not found. The serum bilirubin was 0.7 mg./100 ml., the alkaline phosphatase 16 K.A. units/100 ml. and the flocculation tests were normal. In the xylose absorption test, 5 g. xylose were excreted in the urine in five hours. A three day test of fat excretion in the stools showed an average of 2.8 g./24 hours.

Progress Nine days after admission the hæmoglobin had fallen to 7.2 g./100 ml., the white cells numbered 4,100 and the reticulocytes were 6%. The direct Coombs' and Schumm's tests were now negative, but serum haptoglobins were absent.

Eighteen days after admission, the hæmoglobin was 9.5 g./100 ml., and the reticulocytes 12%. The bone marrow contained fewer megaloblasts and a greater number of polymorphs, the differential count being: Blast cells 5%, myelocytes and metamyelocytes 18%, polymorphs and band cells 33%, proerythroblasts 6%, normoblasts 27%, megaloblasts 8%. There was still a large amount of FIGLU in the urine.

Six weeks later the hæmoglobin was 12.4 g./100 ml., and the reticulocytes 1%. Autohæmolysis was normal. FIGLU was still present in the urine, but the amount was much less than previously. The serum vitamin B₁₂ level had risen to 220 µg./ml. The spleen was not palpable, and he had gained 12 lbs in weight.

In January 1963, the hæmoglobin was 12.8 g./100 ml. The stained blood film showed a normal appearance of the red cells, but there were a large number of polymorphs with hypersegmented nuclei, 35% having 5 lobes, 13% 6 lobes and 3% 7 lobes. A slight trace of FIGLU was detected in the urine, and the serum haptoglobins were absent.

He was then given 15 mg. folic acid by mouth daily for four weeks. Following this treatment, the hæmoglobin rose to 14.8 g./100ml., 14% of the polymorphs had 5-lobed nuclei and none had 6- or 7-lobed nuclei. There was no FIGLU in the urine. The Coombs, and Schumm's tests remained negative, but haptoglobins were still absent in the serum.

Discussion

At the time of this patient's admission to hospital

the evidence for hæmolysis was not particularly obvious, there being no reticulocytosis, polychromasia or raised serum bilirubin, and the initial diagnostic problem was that of a young man with a megaloblastic anæmia. Hæmolysis was confirmed by a positive Schumm's test, and the transiently positive direct Coombs' test suggests an auto-immune mechanism. Hasty treatment with folic acid or vitamin B₁₂ could have obscured the correct interpretation of the situation, as the delayed reticulocytosis might then have been attributed to the treatment. This case, therefore, illustrates the importance of looking for evidence of an associated hæmolytic anæmia in patients with megaloblastic erythropoiesis.

The short duration of the symptoms, and the absence of a reticulocytosis until several days after admission suggest that the hæmolysis had only developed recently, and that this rapidly produced severe folic acid deficiency. It has been shown that in normal subjects fed on diets deficient in folic acid, the stores of folic acid become sufficiently depleted to give abnormal histidine loading tests in four to six weeks (Knowles, Prankerd and Westall, 1961). It is not remarkable, therefore, that in this patient, who never ate green vegetables, deficiency of folic acid developed rapidly and that after hæmolysis ceased the folic acid deficiency was largely corrected by a normal diet. However, although the development of folic acid deficiency in hæmolytic anæmia has frequently been observed, spontaneous recovery has not been reported previously.

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TWO CASES OF ACUTE IDIOPATHIC CIRCUMSCRIBED GANGRENE

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THE association of peripheral gangrene with diabetic or atherosclerotic vascular disease is well known. Other causes include the action of drugs such as ergot, direct contact by chemicals, frostbite and

burns. Polyarteritis nodosa affecting the arterial tree at any level down to the arterioles may cause gangrene, as may occlusion of the venous blood flow (venous gangrene). These characteristically

affect the tips of the fingers or toes first and spread proximally. Any other distribution is rare. Gangrene of the scrotum (Fournier's disease) or vulva may result solely from infection but these and cancrum oris are now rarely seen. Emboli, usually arising from the left side of the heart, may cause gangrene (while it may occur in myocardial infarction without embolism, as a result of hypotension and vascular spasm (Cohen, 1961)), but these again usually affect the tips of the extremities first.

