only in the group of low refractive error (which includes two cases with a low myopic correction) that there is an appreciable excess of non-central fixation; this suggests that it is the non-accommodative squints that tend to have non-central fixation when first examined. Analysis of the interval between onset and first examination of these cases (Fig. 10), however, shows that a greater proportion of the patients with low refractive error attended in the later interval groups, and it appears, therefore, that the apparent increase in non-central fixation in these patients may be due to this relatively long interval before attendance. Once again the association of a long interval with increased incidence of non-central fixation is shown in both refractive groups. There was no significant association in this series between the refractive error and either the age at onset or the degree of anisometropia.

Discussion

The overall incidence of non-central fixation (22.4%) found in this series of young patients with unilateral convergent squint indicates that this defect in fixation constitutes a considerable factor in the management of the amblyopia of squint.

The analysis in this paper has shown that one of the main factors influencing the incidence of non-central fixation is the interval between the onset of the squint and the time of first examination; if this interval is short, there is a low incidence of non-central fixation. This has been confirmed by a similar analysis of the patients attending the school clinic, which will be published elsewhere (Scully, 1961). Moreover, evidence is accumulating to suggest that if occlusion treatment can be instituted early it may result in a re-establishment of central fixation, whereas it is generally agreed that well-established non-central fixation will not respond to such simple measures. Treatment, which can be instituted only at an age of not less than 7 years, is by complex methods involving projection of after-images (Cüppers, 1956), or direct stimulation of the macula (Bangerter, 1953). This treatment may require from 30 to 120 attendances and is expensive both in the time spent by the patient and in the personnel and facilities required. The prevention of non-central fixation is therefore clearly desirable.

The interval between onset and examination on which the incidence of non-central fixation is so clearly dependent is a factor largely under the control of the family doctor. Since this factor appears to be independent of the others it is reasonable to assume that if all patients could be seen with the minimum of delay after the onset of squint the incidence of non-central fixation would be very much smaller. It cannot be emphasized too strongly that as soon as a child is seen to squint it should be referred for examination. This applies to infants, to the toddlers of pre-school age, and to children of school age. There should be no hesitation in referring the child on the grounds of age or of the intermittency of the squint. Early treatment can then result in a saving of much time and energy on the part of both the ophthalmic specialist and the orthoptic department, as well as a considerable economic saving to the patient's family.

Summary

A survey of the incidence of non-central fixation, which is associated with one of the more intractable forms of amblyopia, in children with squint attending an eye hospital for the first time shows that a short interval between the onset of squint and attendance for examination is associated with a low incidence of non-central fixation. The incidence is also low in those patients with a late age of onset and in those with a low degree of anisometropia. These findings are similar to those in a parallel series attending a school clinic.

It is concluded that referral of children with squint to a hospital eye department or school ophthalmic clinic as soon as the squint is noticed can be expected to minimize the incidence of non-central fixation, and therefore to make a major contribution to the prevention of loss of vision.

We are indebted to the surgeons of the Manchester Royal Eye Hospital for allowing us to investigate these patients under their care, and we gratefully acknowledge the helpful criticisms of Dr. A. Stanworth, Reader in Ophthalmology, University of Manchester, in the preparation of this paper.

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ERYTHEMA MULTIFORME AND NEPHRITIS

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Erythema multiforme is a reaction of the skin and mucous membranes to various agents, among them drugs such as the sulphonamides, codeine, and the hydantoins. It is seen fairly often in dermatological practice in this country, and is characterized by erythema (which may assume the classical "target figure" form), purpura, and sometimes vesicles and bullae. There is usually systemic upset with fever and malaise, and in the severe form (so-called Stevens–Johnson syndrome) the mucous membranes of the mouth, eyes, and genitalia may be affected. Histologically there is a cellular infiltrate, particularly around the dilated vessels, with oedema of the dermis and prickle-cell layer, which may proceed to vesicle formation. Certain infections, especially streptococcal, may precede erythema multiforme, and some investigators maintain that the common recurrent type is a hypersensitivity reaction to streptococci (Welsh, 1948). Most dermatologists do not accept this view, and many think a viral cause more likely. Herpes labialis is a common accompaniment of erythema multiforme,

and the herpes simplex virus has been isolated on occasion both from vesicles (Foerster and Scott, 1958) and from the lungs (Finland *et al.*, 1948).

