was normal. One of these was treated with folic acid 5 mg. t.d.s., but there was no haematological improvement after four weeks of therapy. Injections of vitamin B₁₂ were then given with good results. Malabsorption of vitamin B₁₂ can probably be excluded as the cause of the deficiency in this patient, as absorption of radioactive vitamin B₁₂ was normal several months after delivery.

The cause of the low serum vitamin-B₁₂ levels found in pregnancy is obscure. A progressive decrease in the serum vitamin-B₁₂ levels of normal women as pregnancy progressed was found by Lowenstein *et al.* (1962), but the total circulating serum vitamin B₁₂ did not change significantly. A low serum vitamin B₁₂ was associated with megaloblastic erythropoiesis in a high proportion of their cases, however, and they felt that this probably indicated true vitamin deficiency. Vitamin-B₁₂ absorption has been shown to be normal in megaloblastic anaemia in pregnancy by Badenoch *et al.* (1955). It is therefore unlikely that these low levels are due to poor absorption, but rather are the result of excessive utilization by the foetus or are secondary to a deficiency of folic acid. This may not be true in every case, however, as one patient with low serum vitamin B₁₂ investigated before this study started has since been shown to have a true absence of intrinsic factor in spite of her haemoglobin returning to normal after delivery.

There is evidence to suggest that folic-acid deficiency may exist during pregnancy without megaloblastic erythropoiesis developing (Chanarin *et al.*, 1959), in which case it is likely that anaemia due to folic-acid deficiency may be commoner than is at present thought. If this is so it would be of interest to know whether increased Figlu excretion gives an indication of such deficiency. Our own data suggest that this is unlikely, as there is no correlation between Figlu excretion and serum F.A.A. in patients with a normoblastic bone-marrow (Fig. 1). Furthermore, 3 of the 20 patients with a normal haemoglobin concentration had increased Figlu excretion, a proportion similar to that found by Berry *et al.* (1963), who did serial estimations of urinary Figlu in a group of normal pregnant women. It is clearly important to determine whether a normoblastic anaemia which responds to treatment with folic acid does occur in pregnancy. We believe that this point can be settled only by means of a controlled therapeutic trial, and such a trial is in progress.

Summary

In the present study the urinary excretion of Figlu has been estimated in 102 pregnant women and correlated with the haematological state, including the bone-marrow appearance in every case and the serum folic-acid activity and serum vitamin-B₁₂ levels where available. Estimation of Figlu excretion was of little value in the diagnosis of the type of anaemia and was no substitute for bone-marrow biopsy; the serum folic-acid activity was found to be a better guide to the type of erythropoiesis. A number of patients were found to have low serum vitamin-B₁₂ levels in association with normal Figlu excretion and a significant proportion of these had megaloblastic or transitional erythropoiesis.

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Nephritis and Common Skin Diseases

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Glomerulonephritis may accompany some common dermatoses, especially those in which haemolytic streptococci play a part. In anaphylactoid purpura renal involvement is well documented, but in erythema multiforme, erythema nodosum, acute guttate psoriasis, and those pyoderms which harbour streptococci the occurrence of glomerulonephritis is less well appreciated.

The following case histories show how glomerulonephritis may accompany apparently benign skin diseases.

Case Histories

Case 1. Acute Nephritis; Insect Bites; Erythema Multiforme

A woman aged 51 had had an itchy eruption on the shins, thighs, buttocks, and forearms, with malaise and pains in the elbows, knees,

and ankles for two weeks. There was no history of recent sore throat, herpes simplex infections, or drug ingestion. She was a chronic alcoholic. In 1957 she had been treated for syphilis and gonorrhoea, and in 1962 for body lice; in early 1963 she had had an urticarial reaction after eating crab, and at the end of 1963 had eaten fish roes a few days before the symptoms which led to her admission to hospital. The skin on the ankles, calves, and buttocks had a number of erythematous papules 0.5–1 cm. in diameter with central haemorrhagic puncta. Some were arranged in lines and were bed-bug bites. She also had lesions of erythema multiforme on the legs and forearms; some were bullous (1–2 cm. diameter) and others target-like. Pubic lice were present. The joints of the ankles, knees, and elbows were painful and at times swollen. The liver was palpable, the blood-pressure 120/70, and the urinalysis normal.

