Textbook of Dermatology

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IN TWO VOLUMES

VOLUME TWO

SECOND EDITION

BLACKWELL SCIENTIFIC PUBLICATIONS

OXFORD LONDON EDINBURGH MELBOURNE

Osney Mead, Oxford
3 Nottingham Street, London, W1
9 Forrest Road, Edinburgh
P.O. Box 9, North Balwyn, Victoria, Australia

ISBN 0 632 09830 9 (for the two-volume set)
ISBN 0 632 08240 2 (volume 1)
ISBN 0 632 08870 2 (volume 2)

First published 1968
Reprinted 1969
Second edition 1972

Distributed in the U.S.A. by F. A. Davis Company,
1915 Arch Street, Philadelphia, Pennsylvania

Printed and bound in Great Britain by
WILLIAM CLOWES & SONS LIMITED, BECCLES, COLCHESTER AND YARMOUTH

Preface to Second Edition

The generous reception accorded internationally to the first edition of this book has imposed on us the obligation to prepare a second edition considerably sooner than we had expected. The general plan of the book remains unchanged, but in some fields of dermatology very important advances have taken place in the past five years and in consequence most chapters have been extensively revised and very many have been entirely rewritten. It has not always been possible to omit old material to give place to new and despite our strenuous efforts to restrain its growth this edition is therefore considerably larger than the first.

Some of the contributors to the first edition wished to reduce the number of chapters for which they were responsible. We are happy to welcome the new authors who have joined our team. Some of them have chosen completely to rewrite the chapters they have taken over, others have, with the approval of its authors, incorporated parts of the original chapter. Dr. Naylor and Dr. Wells have been compelled by other commitments to leave the team but the chapter on bacterial infections still owes much to Dr. Naylor. Dr. Wells' contributions to the original chapter on Genetics and the Skin have been revised in this chapter in the present edition although he no longer appears as its co-author and is therefore not responsible for any errors which may have found their way into it.

We are grateful to the many reviewers and correspondents who have helped us by constructive criticism or by drawing our attention to errors or omissions. We hope that we have profited from their suggestions, and we look forward to receiving more. It is only with such cooperation that we can hope to achieve our objective of providing a textbook which is scientifically based but is nevertheless essentially a practical work of reference for the serious student of dermatology whose main responsibility is the clinical care of patients.

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Acknowledgements

The preparation of this textbook would have been impossible without the willing cooperation of a great many colleagues. Most chapters have been submitted to the criticism of several members of our team and this mutual assistance has been greatly appreciated. Some contributors have sought the advice of other authorities on technical or specialized aspects of their chapters. We should like to express our gratitude to all those who have helped us in this way and in particular to Professor Denis Bellamy of the Department of Zoology, University of Wales, who has contributed the introduction to Chapter 64 and has given his advice on certain biochemical matters in this chapter; Dr. John Smart, Department of Zoology, University of Cambridge, for his advice on entomological problems; Dr. Eric Waddington, Cardiff Royal Infirmary, whose account of the clinical features of variola, written for our first edition in the light of his extensive personal experience, has required little revision; Dr. Joseph Marks of Cardiff, who offered very helpful suggestions in the field of mycobacterial infections; Mr. P.G.Watson, who gave his advice on matters of common interest to ophthalmologists and dermatologists, Dr. Thelma Bates of St. Thomas's Hospital, for her valuable comments on radiotherapy; Dr. J.N.S. Mitchell, who has given us valuable assistance in the selection of new illustrations and in proof reading; and Dr. V.Kirton, Dr. T.W.Turner, Dr. D.Boxley and Dr. J.G.Reid, who have also helped in many ways.

The source of almost every photograph or diagram is acknowledged in the legend which accompanies it. We are grateful to the publishers, editors and authors who have given us permission to reproduce those few illustrations which are not original. The unacknowledged photographs in Chapters 24 and 44 are from the authors' own collections.

A large proportion of the photographs are from the collections of Addenbrooke's Hospital, the hospitals of the Aylesbury and High Wycombe Group and St. John's Hospital. We are very grateful to all those consultants who have allowed us to use photographs of their patients and apologise if we have inadvertently omitted any individual acknowledgement. The late Professor J.T.Ingram, Professor F.F.Hellier and Dr. S.T.Anning have kindly permitted photographs of their patients to be included in Chapters 35 and 36. The Addenbrooke's photographs are the work of our art editor, Mr. Leonard Beard, or of his predecessor, Mr. Vince. Mr. D.G.Standen provided most of the photographs from Stoke Mandeville Hospital. The St. John's photographs are the work of Mr. R.B.Phillips, Director of the Department of Medical Illustration and Lecturer in Medical Illustration at St. John's Hospital, or of his predecessor, Mr. R.J.Lunnon. Mr. A.L.Pegg and Mr. W.Blackledge are responsible respectively for the clinical photographs and photomicrographs in Chapter 36. We are grateful to them all for their cooperation and technical skill. Messrs. Glaxo have kindly covered the cost of Figure 24.4.