That organs other than the skin may be affected has long been recognized, and special attention has been paid to the pulmonary complications. Few observers, however, have recorded nephritis in this condition, and the majority seem unaware of such an association. Von Hebra (1866) did not include visceral complications other than pneumonia in his early description. The otherwise comprehensive review of the Commission on Acute Respiratory Diseases (1946) stated that " nephritis is not known in this syndrome." None of the standard textbooks of dermatology or general medicine mention nephritis in this condition. Lever (1944) stated that " no renal involvement occurs save transient albuminuria." Ashby and Lazar (1951) reported four cases of erythema multiforme and reviewed the literature to that date but did not mention nephritis.

Osler (1888, 1900), however, was at pains to emphasize nephritis as a serious complication in 6 of his 16 cases of " erythema multiforme." Later authors pointed out the diversity of these cases, and Osler (1914) himself later agreed that some (but not all) were certainly examples of Schönlein–Henoch syndrome. Nephritis is a well-recognized complication of this syndrome (Gairdner, 1948).

Scattered reports since Osler's time record features which indicate renal involvement in some patients with erythema multiforme. Costello (1947) described the case of a man of 36 with severe erythema multiforme whose urine contained a large amount of albumin. At necropsy the kidneys showed the following: " Extensive severe finely granular degeneration, bordering on necrosis. There were areas of interstitial oedema. Large hyaline casts were present in a number of collecting tubules. Many small arterioles, especially the afferent, show hyalinization of the walls, but only a few obliterated capillaries are seen. The glomerular tufts were congested. The walls of the capillaries were thick, of ' wire loop ' type, but patent and not fused. Occasional protein was present in the glomerular capsule." There is no record of a blood-urea estimation in life.

Another of Costello's patients, a woman of 25, had frank haematuria and her urinary deposit contained casts and leucocytes. Robinson and McCrumb (1950) described 11 cases, 2 with severe albuminuria ; one developed oedema and died. He did not record blood-urea estimations or other renal investigations. Ustvedt (1948) in his review reported the case of a boy of 10 years with severe erythema multiforme who developed acute nephritis. He had haematuria, and cylindruria, and a blood-urea level of 86 mg./100 ml. but his blood-pressure was normal. Levitt and Burbank (1953) described the case of a man of 58 with bilateral pulmonary tuberculosis who developed purpuric lesions after an injection of penicillin for pharyngitis, which later became haemorrhagic. The skin lesions progressed to bulla formation. Signs of nephritis then appeared ; the urine contained visible blood, albumin, and casts, and the blood urea rose to 100 mg./100 ml. The patient died of pulmonary tuberculosis. Levitt and Burbank listed the case as Schönlein–Henoch syndrome ; but in view of the patient's age, the bullous lesions, and the severe haemorrhagic pharyngitis, the description more closely resembles the purpuric form of erythema multiforme.

Dresner (1949) reported the case of a man of 27 with severe erythema multiforme who had heavy albuminuria for 21 days, with occasional red blood cells and leucocytes in the urinary deposit. There was no balanitis or urethral discharge and the urine was sterile throughout.

Many other individual case reports mention albuminuria, and occasionally haematuria, but do not record urine microscopy or blood-urea levels. It is clear that little significance is usually attached to albuminuria in this condition and that it rarely leads to fuller investigation, even in the most severe cases. Perhaps the vague term " febrile albuminuria " has diverted attention away from this important finding.

That renal involvement may occur in erythema multiforme, and be an early and serious feature affecting prognosis, is illustrated by the following case reports.

