SURGICAL PROGRESS
1958

BRITISH SURGICAL PRACTICE

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PUBLISHERS' ANNOUNCEMENT

THIS 1958 Progress Volume is the eighth of an annual series of supplements to *British Surgical Practice*. By this means the eight volumes of the main work are kept up to date in the ever increasing field of surgical knowledge, by original articles, critical surveys and abstracts.

The original articles are followed by general surveys of selected systems and specialties; these surveys are followed by abstracts relating to the subject.

The Noter-up section will guide the reader from the main work to the supplementary material which appears in this or previous Progress Volumes. The purpose of the Noter-up remains the same as in previous years. The reader should first of all refer to the material in the main volumes of *British Surgical Practice*. Then, in order to ascertain the advances and changes which have been discussed in this or previous Progress Volumes, he should refer, under the same heading or key number as that consulted in the main work, to the Noter-up in the latest Progress Volume. There he will find details of the articles, surveys and abstracts relating to the subject which have appeared in the Progress Volumes. Regional or system surveys naturally cover a wider field than in previous volumes and individually apply to more than one chapter in *British Surgical Practice*. Because of this, the main subject headings within the surveys have been linked in the Noter-up to the appropriate chapter titles of the main work. Thus by reference to the Noter-up, the reader of the main volumes is easily able to locate any new material on a particular subject even though it may be contained within a survey. The nature of surgical advance has necessitated the inclusion of new titles in the Noter-up, and for convenience and ease of reference, these are as follow: Abdomen; Antibiotics; Brain—Vascular Anomalies; Carpal Tunnel Syndrome; Collagen Diseases; Electronics; Fluid and Electrolyte Balance; Gynaecology; Kidney and Ureter—Nephrectomy; Kidney and Ureter—Surgical Aspects; Lung—Surgery; Obstetrics; Organ Transplantation; Pelvic Organs—Viscerectomy; Pituitary Gland; Plastic Surgery—Correction of Facial Deformity; Thorax—Congenital Deformities; Ureter—Replacement of.

PUBLISHERS' ANNOUNCEMENT

Non-subscribers will find the Noter-up section of value in that it is alphabetically arranged and gives at a glance information as to the presence or absence of recent material on any particular subject. Consequently, the book can be used independently.

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INTRODUCTION

THE MATERIAL in this Progress Volume may be classified under three headings: subjects which have not appeared previously in *British Surgical Practice*; subjects which have been dealt with before but which need to be brought up to date; and critical reviews of current surgical literature.

In the first category are the collagen diseases which, though perhaps primarily "medical" frequently confuse surgical diagnosis; operative cholangiography, the use of which is still a matter of opinion and argument; the carpal tunnel syndrome, which can be so simply relieved provided the diagnosis is beyond question; the use of the ileum in urology, requiring mature surgical judgment based on sound physiological principles; and preclinical carcinoma of the cervix, a condition the nature of which is still open to dispute, but which is convincingly portrayed by Professor Carey of Auckland.

In the second and largest group are blood transfusion, fluid and electrolyte balance, Crohn's disease, the indications for and management of ileostomy for ulcerative colitis, the surgery of the oesophagus, septal defects in the heart, the surgical induction of labour, the management of acute head injuries, and the surgery of glaucoma and of the spinal cord and cervical rib. All these subjects have been described in *British Surgical Practice*, but since the original articles were written advances have been made in treatment based on a better understanding of the pathology of the diseases or of their effects upon physiological processes in the body, and therefore the time has come to bring the articles up to date.

Finally there are thoughtful critical surveys of recent work in the surgery of the stomach and duodenum, in pulmonary surgery and in the surgery of the central nervous system, and it is our hope that our readers will benefit, not only from the opinions expressed by the authors of these articles, but also from the abstracts of current literature which are appended to many of the chapters.

An introduction is scarcely necessary—the list of articles with the names of their authors is an introduction in itself; but it is necessary for us to express to those who have so generously given their time and their thought to the preparation of these articles our deep appreciation of and gratitude for their understanding and co-operation.

