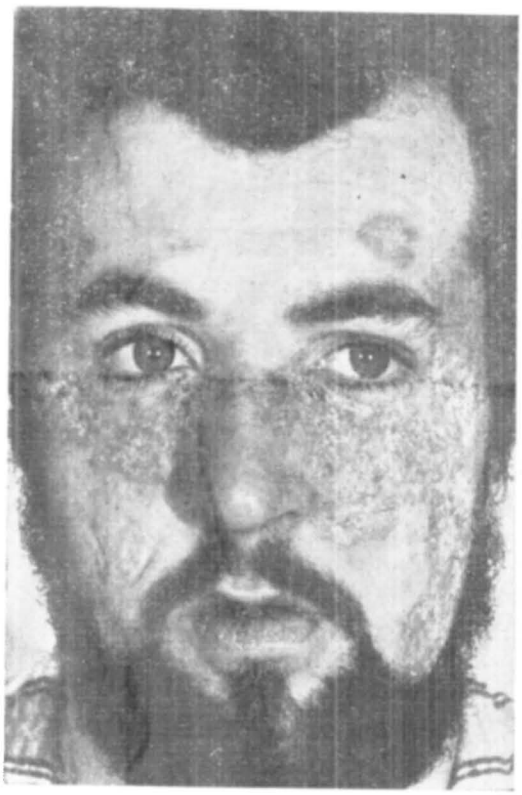


Fig. 1
L. E. discoides of the face.

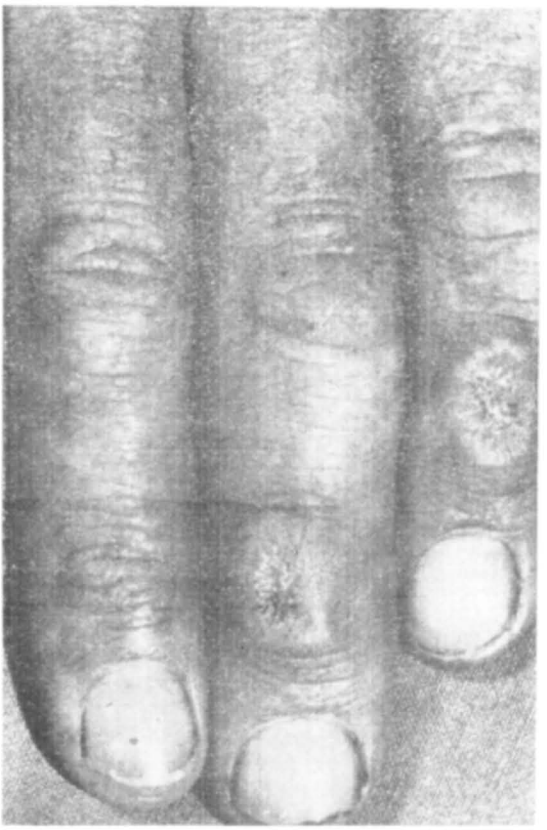


Fig. 2
L. E. discoids of the fingers.

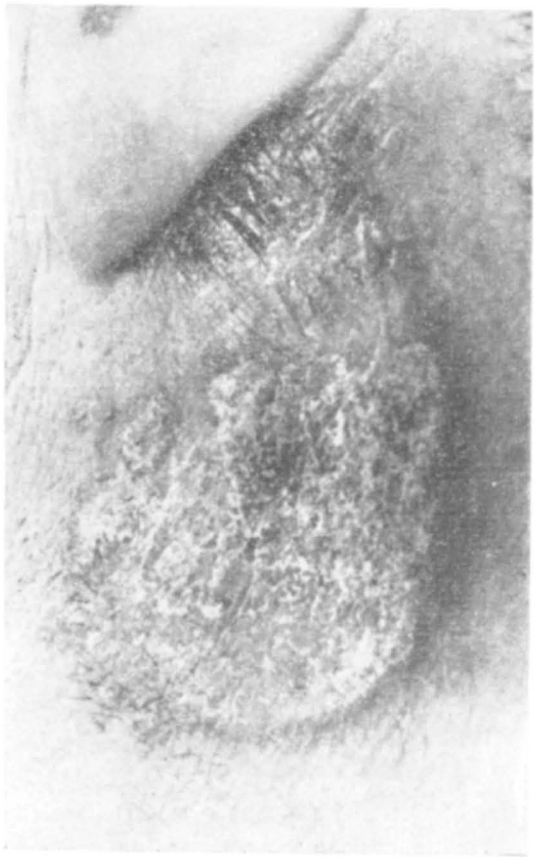


Fig. 3—L. E. discoides under the left ear.