Case 1

A housewife of 58 was admitted to the Royal Victoria Infirmary on February 10, 1960. She had been well until seven days previously, when she developed soreness of the eyes and mouth. On the next day lesions appeared in the mouth and on the eyelid margins, and, on the day after, an erythematous macular eruption occurred, spreading rapidly over the whole body. She developed haematuria, dysuria, cough, sputum, and haemoptysis. She had taken no drugs prior to the onset of the illness.

On examination she was an obese, ill-looking woman virtually covered with the typical rash of erythema multiforme. In many areas the classical target figures predominated, but in others there were purpuric lesions. Friction had removed the top layers of the skin from coalescing lesions, leaving raw denuded areas. Erosions were present on the lid margins and in the nose, mouth, and vulva, with bleeding and crusts. The blood-pressure was 140/80 mm. Hg. Scattered rhonchi were heard in the chest. Her urine was smoky and there was moderate albuminuria. Numerous red cells and leucocytes were present in the deposit, and coliform organisms were cultured from a clean midstream specimen. Her blood urea was 30 mg./100 ml. ; plasma electrolytes were normal ; the serum albumin was 3.1 and globulin 3.1 g./100 ml., with a well-marked increase in α_2 globulin on electrophoresis. Chest *x*-ray examination was negative, but pneumococci and staphylococci were cultured from her sputum.

Treatment with dexamethasone 1 mg. six-hourly and tetracycline 250 mg. six-hourly was started on February 15. The blood urea rose to 198 mg./100 ml. by February 23. Plasma potassium rose to 6.9 mEq/l. the same day, and treatment with resonium A was necessary. Her skin condition improved, but ankle oedema appeared, albuminuria persisted, and the blood urea continued to rise. On February 27 she suddenly complained of violent abdominal pain, became cyanosed, and died within 10 minutes. Permission for necropsy was refused.

Case 2

A housewife of 42 was admitted to the Ipswich and East Suffolk Hospital on November 23, 1958. Her past history had been uneventful and her blood-pressure and urine examination were normal at an obstetric examination in 1952. She had felt vaguely unwell for six weeks, and three weeks before admission had left-sided abdominal pain, followed the next day by the appearance of red spots over the arms and legs. The skin lesions evolved with the formation of blisters, some with blood in them, and pains occurred in several joints. She was seen on November 20 by a dermatologist (Dr. J. B. Lyon), who diagnosed erythema multiforme. The mucous membranes were not involved. There was no history of drug-taking apart from occasional aspirin tablets. Her pulse was 100, but her temperature,

Hb, W.B.C., E.S.R., and chest *x*-ray films were normal. On November 22 she developed severe diarrhoea, which led to her admission the next day to a medical ward, under the care of Dr. J. W. Paulley.

On examination on November 23 she had a rash on her legs, arms, wrists, and face, and looked ill. There were some petechiae, but the predominant lesions were haemorrhagic bullae, with some secondary infection, and a diagnosis of erythema multiforme was again recorded. This was confirmed by skin biopsy, on which Dr. A. B. Lintott reported: "The skin lesion is a subepidermal bulla containing fibrin, polymorphs, and red cells. There are patchy areas of extravasation of red cells into the dermis at the edge of the bulla. There is a patchy perivascular inflammatory exudate, consisting of lymphocytes and neutrophils, in the neighbourhood of the lesion. Only scanty eosinophils are seen. Histologically this is bullous erythema multiforme."

Her urine contained albumin (70 mg./100 ml.) and a small number of hyaline and granular casts; it was sterile. Blood urea was 40 mg./100 ml., serum albumin 3.2 and globulin 3.5 g./100 ml., with increase in α_1-, α_2-, and β-globulins on electrophoresis. The antistreptolysin (A.S.O.) titre was 100 units/100 ml. Her stool contained occult blood persistently, but bleeding and clotting times and platelet count were normal. Muscle biopsy was normal.

