LUPUS ERYTHEMATOSUS

By STEPHEN GOLD, M.R.C.P.

Physician to Skin Department, Hammersmith Hospital; Lecturer in Dermatology to Postgraduate Medical School, etc.

The word 'lupus,' originally applied to any ulcerative lesion of the skin remotely resembling a wolf bite, has been in current usage since the 13th century. With recognition of cancerous processes the term was more specifically applied to tuberculous infection of the skin (lupus vulgaris), while the 'red' lupus probably first described in 1827 by Rayer was termed lupus erythematosus by Cazenave in 1851. No recent observations have added to the morphological features described by these earlier writers.

CUTANEOUS LUPUS ERYTHEMATOSUS

The earliest sign of such a process is an erythema which at first is superficial and remains well circumscribed. With progress, scaliness occurs and the scales so formed are adherent and tend to plug the dilated pilo-sebaceous orifices. When the scales are removed, projecting spines may be seen on their under surfaces, the so-called 'tin-tack' plugging. Where scales are not evident, this plugging of follicles may still be obvious; the concretions are of cheesy sebaceous material whose surfaces have not been blackened as in the usual comedo, give a stippled effect. It is usual to see patches enlarge centrifugally, the edge being raised and scaly while the centre becomes atrophic; telangiectatic vessels are frequently seen coursing in these atrophic areas.

Frequently erythematous plaques do not progress to the atrophic stage, in which case they may disappear without leaving any sign. It is these early, superficial lesions which present diagnostic difficulties. It may, in fact, be impossible to make a diagnosis until after a period of observation, when other of the classical signs, such as plugging, scaling, telangiectasia and atrophy, may have become apparent.

These discoid lesions may be discrete or confluent and appear usually on the exposed parts of the skin. They are characteristically seen on the face, particularly over the nose and cheeks, giving the well-known 'bat's wing' or 'butterfly'

appearance, but occur also on the forehead, eyebrows, ears and scalp. Occasionally the vermillion border of the lips may be involved, giving a streaked silvery appearance. It is important to inspect the mucous membranes, particularly of the palate and tongue, which may present red erosions later becoming shrivelled and white. The exposed part of the neck is often affected in women, while the dorsal surfaces of the hands frequently show similar changes.

It is usual for a patient to develop a number of such lesions, for the most part confined to the face and ears. In extensive cases, however, they may be distributed widely over the body.

The disease may occur at any age, but the maximum incidence is in the third and fourth decades. It affects females about five times more commonly than males.

Precipitating Factors

Sunlight is by far the most important factor in determining the areas affected. It is obvious that these sites are the same as those involved in pellagra and in actinic eruptions. It is not unusual for patients to date the onset of their disease to a prolonged exposure to the sun, particularly at the seaside. It is also common to notice the aggravating effect of sun on existing lesions.

Other types of physical trauma, particularly cold, may also be responsible. It has been shown that most of the patients have a poor peripheral circulation and are subject to chilblains. Changes confined to the chilblain areas (fingers, nose and ears) is a well recognized type, described by Hutchinson as 'chilblain lupus.' Occasionally the process may start at the site of a skin injury or as a sequel to a subcutaneous injection.

Aetiology

Earlier observations, particularly of Continental workers, led to the assumption that the condition was tuberculous in origin. Confusion between it and lupus vulgaris further supported this view. It was suggested that chronic lupus erythematosus

represented a localized skin reaction to a tuberculous focus elsewhere in the body, a hypothesis based on post-mortem evidence where association of a tuberculous lesion in the lungs, glands or elsewhere was taken as proof of their intimate connection. British workers suggested the culpability of streptococcal infections. By removal of septic foci, Barber obtained resolution in some cases.

Modern views on the aetiology remain mixed. Most workers agree that some cases are undoubtedly tuberculous in origin, the development of lupus erythematosus with other tuberculides following close upon a primary lung or gland infection having been seen too frequently to be insignificant. There is much evidence, however, to support other cases as being due to a streptococcal focus. It is possible also that other focal abnormalities, conceivably not infectious in type, are at the basis of this process. It appears that certain conditioning factors are essential. A poor peripheral circulation has already been mentioned, whilst another is endocrine imbalance. It is not unusual, for instance, to see lupus erythematosus or other collagenoses develop after castration.

