Aetiology

The pathological changes in all the cases previously described have been those of areas of necrosis surrounded by a zone of new granulation tissue and a zone of infiltration with inflammatory cells, mainly lymphocytes, with an occasional giant cell. Hargrove *et al.* drew attention to a state of obliterative arteritis affecting the blood vessels beyond the infiltrated area. Stewart (1933b) reviews 10 cases, and in summing up the findings says: "The disease is not one of formation but of destruction." He also draws attention to the complete absence of resistance of the patient to infection. The course of the present case excluded a malignant growth, since the radiotherapy given was not of such dosage as to control a neoplasm. The disease must then be ascribed either to an organism not yet discovered or to an unusual tissue response to infection with known pyogenic organisms.

We believe that the staphylococcus which was found so consistently in the lesion in our case played a prominent part in the cause of the ulceration and was not just a secondary invader. The spread of infection was controlled by aureomycin—rapid extension occurring when the antibiotic was stopped—and during the change-over of treatment to chloramphenicol. When adequate doses of chloramphenicol were given the staphylococcus could not be isolated from the lesion, and healing continued. The slight recurrence was due to infection with a staphylococcus of different sensitivity to antibiotics, and was therefore presumably a fresh strain. This suggests that the granulomatous overgrowth is a non-specific reaction to staphylococcal infection and not to any one particular strain of the organism. Such a theory would explain the occurrence of two attacks separated by an interval of 23 years, as occurred in Hoover's Case 3 and in Lierle's case when a recurrence was precipitated by a blow on the nose. Reinfection with a rare organism would be too great a coincidence. The absence of regional lymph-node enlargement, of leucocytosis, and, in our case, of pyrexia, suggests a failure of the defence mechanism.

That staphylococci are capable of producing indolent inflammatory lesions of the skin has long been known—this is perhaps best characterized by acrodermatitis perstans of Hallopeau; and the common pyogenic granuloma is a good example of exuberant granulation tissue stimulated by staphylococcal infection. Of 17 published cases in which bacteriological findings are given, staphylococci either alone or with streptococci were found in 15: although staphylococci can be isolated by nasal swab from many people, this finding is compatible with our theory.

Summary

A case of progressive granulomatous ulceration of the nose and face is described.

A penicillin-resistant *Staph. pyogenes* was isolated from the lesion, at first in combination with a haemolytic streptococcus and an avirulent corynebacterium; later the staphylococcus was obtained in pure culture.

Aureomycin prevented an extension of the infection, but a staphylococcus sensitive to the drug *in vitro* could still be recovered from the lesion.

Chloramphenicol produced a gradual but complete recovery, with coincident disappearance of the staphylococcus from the ulcer.

The aetiology of the condition is discussed and the suggestion put forward that it is a non-specific but unusual response to staphylococcal infection.

It is suggested that chloramphenicol may be as good as, if not superior to, aureomycin in the treatment of staphylococcal infections.

We should like to express our thanks to Mr. J. H. Cobb for his co-operation and for drawing our attention to the previously published work on the subject.

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PURPURA AND PANCYTOPENIA COMPLICATING ARSENOTHERAPY

BY

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Purpura and other blood disorders are rare complications of the treatment of syphilis by organic arsenicals. The possibility that these drugs might be responsible for the purpuric manifestations was suggested by Labbé and Langlois (1919) only nine years after their introduction. The first to be incriminated was arsphenamine, and Loveman (1932) described 14 cases in the literature up to that date, and added one case of his own which showed a pancytopenia, with thrombocytopenic purpura, agranulocytosis, and aplastic anaemia. Falconer and Epstein (1940) described eight of their own cases of purpura occurring during arsenical treatment. All the organic arsenicals employed in the treatment of syphilis have been suspect, but neoarsphenamine has been involved more often than any other—in part, perhaps, because of its more widespread use. "Mapharsen" was introduced in 1936, but purpura associated with this form of arsenical has been relatively uncommon. However, Wintrobe (1946) mentions having seen three cases, and one further case was reported by Schwartz and Vonder Heide (1945).

Though these complications of arsenotherapy are rare, four cases were admitted to the Royal Victoria Hospital during a period of nine months. These cases had a similar clinical picture but somewhat dissimilar haematological findings, and three ended fatally. These cases are thought worthy of record.