Treatment with prednisone 10 mg. eight-hourly was begun on November 29, but the rash spread, and by December 1 involved her buttocks, back, and palate. A throat swab yielded Vincent's organisms only. On December 12 her urine contained albumin, hyaline casts, red cells, and leucocytes; A.C.T.H. was added to the therapy. By December 15 the rash and abdominal pain was clearing, and blood urea had fallen to 35 mg./100 ml., but she then developed a nephrotic syndrome with albuminuria of 12 g./l., serum albumin 1.9, globulin 2 g./100 ml., and moderately severe oedema of legs and sacrum. Blood urea rose again to a maximum of 160 mg./100 ml. on January 1, 1959. Blood-pressure readings were consistently normal.

Withdrawal of corticosteroids on January 5 was followed by a brisk diuresis and a fall in blood urea to 32 mg./100 ml. by January 19. Oedema and albuminuria disappeared and her general condition improved. She has been followed since discharge, and there have been no further symptoms referable to skin or urinary tract. When last seen (November 30, 1960) she was well, and the blood urea, Hb, and E.S.R. were all normal.

Case 3

A man of 63 was admitted to Addenbrooke's Hospital on December 8, 1959. He was receiving digitalis and mersalyl consequent upon a myocardial infarction four years previously, and took an ipecacuanha mixture for chronic bronchitis. There was no history of recent infection or the administration of other drugs. Six days before admission he developed a rash on his thighs and face, spreading to the trunk. Two days later lesions appeared in the mouth. His temperature was 99° F. (37.2° C.), B.P. 95/70 mm. Hg, and some crepitations were present at both bases. The typical rash of erythema multiforme was present, but glans and urethra were not involved.

There was moderate albuminuria and some granular casts were found in the deposit. Blood urea was 104 mg./100 ml., E.S.R. 33 mm./hr., Hb 13.2 g./100 ml., and W.B.C. 11,000/c.mm. Electrophoresis showed relative increase in α_2- and γ-globulins. There was mottling of the right lower zone on the chest *x*-ray film. Pathogens were not grown from a throat swab, but A.S.O. titre was 320 units/100 ml.

He recovered without treatment, and the blood urea fell to 48 mg./100 ml. five days later.

Case 4

A housewife was first seen at the Royal Victoria Infirmary in 1949, when she underwent lobectomy for localized bronchiectasis. Her mother had suffered from severe rheumatoid arthritis, and the patient herself developed typical widespread rheumatoid arthritis in 1948, when aged 32. Her joint symptoms continued to trouble her until the start of prednisone therapy in 1960. The diagnosis was later confirmed by the development of characteristic deformities, rheumatoid nodules, and a positive (1:128) Rose–Waaler test. Her treatment to 1956 included salicylates and four courses of sodium aurothiomalate ("myocrisin"). She was treated with low doses of prednisone and supplementary injections of corticosteroids into individual joints on a number of occasions between 1956 and 1960. A skin rash was noted on the forearms when she attended the rheumatoid clinic in February, 1959, and this led to a search for lupus erythematosus (L.E.) cells in the blood. L.E. cells were not found then, nor on six subsequent occasions over the next 18 months. The E.S.R. was persistently raised to about 90 mm./hr. Her blood-pressure was normal (140/75 mm. Hg), and albuminuria was not detected at an examination in February, 1959.

On October 4, 1959, she was referred to the skin department and seen by Professor J. T. Ingram on account of an eruption on her face, lips, arms, legs, and inside the mouth, which was diagnosed as severe erythema multiforme. She gave a history of similar attacks recurring every few months over the preceding two years. She was seen again by Professor Ingram on December 2, when a further attack with sore throat occurred two weeks after an intra-articular injection. The eruption was a typical widespread erythema multiforme. She gave a history of the development of mouth ulcers, without skin rash, at a similar interval after previous injections. Her blood-pressure was 140/100 mm. Hg., Hb 9.2 g./100 ml., and electrophoresis showed a well-marked increase in α_2- and γ-globulins. Another intra-articular injection of prednisone was given in August, 1960, after preliminary skin-testing. In spite of a negative intradermal test, further eruption appeared three weeks later. On this occasion she was found to have moderate albuminuria, a blood urea of 104 mg./100 ml., and a blood-pressure of 210/120 mm. Hg, and was admitted to the medical unit under Professor G. A. Smart for further investigation.