To suggest that two or more distinct organisms can be responsible for the same morphological entity is not without precedent. Erythema induratum is accepted to be of a tuberculous nature in young girls, while in older age groups (Whitfield type, nodular vasculitis) it is of streptococcal origin. Similarly, erythema nodosum is accepted as being associated with primary tuberculous infection or with streptococcal tonsillitis. It seems not unreasonable to suggest that in lupus erythematosus these two organisms may also be culpable, the conditioning factors determining the morphological response (erythema induratum, erythema nodosum, lupus erythematosus) being the variants.

Prognosis

It has been stated that in one third of the patients resolution is complete, one third are improved by treatment and one third progress unchanged. This is a fairly accurate assessment. Less than 1 per cent. progress to the 'systemic' form.

Treatment

Early lesions should be soothed with simple preparations containing calamine. It is important to give strict advice on avoidance of sunlight; the use of a wide brimmed hat and protective clothing, with the applications of various sun screen preparations, is helpful.

The natural process of atrophy can be hastened

by the applications of caustic such as pure phenol. Local application of carbon dioxide snow is also helpful; it may be used as a solid stick or, with acetone, painted on as slush.

On the assumption that some cases are streptococcal in origin sulphonamides and other antibiotics have been used. Early results with the former suggested that they might be useful in treatment. It has now become apparent, however, that the danger of producing systematization is too great and should preclude their use completely. The results obtained with penicillin, streptomycin and more recent preparations have not been convincing.

Administration of bismuth either by injection or by mouth has been a safe and relatively helpful procedure. In this country bismuth is given in courses of eight or ten weekly intramuscular injections. Gold is used, probably with greater success but certainly with more hazard. It may be administered intramuscularly or intravenously, dosage is as for rheumatoid arthritis. It is usual for courses to consist of eight injections and to be followed by a period of rest from four to six weeks. Albuminuria, granulopenia, toxic rashes (exfoliative dermatitis) and systematization are possible complications which must always be kept in mind.

SYSTEMIC LUPUS ERYTHEMATOSUS

It has been recognized since the earliest observations of Kaposi that occasionally disseminated lupus erythematosus may assume an entirely new appearance, associated with severe bodily illness. It appears that few patients with the chronic disease behave in this manner. Generally there is a provoking factor to account for it. Exposure to sunlight, drugs (particularly the heavy metals) and infectious conditions are factors known to play a part in causing dissemination.

This alteration is characterized by a spreading of the rash, severe prostration, high fever, pains in the joints and other features to be discussed later. However, it should be clearly understood that of all these 'systemic' types, only a minority have suffered from preceding chronic lupus erythematosus, the majority occurring *de novo*. It is the opinion of some that they do not even represent the same process.

This condition is primarily one of women, occurring between puberty and the menopause. Its occurrence in men is extremely rare. The onset may be vague or it may be abrupt. In the former general lassitude and rheumatic pains are the usual premonitory symptoms, followed by fever with blotchy erythematous rashes. In the latter high fever with marked toxæmia, albuminuria, anaemia, leucopenia and pleural or pericardial effusions lead on inexorably to death.

FIG. 1.—Chronic lupus erythematosus.

FIG. 2.—Gross scarring in chronic lupus erythematosus.

FIG. 3.—Chronic lupus erythematosus of superficial type.

FIG. 4.—Lichenoid lesions in chronic stage.

FIG. 5

Symptomatology

Cutaneous Manifestations

Those patients who have suffered previously from the chronic disease will show evidence of discoid lesions which have increased in size and become redder. More commonly the rash is non-descript, though there are several well recognized types. Again it is seen that the areas exposed to light are those maximally affected; blotchy erythema of the face with slight scaling is usual. This type of eruption is commonly macular, the central area of the face being involved. The colour may vary from pink to red or a cyanotic tint. When the rash is oedematous, individual lesions may be papular, vesicular or even bullous.

A well recognized feature is erythema localized around the nail folds, a sign also present in dermatomyositis and scleroderma. Subacute types often reveal telangiectasia around the nails. Red macules are seen on the palms and occasionally small, painful nodules, not unlike Osler's nodes.