Case 1

A married woman aged 30, with one child aged 8, was first seen by her doctor in July, 1948, having a sore on the vulva. This was treated with penicillin ointment locally and a sulphonamide by mouth; her blood was serologically positive for syphilis. She was referred to the V.D. out-patient department, but refused examination. She was seen again in August, when she had developed a copper-coloured rash, which had been noticed for one day. It was distributed over the chest and abdomen, and to a less extent on the arms and inner sides of the thighs. The cervical and inguinal lymph nodes were enlarged. A small ulcer present on the vulva showed *Treponema pallidum* on dark-ground examination. Her Kahn reaction was ++++, W.R. ++, and Dreyer reading 108. She denied extramarital intercourse, but stated that her husband, who was in the Army, had been home on leave in May of that year.

Penicillin treatment, 3,000,000 units in 10 days, was given. This was followed by courses of combined bismuth and arsenic injections. Over a period of somewhat less than a year she received 3 g. of bismuth, 0.86 g. of mapharsen, and 7.2 g. of neoarsphenamine. Serological tests for syphilis were negative in January, 1949. During the third course of

arsenic and bismuth, in March, 1949, she noticed a dark rash on her body and bleeding from her gums, and she was immediately admitted to the hospital.

On examination she was seen to be a somewhat pale woman of average height and normal build. An extensive petechial rash, almost confluent, was scattered over her face, arms, and legs, being most extensive on the limbs. She was bleeding from her gum margins, and numerous blood-filled vesicles were seen in her mouth. There was no haemoptysis, haematuria, haematemesis, or melaena. Her liver and spleen were not palpably enlarged and there were no haemorrhages into her optic fundi. Pulse was normal, and blood pressure 90/70 mm. Hg. Her blood showed a prolonged bleeding-time and a thrombocytopenia without gross anaemia or leucopenia (see Table).

Penicillin was started, but had to be discontinued after one day because of the development of haematomata at the sites of injection. On the day after admission she had a slight haematemesis and melaena, but the purpuric rash began to fade, and in the absence of further evidence of bleeding no treatment was given. The patient was discharged completely well seven days after admission.

Findings in the Blood of Case 1

	At Onset	After Recovery
Haemoglobin (g./100 ml.)	12·0	17·0
R.B.C. (per c.mm.)	4,300,000	5,950,000
W.B.C. (per c.mm.)	5,700	5,700
Platelet count (per c.mm.)	54,000	240,000
Bleeding-time	25 minutes	3 minutes
Clotting-time	10	11 ,,
Prothrombin	100%	—
Capillary fragility	Increased	Normal

At biopsy the bone marrow had a total nucleated count of 44,000 cells per c.mm., but the myeloid and erythroid series showed a normal average differential count. There was no eosinophilia suggestive of an allergic reaction. The megakaryocytes were found to be reduced. They averaged 1 per 10,000 nucleated cells of the bone marrow, as against the normal average of 17 per 10,000, and showed a slight reduction of mature megakaryocytes capable of active platelet production.

Case 2

A merchant seaman aged 26 noticed a sore on his penis when in Indo-China in November, 1948. He was referred to a hospital in Saigon, where *Tr. pallidum* was found in the penile sore. He was then referred to Singapore, where he received a combined course of arsenic and bismuth to a total of 6 g. of neoarsphenamine and 1 g. of bismuth. He returned to this country and first appeared in the venereal diseases out-patient department of the Royal Victoria Hospital in April, 1949. The ulcer had now healed and serological tests for syphilis were entirely negative. He received a course of penicillin consisting of 6,000,000 units in 10 days, after which arsenic and bismuth injections were then recommenced. He was given 2.1 g. of "stabilarsan," 2.25 g. of neoarsphenamine, and 1 g. of bismuth.

In July he noticed that he bruised readily, that he had developed a generalized dark rash over his body, that his gums bled readily, and that his urine was dark red in colour. He did not appear to be ill on admission, and was alert, co-operative, and intelligent. He was not anaemic, cyanosed, or jaundiced. There was a general petechial rash on his trunk and limbs, and he was bleeding freely from his gum margins. The urine was a dark reddish colour, and on examination contained albumin and red blood cells. The liver and spleen were not palpably enlarged, and nothing abnormal was found on physical examination of the other bodily systems.