Her rash faded soon after admission to hospital, but the blood urea remained above 100 mg./100 ml., and the albuminuria and the presence of red cells and leucocytes in the urinary deposit persisted. There was no splenomegaly, and the white blood cell count was normal on several occasions. Needle biopsy of the kidney (Fig. 1) showed sclerosis of many glomeruli, crescent formation, and round-cell

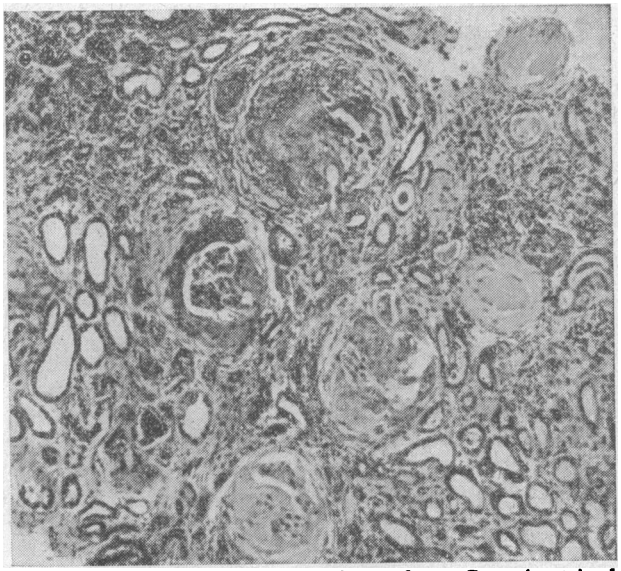

FIG. 1.—Needle biopsy of the kidney from Case 4, stained haematoxylin and eosin, showing crescent formation and destruction of glomeruli. (×100.)

infiltration of the periglomerular interstitial tissue. The typical "wire loop" lesions of advanced lupus nephritis were not seen, and stains for amyloid were negative. Culture of blood from the biopsy needle was sterile, but coliform organisms were grown from the post-biopsy midstream urine.

She was treated with an increased dose of prednisone (30 mg./day) which caused a dramatic improvement in her arthritis. During the six-months follow-up the albuminuria has been reduced to a faint trace (30 mg./100 ml.), the urinary deposit has returned almost to normal, but no reduction in the blood-urea level or blood-pressure has occurred. During September, 1960, her prednisone dosage was temporarily reduced because of side-effects, and during this period the rash recurred. On this occasion there was no vesiculation, and a skin biopsy showed endothelial swelling of arterioles and extravasation of red blood cells and leucocytes into the upper dermis similar to that found in anaphylactoid purpura.

Case 5

A housewife of 59 was first seen in the skin department of the Royal Victoria Infirmary on October 17, 1960, with a history of recurrent attacks of erythema multiforme for five years after an attack of shingles. The episodes lasted two to three weeks, and were separated by intervals of about six weeks. Her urine did not contain albumin, and was normal on microscopy. She returned on October 28 during a typical attack, with target lesions on the skin and ulcers on the tongue. Her urine contained a trace of albumin. Haemolytic streptococci of Lancefield group A were cultured from a throat swab. Her Hb and white cell count were normal, E.S.R. 25 mm./hr., blood urea 41 mg./100 ml. She was treated with sulphamethoxypyridazine 0.5 g. daily, but the rash spread, her temperature rose to 101° F. (38.3° C.), and she was admitted on November 7.