'Erysipelas perstans faciei,' a papular rash of livid hue affecting the face, was described by Kaposi. Purpuric and petechial lesions are often seen and, in the absence of thrombocytopenia, indicate localized vascular damage; pigmentation is a common sequel where there has been much extravasation of blood. Erythematous or petechial areas often occur in the mucous membranes of the mouth; they soon develop into shallow ulcers.

FIG. 6

FIGS. 5 AND 6.—Systemic lupus erythematosus (sub-acute) associated with thrombocytopenia.

The rashes are therefore polymorphic. There may be urticaria, erythema, purpura, or bullous features. A generalized alopecia is usual during the acute phase, unlike the cicatricial type seen in the chronic form.

Joint Symptoms

Most patients suffering from the systemic disease have, at one time or another, painful and swollen joints. This arthritis subsides rapidly and the association with peri-arthritis, synovitis and fibrositis may make differentiation from rheumatic fever difficult. If acute symptoms persist, the residual arthritis may resemble the subacute infective type. It is unusual to see radiographic changes or permanent joint deformity. These symptoms are often relieved by rest and salicylates, though the latter do not affect the fever.

Renal Findings

It has long been recognized that renal disease is a common association. Abnormal urinary findings occur in 75 per cent. of the patients, commonly without hypertension.

Albuminuria, casts and red and white cells are commonly found in the urine. Renal failure is unusual. Even in the absence of albuminuria, renal function tests frequently show impairment.

Cardiovascular Symptoms

Clinical enlargement of the heart is rare and cardiac murmurs cannot be taken as evidence of verrucous endocarditis. Tachycardia, arrhythmias and murmurs occur as in any severe illness. Pericarditis and pericardial effusions may be detected. Cardiac failure, except as a terminal event, is not a feature. Electrocardiographic findings are again not characteristic; it is usual to see low voltage curves and occasionally abnormal T wave formation; delay in conduction has been reported.

Gastrointestinal Symptoms

Diarrhoea and vomiting may occur and the simulation of an acute abdominal emergency is not unknown.

Central Nervous System

Epileptiform seizures and toxic psychoses have been reported and, in fact, any focal reaction may occur.

Reticulo-Endothelial System

Enlargement of the liver is uncommon but when it does occur is a result of cloudy swelling, pylephlebitis or abscess formation.

In the literature there have been numerous reports of splenomegaly and some authors have found it regularly in their cases. In my own ex-

perience, enlargement of the spleen is uncommon except in children. Lesser degrees of splenomegaly may easily be missed through lack of regular examination.

Widespread enlargement of the lymphatic glands is a common feature. It is probable that enlargement of some glands is present in over 60 per cent. of cases; it has also been suggested that such a finding indicates chronicity. The glands, when enlarged are discrete, soft and often tender; they do not break down.

Serous Membranes

Inflammatory changes are most commonly found in the pleura. Small effusions are not infrequent; they may clear up spontaneously only to reappear later. At times the degree of effusion may completely dominate the clinical picture; in others obliterative changes occur which may be associated with a similar process in the pericardium. Although pleural involvement is infinitely more common than primary changes in the lung, small patches of pneumonia are not infrequently to be found underlying a pleural reaction. Effusions in the pericardium, though less common, may be as marked as those in the pleura; fibrosis occurring in small patches indicates previous inflammation. Peritoneal effusions are rare.

Eye Changes

Conjunctivitis of an allergic type occasionally occurs. The injection is often violaceous. Retinal lesions are well recognized but no single fundal picture can be considered diagnostic. The features most commonly noted include small white fluffy areas lying superficially in the retina (cytoid bodies), small superficial haemorrhages and papilloedema. These fundal changes, probably a manifestation of widespread vascular injury, sharply distinguish the condition from rheumatic fever or rheumatoid arthritis.

Diagnosis

Diagnosis of a typical case presents no difficulty. The occurrence of a characteristic rash on the face and hands of a woman who is febrile and complains of pain and stiffness in various joints is an unforgettable picture. Should there be an associated renal involvement or effusion from serous membranes the syndrome is virtually complete.