E. ROCK CARLING
J. PATERSON ROSS

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NOTER-UP, 1958

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COLLAGEN DISEASES

By R. E. TUNBRIDGE, O.B.E., M.D., M.Sc., F.R.C.P.
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INTRODUCTION

The term collagen diseases was introduced following the work of Klemperer, Pollack and Baehr (1942), Klemperer (1950), who observed that in a number of diseases of unknown aetiology the common pathological finding was the presence of fibrinoid necrosis and perivascular infiltration. Klemperer was careful to emphasize that a single end organ response did not of necessity indicate a common aetiology. Initially, however, he did suggest that fibrinoid was a degenerative form of collagen or at least derived from collagen break-down and by so doing stimulated interest in the study of the connective tissue system. Some authors use the term collagen disease or collagen disorders to include any disease with widespread involvement of the connective tissue system even if other tissues or whole organs are involved. It is customary to group rheumatoid arthritis, acute and subacute disseminated forms of lupus erythematosus, polyarteritis or periarteritis nodosa, scleroderma and dermatomyositis as collagen disorders. Some authorities extend the list to include rheumatic fever, serum sickness, ankylosing spondylitis, thromboangiitis obliterans and malignant nephrosclerosis.

These disorders have many features in common. They usually run protracted clinical courses, with remissions and relapses, but occasionally present as an acute fulminating illness. Arthralgias, arthritis, deformity, skin lesions of the most varied character, albuminuria, renal disease, general malaise, anaemia and loss of weight are common clinical manifestations. It is very largely on account of the arthritic manifestations, the deformities, muscle wasting, and Raynaud's phenomenon, that the diseases mentioned present diagnostic problems for the surgeon.

The nature of the fibrinoid lesion is still not fully understood. Several workers, notably Bien and Ziff (1951), have shown that collagen fibril degeneration plays little part in the formation of fibrinoid, whereas Strukov and Orlovskaya (1957) considered that the break-down products of collagen, particularly the mucopolysaccharides, contribute greatly to the formation of fibrinoid. Glynn and Loewi (1952) have shown that fibrin contributes very little to the formation of fibrinoid; but there is little doubt that blood products and mucopolysaccharides, probably from the connective tissue matrix, contribute towards the formation of fibrinoid

material. The other pathological feature stressed by Klemperer, perivascular infiltration, is likewise not confined to the collagen disorders.

Nature of the connective tissue system

The mistake has been in focussing attention upon the collagen fibres and fibrils, important though they are, both qualitatively and quantitatively. The connective tissue system also contains other fibres, elastic and reticular; cells, fibroblasts, histiocytes and mast cells, and matrix. Recent research has concentrated upon the fibre components. Astbury and Bell (1939), as a result of their investigation into the structure of protein fibres, were able to divide them into two main groups, the k.m.e.f. (keratin, myosin, epidermin, fibrinogen) group and the collagen group. Each group has a distinctive x-ray diffraction pattern as well as physical and chemical properties. The position of the elastic and reticular fibres remained in doubt but recent work (Hall and his colleagues, 1955) suggests that they are essentially members of the collagen group. The constant x-ray diffraction findings, chemical composition, and characteristic structure under the electron microscope, with a constant banding of 640 Ångström units—what Gross has referred to as the finger printing of collagen—has tended to lead to the concept of collagen as a uniform structure of constant chemical composition and configuration. The comparatively slow rate of turnover of labelled glycine in mature rat tail tendon tended to confirm this view.

More recent work has shown that there are definite differences in the collagen fibrils from different tissues both as regards size (Schwarz, 1957) and their reaction to enzyme, *p*H and electrolytes. The age of the fibres is also a determining factor in their response to stimuli. Collagen fibrils from the skin of young subjects are more vulnerable to the action of collagenase than are corresponding fibrils from the skin of an adult of 24 years or more (Keech, 1955). The author's colleagues have brought forward evidence to suggest that collagen and elastin are members of the same family of proteins and have succeeded in producing a range of morphological products indicative of a possible transformation of collagen into elastic-like material (Hall and his colleagues, 1955). The complete chemical proof of such change has not yet been obtained but the studies so far made would suggest that collagen and elastin are really at different ends of a broad spectrum of substances and that the term collagen is not an indication of a single protein compound but rather a group of protein fibres with similar, but not necessarily identical chemical composition, and with similar, but not necessarily identical physical properties. Furthermore, in living tissues polysaccharides are very closely associated with the collagen and elastic fibres, if not an integral part of their structure, and the mucopolysaccharides play an important role not only in forming but also in maintaining the structure of the fibres. The reticular fibres have been shown to be composed of a core of collagenous fibrils surrounded by a special sheath containing a high percentage of fatty acids, myristic acid and polysaccharides (Windrum, Kent and Eastoe, 1955).