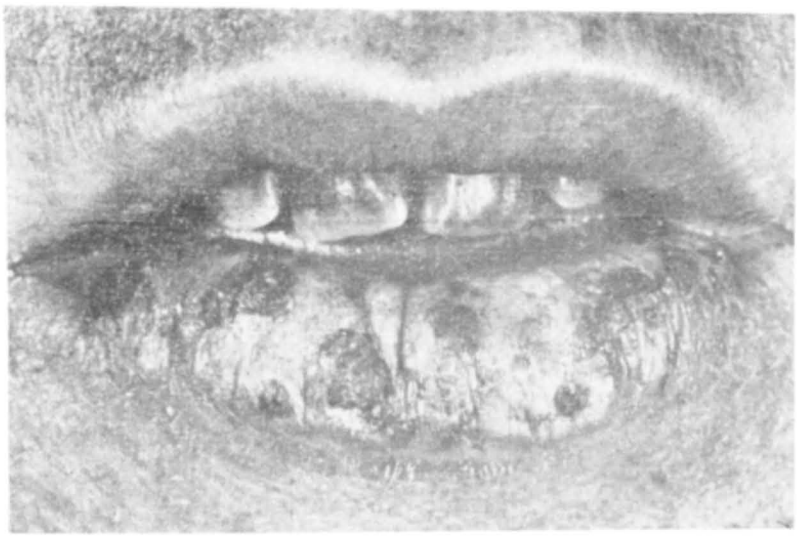


Fig. 4—L. E. discoids of the lover lip.

cells in these cases is small and the L. E.–like symptoms are reversible. As BRUNSTING et al have expressed it, the L. E. test is a very valuable aid in the diagnosis of acute L. E.; individual clinical assessment of every patient is however the most important element, since the prognosis depends on many factors, of which the outcome of the L. E. test is only one.

A patient who suffers from acute L. E. is very apt to produce, not only antibodies against his own cells and components of his own tissues, but also against those of others, and transfusion reactions are therefore often observed in these patients.

MICROSCOPICAL FEATURES

The essential lesion is the fibrinoid degeneration of collagen; as a rule this is not very apparent in the skin, the phenomenon being most evident in the internal organs.

In the skin lesions we sometimes observe, in addition to a degree of hyperkeratosis, some hydropic degeneration of the basal layer. Some lymphocytic infiltration is visible around the vessels and occasionally the vessel walls show slight fibrinoid degeneration.

The basal membrance may be swollen, and the local collagen homogenized. The visceral lesions comprise fibrinoid degeneration of the subendothelial connective tissue, with slight aspecific inflammation.

Often there is also some peri–arterial fibrosis; in certain cases, the degenerative changes are also evident in the vascular walls.

Small foci consisting of amorphous nuclear material are also found in various organs, particularly in the kidneys and the endocardium.

If skin lesions are present, they show as a rule few characteristic features.

FLUORESCENCE MICROSCOPY

It has been shown (CORMANE and KALSBEEK) that in acute L. E. the same fluorescence of the basal membrane is present in the skin lesions as in chronic L. E. (see above).

Further it was found that this fluorescence was present, though to a slightly lesser degree, in the normal skin of patients with acute L. E., even where macroscopical and microscopical skin lesions were entirely absent. These authors have hence discovered a new diagnostic element.

THE RELATIONSHIP BETWEEN DISCOID L. E. & ACUTE L. E.

Occasionally, discoid L. E. precedes or follow the symptoms of acute L. E. SCOTT et. al. (see table) have attempted to classify 116 L. E. patients into a number of groups.

Group A consisted of 16 patients, who presented the typical symptoms of acute L. E. with many internal complications; none of these patients had ever

suffered from discoid L. E., although 56% of them had experienced transient erythemata.

Group B consisted of 14 patients; these were suffering or had suffered from discoid L. E., although they all presented the extensive symptom complex of acute L. E.

In 70% of the patients, the discoid L. E. had preceded the first acute symptoms by a period varying from 18 months to 18 years.

Group C and D, consisting of 11 and 77 patients respectively, presented the classical signs of discoid L. E.

The patients in group D presented no internal symptoms which could be attributed to acute L. E., whilst the patients in group C each presented one or more symptoms of acute L. E. but could nevertheless not be considered as suffering from true acute L. E. The classification of the patients into group B or into group C was probably here and there somewhat arbitrary.