We describe two cases of cutaneous gangrene with unusual distribution in which none of the above causes could be seen to operate.

Case 1

Mr. C. A., aged 69, a retired decorator, was admitted to hospital on 15.1.61 complaining of severe bruising of the face and arms for 24 hours. He had been well until 10.12.60 when he had had some left pleuritic pain which was treated successfully by his general practitioner (drugs prescribed not known). On 6.1.61 he developed a sore throat with generalized aching pains and a discharging right eye, his temperature being 101.6°F. (38.7°C.). He was treated with tetracycline but a few days later painful blisters appeared on the scrotum and thighs followed by the purple discoloration of the face.

In the past he had been admitted to another hospital (1957) with gangrene of the left ear and part of the skin of the left forearm. This was found to be associated with granulocytopenia and hepatosplenomegaly. On prednisone (60 mg. daily) his white cell count rose from 850 to 4,600 cells/cu.mm. and the skin lesions healed. He was readmitted in March 1959 with recurrent small hæmatemeses, moderate jaundice and persisting hepatosplenomegaly. He had a hæmolytic anaemia with a hæmoglobin of 6.35 g.% (43%) and a positive Coombs' test. He was still taking prednisone. The dosage of prednisone was increased and following some improvement in blood counts a splenectomy was performed, the spleen weighing 250 g. Following operation his blood counts remained satisfactory and prednisone was gradually discontinued. He had remained well until December 1960.

On examination the most striking feature was the multiple purple areas with reddened borders which covered the left ear, left side of the face, right cheek and both upper arms. Similar, though smaller, lesions were present on the forehead, upper lip and right nipple. (Figs. 1 and 2.) There were thin white scars on the left ear and left forearm where the skin had undergone necrosis in 1957. The temperature was 99.6°F., pulse 90/min. and regular, blood pressure 140/90 mm. Hg. and the heart sounds were normal. There was no abnormality of the respiratory or nervous systems. The abdomen was soft, with an incisional hernia of the splenectomy scar; the liver was palpable 3 cm. below the costal margin, but no other masses were palpable. There was a healing bullous eruption of the scrotum.

Investigations: Hb. 13.6 g.% (92%), with a normal white cell and differential count and ESR. The platelet count was also normal and no cold agglutinins were detected in the serum. The serum proteins were 7.7 g./100 ml., with a decrease in the albumin and beta-globulin content. Wassermann and Kahn tests were negative. L.E. cells could not be found in three blood specimens. Urinalysis was normal except for the presence of urobilin in excess. Blood urea 42 mg./100 ml. ECG normal, but the chest X-ray showed shadowing in the left upper lobe.

FIG. 1.—Case 1.

FIG. 2.—Case 2.

He was treated with penicillin, 500,000 units six-hourly, and prednisone, 40 mg./day, but although his temperature returned to normal the skin lesions continued to spread until they were affecting the outer aspects of both arms and legs and the 'butterfly area' of the face. No gangrene occurred on the tips of the fingers or toes. Eight days after admission the deep purple colour of the lesions had been replaced by a dry black gangrene with occasional bullæ which were sterile to culture. The patches of gangrene enlarged relentlessly and the patient lapsed into coma and died on 26.1.61.

Post Mortem Examination. There were scattered patches of skin gangrene on the cheeks, nose, hands,

lower legs and feet. There was severe oedema of the lungs, more marked at the bases than at the apices, and sections showed extensive bronchopneumonia. The surfaces of the mitral and aortic valves were smooth and there was only mild atheroma of the aorta and coronary arteries. There was no thrombus in either atrium, nor was there evidence of old or recent infarction. The other organs showed no significant abnormality; in particular, there was no evidence of infarction in organs other than the skin and no site of embolus formation could be found.