Examination of the blood showed a normochromic anaemia, haemoglobin 9.5 g./100 ml., a leucopenia (3,600 per c.mm.), a slight thrombocytopenia, and a prolonged bleeding-time. Bone-marrow biopsy revealed a marrow hypoplasia.

To relieve the purpura the patient was transfused with 1 pint (570 ml.) of perfectly fresh compatible blood. The next day he was much better and the purpura had almost completely disappeared. Three days later, however, the bleeding from the gums recommenced and fresh purpuric spots appeared on the thighs. A further pint (570 ml.) of fresh blood was transfused. Eight days after admission tonsillitis developed and examination of the blood again showed a normochromic anaemia with a leucopenia (1,900 per c.mm.) and agranulocytosis with thrombocytopenia. One pint (570 ml.) of blood was withdrawn from a case of chronic myeloid leukaemia under treatment in the wards (W.B.C. 112,000 per c.mm.), tested for compatibility, and this was transfused into the patient. This did not produce any significant rise in the neutrophil polymorphs of the peripheral blood. The patient had been on penicillin since the onset. A swab of the tonsillar area gave a pure growth of a streptomycin-sensitive *Bact. coli*, and penicillin was therefore stopped and streptomycin therapy instituted on his ninth day in hospital. Two days later he was clinically very much better; his throat was easier and less inflamed, and the purpura had subsided. On the following day, however, an ecchymosis developed on the left eyelid and spread to involve the whole of the left orbit, and this was followed two days later by a haematemesis, after which the patient became very shocked and cold. Evidence of cerebral involvement quickly followed with severe headache and stiffness and rigidity of the neck. Despite the transfusion of 2 pints (1.14 litres) of fresh blood the patient drifted into coma and died.

Post-mortem Summary.—Aplastic anaemia and purpuric haemorrhages into heart, renal pelves, skin, stomach, and brain, following arsenical therapy. Aplasia of vertebral marrow, confirmed histologically. The immediate cause of death was a massive intracerebral haemorrhage into the cerebellum and occipital lobes of the cerebrum, with subarachnoid extension into the posterior fossa. There was associated cerebral oedema and bilateral tentorial herniation, but no evidence of any disease of the cerebral vessels.

Case 3

A man aged 37 first attended the venereal diseases out-patient department of the Royal Victoria Hospital in March, 1947. His wife, who had sero-positive syphilis, was already attending at this time. He himself had no complaints; no history of gonorrhoea or syphilis, and the last extramarital exposure had occurred four years previously. On examination there were no clinical signs suggestive of syphilis, and serological tests for syphilis were negative. His cerebrospinal fluid was found to be normal. Accordingly no treatment was instituted, but he was kept under observation. In March, 1949, serological tests were positive: Kahn +++, W.R. ++, and Dreyer reading 5.4, and he received a ten-day course of intramuscular injections of penicillin to a total of 6,000,000 units. This was followed by combined courses of arsenic and bismuth injections, and at the end of the second course the serological tests for syphilis were again negative.

When the patient reported for the third injection of his third course in September, 1949, petechial haemorrhages were noted on the skin and he was admitted to hospital. By this time he had received 7.65 g. of neoarsphenamine and 1.8 g. of bismuth. He stated on admission that he had been feeling vaguely unwell for about two months. For about the same time he had also noticed a rash on his face and hands. This had been treated by his own doctor with penicillin cream, gentian violet, and other remedies, without benefit. He complained of some aching in his abdomen and of low back pain. Petechial spots had been noted for a few days before admission and he had had one attack of severe epistaxis. He was an epileptic and had been on phenobarbitone, ½ gr. (32 mg.), night and morning since he was 14. He had received no other drugs, and had suffered from no illnesses apart from an attack of pneumonia in 1937.