The majority of cases, however, particularly those of insidious onset, never present such a simple problem. Similarity to other collagenoses is apparent and, in fact, mixed types are not infrequent; there may well be a common denominator in these disorders. So long as the possibility is present in the clinician's mind it is unlikely that the diagnosis will be missed. The

following syndromes have been enumerated by Gross (1940), as being symptom complexes in which such a diagnosis should be carefully considered:—

1. 'Rheumatic fever' with pericarditis and petechiae.
2. 'Rheumatic fever' with nephritis, raised blood urea and normal blood pressure.
3. 'Rheumatic fever' with purpura.
4. 'Rheumatic fever' with leucopenia in spite of fever.
5. 'Subacute bacterial endocarditis' with negative blood culture and no embolic phenomena.

Pathological Findings

1. Haematological

(a) Hypochromic or normochromic anaemia is usual.

(b) Leucopenia is an important diagnostic sign. When there is a raised white count and no associated infectious process to account for it, a strong doubt is cast on such a diagnosis. It is usual to see a relative lymphocytosis.

(c) The sedimentation rate is always increased, often to a marked degree.

(d) Diminution of platelets is observed occasionally, particularly in those with an associated purpura.

(e) A positive direct Coomb's test occasionally occurs and an interesting and probably connected feature is the ability of these patients to form multiple antibodies to transfused blood.

(f) Sternal marrow obtained from patients in an acute phase, particularly if heparinized, reveals a peculiar cell now known as the 'lupus erythematosus cell' (Hargraves *et al.*, 1946). This cell represents one of the granular series which has ingested round, amorphous, basophilic masses. The cell nucleus has frequently been pushed aside so as to envelop these ingested masses to give a horseshoe appearance. In association with these specific cells the amorphous bodies are seen lying free; there is also a tendency of white cells to clump together.

These lupus erythematosus cells have now been demonstrated in peripheral blood. It appears that heparin or other anticoagulants are unnecessary for their production. The ingested material is probably nuclear in origin and is possibly derived from degenerating lymphocytes. They are seen in other conditions particularly where there is wholesale nuclear destruction as in leukaemia, but never in such quantity as in acute lupus erythematosus. They have, therefore, been regarded as an important aid to diagnosis.

It has been possible, by using healthy white cells and patients' serum to reproduce this effect, but when the serum is heated to 65° C. the effect

is lost. It seems probable that nuclear debris lying free in patients' serum soon becomes phagocytosed by scavenging white cells, a process requiring some activity of the abnormal globulin (see below), as it will not occur after heating or specific absorption of the globulin.

(g) Blood cultures are invariably sterile until near death, when a terminal septicemia is often noted.

2. Biochemical

(a) The most striking feature of this condition is the marked alteration of serum protein distribution; the albumin fraction is often decreased especially if there is concomitant albuminuria whilst the globulin fraction is increased so as to produce reversal of the albumin-globulin ratio. This increase in globulin is largely due to a specific increase of the γ fraction which may diminish during a remission and rise again in an exacerbation.

It is probable that this γ globulin represents antibody, possibly produced in response to a bacterial antigen or possibly to an auto-antigen.

(b) Cold agglutinins are frequently present and they may be of such high titre as to cause immediate agglutination following venepuncture.

(c) A factor present in patients' serum will cause agglutination of sheep's red cells which have been previously sensitized by the addition of 'anti-sheep's' red cells serum.

(d) Borrie (1951) has demonstrated an undue tolerance to injected heparin and suggests that this was due to a neutralization of the heparin by the γ globulin.

Serological tests for the detection of syphilis frequently give positive results, again probably due to the presence of this abnormal globulin. If repeated tests are made it is apparent that there is a variation in titre from time to time, a finding not apparent in untreated syphilis.

It is probable that all the findings in this group are basically due to the presence of abnormal globulin. Whether we are dealing with a condition of hypersensitivity or altered immunity or a combination of the two is speculative.

(e) The serum calcium is usually slightly reduced in acute cases.

(f) The excretion of ascorbic acid after large doses by mouth is subnormal.