Sections of an early gangrenous patch on the ulnar border of the right hand showed a sharp transition from viable to necrotic epidermis. In the necrotic epidermis occasional nuclei still retained their basophilia and these were mainly in the basal and granular layers. The transition from normal to abnormal dermis was less sharp. The dermal collagen fibres were swollen and there was interstitial hæmorrhage. Just below the junction of normal and necrotic epidermis there was a narrow zone of oedema and neutrophil leucocyte infiltration. Of the veins and arteries some were occluded by mixed thrombi while showing intense congestion. The capillaries were dilated and congested.

Case 2

Mrs. M. W., aged 68, a housewife, was admitted to hospital on 27.4.61. Three weeks before she had developed a crack in the left side of her mouth which had become infected, and also a sore throat. During the time up to her admission her mouth and throat had become increasingly infected and the inflammation was so severe that she was unable to swallow. She also developed a red rash on the outside of both upper arms.

In 1959 she had been treated for thyrotoxicosis by her general practitioner with methyl thiouracil, 50 mg. q.d.s. She stopped taking the drug late in 1960. However, in March 1961 her doctor found further signs of thyrotoxicosis and prescribed some more tablets. Shortly afterwards she began to feel unwell and moved to another town to stay with friends. She continued to take the 'white tablets' until the day of admission; these tablets almost certainly were methyl thiouracil.

On admission she was very ill, temperature 99.6°F. The fauces were inflamed and there was thick pus in the mouth. The cervical lymph nodes were tender and enlarged. There was a purpuric rash on the outer aspect of both upper arms, and Hess's test was strongly positive. The thyroid was not palpable, but there was moderate exophthalmos and a fine tremor of the hands. The pulse was rapid (124/min.) and regular, the blood pressure was 125/70 mm. Hg. and there were no signs of cardiac failure; a soft systolic murmur was heard, maximal at the apex. Examination of the chest was normal. There were no physical signs in the CNS.

Investigations: WBC 1,200/cu.mm., 54% neutrophils and 46% lymphocytes. The platelet count was found, and confirmed, to be 650,000/cu.mm. Hb. 10 gm.% (68%), ESR was 46 mm./hr. (corrected Westergren). Wassermann and Kahn tests negative. Serum proteins 5.7 g./100 ml., electrophoresis showing a big decrease in albumin and an increase in alpha-2 globulin. Blood urea 22 mg./100 ml. The direct Coombs' test was negative and no cold agglutinins were present in the serum. Urinalysis normal apart from an excess of urobilin. ECG: sinus tachycardia only.

A diagnosis of leucopenia due to methyl thiouracil was made. She was given intravenous fluids as she was unable to swallow, and intravenous erythromycin. During the next few days she improved remarkably. Her mouth cleared up completely and she was soon able to take oral fluids. However, on 30.4.61 a painful area of

FIG. 3.—Case 2.

skin necrosis appeared which extended from the knee to the ankle of the right leg and was a dark purple in color. It was not cold to the touch. Further lesions began to appear; these consisted of purple-black patches on the outside of both arms, behind the left knee, on both cheeks, the left nostril and the edges of both ears, as well as the original lesion on the right leg (Fig. 3). The larger lesions became bullous with serous exudate containing a few leucocytes but no organisms.

After the appearance of the necrotic skin lesions, specimens of blood were examined for L.E. cells, and moderate numbers of these were demonstrated. A sternal marrow smear showed normal bone marrow except for a high plasma cell count, consistent with a 'collagen disease'. The white cell count rose to 3,500 cells/cu. mm. with a normal differential count, and remained at this level.

A biopsy was taken of a typical lesion. Histologically this showed necrosis of the epidermis which was confined to the upper half of the rete Malpighi except for a small area centrally where it involved the whole thickness of the epidermis. The necrotic epidermis had separated from the underlying dermis. The dermal veins, but not the arteries, contained fibrinous thrombi which formed endothelium-covered projections into the lumina.