Examination showed that he was well nourished, with some pallor of his mucous surfaces. Papular and excoriated eczematous lesions with crusting were present on his beard region, especially on the left side of the chin, with enlargement of the submental lymph nodes. Chronic scaly fissured patches were present on the webs of the thumb and index fingers of both hands, and there were a few patches on the legs. This was considered to be an arsenical dermatitis. Numerous petechiae were scattered over both legs below the knee, with less numerous patches on the back, shoulders, and buccal mucosa. The tongue showed a few petechiae, and there was slight bloody oozing from the gums. The spleen was not palpably enlarged and there were no other bodily abnormalities. Examination of the blood on admission showed: haemoglobin, 10.6 g.%; red cells, 3,230,000; white cells, 2,300 (polymorphs 8%); platelets, 86,000; bleeding-time, 15 minutes; clotting-time, 4 minutes; capillary fragility, positive. Bone-marrow biopsy showed a grossly aplastic marrow with 3% developing myelocytic cells and 2% normoblasts.

A course of dimercaprol (B.A.L.), 1.2 g. in six days, was given. This had little effect on the arsenical dermatitis and none on the marrow aplasia. On the day after admission he was transfused with 1 pint (570 ml.) of fresh compatible whole blood. The next day he complained of a sore throat, and a necrotic ulcer was found on the right tonsil. This was associated with a pyrexia of 101° F. (38.3° C.). A swab from the ulcer showed no microscopical evidence of fusospirochaetes, but on culture gave a profuse growth of penicillin-sensitive haemolytic streptococci. The faucial condition improved and the temperature fell in 24 hours on intramuscular injections of penicillin, 500,000 units daily. On the eighth day another pint (570 ml.) of compatible fresh blood was given, to which he had a pyrexial reaction—temperature 101° F. (38.3° C.)—but without haemoglobinuria. The following day he complained of crampy abdominal pain, with pain and tenderness in the right iliac fossa but no rigidity. This was associated with melaena.

He was maintained with blood transfusions, but on the thirteenth day in hospital he had a haematemesis of about 1 pint (570 ml.). The melaena persisted and blood clots appeared in the faeces. He looked ill and drawn, had abdominal pain, and the abdominal tenderness became more marked. It was considered that he had probably developed an intramural haemorrhage into the intestinal tract. Despite the transfusions his condition deteriorated and he died on the fourteenth day after admission to hospital.

Post-mortem Summary.—Aplastic anaemia following arsphenamine therapy, generalized purpuric haemorrhages into skin, lungs, heart, kidneys, and intestines. Oedema of lungs. The immediate cause of death was massive haemorrhage into the intestinal tract, which was associated with a gross intramural haemorrhage into the hepatic flexure region of the colon, with extension into the perinephric fat of the right kidney. The brain was remarkably free from any evidence of petechial haemorrhages. The bone marrow showed extensive replacement with fat, and only a few basic reticulum cells, plasma cells, and lymphocytes were present.

Case 4

A woman aged 48, with a family of six children, all alive and well, plus one child who died eight years previously, had no history of miscarriages, though her husband had been attending the venereal diseases department since 1939, originally with a sore on the penis and with Kahn ++ and W.R. +++. In January, 1949, she also attended the department with perforation of the hard palate, the only other physical findings on complete examination being the presence of hyperkeratosis of the feet and leucoderma colli. Serological tests were: Kahn ++ and W.R.++. She received three courses of treatment consisting of 13.65 g. of neoarsphenamine and 3 g. of bismuth. The tests remained strongly positive throughout the therapy.

One month after antisyphilitic therapy was started it was noticed that the patient was somewhat anaemic. Examination of the peripheral blood revealed haemoglobin 77% (Haldane) and red cell count, 4,200,000, so she was put on ferri sulph. co. (*N.F.*) 3 gr. thrice daily. The anaemia did not respond to this, and in November, 1949, she was admitted to hospital with severe pallor, nausea, and anorexia, a feeeling of tiredness, and breathlessness on exertion.

Examination showed her to be pale, anaemic, well nourished, and without enlargement of the superficial lymph nodes. She was breathless on the slightest exertion, somewhat listless, but co-operative. The tongue was smooth and the abdomen lax. The spleen was enlarged two fingerbreadths below the costal margin, but the liver was not palpable. Pulse rate was 90 and B.P. 140/90. The heart showed some enlargement to the right, with a harsh systolic murmur at the apex. On admission the haemoglobin was 21% (Haldane) (3.1 g./100 ml.), red cell count 950,000, white cell count 575, of which 63% were neutrophils. Van den Bergh 1.25 mg. per 100 ml. Bleeding and coagulation times were within normal range. The bone marrow showed aplasia, with marked reduction in the erythropoietic series.