Our registrars have given us valuable assistance in many ways. We ask them to accept this collective acknowledgement of our appreciation.

In conclusion, on behalf of ourselves and the many contributors who are his former pupils we wish to place on record our indebtedness to Dr. G.B.Dowling and our gratitude for his teaching and example.

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Contents

VOLUME ONE

VOLUME TWO

CHAPTER 36

Lupus Erythematosus, Scleroderma and Dermatomyositis

THE 'COLLAGEN' OR 'CONNECTIVE-TISSUE' DISEASES

N. R. ROWELL

The title of this chapter is evidence of the failure of the author and editors to find any term which all could accept as accurate and appropriate for this important group of diseases. The term 'connective-tissue diseases' [10] has frequently been used in recent years, but whilst some authorities equate it with the older term, 'collagen diseases', others [4] apply it to all inherited or acquired disorders of the connective-tissue system. 'Collagen disease' is unacceptable, since there is no evidence that collagen is primarily at fault. The increasing emphasis on immunological abnormalities in these conditions has brought the terms 'auto-immune diseases' [8] and 'immunological diseases' [13] some popularity, but both are too comprehensive. To avoid the premature coining of a confusing new term, we have preferred to continue to refer to connective-tissue disease, wherever the use of a collective term is unavoidable.

That disease can involve the whole of the connective-tissue system is a relatively recent concept. In 1933, Klinge [7] was the first to propose that rheumatic fever and rheumatoid arthritis were disorders of the entire connective tissue. The changes in the intercellular components of the connective tissue, the presence of fibrinoid necrosis in collagenous tissue and the myxomatous swelling of ground substance were similar to those seen in experimental animals made hypersensitive to foreign protein, and for these reasons he concluded that the rheumatic diseases were due to hypersensitivity. He included other conditions in which fibrinoid necrosis was a feature, such as polyarteritis nodosa, dermatomyositis and malignant hypertension. The presence of widespread fibrinoid change in the vessels led to the inclusion of systemic sclerosis by Masugi & Yä-Shu [9], and also of systemic lupus erythematosus. However, Klemperer and his colleagues [6], with whose work the term collagen disease is associated, struck a note of caution by pointing out that fibrinoid necrosis could be seen in the absence of hypersensitivity mechanisms, for example, in the base of peptic ulcers. It has been stated [1] that the presence of fibrinoid degeneration does not warrant the grouping of the conditions showing this change, nor does it imply an allergic mechanism. It is now recognized that there are various types of fibrinoid with somewhat similar staining properties. They have a multiple origin from the degeneration of collagen, from the ground substance, muscle, and fibrin and other plasma proteins.

In 1950, Klemperer [5] stated: 'the term diffuse collagen disease was originally applied to acute and chronic maladies which are characterized anatomically by generalized alterations of the connective tissue, particularly by abnormalities of its extracellular components. In this case the term can include rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, acute lupus erythematosus, generalized scleroderma and dermatomyositis'. Klemperer emphasized his dissension from the widespread indiscriminate use of the term collagen disease for disorders with unusual clinical or pathological features. He confirmed that his sole intention was to put forward the concept that 'in certain diseases anatomical investigations reveal conspic-

uous alterations in the intermediary substances of the connective tissue in a systemic manner'. It is now realized that the connective tissue is not the only tissue involved in these disorders.

It has been customary to consider that systemic and discoid lupus erythematosus, systemic sclerosis, localized and generalized morphoea, polyarteritis nodosa, Wegener's granulomatosis, giant-cell arteritis, dermatomyositis, rheumatoid arthritis and Sjögren's syndrome should be grouped together, and this has been supported by evidence of clinical, pathological and immunological overlap. But this grouping may not be justified, and may even hamper our understanding of these diseases. Subgroupings may be distinguished. It appears that the connective-tissue disorders can be divided into two groups on the basis of the antinuclear factor test [11]; those such as lupus erythematosus and systemic sclerosis in which antinuclear antibodies are frequently found in high titre, and those like polyarteritis nodosa, various types of cutaneous vasculitis and dermatomyositis in which antinuclear antibodies are usually absent.