Investigations.—Four days after admission the blood-pressure had risen to 175/115, reaching a maximum on daily testing of 180/120,

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and remaining at about this level for over three weeks. There was oliguria; the urine contained protein (4+), with granular casts, red blood cells (3+), and white blood cells; culture was sterile. The daily urinary output of protein was between 2.7 and 14 g. per 24 hours. The blood urea rose from 36 to 60 mg./100 ml. Other investigations were normal: blood count, E.S.R., serum proteins, W.R., antistreptolysin (ASO) titres, throat swab, serum bilirubin, lupus erythematosus cells, antinuclear factors, occult blood in the stools, radiographs of the chest, and renal areas.

The blood-pressure, urinary output, and blood urea returned to normal and the skin healed after four weeks, but some proteinuria and casts remained.

Case 2. Nephrotic Syndrome and Infected Seborrhoeic Eczema

A storekeeper aged 61, with no past history of skin or kidney disease, developed a rapidly spreading seborrhoeic dermatitis. After two weeks he was admitted to hospital with extensive impetiginized areas, particularly around his ears and axillae. Two weeks later he was oedematous, his weight had increased by 31 lb. (14 kg.), and his urine contained protein, granular and hyaline casts, and "numerous" red and white blood cells. His blood-pressure, which was 140/80, never rose above 150/90. The urine, tested daily, contained between 1 and 4 g. of protein per litre (Esbach) and the highest of four blood-urea estimations was 45 mg. There was no evidence of diabetes mellitus or connective tissue disorder.

Eighteen months later, after systemic corticosteroids and diuretics had been considerably reduced, he returned to work. He had slight proteinuria and minimal eczema; his weight was normal.

Case 3. Focal Nephritis, Acute Guttate Psoriasis, and Erythema Nodosum

A machinist aged 33 developed generalized guttate psoriasis and erythema nodosum of the shins 10 days after an acute tonsillitis which had been treated with oral penicillin. He had had acute rheumatism at the age of 12, and recurrent tonsillitis which was treated by tonsillectomy at 23. He gave no family history of psoriasis.

Investigations.—Blood-pressure 130/80 and urinary output normal. Urine contained protein (+), R.B.C.s, W.B.C.s, and hyaline casts (+); culture was sterile. Blood urea 26 mg./100 ml. Throat swab (after penicillin treatment) was sterile, but ASO titre was 250 units/ml. Hb 13.6 g./100 ml., W.B.C.s 9,850/c.mm., with normal differential. Serum proteins normal. No L.E. cells.

The renal exudate persisted for three weeks, the erythema nodosum for two weeks, and the guttate psoriasis had gone after eight weeks.

Case 4. Recurrent Focal Nephritis and Acute Guttate Psoriasis

A housewife aged 46 had had three attacks of generalized guttate psoriasis during the past two years. Each followed two to four weeks after beta-haemolytic streptococcal tonsillitis. During the last two attacks her urine had contained protein (+), R.B.C.s (+), and W.B.C.s (+); culture was sterile. Her blood-pressure and blood urea were normal throughout each attack.

The renal exudate cleared after three weeks.

Case 5. Focal Nephritis and Generalized Exfoliative Psoriasis

A schoolteacher aged 32 developed acute guttate psoriasis three weeks after acute tonsillitis which was treated with penicillin. He was subject to recurrent tonsillitis. The urine contained albumin (+), R.B.C.s (+), and W.B.C.s (+); culture was sterile. Blood-pressure 120/80. Blood urea 20 mg./100 ml. ASO titres were 50, 90, and later 100 units/ml. The skin lesions progressed to a generalized exfoliative psoriasis.