3. Histopathological

At post-mortem, macroscopic changes are remarkable by their absence. In a small percentage of patients more especially those under 20, verrucous endocarditis (Libman-Sacks) may be evident. These coarse vegetations are larger, more fragile and often have a broader base than those seen in

rheumatic fever. Bacteriologically they are sterile. They may affect any or all of the four cardiac valves and a characteristic feature is their tendency to spread up on to the mural endocardium. Furthermore, patches of mural endocarditis, quite distinct from the valvular lesions, are often seen in the right auricle or in either ventricle. Macroscopic vegetations are present in 40 per cent. of patients and it is probable that microscopic evidence is present in a further 20 per cent.

Apart from associated lymphadenopathy, splenomegaly and other non-specific findings, the only other striking gross abnormality is a peculiar alteration of the mediastinal and peritoneal fat. This is often of a peculiar, gelatinous consistency and is particularly striking when present around the pericardium. The kidneys, which are generally of normal size, frequently show scattered petechial haemorrhages on their surfaces.

When considering the microscopic changes of all processes in which collagen is predominantly affected, it becomes apparent that, throughout, two distinctive processes are in operation simultaneously, the degenerative and the proliferative. Thus, in rheumatic fever and polyarthritis nodosa, cellular proliferation dominates the picture and 'fibrinoid' areas are soon converted into scar tissue. In systemic lupus erythematosus 'fibrinoid' changes dominate the picture and cellular proliferation is minimal. The lesions are widely distributed though there are definite sites of predilection (skin, joints, serous membranes, etc.). As well as this 'fibrinoid' change in collagen there is a corresponding alteration in the intercellular cement substance. This is normally invisible in healthy tissues but here it becomes apparent and stains metachromatically.

As blood vessels contain all elements of connective tissues in their walls it is obvious that vascular lesions can occur at any site. This, in fact, explains the widespread and often focal reactions seen in such sites as the gastro-intestinal tract. Vascular alteration may be the sole evidence of collagen damage. Changes vary from complete necrosis of an arteriole involving all its coats to the slightest deposition of 'fibrinoid' material within the intima. There is always a simultaneous proliferation of fibroblasts, which in smaller vessels can lead to extreme narrowing. As the process progresses concentric 'fibrinoid' rings are laid down in the intima, raising the endothelium and causing

blocking of the lumen. Changes that are seen in individual sites are all variations of this pattern. The typical 'onion skin' appearance of the splenic vessels and the 'wire-looping' of the glomerular capillaries, the latter representing a 'fibrinoid' change of basement membranes, are all examples of this process.

Treatment

From the earliest observations it was apparent that treatment was of little avail. At best reliance on good nursing and a relief of individual symptoms was all that could be achieved. Various drugs have been tried and those perhaps which have found most favour are iodine and quinine by mouth and bismuth by injection. Reports of individual cases benefiting from the use of sulphonamides, penicillin, streptomycin and other antibiotics are numerous, though the results are far from consistent, and occasionally it appears that their use has aggravated the condition (Gold, 1951).

Blood transfusions and a high protein diet are helpful supporting measures. Salicylates are useful in controlling joint symptoms; antihistamines have not proved of value and it should be noted that these patients often display marked hypersensitivity to any drug taken internally. The administration of hormones or even castration have only proved temporarily helpful.

With the advent of ACTH and cortisone it appeared at first that the treatment of this uniformly fatal condition would be revolutionized. It now seems that their effect, though profound at first, is not permanent. When these drugs are withdrawn the condition relapses often in a more violent form than before. At best it seems that they should be used only during an acute phase in the hope of a natural remission. After their initial administration there is a striking response in fever and joint symptoms, and later the rash may disappear. A remarkable sense of well-being descends upon the victim, appetite improves and mild euphoria is frequent. The usual biochemical and haematological responses are observed. Frequently the patients' hopes are buoyed up and their relations witness a dramatic recovery only to realize later that the benefit is not maintained.

General opinion on the use of these substances in the treatment of systemic lupus erythematosus is unfavourable.

BIBLIOGRAPHY

- BORRIE, P. F. (1951), *Brit. J. Derm.*, 63, 21.
 GOLD, S. (1951), *Lancet*, 1, 268.
 GROSS, L. (1940), *Am. J. Path.*, 16, 375.
 HARGRAVES, M. M., RICHMOND, H., and MORTON, R. (1946), *Proc. Mayo Clinic*, 23, 25.