It will thus be seen that collagen fibrils, and in fact the whole connective tissue system, are not a static tissue but one comprised of elements which are extremely varied in their chemical structure and in their reaction to enzymatic and other agents. Before discussing the changes brought about by disease it is essential to

know the state of the tissue at the time of attack, because the response will be determined as much by the state of the tissue as by the invading organism or its products.

From this brief survey of the connective tissue system it will be seen that there is little ground for calling the diseases under discussion collagen disorders, even if the pathological changes were confined to the connective tissue system.

Steroid therapy and hypersensitivity

Two further arguments have been advanced in favour of retaining the title, namely, their response to steroid therapy and the frequent association of the hypersensitive state with the collagen disorders. The experimental work of Rich of Baltimore (1952) in relation to serum reactions and to sulphonamide sensitivity resulted in the production of pathological changes very similar to those described by Klemperer as being a feature of the collagen diseases. There are recorded cases in which the onset of collagen diseases appeared to follow on drug sensitization, the injection of vaccines, of sera, or after exposure to sunlight and to radiation. It has also been claimed that the disorders are much more frequent today than formerly, and that this is the result of the widespread use of sulphonamides and antibiotic preparations. These are difficult views to refute but the increased prevalence could equally well be due to greater awareness of the conditions and to improved diagnostic aids.

The therapeutic role of the steroids has been mainly one of suppression of symptoms in rheumatoid arthritis both for short-term and long-term therapy, if we are to accept the conclusions of the Medical Research Council and Empire Rheumatism Council trials. There is little evidence to suggest that cortisone does much more than bring about relief of symptoms.

RHEUMATOID ARTHRITIS

Clinical diagnosis

Rheumatoid arthritis presents in many forms and the criteria for diagnosis have until recently been mainly clinical. The usual onset in some 60 per cent of cases is insidious, beginning with stiffness in the smaller joints of the hands or of the feet, usually symmetrical and worse first thing in the morning, followed by the development of pain and swelling and ultimately deformity. The progression of the arthritic manifestations is often associated with general malaise, anaemia and a raised sedimentation rate. Contrary to popular opinion the condition occurs at all ages and the onset is most frequent between the ages of 40 and 50 years. In a percentage of cases the clinical manifestations are similar to those described but the onset is acute and fever is prominent, the condition being essentially an acute polyarthritis. In this latter group of cases the differential diagnosis has to be made from other forms of acute polyarthritis, including rheumatic fever.

When the acute form is confined to the wrists and hands and the subject is aged 40 or more years, the possibility of the "arthritis" being due to hypertrophic pulmonary osteoarthropathy should not be overlooked. The author has seen cases of carcinoma of the bronchus present in this way and even admitted to hospital as rheumatoid arthritis.

Differential diagnosis with major joint involvement

Some cases of rheumatoid arthritis present initially with only major joint involvement. Here the differential diagnosis between traumatic arthritis, Reiter's syndrome, gonococcal arthritis (fortunately a rare disease today) and an atypical ankylosing spondylitis, can be difficult. The majority of American authors consider rheumatoid arthritis and ankylosing spondylitis as manifestations of the same disorder but in Great Britain, largely owing to the work of Buckley, they are considered as separate entities. Buckley (1931) clearly demonstrated that Bechterew's disease and the Marie-Strümpell disease were not two disorders but one and the same disorder, now called ankylosing spondylitis. The incidence of peripheral joint involvement in ankylosing spondylitis varies considerably. The majority of authors place it in the range of 5–15 per cent. This figure is an overall figure and does not indicate the percentage of cases of ankylosing spondylitis presenting as an arthritis of one of the major joints. The review of Sharp and Easson (1954) suggested that peripheral joint involvement is more frequent in the atypical cases of ankylosing spondylitis. A history of familial incidence of arthritis and the radiological changes in the sacro-iliac joints usually clinch the diagnosis, but when a patient presents with a monarticular arthritis the possibility of ankylosing spondylitis is sometimes overlooked. Reiter's syndrome is the most common form of arthritis found in patients attending venereal disease clinics today. The other members of the triad of presenting lesions, conjunctivitis, urethritis, are not always obvious. Iritis and iridocyclitis are stated by Buckley (1948) to be relatively common in ankylosing spondylitis and possibly to be more frequent amongst older patients. A history of eye trouble associated with arthritis therefore requires to be looked into very carefully before making a final diagnosis. The differential diagnosis between the various arthritic conditions has been helped by the development of the differential agglutination test. The test, as is seen later, gives a high percentage of positive results in rheumatoid arthritis but only rarely a positive result in cases of ankylosing spondylitis or Reiter's syndrome.