The renal exudate cleared in four weeks.

Case 6. Focal Nephritis and Anaphylactoid Purpura

A printer aged 54 had had a purpuric eruption with macular and urticarial lesions 0.5–1 cm. in diameter on his legs and buttocks for six weeks. This had followed four weeks after a sore throat treated with aspirin. He had no joint, gut, or kidney symptoms. In adolescence he had had rheumatic fever.

Investigations.—Blood-pressure 160/90 (fat arm). Urine contained protein (2+), R.B.C.s (+), W.B.C.s (+); hyaline and granular casts (+); culture was sterile. ASO titre 250 units/ml. Blood urea 39 mg./100 ml.

Physical examination normal. Capillary fragility (Hess's test) negative. Hb 15.2 g./100 ml. W.B.C.s 7,300/c.mm. with normal differential. Platelets normal. E.S.R. (Westergren) 12 mm. in one hour, serum proteins normal, W.R. negative, no L.E. cells, antinuclear factors negative. Radiograph of chest normal.

The eruption cleared after three weeks. The urinary deposit persisted for five weeks, but the albuminuria remained.

Discussion

Glomerulonephritis is a term which implies a delayed hypersensitivity reaction affecting the glomerular vasculature. It is a syndrome initiated by different stimuli, involving many complex immunological mechanisms, though commonly streptococci are responsible (Peters, 1963). In susceptible individuals initial attacks result from only a few serological types of group A beta-haemolytic streptococci, but exacerbations may be caused by any type (Rammelkamp, 1962). Marked biological variance of immune response to antigens in normal and diseased persons explains the range of effects from benign inapparent subclinical to fulminating (Peters, 1963).

Four groups of diffuse glomerulonephritis are well defined: post-streptococcal acute glomerulonephritis, nephrotic syndrome, and subacute and chronic glomerulonephritis. Now a fifth group, focal nephritis, is accepted as a definite entity on clinical and histological grounds (Wilson, 1962; Heptinstall and Joekes, 1963). The classical manifestations of diffuse nephritis—oedema, hypertension, renal failure—are absent in focal nephritis, where the sole sign may be a minimal and transient renal exudate. The implication, now proved histologically, is that only a few glomeruli are pathologically affected.

In anaphylactoid purpura the incidence and outcome of the renal lesions are very variable (Heptinstall and Joekes, 1963). The renal pathology is similar to acute glomerulonephritis, but the lesions are commonly focal and not generalized (Milne, 1962).

Erythema multiforme is a clinically distinct syndrome of multiple aetiology affecting the skin and mucous membranes, and rarely the kidneys (Comaish and Kerr, 1961), producing lesions with some histological similarities to acute nephritis, although the normal blood-pressure, transient arthralgia, and occult blood in the stools may suggest anaphylactoid purpura syndrome. Drugs, sera, streptococci, viruses, mycoplasma pneumoniae (Ludlam *et al.*, 1964), and chemical substances (Yaffee and Stargardt, 1963) have been blamed—as they have in all the necrotizing "allergic" angitiides (Winkelmann and Ditto, 1964). It is possible to link nephritis and erythema multiforme in Case 1, imputing as an antigen the foreign material from the insect bites or the fish. The course of the patient's disease was similar to that of experimental foreign protein nephritis, where there is a generalized polyarteritis with manifestations of serum sickness (Peters, 1963).

Erythema nodosum is a well-known sequel of streptococcal infection, although other causes are more usual at the age of our patient in Case 3 (James, 1961). Likewise acute guttate psoriasis, both in initial and subsequent attacks, has been shown to follow streptococcal throat infections, although the mechanism is poorly understood (Norlind, 1950; Nørholm-Pedersen, 1952). One possible explanation is that a streptococcal "toxin" damages the capillaries of the dermis, which are

abnormal in individuals with an inborn tendency to psoriasis, thus after an interval of 10 to 15 days producing the lesions of psoriasis (Whyte and Baughman, 1964). An antigen-antibody reaction centred on the dermal capillaries, similar to that which occurs in the glomerular capillaries in acute nephritis, seems unlikely, as fluorescent antibody studies carried out on psoriatic skin have been negative (Raskin, 1964).