Nevertheless the classification into these groups A, B, C, and D, shows that in the examination of a patient suffering from discoid L. E., a study of the condition of the skin is never in itself sufficient; complete internal examination is absoluiely indicated. The validity of this statnment is evident from the fact that out of 102 patients who were suffering or had suffered from discoid L. E. of the skin, 25 had one or more internal symptoms of acute L. E.

THE RELATIONSHIP BETWEEN ACUTE L. E. AND CERTAIN OTHER PATHOLOGICAL CONDITIONS.

An additional difficulty in the diagnosis of acute L. E. is created by the fact that this disease is sometimes associated with other so-called "collagen diseases", such as periarteritis nodosa, dermatomyositis, and diffuse sclerodermia. At the dermatological clinic of the University of Utrecht we have ourselves observed certain striking examples of these combinations.

In acute L. E., one can very often observe livedo reticularis, which is generally regarded as a symptom of associated arteritis.

The above-mentioned conditions have sometimes been grouped together under the heading of "collagen diseases", which allegedly have as their common element a fibrinoid degeneration of collagen. However, it remains an open question whether this feature is specific and also, whether it is present in all these diseases.

It is not improbable that an auto-immune process plays a part in all these diseses, but they can virtually always be clearly distinguished from one another on the basis of the clinical picture, even though a certain number of transitional forms and combinations are known.

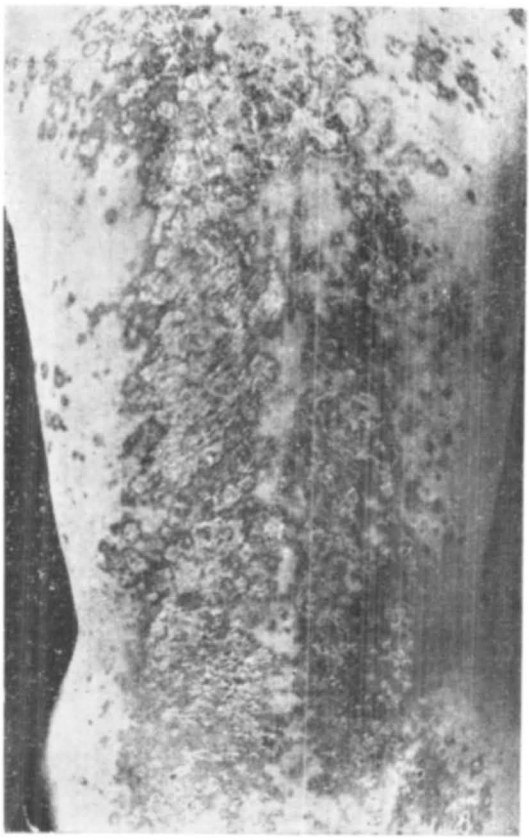


Fig. 5
L. E. discoids, acute dissemination over the trunk.

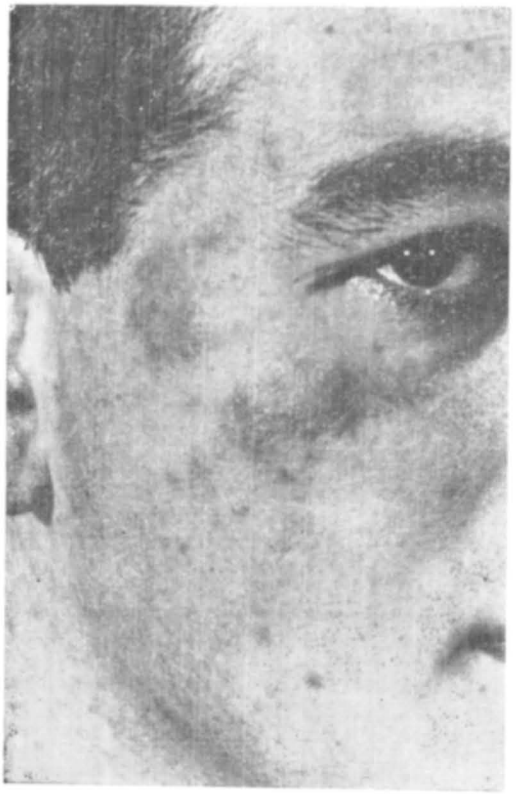


Fig. 6—Erythema perstans (L. E.)