Psoriasis and rheumatoid arthritis

The association of psoriasis and rheumatoid arthritis has long been observed. A recent review by Wright (1956) suggested that although there is an association of the two diseases there is much evidence to suggest the possibility of a distinct clinical entity. The psoriasis is usually well marked and mainly confined to the nails, and the arthritis largely confined to the terminal interphalangeal joints. Furthermore, there is a close correlation between the development of the psoriasis of the nails and the progression of the arthritic changes. Finally, the differential agglutination test was only occasionally positive in cases where the two diseases were associated.

Tendon lesions

Tendon lesions are a very frequent finding in rheumatoid arthritis and their pathology and relationship to the rheumatoid arthritis nodule have been described by Kellgren and Ball (1950). These tendon lesions and the contraction of the fingers that they produce can occasionally be the presenting sign or symptom of rheumatoid arthritis. It is in such instances that the differential diagnosis between nerve

lesions such as ulnar palsy, Dupuytren's contracture, scleroderma and dermatomyositis, may present a problem.

Lesions of the tendon, due to the accumulation of uric acid in gout and muscle disorders, have also to be considered. Thickening of the tendon causing snapping fingers is probably the most common single lesion, but the rheumatoid nodules may occur on several fingers, usually involving the long flexor tendons. Sometimes nodules form on the back of the wrist and may be difficult to distinguish from synovial cysts. They are usually composed of granulation tissue and the only treatment is surgical removal. Where rheumatoid nodules are the presenting feature surgical treatment should still be undertaken if contractures are developing, but therapy designed towards the management of the general condition of the patient should also be prescribed.

Occasionally hypersensitivity to drugs, and particularly to penicillin, may give rise to an acute polyarthritis which has many features of the early stages of rheumatoid arthritis. There is usually a definite history of chemotherapy and the differential agglutination test is negative.

Diagnostic criteria

Until recently the diagnosis of rheumatoid arthritis had been based almost entirely upon a combination of clinical and clinicopathological data of a non-specific character. A Committee of the American Rheumatism Association (Ropes and his colleagues, 1956) have drawn up a list of 11 diagnostic criteria of rheumatoid arthritis and they considered that a 6 weeks' history of symptoms in the presence of 5 of the 11 criteria is adequate for the diagnosis of rheumatoid arthritis in the absence of positive findings of another disease process. The 11 criteria are as follows.

(1) Morning stiffness.
(2) Pain on movement or tenderness in at least one joint (observed by a physician).
(3) Swelling (soft tissue thickening or fluid—not bony overgrowth alone) in at least one joint (observed by a physician).
(4) Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms between the two joint involvements may not be more than 3 months).
(5) Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body, bilateral involvement of mid-phalangeal, metacarpophalangeal or metatarsophalangeal joints is acceptable without absolute symmetry. Terminal phalangeal joint involvement will not satisfy this criterion.
(6) Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces or in juxta-articular regions.
(7) Radiological changes typical of rheumatoid arthritis, which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes—degenerative changes do not exclude patients from the group of rheumatoid arthritis.
(8) Positive sheep cell agglutination (Rose and Ragan, or Heller test) or positive streptococcal agglutination test.
(9) Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).
(10) Characteristic histological changes in synovial membrane with 3 or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form "lymphoid nodules"; deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.
(11) Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

Rose-Waaler test

Two features of the list should be noted, the absence of reference to the erythrocyte sedimentation rate and the inclusion of the sheep cell agglutination test (D.A.T.) or the Rose-Waaler test. The original observations of Waaler were made in 1940 but were not followed up until the publication of Rose and his colleagues in 1948. Since then numerous papers have been published indicating the value of the test in the diagnosis of rheumatoid arthritis. Earlier reports suggested the test was positive in some 50 per cent of cases of rheumatoid arthritis, but a high percentage of positives was also obtained in lupus erythematosus and to a lesser extent in acute rheumatic fever. Modifications in the technique, the use of tanned red cells, latex particles and Bentovite have not only facilitated the procedure, but have tended to increase both the selectivity and the sensitivity of the test.