On admission she looked ill, but physical examination was normal apart from the rash, which had spread and become confluent in some areas on the limbs, face, and trunk. The fauces were reddened, but there was no ulceration of the mouth or vulva. Her blood-pressure was 130/80 mm. Hg. Her urine contained moderate amounts of albumin, many red cells, and some leucocytes and granular casts. Basal crepitations were noted on November 8, but the chest *x*-ray picture was normal and she had no cough or sputum. Prednisone 10 mg. eight-hourly was begun on November 11, and within 24 hours her rash was fading and her temperature had settled to normal. The urine output remained reasonable (about 800 ml./day), but she became breathless and developed oedema, pleural effusions, and raised venous pressure. The heart was not significantly enlarged, and E.C.G. was normal. The blood urea had risen to 103 mg./100 ml. and plasma sodium had fallen to 119 mEq/l. by November 12. On the 16th, when her blood urea was 250 mg./100 ml., she was transferred to the artificial kidney unit and treated with the standard conservative regime of low-protein diet and fluid restriction (Elliott *et al.*, 1960). The same day she developed signs of a right-lower-lobe pneumonia, and a resistant staphylococcus was isolated from her sputum. Tracheotomy was required next day for severe respiratory distress. She improved after a haemodialysis on November 20 and passed into the early diuretic phase of acute renal failure, but she died of a further exacerbation of her chest infection on November 27.

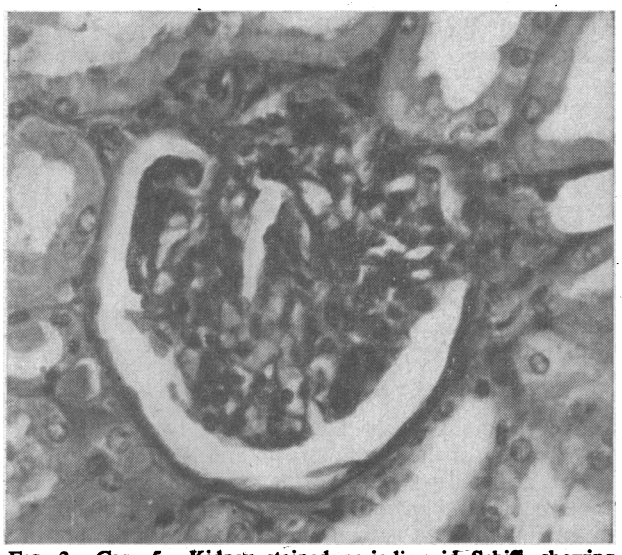

FIG. 2.—Case 5. Kidney stained periodic-acid Schiff, showing acute tubular damage and adhesion of glomerulus to Bowman's capsule. Specimen taken with biopsy needle 10 minutes after death. (×360.)

Necropsy revealed severe tracheobronchitis and pneumonia, venous congestion, and large pale kidneys with prominent glomeruli. On microscopy (Fig. 2) there were degenerative changes in the convoluted tubules typical of "acute tubular necrosis," and some glomerular changes not typical of that condition. There was some increase in the cellularity of glomeruli with reduction in capillary lumina and adhesions between capillary loops and Bowman's capsule. There was no crescent formation or cellular infiltration of the type seen in Case 4.

Discussion

The only satisfactory classification of disease is one based on aetiology. Erythema multiforme is a skin reaction which is clinically distinct but of multiple aetiology; in other words, it is a syndrome, not a disease. We believe that this syndrome is associated with a renal lesion more commonly than is generally realized. Four of the five cases described were seen by one of us (J.S.C.) during two years of mixed general medical and dermatological practice. It is our impression that in the past the possibility of renal complications has not been sufficiently appreciated, and consequently full urine examination and blood-urea estimation have seldom been performed. Albuminuria, when present, has usually been attributed to fever or local lesions of the urethra and surrounding structures. Only one of our patients (Case 1) had urethral involvement; this could not in any case account for the uraemia.

Both the clinical features and the histological abnormalities in our patients may be found in a number of different diseases involving the kidneys. We have therefore considered the possibility that our patients were suffering coincidently from the rash and unrelated renal diseases. The close association in time between the dermal and renal manifestations makes this very unlikely. Ascending urinary infection might be expected to accompany erythema multiforme in some patients with genital involvement, and a positive culture was in fact obtained from a midstream urine specimen in the one patient with vulval lesions. However, none of our patients had the typical clinical or histological features of urinary infection, and none had pyuria. The positive culture immediately after biopsy in Case 4 is of unknown significance; we have found this in several patients with glomerulonephritis. Several other possible causes of renal damage were suggested by the history in Case 4; however, amyloid was excluded histologically and systemic lupus erythematosus is unlikely in view of the persistently negative L.E. cell test. The urine and blood-pressure were known to be normal three years after her last course of gold injections, and her renal abnormalities appeared after the onset of her rash.