There is an urgent need for precise and universally acceptable criteria for diagnosis. When adequate criteria and modern investigational techniques are used it is apparent that each disorder can be distinguished as a separate entity. For example, evidence has been produced that discoid lupus erythematosus is a separate disorder and not a benign variant of systemic lupus erythematosus [2,12]. Moreover, on keeping an open mind when analysing well-documented data, certain diseases appear to consist of more than one separate condition. Thus it appears that rheumatoid arthritis consists of at least two distinct entities—inflammatory polyarthritis, diagnosed clinically, and erosive arthritis, diagnosed radiologically [3].

It must be admitted that diagnosis of these disorders is sometimes far from easy, and extensive investigation may be required. A diagnosis of 'collagen vascular disease' or 'collagenosis' in a patient suffering from an illness with obscure symptoms and signs, possibly associated with an elevated erythrocyte sedimentation rate which responds to corticosteroids, is the resort of the intellectually destitute and must be avoided. It is usually possible to make a precise diagnosis, and this is very important for modern epidemiological and statistical techniques. However, it is more than an academic exercise as, in the future, specific therapy may well depend on the precision of diagnosis.

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LUPUS ERYTHEMATOSUS

Lupus erythematosus is usually subdivided into two main types—discoid and systemic. Some authors [10,14] subdivide discoid lupus erythematosus into a localized form in which lesions are confined to the face above the chin, the scalp and the ears, and a disseminated form in which lesions also occur elsewhere on the body. Although haematological and serological abnormalities occur slightly more frequently in the disseminated form, the natural history of the two subgroups is similar and in the author's view they are the same disorder.

The more controversial point is whether discoid and systemic lupus erythematosus are variants of the same disease. The evidence in favour of this thesis may be summarized as follows:

(i) The cutaneous lesions of systemic and discoid lupus erythematosus may be clinically and histologically indistinguishable.
(ii) Certain clinical features are found in both conditions (see Table 36.1).
(iii) Similar haematological, biochemical and immunological abnormalities can be demonstrated in both conditions (see Table 36.1), although the incidence of abnormalities is lower in discoid lupus erythematosus.
(iv) Patients with discoid lupus erythematosus occasionally develop evidence of overt systemic lupus erythematosus.
(v) Patients with systemic lupus erythematosus may develop typical lesions of discoid lupus erythematosus when the active phase subsides [11].

TABLE 36.1. Comparison of data on a personal series of patients with discoid and systemic lupus erythematosus

	Discoid lupus erythematosus	Systemic lupus erythematosus
Number of cases	120	40
Rash	100%	80%
Joint pains	23%	70%
Fever	0%	40%
Raynaud's phenomenon	14%	35%
Chilblains	22%	22%
Poor peripheral circulation	26%	32%
E.S.R. > 20 mm in first hour	20%	85%
Serum globulin > 3G%	29%	76%
L.E. cells	1·7%	83%
Antinuclear factor (s)	35%	87%
Homogeneous	24%	74%
Speckled	11%	26%
Nucleolar	0%	5·4%
Precipitating auto-antibody (ies)	4%	42%
Wasserman reaction positive	5%	22%
Rheumatoid factor test positive	15%	37%
Direct Coombs' test positive	2·5%	15%
Leucopenia	12·5%	37%
Thrombocytopenia	5%	21%

This seems to be formidable evidence but the following observations require explanation.

1. The risk of a patient with discoid lupus erythematosus developing overt systemic lupus erythematosus is small. It varies from 1·3% [9] to 5% [17]. My own observations suggest that despite the fact that 55% of patients with discoid lupus erythematosus show some haematological or serological abnormality the risk of such conversion is less than 5% [1,16A]. In some series [12,15,18] such conversion was not encountered despite follow up for nearly 30 years. A retrospective study [16] of 127 patients with systemic lupus erythematosus showed that eight patients had had discoid lesions from 2 to 29 years.

2. The presence of laboratory abnormalities in discoid lupus erythematosus does not appear to predispose to the development of systemic lupus erythematosus [1]. Haematological abnormalities were still present in 50% of 77 patients with discoid lupus erythematosus, 5 years after initial assessment, yet none had developed systemic lupus erythematosus in the same period [15]. The same prognosis was found in a subgroup intermediate between discoid and systemic lupus erythematosus as in patients with uncomplicated lupus erythematosus [18].