Rothermich and Philips (1957) using the latex method obtained a positive result in 84 per cent of cases of rheumatoid arthritis. The percentage of false positives was low, 26 in 616 of the above series. Eleven of these positives were in cases of non-rheumatic disease, and the remaining 15 in cases that were clinically non-rheumatoid arthritis. There were 2 positives in a series of 17 cases of lupus erythematosus examined, a much lower percentage than in any other reported series. The test appears to be an antigen-antibody reaction. Svartz and Schlossmann (1955) showed that the haemagglutinating factor (for rheumatoid arthritis) was precipitated in the cold but very seldom in other diseases and they considered the test to be specific for rheumatoid arthritis. Svartz (1957) has shown that the factor is associated with the *gamma*-globulin and is a macro-globulin but has not yet succeeded in separating the factor. The demonstration of an inhibitor of the haemagglutinating factor by Ziff and his colleagues (1954) as well as by Heller and his colleagues (1952) has confirmed the specificity of the test. It has already proved a valuable aid in diagnosis and should serve to throw more light upon the aetiology of rheumatoid arthritis.

The test has, however, certain interesting clinical associations. It is rarely positive during the first 3 months of the disease and is often not positive until 6 months after the initial symptoms have appeared. In some patients the test is variable, positive on one occasion, negative on another and *vice versa*. The significance of this change is not understood, especially as in many long-standing cases of rheumatoid arthritis the test is positive. Furthermore, positivity seems to bear no close correlation to clinical severity or to the erythrocyte sedimentation rate. Kellgren and Lawrence (1956) used the test in their survey of the incidence of arthritis and rheumatic conditions in Leigh, Lancashire, and found it to be a useful confirmatory diagnostic aid.

Radiological diagnosis

Experience resulting from the population surveys and the therapeutic trials arranged by the Empire Rheumatism Council have assisted in clarifying opinion on the radiological changes in rheumatoid arthritis. The terminal interphalangeal joint has been found to be useless as a basis of assessment, and the changes in the wrist joint proved to be ones most likely to lead to disagreement and misinterpretation. At the Ninth International Congress on Rheumatic Diseases, held in Toronto in June, 1957 (Kellgren and Lawrence, 1957), experts from different coun-

tries were asked to grade films in relation to four factors, osteoporosis, erosions, rheumatoid arthritis and osteoarthritis. There was considerable unanimity for the severe case of rheumatoid arthritis, but in the moderate degrees of involvement the differences in interpretation were appreciable. The greatest discrepancy between observers was found in the assessment of erosions. The value of the report lies in the indication of a growing agreement as to the essential radiological diagnostic criteria. Intra-articular narrowing, of less than one millimetre, has been shown to be significant in the Empire Rheumatism Council trials and was not listed as a specific test at Toronto but was included for the overall assessment.

LUPUS ERYTHEMATOSUS

Lupus erythematosus is perhaps more familiar to the dermatologist than to the general physician, although as long ago as 1872 Kaposi described the acute form of the disease and the varied clinical manifestations. The localized discoid tumours of the skin are considered by many dermatologists to be a distinct disorder and not a localized manifestation of a more general disease. Gold, in his review of this disorder, and also most of the American authorities, do consider that there is no clear-cut distinction between the localized and generalized forms of the disease. For practical purposes the classification of O'Leary into chronic discoid, generalized discoid, subacute and acute disseminated forms of lupus erythematosus is generally used as a working basis. The skin lesions may be found in all parts of the body but are very common on the face, particularly round the eyes. They usually appear in the disseminated forms of the disease as erythematous macules on the bridge of the nose which tend to coalesce and form the so-called butterfly erythema. Erythematous macules in the fingers are also frequently present in the acute disseminated forms. In addition to the rashes, arthralgias, arthritis, leucopenia, visceral involvement, pericarditis, pleurisy, anaemia, and renal damage are prominent features in the disseminated forms of lupus erythematosus. The condition also differs from the other "collagen diseases" in having a very high incidence amongst women. Some 80–90 per cent of the cases occur in women and particularly in the age group 20–40 years. The renal changes are also important. When atypical rheumatoid arthritis occurs in a young woman with anaemia, leucopenia, and the presence of albumin or red cells in the urine, a diagnosis of lupus erythematosus should be suspected. Great prominence was given to the involvement of the heart following the report of Libman and Sacks (1924) of 4 cases with vegetations on the heart valves. Certainly lupus erythematosus has to be considered in the differential diagnosis of bacterial endocarditis and in some cases of rheumatic fever, but most of the clinicopathological reports would suggest that involvement of the heart valves is not a common feature of disseminated lupus erythematosus. Far more important is the development of acute haemolytic anaemia or, in a supposed case of rheumatoid arthritis, of pleurisy, pericarditis or visceral involvement.

