Discussion

Although none of the cases recorded by Rauchwerger *et al.* had had less than eight months' exposure to streptomycin before they developed skin lesions, Strauss and Warring recorded one case after only one month. In our own cases symptoms developed between six weeks and six months after the exposure to streptomycin began. The sites of the lesions have been much the same in all three series, though our cases are remarkable in that the hands or fingers were affected in only one of the four.

Rauchwerger and his colleagues considered that intradermal tests were more reliable than patch tests and were negative in those not exposed to streptomycin. We also had no positive reactions in the controls.

An exacerbation of the lesions during the skin reaction to the patch test occurred in three out of four of Strauss and Warring's cases and to the intradermal test in at least one of those recorded by Rauchwerger *et al.* A definite flare-up was seen in three of our four cases during the intradermal test, and the development of a rash on the wrist in the fourth case may have been a similar manifestation.

We consider that the occurrence of both local and general reactions in the four nurses on skin testing supports the clinical impression that their skin lesions were due to handling streptomycin.

Prevention.—Nurses and others should be warned to avoid soiling their skin with the powder or solution and instructed to wear rubber gloves when handling streptomycin. They should wash their gloves, hands, and arms thoroughly afterwards. It appears that, even if sensitized, a nurse can continue to work with streptomycin if these precautions are taken (Strauss and Warring, 1947). Skin-sensitivity tests should be done to confirm suspected streptomycin sensitivity and those proved sensitive warned to take full precautions and to inform the doctor of the sensitivity if streptomycin should ever be advised for them as patients.

Summary

Four nurses out of approximately 80 handling streptomycin at Brompton Hospital, London, during a period of 18 months, developed a dermatitis. Their exposure varied from six weeks to six months.

The dermatitis consisted of an itchy papular erythema of the skin round the eyes and over the elbow flexures. In only one nurse were the hands involved.

Skin-sensitivity tests, using 50 µg. of streptomycin in 0.1 ml. of saline, were positive in the four affected nurses but negative in controls.

People handling streptomycin should wear rubber gloves and avoid soiling their skin with the material.

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Specific recommendations for combating malaria on a world-wide scale were drawn up by the Expert Committee on Malaria of the World Health Organization, which met in Washington, D.C., on May 19–25. Its report outlines methods to implement the policy already advanced by the W.H.O. The Committee on Malaria was presided over by Dr. Arnaldo Gebaldon (Venezuela). Among the members who attended were Major-General Sir Gordon Covell (United Kingdom), Dr. Paul F. Russell (U.S.A.), Medical General Marcel Vaucel (France), and Dr. D. K. Viswanathan (India). Dr. Wallace R. Aykroyd officially represented the Food and Agriculture Organization on the committee, and Dr. Emilio Pampana, of the W.H.O., acted as secretary. Attending as observers for the Pan-American Malaria Commission were Dr. Carlos A. Alvarado (Argentina), Dr. Paulo C. A. Antunes (Brazil), and Dr. Luis Vargas (Mexico).

IDIOPATHIC HYPERSPLENISM

REPORT OF A CASE

BY

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Recent work has thrown more light on the functions of the spleen in regulating the levels of the three formed elements in the blood—red cells, white cells, and platelets.

The destructive action of the spleen on the white blood cells is stressed by Wiseman and Doan (1939), who described three cases of chronic neutropenia with oral ulceration associated with splenomegaly. Along with this neutropenia were variable purpura and thrombocytopenia. The bone-marrow, in contrast to the peripheral blood picture, showed a pronounced hyperplasia. Removal of the spleen resulted in a return of the white cell count to normal, and examination of the spleen by supravital methods showed excessive phagocytosis of neutrophils by clasmatocytes. These workers termed this condition chronic splenic neutropenia. Two further cases were described by them in 1942. Similar cases have since been recorded by others. Langston *et al.* (1945) found evidence of excessive phagocytosis in their case, and Muether *et al.* (1941), describing one case, found groups of degenerate white cells lying free in the splenic sinuses. Doan and Wright (1946) consider that a similar splenic effect on platelets is the cause of thrombocytopenic purpura.

A destructive action on the red cells has also been described. Doan and Wright (1946) described two cases of "splenic panhaematopenia" and charted the haematological findings in five others. Panmyeloid hyperplasia was a feature in these cases. Splenectomy resulted in a return of the blood picture to normal. These workers found diffuse endothelial hyperplasia in the splenic sinuses and evidence of excessive sequestration and destruction of red cells, white cells, and platelets in supravital sections of the spleen.