Repeated transfusions of fresh whole blood and a course of dimercaprol were given. She also received injections of 20 μg. of vitamin B_{12}, one ampoule of vitamin K, and 300 mg. of ascorbic acid daily. Six transfusions brought no significant reaction. The seventh transfusion resulted in a marked rigor, so transfusion was stopped. There was no significant improvement in the haematological picture despite the therapy: the white cell count remained low, the haemoglobin ranged between 50% and 29%, and there was constant thrombocytopenia. The patient gradually deteriorated, and died on the 28th day after admission.

Post-mortem Summary.—Aplastic anaemia, haemosiderosis of spleen, slight haemosiderosis of liver, chronic pyelonephritis, and cystitis. The bone marrow showed marked aplastic replacement of both erythroid and myeloid series of cells by fatty tissue.

Discussion

Case 1 is a pure thrombocytopenic reaction to arsphenamine, however this is produced. It showed the characteristic findings peculiar to this type of case—namely, free bleeding from mucous surface, marked fall in circulating platelets, and increased capillary fragility as shown by skin purpura and a positive Hess test. The bone marrow showed no abnormality of the myeloid or erythroid series, and no evidence of the eosinophilia which is usually present in allergic disorders affecting the bone marrow. The megakaryocytes were depressed—few in number, and with maturation arrest—suggesting a direct toxic effect of the drug on the mother cells of the circulating blood platelets. As in most cases of this type, there was a rapid and spontaneous return to normal associated with a rise in the platelet count, which usually begins in 24–48 hours and returns to normal in four to seven days. This good prognosis has been noted in all cases showing this complication of arsenical treatment, and so far no fatalities have been recorded. This differs from the other blood reactions to arsenicals.

Cases 2 and 3 at the onset superficially resembled Case 1, since they developed melaena with bleeding into the skin during the treatment of syphilis with standard courses of bismuth and arsenic by weekly injection. They showed a mild degree of anaemia, with moderate leucopenia, mainly affecting the polymorphonuclear leucocytes, a thrombocytopenia, and prolonged bleeding-time. Despite treatment the haemorrhagic diathesis persisted and the leucopenia progressed to an agranulocytosis with pyrexia and faucial manifestations. This peripheral pancytopenia was associated with a marked aplasia of the bone marrow (panmyelopathy), which affected all elements and was unassociated with any increase in the eosinophil myelocytes, whose increase would have suggested a possible allergic basis for the bone-marrow inhibition. This tendency to massive rather than selective damage of the bone marrow by organic arsenicals has been noted by Plum (1937), who showed that of 47 cases with leucopenia 33 were associated with anaemia or thrombo-

cytopenia. He also pointed out that in arsenical agranulocytosis, in contradistinction to agranulocytosis produced by other heavy metals, there were a relatively high leucocyte count at the onset; a lower age incidence, and a higher incidence in males.

It has been established that heavy metals (including arsenic and gold) exert their toxic effects on a biological system by reacting with the sulphydryl groups of the protein fraction of cellular enzymes to form mercaptides. The sulphydryl groups in the dithiol B.A.L. (dimercaprol; 2:3-dimercaptopropanol) compete with the dithiol protein–metal complex in the tissues, thus combining with and eliminating the offending metal. This restores the enzyme system. The therapeutic efficacy of dimercaprol in some of the toxic manifestations of arsenical poisoning has been dramatic. Its effect on arsenical dermatitis has been good (Carlton *et al.*, 1948), and on gold thrombocytopenia and granulocytopenia encouraging (Lockie *et al.*, 1947; Cohen *et al.*, 1947; Ragan and Boots, 1947).

The results of dimercaprol therapy on the haematological disturbances occurring during arsenotherapy are variable. In 12 cases of agranulocytosis following intensive arsenic treatment for syphilis Fisher, Holley, and Fein (1947) reported good results with combined therapy including dimercaprol. Eagle (1946) treated 11 cases of arsenical agranulocytosis with dimercaprol, and 10 recovered; he found, however, that dimercaprol had no beneficial effect on three cases of aplastic anaemia caused by arsenic poisoning.