The L.E. cell

The diagnosis of lupus erythematosus rested in the past very largely on the varied clinical presentation associated with the development of a rash until the discovery in 1948 by Hargreaves, Richmond and Morton, of the Mayo Clinic, of the so-called L.E. cells. These cells were first discovered in the bone marrow, but now numerous

techniques have been devised for demonstrating their presence in the peripheral blood. In the L.E. cell, a leucocyte, is a large, homogeneous mass now thought to be ingested nuclear material which stains with Feulgen's solution, a reaction which is indicative of the presence of desoxyribose nucleic acid. The test is an *in vitro* and not *in vivo* test, and requires three constituents: (1) a source of nuclear protein, (2) a factor in the serum or plasma of a patient suffering from lupus erythematosus, and (3) active phagocytes. It is usual for the blood to be incubated, but sometimes fresh blood can be used and sometimes heparinized blood. For a discussion of the relative merits of the different techniques, it is necessary to consult the respective authorities. The greatest difficulty in the interpretation of results has been over the criteria that constitute an L.E. cell. Numerous errors have been made in the past, particularly mistaking tart cells, erythrophagocytosis, platelet aggregations and even amyloid bodies as L.E. cells.

Systemic lupus erythematosus is of most concern to the surgeon when it presents as an atypical arthritis, pyrexia of unknown origin, haemolytic anaemia, Raynaud's phenomenon, or as an unexplained albuminuria. The discovery of the L.E. cells has raised almost as many problems as it has solved and more particularly the problem as to the precise significance of the finding. Harvey and his colleagues (1954), in a review of the condition, fully discussed the specificity of the L.E. cell. Criteria for the cells are now generally accepted and it is usually recommended that the finding of 4 cells on a slide on at least two occasions is a minimum requirement for considering the test as positive. The L.E. cells have been reported in numerous conditions (Bateman, Malin and Meynell, 1958), although the most important consideration is the significance of their occurrence in rheumatoid arthritis. The Dutch workers, Kievits and his colleagues (1956), found L.E. cells in 17 per cent of 618 cases of rheumatoid arthritis. The group with L.E. cells showed a higher percentage of splenomegaly, diseases of the lower respiratory tract, abnormal urinary sediment, anaemia, and false positive tests for syphilis, but the authors could not find any evidence that the patients with L.E. cells had a specific clinical picture different from those cases of rheumatoid arthritis in which no L.E. cells were observed. In another series (Bateman, Malin and Meynell, 1958) L.E. cells were found in 28 cases of rheumatoid arthritis. Systemic lesions in keeping with a diagnosis of lupus erythematosus occurred in 15, but in 13 arthritis was the only symptom. In one fatal case autopsy revealed no characteristic lesions of systemic lupus erythematosus. It is conceivable that these cases in the above series might have had both lupus erythematosus and rheumatoid arthritis. The similar association of a relatively high proportion of positive D.A.T. tests in lupus erythematosus might be regarded as further evidence of a tendency to association of the two diseases or to some common pathological process, that is, something in the serum capable of destroying desoxyribose nucleic acid.

The discovery of the L.E. cell has provided a valuable diagnostic aid and the evidence would suggest that its finding has a considerable degree of specificity.

It is interesting to note that following therapy with cortisone or cortisone-like substances and with nitrogen mustard L.E. cells have, in some cases, disappeared and in others been reduced to a very low count. Also, exacerbations of the disease are frequently associated with an increased prevalence of L.E. cells in the peripheral blood. The fact that cortisone and similar chemical compounds can lead to a