3. Immunoglobulins and complement are present in uninvolved skin of patients with systemic lupus erythematosus and absent in patients with discoid lupus erythematosus [19].

4. Most patients with discoid lupus erythematosus exposed to ultraviolet light, stress, trauma, etc. do not develop the systemic disease.

5. The age and sex distribution of systemic lupus erythematosus [4,13] is strikingly different from that of discoid [3,16].

It has recently been proposed [3,4,5,6] that both systemic and discoid lupus erythematosus are initiated by the occurrence of somatic mutations in lymphocytic stem cells of predisposed individuals (see diagram 36.1, p. 1079), and that they are genetically distinct. There are at least three, and probably four, genotypes in discoid lupus erythematosus [6]. It has long been recognized that the sex ratio is markedly different in the two diseases. The female:male ratio of carriers at birth in systemic lupus erythematosus is about 4·5:1 [4], although it may vary between countries [6], and it has been proposed that the genotype in systemic lupus erythematosus involves three dominant X-linked alleles. By contrast the sex ratio (female:male) of carriers at birth in discoid lupus erythematosus is about 1·2, 1·4 and 2·6:1 in the three genotypes

[5] and it seems likely that there is only one X-linked allele involved in genotype 2 and two in genotype 3. Autosomal predisposing alleles are probably also present in all the genotypes in both systemic and discoid lupus erythematosus.

The age distribution of the onset of the two conditions also differs. The age distribution in each sex in systemic lupus erythematosus is consistent with the hypothesis that the condition is initiated in genetically predisposed individuals by the occurrence of somatic mutations affecting three X-linked loci in lymphoid stem cells. In discoid lupus erythematosus the number of mutations required to initiate the disease depends on the genotype. Three somatic mutations affecting autosomal genes in a single stem cell are required in the first genotype (early onset cases), whereas four mutations, one X-linked, are needed in the second genotype and five mutations, one X-linked, in the third genotype (late onset cases). However, it must be pointed out that more extensive data are required for definitive interpretation. On the simplest interpretation three forbidden clones [7] of lymphocytes synthesizing cellular auto-antibodies develop in systemic lupus erythematosus, whereas only one forbidden clone is involved in discoid lupus erythematosus.

If this genetic analysis is confirmed the few patients who 'convert' from discoid into systemic lupus erythematosus, and vice versa, must be genetically predisposed to both diseases. Those patients with only a genotype for discoid lupus erythematosus will never convert, even when subjected to environmental factors, such as drugs, bacterial or viral infections, ultraviolet light and stress.

At present it is not possible to determine the genetic pattern of individual patients or to predict with any accuracy the small proportion of patients with discoid L.E.-like lesions who will develop systemic lupus erythematosus. Humoral auto-antibodies are not pathogenic in these diseases [2], but they probably reflect the underlying cell-bound auto-immunity which causes the disease. The ability to synthesize particular antinuclear antibodies may depend on additional genetic factors, and this could account for the absence of such antibodies in certain patients with active disease. If the possession of a serological abnormality in discoid lupus erythematosus implies a predisposition to transformation into systemic disease, we would expect the sex ratio of this group to be similar to that for systemic lupus erythematosus. This is not the case [1]. The sex ratio in patients with discoid lupus erythematosus and laboratory abnormalities is not significantly different from the sex ratio in patients without abnormalities.

From consideration of the clinical features, the natural history, and the age and sex distribution, it is concluded that patients with discoid lupus erythematosus and haematological and serological abnormalities are not cases of systemic lupus erythematosus in disguise, but are cases of discoid lupus erythematosus, which is a separate entity from systemic lupus erythematosus, and has a different genetic background.

It has been proposed that cutaneous and multisystem lupus erythematosus are better terms for these disorders [8], but because of established usage the terms discoid and systemic lupus erythematosus are retained here.

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DISCOID LUPUS ERYTHEMATOSUS

SYN. CUTANEOUS LUPUS ERYTHEMATOSUS; CHRONIC DISCOID LUPUS ERYTHEMATOSUS

Definition. Discoid lupus erythematosus is a relatively benign disorder of the skin, most frequently

involving the face and characterized by various sized, reddish, well-defined, scaly patches, sometimes with hyperkeratosis, which tend to heal with atrophy, scarring and pigmentary changes. There are haematological and serological changes in about half the patients, and these changes, with other evidence, suggest an auto-immune aetiology.