Pyoderma in patients with seborrhoeic eczema is a very common complication; it is much rarer in atopic eczema, yet 4 out of 492 patients suffering from atopic eczema were found to have glomerulonephritis on presentation (Roth and Kierland, 1964). Impetigo has been reported as a common precursor of glomerulonephritis in the U.S.A. (Blumberg and Feldman, 1962). This could be true in this country: over the past two years in our department half the cultures from 24 patients with impetigo grew beta-haemolytic streptococci.

It is interesting that two of our patients (Cases 3 and 6) had acute rheumatism in adolescence—a further manifestation of their streptococcal hypersensitivity.

Summary

Nephritis may occur with common skin diseases. Examples of various types of nephritis associated with anaphylactoid

purpura, erythema multiforme, erythema nodosum, acute guttate psoriasis, and infected eczema are given.

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Variations in Small-intestinal Villous Shape and Mucosal Dynamics

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The small-intestinal mucosa maintains a constant appearance while being in a continuous state of proliferation and loss. The crypts of Lieberkühn contain immature cells showing frequent division, and from them epithelial cells stream up the villi in a regular fashion to be lost at the tips (Leblond and Stevens, 1948; Creamer *et al.*, 1961). The whole small-intestinal epithelium is replaced in this way about every two days. The rates recorded by observers using many animal species have been remarkably constant, and in man Bertalanffy and Nagy (1961) have estimated the duodenal turnover time to be two days. If the production of new cells is abruptly stopped by either antifolic drugs or x-irradiation the normal villous structure collapses (Philips and Thiersch, 1949; Wiernik *et al.*, 1962). Within two to three days sheets of epithelial cells are shed and stunted broad villi or a flattened surface is left. This suggests that the structure of the small-intestinal mucosa is plastic and that variations in epithelial-cell turnover may well determine the shape and size of the villi.

The so-called normal appearance of the small-intestinal villi as viewed under the dissecting microscope is finger-shaped, but many healthy people show some leaf-shaped villi. In pathological conditions a whole range of appearances is seen, from normal finger villi to leaves, to convolutions, and in some cases to a completely flat mucosa (Holmes *et al.*, 1961). The purpose of the present study was to see if the change in villous shape from fingers to convolutions could have an explanation in the dynamics of the intestinal epithelial cells. The problem of idiopathic steatorrhoea and the production

of a flat mucosa has been considered previously (Creamer, 1962).

Materials and Methods

Twenty small-intestinal biopsies were examined. They were selected solely because they showed a variety of changes from finger villi to convolutions. None of the patients had idiopathic steatorrhoea, but some had gastrectomies, Crohn's disease, or other intestinal disease. Seventeen were obtained perorally and three were surgical specimens, of which two came from the jejunum at a gastrectomy and a gastroenterostomy stoma under revision.

The sections were all well orientated, so that the crypts were cut longitudinally. On each section a count was made of at least 2,000 epithelial cells, recording separately crypt cells, adult cells, and metaphase mitotic figures. From this the ratio of adult cells to crypt cells was calculated. The mitotic rate was expressed as metaphases per hundred crypt cells.

Where leaf-shaped villi are present the section may be cut through the long axis of the leaf A-A or across the short axis B-B (Fig. 1). If a cell count is made through a long axis A-A fewer adult cells are recorded than if a number of leaves are cut through the short axis B-B. In one case this was done, and the proportion of adult cells to crypt cells was exactly half when a leaf villus was cut down the long axis compared with a similar area where the leaves were sectioned through the short axis. Because of this, an area was always chosen where leaf-like villi were sectioned through the short axis.

The crypt length was estimated by counting the number of cells down one side of a crypt, the average of several crypts

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