Doan (1945) and Doan and Wright (1946) believe that selective destruction by the spleen of red cells leads to congenital acholuric jaundice, of white cells to chronic splenic neutropenia, and of platelets to thrombocytopenic purpura. These blood elements may be involved singly or in combination.

Similar clinical pictures have been described by others, who, however, have failed to find evidence of excessive splenic destruction of the circulating blood elements. These others believe that the main factor is an inhibitory action of the spleen on the marrow. Singer, Dameshek, and Miller (1941), studying the effect of splenectomy on the blood picture in a variety of conditions, came to the conclusion that the spleen exerts some influence on haemopoiesis.

Rogers and Hall (1945) and Salzer *et al.* (1945), each describing one case of chronic neutropenia relieved by splenectomy, could find no evidence of excessive phagocytosis of granulocytes. Splenomegaly in various other unrelated conditions may also be accompanied by leucopenia. Engelbreth-Holm (1938), in his study of tuberculous splenomegaly, noted the association of anaemia and leucopenia with a hyperplastic marrow which returned to normal after splenectomy. Schousboe (1940) described similar findings in lymphogranulomatosis and syphilitic cirrhosis with splenomegaly and anaemia. These authors suggested a splenic control of the emission of cells from the marrow.

Dameshek and Miller (1946) studied the bone marrow in cases of idiopathic thrombocytopenic purpura before

and after splenectomy. Before splenectomy they found a greatly increased number of megakaryocytes in the marrow. Platelet production was evident in only a small proportion of them compared with normal controls. After splenectomy a high proportion of the megakaryocytes showed platelet production and the platelet count rose. These workers suggested an inhibitory splenic effect on platelet production. This concept might be extended to include an inhibitory effect on other haemopoietic tissues.

It seems evident that an effect on the maturation of the blood cells may be an outstanding feature of this so-called hypersplenism. The following case is presented as an apparent example of this condition.

Case Record

An unmarried dairymaid aged 45 was admitted to Aberdeen Royal Infirmary on Dec. 30, 1946, under the care of Prof. R. S. Aitken. She had enjoyed excellent health until three months before admission, when she began to tire more easily, felt weak, and her skin became yellow. She complained of breathlessness and palpitation on exertion and intermittent oedema of the ankles. Menstruation was scanty. All these symptoms became progressively more severe. In the month before admission she had been receiving large doses of "anahaemin" and other liver extracts without improvement. Past history and family history were not relevant. Her diet had always been satisfactory.

Examination revealed a heavily built woman with a slightly yellowish tint of the skin and sclerae. There was some diffuse brown pigmentation of the backs of the hands, the extensor aspects of the elbows, and the patellar regions. There were a few discrete brown spots on the face, but none was seen inside the mouth. The mucous membranes were pale. The nails were slightly brittle and the hair was coarse. The tongue was normal. The neck veins were distended 2 cm. above the sternal angle, and there was slight oedema over the sacral and pretibial regions. No abnormality was detected in the heart or lungs. The blood pressure was 142/80. The spleen was palpable and firm, two fingerbreadths below the costal margin. The liver edge was not felt. Two small retinal haemorrhages were noted. The urine contained a trace of urobilinogen. Physical examination was otherwise negative. The blood picture was as follows: red cells, 1,030,000 per c.mm.; haemoglobin, 24% (Haldane); colour index, 1.16; reticulocytes, 2.4%; white cells, 2,800 per c.mm. (polymorphs 64%, lymphocytes 19%, monocytes 17%). The red cells showed moderate anisocytosis; there were some macrocytes and microcytes, but most were normal. Red-cell fragility was normal. The platelet count was not done at this time, but later it was found to vary between 147,000 and 205,000 per c.mm. Examination of the sternal marrow by aspiration showed a marked normoblastic hyperplasia: myeloblasts 0.8%, premyelocytes 4.4%, myelocytes (neutrophils 11.2%, eosinophils 2%), metamyelocytes (neutrophils 24%, eosinophils 1.2%), segmented forms (neutrophils 4.8%, eosinophils 0.8%), lymphocytes 7.2%, haemocytoblasts 3.6%, normoblasts 40%. Detailed haematological findings are given in the Table. A fractional test meal showed a normal acid curve. The icterus index was 12. A galactose-tolerance test gave a normal result. Other investigations included blood Wassermann reaction, radiograph of chest and oesophagus, repeated stool examinations for occult blood, blood-sugar curve, fat-balance test, estimations of plasma proteins, serum chlorides, potassium, sodium, and the blood urea. All gave normal or

negative results. Full doses of anahaemin by injection and proteolysed liver and iron by mouth for three weeks did not alter the blood picture or produce a significant reticulocyte response (see Table). Blood transfusions were given on Jan. 6, 1947, and again on Feb. 5. The blood count gradually returned to its previous level after each one. The diffuse brown pigmentation appeared to increase slightly, but the patient's general condition remained unchanged.