Aetiology. This disorder has a characteristic age and sex pattern. The disease affects twice as many females as males, and in a personal series of 198 patients the peak age of onset was in the fourth decade in females and slightly later in males. Three per cent of a series of 1,045 cases began under 15 years of age, and 2·5% at over 70 years [20]. The condition has started at 83 years. Familial cases do occur [43], but only rarely. Steagall *et al* [65] reported the condition in identical twin sisters, and listed 25 families with two or more members who had discoid or systemic lupus erythematosus. Discoid lupus erythematosus has been noted in three consecutive generations [30]. Hypergammaglobulinaemia was found in four successive generations, including four out of six asymptomatic relatives. It has been proposed (see p. 1063) that genetic factors and somatic mutations are implicated in the pathogenesis of the disease [12–14]. There are at least three genotypes and there is probably a fourth corresponding to those 'transitory' cases [5] in which immunoglobulins are present at the dermo-epidermal junction of uninvolved skin. The relative size of these subgroups may differ between countries, owing to differences in the frequency of the predisposing genes. The genetic predisposition probably involves one X-linked allele in genotype 2 and two X-linked alleles in genotype 3, as well as autosomal alleles. The initiation of the disease results from the occurrence of random events, believed to be a special form of somatic mutation. Somatic mutations occur at X-linked and autosomal loci in a lymphoid stem cell. In the first subgroup of predisposed persons three mutations affect autosomal genes, in the second four mutations occur, one of which affects an X-linked gene, and in the third genotype five mutations occur, one involving an X-linked gene. As a result a forbidden clone of lymphocytes synthesizing cellular auto-antibodies develops. After a latent period of about 4 years in females and 2 years in males, clinical signs of the disease become manifest. Normally, an endogenous defence mechanism appears to be directed against the proliferating forbidden clone. Environmental factors, by interfering with the defence mechanism, can precipitate the onset of the disease, or produce exacerbations once clinical signs have developed. The significance of the finding of tubular structures approximately 20 nm in diameter similar to paramyxoviruses in endothelial cells of dermal blood vessels, perivascular histiocytes or fibroblasts [11,33], particularly of new lesions, is not yet known. If they are confirmed to be viruses, these structures could act as a precipitating factor.

The onset of the lesions may be precipitated by a variety of factors. In my own series, lesions started with trauma in 11%, with mental stress in 12%, sunburn 5%, infection 3%, exposure to cold 2%, and pregnancy 1%. The types of trauma included splashing with hot fat, a scratch on the nose and various types of wounds and scars. In the remainder, approximately two-thirds, lesions started apparently spontaneously. On the other hand, once lesions had developed, exacerbations occur particularly with exposure to sunlight and trauma.

Lodin [45] noted a lower incidence of trauma (2·2%) and included exposure to X-ray, diathermy, and chemical burns and lesions in scars of herpes zoster. He suggested that previous exposure to light may have been necessary. Occasionally, drugs, for example griseofulvin [1], may precipitate lesions of discoid lupus erythematosus. Chronic biological false-positive reactors, with positive serological tests for syphilis in the presence of a negative treponemal immobilization test, may also develop discoid lupus erythematosus [15].

Once lesions have developed, exacerbations may be associated with a variety of factors. In a personal series of 120 patients, a history of exacerbations with sunlight was found in 68%. Other authors [6] have denied the role of sunlight as an exacerbating factor in localized discoid lupus erythematosus. The action spectrum is confined to wave lengths shorter than 320 nm [26]. Epstein *et al* [26] conclude that 'the photosensitivity reaction appears to be an aggravating feature and not a basic factor in the pathogenesis of lupus erythematosus'. Lesions may be produced by repeatedly exposing patients with discoid lupus erythematosus to monochromatic ultraviolet light at 320 nm [29]. Seventeen per cent of patients notice an exacerbation with cold. Sometimes, a history that lesions get worse with sea air and winds is obtained. More than half the patients note that the condition is worse in the summer, but 10% are worse in winter. About 13% of patients say that their lesions deteriorate premenstrually. Lesions may deteriorate in the first 3 months of

pregnancy, improve in the next 6 months, and become worse again after delivery [62], but frequently pregnancy has little effect. There is no doubt that worry and anxiety play a part, and 16% of patients have noticed lesions getting worse at such times.