The first of our cases (Case 2) with agranulocytosis (and aplastic anaemia) did not receive dimercaprol, while the second (Case 3) was given a course of intramuscular injections of dimercaprol in oil to a total of 1.2 g. spread over six days. There was no essential difference in the clinical course of these two cases and no rise in the peripheral cellular counts of the blood, and both ended fatally. The fact that the associated arsenical dermatitis in Case 3 did not respond to dimercaprol suggests that the condition was of long standing (cf. Eagle, 1946). The damage to the bone marrow was severe, as it showed very few developing cells of either the myeloid or the erythroid series, and may have been irreversible.

Case 4 presented as a gross aplastic anaemia from the onset, and purpuric manifestations were not observed, although the platelet count was uniformly low. Despite blood transfusions, oral iron and ascorbic acid, and injections of vitamin B_{12} and of dimercaprol she showed no clinical or haematological response and her condition proceeded inexorably to a fatal termination.

At the onset the clinical manifestations of a thrombocytopenic purpura of toxic origin are essentially similar to those encountered in the more severe cases of toxic pancytopenia in which all elements of the bone marrow are depressed. Yet the former has a good prognosis and the latter a uniformly poor one. As a case of toxic pancytopenia develops, the initial purpura becomes associated with a gradually increasing anaemia and a leucopenia which proceeds to agranulocytosis. If such severe bone-marrow damage occurs during anti-syphilitic therapy with heavy metals it appears that the prognosis is poor, despite treatment with dimercaprol. All cases of purpura developing during treatment for syphilis should be followed carefully, with repeated blood examinations, to distinguish between the benign and fatal forms which may arise during arsenotherapy.

Summary

Four cases of blood dyscrasia resulting from the toxic effects of organic arsenicals are presented.

One case of toxic thrombocytopenic purpura recovered spontaneously.

The three other cases showed a pancytopenia with marrow aplasia and ended fatally.

The administration of dimercaprol to two of the cases had no apparent effect on the severe toxic manifestations.

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CARCINOMA OF THE ADRENAL CORTEX WITH ENDOCRINE MANIFESTATIONS

REPORT OF A CASE

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Functioning adrenal cortical tumours can produce various clinical pictures. In women, a group of symptoms associated with virilism is referred to as the adrenogenital syndrome. When such abnormalities as obesity, decreased sugar tolerance, hypertension, amenorrhoea, and hirsuties appear without virilism the name Cushing's syndrome is employed. Considerable overlapping occurs, and cases of adrenocortical tumour may show features of both syndromes.

An unusual case is described below in which hirsuties, obesity, and cutaneous striae appeared in a girl before puberty, and in whom menstruation began normally and continued regularly until six months before her death from a metastasizing tumour of the right adrenal cortex. Virilism was absent and carbohydrate metabolism was normal.

Case Report

The patient, a social worker, was one of 12 children. Both parents were short and stout, and one grandmother was said to be exceedingly fat. She herself was plump from infancy, but not excessively so. At 8½ years she weighed 61 lb. (27.7 kg.). At 10 years pubic and axillary hair appeared. She was then sent to the London Hospital on account of obesity—weight 95 lb. (43 kg.), height 4 ft. 3 in. (129.5 cm.)—and was dieted. The following year increasing obesity made further schooling impossible. Striae appeared in the loins, and the pubic hair assumed the male distribution. She complained of occasional migrainous headaches.

A year later, aged 12, she entered hospital with pain in the left loin. Examination showed marked obesity; weight 104 lb. (47.2 kg.), height 4 ft. 4 in. (132 cm.), rubicund facies, pubic hair extending to umbilicus, with fine dark hair over shoulders and arms (Fig. 2*a*). Blood pressure was 135/95 to 150/80. Investigations showed: blood urea, 21 mg. per 100 ml.; normal intravenous pyelogram and urea-concentration test; cerebrospinal fluid normal; fundi, visual fields, and radiograph of pituitary fossa normal. Radiography showed no cardiac enlargement. In view of the