Fig. 7
Fluorescence in Subepidermal basal membrane

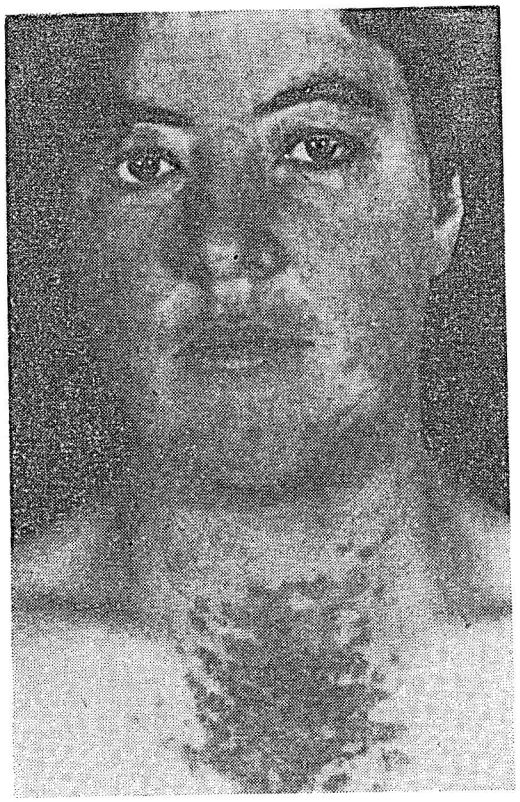


Fig. 8
Patchy redness in L. E. acutus

Recently, attention has been drawn by several investigators to the fact that acute L. E. may be associated with SJÖGREN'S disease; I have myself observed two such patients.

SJÖGREN'S disease is a pathological condition characterized by the loss of the secretory function of glandular tissue and synovia. This results, among other things, in dryness of the mouth, nose and eyes, anhydrosis and articular disorders. It would appear that auto-immunization may also play a part in the causation of this pathological condition.

PROGNOSIS

Acute L. E. is a severe disease the prognosis of which is variously doubtful or unfavourable.

Occasionally, however, its course is unexpectedly benign. For instance, HASERICK has observed 12 patients seriously ill with this disease, for whom the worst was feared in view of the gravity of the symptoms, and who nevertheless were still alive 6 years later. Their health was at that time reasonable; 5 patients could even be said to be in very good condition, and had taken no corticosteroid drugs in latter years.

This author warns against pregnancy, but is of the opinion that once pregnancy has occurred, premature termination is not indicated.

It was found that in the above-mentioned patients L. E. cells, serum proteins and urinary changes had been partially or completely normalized, even though such normalization does not constitute proof of a permanent remission. HASERICK writes: "Stable remissions may occur, but true cures are doubtful in this disease".

Nevertheless, these findings provide a measure of encouragement when instituting therapy; there is no absolute cause for despondency, even in severe cases. It is not necessary nor is it permissible for the physician to resign himself to the prospect of an inevitable downhill course. It is essential, on the other hand, prior to dental treatment and surgical operations and in the course of pregnancy, to resume the corticosteroid treatment, or sometimes increase the dose temporarily, because reactivation of the process is to be expected.

These patients should also be warned against exposure to bright sunlight. A possible complication of discoid L. E., although rare, is the development of a planocellular carcinoma in the cutaneous or mucosal lesions. We have treated a patient with this complication, which necessitated the amputation of both ears and plastic surgery of the facial skin.

THERAPY

The discoid form and the erythema perstans form of L. E. were initially treated with preparations of arsenic, with quinine and sometimes also with injections of gold, later replaced by bismuth. The last-mentioned treatment has in turn been replaced by the synthetic antimalarial drugs, such as chloroquine

(100 mg. 3 times per day), hydroxy-chloroquine (200 mg. 3-4 times per day) and amodiaquine (200 mg. 2 times per day).

Originally it was believed that these drugs were effective because they decreased the patients sensitivity to sunlight; it is now believed that the effect is to be attributed to an aspecific anti-inflammatory action.

Prakken has subjected the treatment of discoid L. E. to a critical evaluation. He found that in one-third to one-fourth of the total number of patients, the symptoms disappear or undergo substantial improvement. A curious finding from his literature studies was that older forms of treatment such as mapharsen, gold and bismuth did not compare unfavourably with the more modern forms of treatment.

From these findings it must be concluded that the question as to whether the modern change of treatment has been justified should be answered exclusively on the basis of the side effects and with reference to the method of administration. It may be said that in general, approx, one-third of the number of patients are cured or improved regardless of the type of treatment employed.