Pathology [49]. The various clinical types of lupus erythematosus show an essentially similar histological picture [46], the salient features of which are (a) liquefaction degeneration of the basal cell layer of the epidermis; (b) degenerative changes in the connective tissue, consisting of hyalinization, oedema and fibrinoid change, most marked immediately below the epidermis; and (c) a patchy dermal lymphocytic infiltrate with a few plasma cells and histiocytes, particularly around the appendages which may be atrophic. The presence of at least two of these is essential to the histological diagnosis of lupus erythematosus. The following other changes may be found, but are less important: thinning and pallor of the epidermis with relative hyperkeratosis and plugging of the follicular mouths; thickening of the basement membrane of the epidermis and sometimes of small vessels; premature elastotic degeneration of collagen in light-exposed areas. In tumid lesions the dermal infiltrate can be very dense, and sometimes almost granulomatous. Occasionally, irregular hyperplasia of the epidermis occurs and there may be clefts, or even bullae, between the dermis and epidermis. Early lesions may not show much hyperkeratosis. Although the keratotic plugs are usually found in the openings of the hair follicles, they may also block the sweat ducts or occur independent of either structure. Sometimes the hair follicles contain concentric layers of keratin instead of hairs. Atrophy of the prickle-cell layer occurs to a variable extent, and sometimes there may be acanthosis. Melanin may be found in the upper dermis as the result of pigmentary incontinence. Blood vessels are dilated and the upper dermis is oedematous. Sections stained with the periodic-acid-Schiff technique show thickening of the basement membrane. Fluorescent antibody techniques show the presence of immunoglobulin and complement in the epidermal-dermal junction in skin lesions of discoid lupus erythematosus, but not in the uninvolved skin as in the majority of cases of systemic lupus erythematosus (see p. 1080). In more acute forms there is less hyperkeratosis and dermal infiltration,

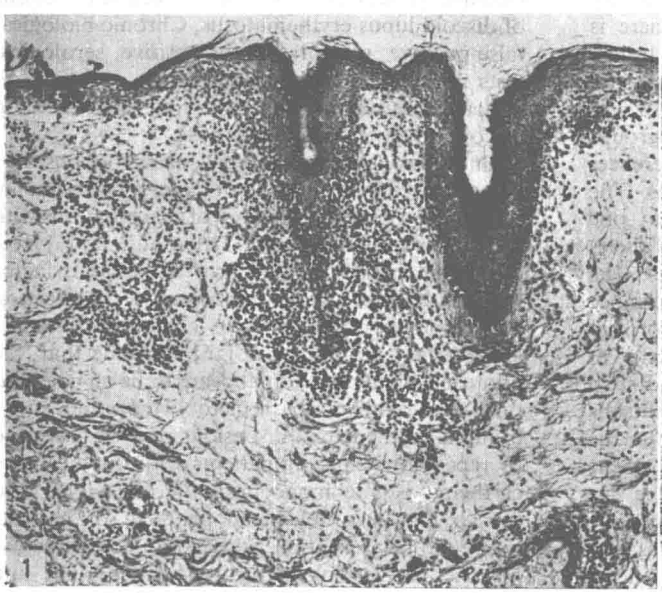

FIG. 36.1. Discoid lupus erythematosus. There is atrophy of the epidermis, keratotic plugging, liquefaction degeneration of the basal layer, oedema and hyalinization of the connective tissue below the epidermis and a marked inflammatory infiltrate. H. & E. ×63 (United Leeds Hospitals).

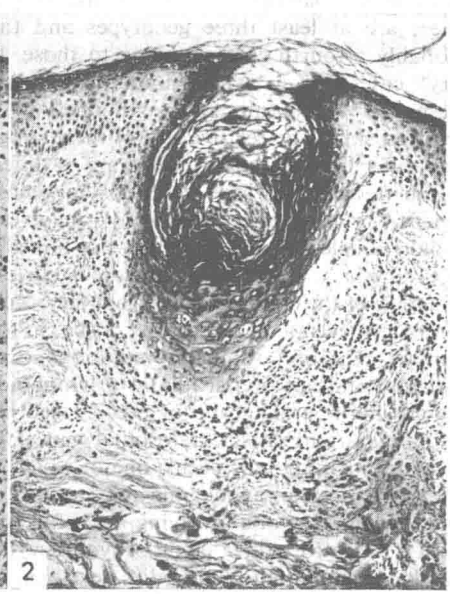

FIG. 36.2. Discoid lupus erythematosus. The keratotic plugging, degeneration of the basal layer and predominantly lymphocytic infiltrate are well shown. H. & E. ×91 (United Leeds Hospitals).