Splenectomy was carried out on April 3 by Mr. Andrew Fowler. Transfusions of packed cells given before and after operation raised the haemoglobin to 70%. At operation the liver was found to be of normal size; the surface was quite smooth and of normal consistency. There was no thrombosis of the splenic vein. Convalescence was uneventful and the patient was discharged home on April 18.

On Dec. 10 (eight months after operation) she was well and was undertaking moderately heavy farm work. The blood picture showed: red cells 3,380,000 per c.mm.; Hb, 76%; C.I., 1.12; reticulocytes, 2.8%; white cells, 5,700 per c.mm.; platelets, 485,000 per c.mm. The red cells showed some anisocytosis, some macrocytosis and hypochromia. A few Howell-Jolly bodies were present.

The patient was seen again on April 7, 1948, when she was feeling very well and was undertaking normal work. Blood examination showed: Hb, 98% (Haldane); red cells, 4,460,000 per c.mm.; C.I., 1.1; reticulocytes, less than 1%; white cells, 7,800 per c.mm.; platelets, 347,500 per c.mm. Examination of the film showed slight but definite macrocytosis with numerous Howell-Jolly bodies.

*Pathological Report on the Spleen (Dr. W. M. Davidson).—*The spleen weighs 470 g. and is therefore some three times the normal weight. It has a firm consistency and a deeply congested cut surface, flecked with prominent glassy nodules about 1 mm. in diameter. These are regularly distributed and represent Malpighian corpuscles. Microscopically there are only two features of note: the very active germ centres in the Malpighian corpuscles and the presence of a moderate amount of iron pigment. Erythrophagocytosis and haemopoiesis are not features. The splenic findings are not typical of a haemolytic anaemia of the acholuric type.

Discussion

The diagnosis in this case presented many difficulties. The presence of gross anaemia in the absence of gastrointestinal bleeding and the apparently normal liver at operation were against Banti's syndrome. As liver biopsy was not carried out it is not known whether it was histologically normal, but microscopically the spleen did not suggest congestive splenomegaly.

Acquired haemolytic anaemia was another possible diagnosis. Although studies of the haemolysin content of the blood were not made, it was thought that a haemolytic process severe enough to reduce the haemoglobin to 24% would result in a high reticulocyte count. The association of a hyperplastic marrow with a reticulocyte count which was only slightly raised did not seem compatible with this diagnosis, and the spleen did not show the microscopical appearances of haemolytic icterus. Also, apart from a trace of urobilinogen in the urine and a slightly raised icterus index, there was no evidence of a high rate of blood destruction.

Haematological Findings

Date:	31/12/46	3/1/47	15/1	30/1	9/2	28/2	6/3	19/3	31/3	3/4	4/4	9/4	8/5	30/5	18/6	20/8	10/12
R.B.C.millions/c.mm.	1.03	1.37	1.62	1.20	2.80	2.37	2.37	2.0	1.62	3.10	—	—	3.10	2.90	2.84	3.20	3.38
Hb % (Haldane)	24	28	36	30	58	46	48	40	36	64	74	78	70	70	68	80	76
Reticulocytes %	2.4	9.5	5.5	4.7	2.5	—	4.7	—	4.5	5.7	5.7	0.5	5	3.5	2.3	<1%	2.8
Platelets/c.mm.				162,500	205,000					147,500	280,000	350,000	515,000	405,000	375,000	307,000	485,000
W.B.C./c.mm.	2,800		1,700	2,400	3,400				3,400	9,600	14,400	3,400	7,400	5,700	13,800	5,000	5,700
Neutrophils %	64		56										64	37	37	37	
Lymphocytes %	17		34										24	40	44	44	
Mononuclears %	17		8										11	23	18		

Blood transfusions were given: 1 pint (568 ml.) whole blood on Jan. 6, 2 pints (1,136 ml.) of packed cells on Feb. 5, 2 pints packed cells and 2 pints whole blood on April 3-4. Full doses of liver extract by injection and proteolysed liver and iron by mouth were given from Dec. 31, 1946, to Jan. 24, 1947.

Haemochromatosis with pigmentation may result in refractory anaemia (Bomford and Rhoads, 1941). No other features of this condition could be demonstrated, and injection of a weak solution of potassium ferricyanide and hydrochloric acid into the skin (Fishback, 1939) produced no iron reaction.