On 2.5.61 the patient was started on prednisone, 40 mg. q.d.s., and from that time started to improve. No further skin lesions appeared, and the steroids were gradually discontinued over the next three months. All the involved skin healed except the largest patch on the right leg, which later required grafting. Three toes on the same leg later had to be amputated. On 18.2.62, however, she became pyrexial, with weakness, malaise and vomiting, and diffuse abdominal pain. Hæmoglobin, serum amylase, serum electrolytes, blood urea and ECG were normal, but the white cell count was slightly raised. Despite intravenous fluids and gastric aspiration she deteriorated rapidly, and it was thought

that she had thrombi in the mesenteric vessels similar to those which had occurred in the skin. She was treated with heparin and phenindione, and given intravenous tetracycline. There was an immediate response to this therapy, but on 24.2.62 she developed atrial fibrillation, which was controlled by digoxin. She was discharged on 21.4.62 but a month later was readmitted with pain in the left cheek, and lumbar pain due to spinal osteoporosis. The latter symptom was relieved by a lumbar corset, anabolic hormones and a high calcium diet. She has now been discharged to an old people's home.

Comment

Reports of similar cases are uncommon. Swarts (1942) described two cases affecting the dorsum of the feet in young men. Both showed similarity to our cases in the sudden onset, the active phase when the purple area becomes vesicular, separation of a gangrenous plaque, and healing in six to eight weeks leaving a white scar. However, our cases both had haematological abnormalities at some stage, i.e. haemolytic anaemia in Case 1 and L.E. cells in Case 2.

The cause of the skin necrosis in these cases is obscure. That both manifested auto-immune processes in the blood might indicate that such a mechanism operated to cause the skin necrosis. Skin necrosis has been reported in disseminated lupus erythematosus (Dubois and Arterberry, 1962)

and in rheumatoid arthritis without L.E. cells in the blood (Bywaters, 1957) but in these there was arteritis affecting the arteries supplying the necrotic skin and the gangrene was of the common distribution commencing at the tips of fingers and toes. Other members of the collagen diseases such as polyarteritis nodosa, thrombotic microangiopathy (Symmers, 1952, 1956) and thrombotic thrombocytopenic purpura seem unlikely as the disease process involved the venules and not the arterioles in Case 2 and in neither case was the platelet count lowered. Drugs might well be to blame, particularly in Case 2, for methyl thiouracil is known to cause both leucopenia and polyarteritis (Richardson, 1961).

Twenty years ago Swarts wrote of his cases: 'I can only speculate as to this peculiar type of cutaneous gangrene. It may be a trophoneurotic phenomenon . . .' While auto-immunity may have played a part in our cases in neither is the cause clear; the features do not correspond completely with any known disease and the resemblance of the cases to each other is incomplete. For this reason we have reported them under the descriptive heading 'Acute idiopathic circumscribed gangrene.'

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TRANVESTISM AND FERTILITY IN A CHROMOSOMAL MOSAIC

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Cross dressing or the wearing of clothes appropriate to the opposite sex was called transvestism in 1910 by Hirschfeld. It is also known as eonism after Chevalier D'Eon de Beaumont, who was a diplomatic agent of Louis XIV and who lived most of his life as a woman. The problem of transvestism is probably a widespread one, particularly amongst men, as is borne out by Hamburger (1953), who received 1,117 letters from distressed patients throughout the western world with features of transvestism. This followed the publication, in the

non-medical Press, of a dramatic case of 'change of sex' treated at his clinic.

Transvestism is known to be linked with fetishism, but the reported frequency of this association varies from author to author. Randell (1959) found only two cases of fetishism amongst 37 male transvestites, while Peabody, Rowe and Wall (1953) underlined the relationship between the two disturbances. Barr and Hobbs (1954) state that transvestism must be distinguished from fetishism. Epstein (1961) suggests the amalgamation of the