If erythema multiforme is indeed a result of streptococcal infection in a substantial proportion of cases, it

would be surprising if it were not sometimes associated with acute glomerulonephritis. The association would not necessarily be very frequent. Acute glomerulonephritis has a different age incidence,, and in this country it almost always follows infection with a single type of streptococcus (type 12). Erythema multiforme may well be a reaction to infection with many different types of streptococci, as rheumatic fever seems to be. Streptococci of group A were isolated from the throat of one of our patients and another had a raised A.S.O. titre as evidence of preceding streptococcal infection. On the other hand, none of our cases followed the typical course of acute glomerulonephritis ; three were normotensive or hypotensive throughout and none had hypertension early in the illness ; no patient had a classical onset with headache, generalized oedema, frank haematuria, and oliguria. These observations apply also to the previously described patients referred to in the introduction. It has been said that acute glomerulonephritis often follows an atypical course in older adults, but this may simply imply that there are several different renal diseases referred to by this title at present (Hall *et al.*, 1961).

The histological changes in Case 4 (Fig. 1) are similar to those in the progressive type of acute glomerulonephritis (Ellis, 1942), but are not specific to this condition ; they have been described in lupus nephritis (Muehrcke *et al.*, 1957) and in the Schönlein–Henoch syndrome (Heptinstall, 1960). The changes in the glomeruli in Case 5 (Fig. 2) are non-specific.

There were some clinical similarities to Schönlein–Henoch syndrome ; two of our patients complained of abdominal pain, and one had persistent occult bleeding from the bowel and transient arthralgia, but the rash in all our patients was unmistakably that of erythema multiforme.

Four of our cases were treated with corticosteroids ; in three the skin rash resolved within a few days of the beginning of therapy and in one it recurred during temporary reduction in steroid dosage. Improvement in the renal condition, when it occurred, was less dramatic and slower ; it may well have been coincidental.

We conclude that an inflammatory renal lesion with some similarities to acute glomerulonephritis accompanies erythema multiforme in a proportion of cases ; that it may lead to fatal uraemia during the acute illness ; and that recurrent episodes may produce chronic nephritis. Further study—clinical, bacteriological, and histological—will be required to determine whether the lesion is identical with acute glomerulonephritis after streptococcal infection. The results may well be important in determining whether long-term prophylactic penicillin is indicated in patients with recurrent attacks.

Summary

Five cases are described in which erythema multiforme was accompanied by the onset of a form of nephritis manifested by albuminuria, microscopical haematuria, cylindruria, and uraemia. Hypertension and oliguria were not features of the acute attack.

Two patients died during the acute attack, one progressed to subacute nephritis with chronic uraemia, one developed a nephrotic syndrome and subsequently recovered, and in one the renal abnormalities subsided with the rash.

The histological features in two cases are described.

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CHRONIC BRONCHITIS

CONTROLLED TRIAL OF ISOPRENALINE AND CHYMOTRYPSIN BY INHALATION

BY

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The aim of the trial was twofold ; firstly, to assess the ability of finely divided chymotrypsin with isoprenaline by inhalation to relieve airways obstruction ; and, secondly, to assess its ability to liquefy sputum and thus increase the quantity expectorated when presented alternatively as a fine dry powder or suspended in an inert propellant.

The patients were admitted to hospital for the duration of the trial. The clinical material consisted of 35 male patients aged 30 to 65 years. All the patients had had winter cough and sputum for at least three years, and had been off work at least once, during that period, with bronchitis.

Method

Every patient received each of the two methods of presentation of the chymotrypsin and isoprenaline for a period of five days. Each of these periods was preceded by three days " control " during which no treatment was given. Whether a patient should start with the powder or with the suspension was determined from a list based on random numbers. None of the patients had antibiotic therapy of any kind.