Prakken remarks: "If you ask me whether I am of the opinion that the synthetic antimalarial drugs are efficacious in ohronic L. E., then I have to answer: I think they are, I certainly hope they are, but I am not sure."

I believe I may conclude from my own experience that most patients respond only slightly or not at all, but that a few respond surprisingly well. The natural course of the disease may influence one's evaluation of the results; I believe that there is a great deal of truth in the remark made by Ehring et al., that chronic L. E. is cured with these drugs only if there is a spontaneous remission.

In certain cases, in which there is a danger of severe mutilation due to scar formation, the treatment is often supplemented by the administration of a smali dose of corticosteroids, for instance 10 to 15 mg. prernisone for a limited period of time; there is no doubt that this supplementary treatment usually has a favourable effect.

Known complications of the treatment with antimalarial drugs include anorexia, gastro-intestinal spasm, diarrhoea, insomnia, psychoses, convulsions, polyneuritis (in particular caused by amodiaquine), pigmentation of the skin, depigmentation and pigmentation of the hair, and toxicodermia. Of a more severe nature are certain ocular complications, such as deposition of the drug in the cornea, or irreversible retinopathies, whilst less severe ocular sequelae include derangements of accomodation.

Methaemoglobinaemia has been reported, as also has leukopenia (reversible as a rule).

Surveying this list of side effects, one might almost be inclined to refrain completely from employing these drugs, particularly if it were to be true that they have little or no favourable effect.

On the whole, however, the side effects are only incidentally observed; regular examination by the ophthalmologist and control of the blood picture is indicated.

For that matter, the end of antimalarial therapy in L. E. would seem to be in sight. For a considerable period of time now we have been treating all chronic L. E. patients primarily with ointment therapy, viz. with synthetic chloro–or fluoro–corticosteroids, and we have found that elsewhere this same method of treatment is nowadays in use. These preparations are well resorbed and have an excellent local effect, while a general effect becomes noticeable only if large portions of the skin surface of the body are treated.

With this therapy it is sufficient as a rule to rub a little ointment into the affected areas three times a day; in refractory cases, this treatment can be supplemented by subsequently covering the area (with thin plastic or elastic collodion), which enhances the absorption.

In acute L. E., the treatment should consist of two phases; one should begin with a " frontal attack ", with immediate oral administration of a corticosteroid in a sufficient dose to bring about disappearance of the symptoms. or at least to arrest their progress; subsequently there should be a gradual transition to " maintenance treatment ", a lower dose level being selected at which the symptoms are as far as possible suppressed without the risk of undesirable corticoid side effects, which are repeatedly underestimated. The treatment of acute L. E. should be carried out in hospital, and in the course of maintenance treatment, periodic clinical checks in hospital should also be performed. With this treatment we must always bear in mind that the treatment must not do more damage than the disease. As mentioned above, it is in certain cases possible to discontinue corticosteroid therapy completely after some time. Finally, it is felt that in addition to this treatment, the antimalarial drugs still deserve a certain place in the therapy of L. E.

We have now arrived at the end of our discussion of this disease, which is far from rare. We have attempted to present to the general dermatologist a review of the nature, symptoms and treatment of the ailment and to call his attention to recent diagnostic techniques.

Many aspects of the subject had to remain undiscussed; nevertheless this communication has grown much more lengthy than was originally intended.

The key to the clinical picture (the "why") is still an unsolved problem. Only when we have deepened our insight into this problem, will it perhaps be possible to develop a more fundamental therapeutic approach.

TABLE

Some data concerning patients with L. E. (follow-up time 5-7 years), derived from SCOTT et al.

	Group A 16 patients L. E. acutus	Group B 14 patients L. E. acutus and L.E. discoides	Group C 11 patients L. E. discoides	Group D 77 patients L. E. discoides
Sex	3 M, 13 F,	3 M, 11 F,	3 M, 8 F,	29 M, 48 F,
Discoid lesions	0	100%	100%	100%
Urticaria	62%	36%	0	0
Transient erythema	56%	0	0	0
Perniosis	18%	86%	73%	31%
Renal disease	50%	29%	27%	0
Rheumatoid arthrititis	89%	64%	27%	5%
Feverperiod	44%	64%	27%	1 patient
Pericarditis	18%	21%	0	1 patient
Pleuritis	25%	29%	0	0
Positive L. E. phenomenon	94%	71%	0	0
Deaths	38%	22%	9%	4%

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