On the evidence available it is difficult to be dogmatic on the aetiology of this condition. The association of a normoblastic marrow with macrocytes in the circulating blood suggested a defect in maturation, in that haemoglobinization of immature normoblasts was occurring. It is of interest to note that a degree of macrocytosis was still present after splenectomy. This indicates that splenectomy has not resulted in a complete return of maturation to normal. The improvement in the blood picture after splenectomy suggests, however, that the spleen was at least partially responsible. This fact seems definite, but any other deduction would be speculative.

It has not been possible in the above case to demonstrate the excessive destruction in the spleen of formed elements which Doan and Wright (1946) and other workers stress. The evidence here supports those who hold that the spleen in such cases exerts an inhibitory effect on maturation. There may, however, have been some increased destruction of abnormal formed elements.

Whatever the cause, removal of the spleen resulted in a great improvement in the blood picture and in the patient's general condition, although it did not result in complete haematological recovery. It enabled a woman with an anaemia so gross as to render her a bedridden invalid, with oedema, and with a 2-cm. congestion of her neck veins to lead an active life. In view of the beneficial effects of splenectomy it is important that cases of this type be recognized.

A suitable name for this condition is difficult to choose. American workers have used such terms as "splenic pannaematopenia" and "idiopathic hypersplenism." Until the cause has been defined the latter seems suitable. Unfortunately the simple term "splenic anaemia" is inappropriate because of its association with Banti's syndrome.

Summary

A case is described of gross anaemia, leucopenia, and splenomegaly associated with a normoblastic marrow picture.

Splenectomy partially relieved the condition.

The pathogenesis is discussed but no definite conclusion is reached.

I wish to thank Prof. R. S. Aitken for permission to record this case, Dr. H. W. Fullerton and Prof. A. Kekwick for much helpful advice and criticism, and Dr. W. M. Davidson for the pathological report.

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PEPTIC ULCER DURING PREGNANCY WITH A REPORT OF A CASE OF PERFORATION

BY

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Although complaints of indigestion are common among expectant mothers the association of peptic ulcer with pregnancy is believed to be most unusual. During the period 1928–37 Sandweiss *et al.* (1943) discovered only one case of proved duodenal ulcer in 70,310 pregnancies collected from five hospitals in Detroit. Over a similar period in New York City one case of gastric ulcer was reported from 348,310 pregnancies. Both cases resulted in death from perforation. Avery Jones (1947) stated that no case of proved peptic ulcer was discovered among 10,000 pregnancies at the antenatal clinic of the Central Middlesex Hospital even in the few cases referred to the dietetic clinic for indigestion.

In view of the almost universal association of digestive disturbances with pregnancy it is not surprising that activity in an unsuspected ulcer is often overlooked until perforation has occurred. Nevertheless the above figures show that it must be extremely rare to meet with this complication. Scott (1945), discussing the differential diagnosis of acute abdominal lesions in pregnancy, does not even mention ulcer perforation as a possibility, although appendicitis, intestinal obstruction, and gall-bladder disease receive full consideration.

The following case, in which perforation of a duodenal ulcer occurred at the 36th week of pregnancy, is reported partly because it is so rare and partly because it affords an opportunity of reviewing the effects of pregnancy upon peptic ulcer in general.

Case History

A primipara aged 24, at the 36th week of pregnancy, was admitted to the North Herts and South Beds Hospital on Aug. 20, 1947, complaining of acute abdominal pain. Four years previously she had been treated in hospital for a duodenal ulcer, and this had been confirmed by an x-ray examination. She had not suffered from any other illness, and did not show any signs of masculine endocrine characteristics. The significance of this is referred to in the commentary below. During her pregnancy she had had two severe attacks of indigestion relieved by alkalis. A third attack began a few days before admission, and she finally collapsed with a very severe pain in the epigastrium.

When first seen, eight hours after the onset of the acute pain, she complained of continuous pain all over the abdomen and had vomited twice. Her temperature was 100° F. (37.8° C.) and her pulse rate 84. The size of the uterus corresponded with the dates, and it contained a live foetus presenting by the vertex. There were no signs of toxæmia, but generalized abdominal tenderness and some rigidity were present in the right side of the epigastrium. No peristalsis could be heard.

Having excluded the possible causes of pain due to the pregnancy, the diagnosis appeared to rest between a perforated duodenal ulcer and a perforated appendix displaced upwards by the enlarged uterus.

Laparotomy was performed ten hours after the onset of the acute pain. A high paramedian incision was made and free fluid was encountered. A small perforation about 4 mm. in diameter was found on the anterior surface of the duodenum. This was closed and a small portion of omentum sutured over it. A brief search for the appendix served only to show the extreme difficulty of locating this organ late in pregnancy, and in order not to disturb the uterus, the surface of which was