It has been shown that in practice the transport of blood in non-refrigerator vehicles between donor session and centre was satisfactory, in that over a period of seven years about 500,000 bottles have been so collected with only one fatality due to infection that was caused by an organism which grows in blood at 4° C. Blood contaminated with cold-growers which caused the other seven deaths reported in England and Wales during the last ten years was collected by services which employ refrigerator transport between donor session and centre.

In spite of experimental evidence that some samples of blood contaminated with these organisms will yield growth slightly earlier during storage if not immediately refrigerated, the remoteness of this hazard in practice explains the good results obtained with non-refrigerator vehicles.

Provided that blood can be refrigerated within eight hours of collection there would appear to be no evidence that refrigeration at the collecting session or during transport is essential in temperate climates. Experimental incubation of blood for two hours immediately after collection suggests that in the tropics it will come to no harm if left for at least two hours unrefrigerated.

It seems that one reason why accidents from infected blood are not more common may be that blood for transfusion is a poor culture medium.

Summary

The problem of contamination of blood for transfusion was investigated, particularly with regard to the effect of temperature after collection on contaminating organisms.

Bacteria which grow at 37° C. and two strains isolated from infected blood which grow at 4° C. were inoculated into samples of freshly drawn blood in an attempt to reproduce the actual mode of infection during donation.

It was demonstrated that, although experimentally there are slight advantages in refrigerating blood within 30 minutes of collection, in practice refrigeration in temperate climates is not essential until at least eight hours after collection.

Some samples of blood held at 37° C. for two hours immediately after donation killed small numbers of contaminating bacteria; none of the strains tested multiplied in blood during this time.

Prevention of contamination by cold-growing bacteria is discussed and a method is recommended for the examination of blood suspected of infection.

We wish to thank first the blood donors who volunteered for these experiments, without whom the work could not have been done. Acknowledgments are due to Professor Wilson Smith for his encouragement and advice, to Dr. P. L. Mollison for the estimation of red-cell survival, to the staff of the North London Blood Transfusion Centre, particularly Dr. P. B. Booth and Dr. G. Plaut, and to Mr. T. D. Whittet for the pathogenicity and pyrogen tests in rabbits.

ADDENDUM.—Since this paper was completed, results of experiments on the survival and growth of bacteria in bank blood incubated at 37° C. for short periods before refrigeration have been published by Geller, P., Chandler, L., and Jawetz, E., *J. Lab. clin. Med.*, 1957, 49, 573. So far as the results can be compared, they are in agreement.

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SPLENECTOMY IN ACQUIRED GENERALIZED MYELOSCLEROSIS

BY

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Acquired generalized myelosclerosis with associated myeloid metaplasia is an uncommon but well-recognized disorder which has been described under a variety of names, including osteosclerotic anaemia, myelophthisic anaemia, megakaryocytic myelosis, and agnogenic myeloid metaplasia. It is regarded as distinct from the hereditary osteopetrosis or marble bone disease of Albers-Schönberg, which occurs in childhood and young adults. Acquired myelosclerosis is not familial, and is seen in patients of both sexes more commonly after the age of 40. The clinical features are an insidious progressive anaemia, usually of leuco-erythroblastic type, and gross splenomegaly. The anaemia may later show a haemolytic component or may be associated with neutropenia or thrombocytopenia. Radiographs of the bones sometimes show mottled rarefaction or irregular condensations in the cortical portions and splintering or elevations of the periosteum (Rosenthal and Erf, 1943). The prognosis is poor, death occurring usually within five years from cardiac failure, intercurrent infection, or haemorrhage. At necropsy there is replacement of the bone marrow by fibrous or osseous tissue and extramedullary haemopoiesis, myeloid metaplasia occurring in the spleen, in the liver, and sometimes in the kidneys and lymph nodes.

Aetiology

The cause of the condition remains uncertain, but in a few cases it has been reported in association with carcinomatous deposits in the marrow, myeloma, Hodgkin's disease, and diffuse tuberculous infection. Wyatt and Sommers (1950) reviewed a group in which they suggested that the changes were a result of intoxication by various organic chemicals. Donhauser (1908) was the first to regard the myeloid metaplasia as a compensatory extramedullary haemopoiesis and the spleen as the most important source of red cells, granulocytes, and platelets. If this is a correct hypothesis, splenectomy would be clearly contraindicated (Scott, 1949; Wintrobe, 1951; Learmonth, 1951; Chatterjee, Meza Arrau, and Dameshek, 1952; Hickling, 1953).

An alternative hypothesis supported by Vaughan and Harrison (1939), Dameshek (1951), Hutt, Pinniger, and Wetherley-Mein (1953), and Richardson and Pinniger (1953) regards the myelosclerosis and the myeloid metaplasia as part of a proliferative disorder of mesenchymal tissue, in response to an as yet unknown stimulus. As the mesenchymal cell is multipotential and may differentiate into a fibroblast, erythroblast, myeloblast, or megakaryoblast, the clinical and haematological pattern depends upon the predominant cell group and the stage of development involved. Myelosclerosis has been described in association with polycythaemia vera in a number of cases reviewed by Beattie and Withey (1953), since when further reports have been added by Robson (1953) and Korst, Clatanoff, and Schilling (1956). Cases of myeloid leukaemia with myelosclerosis have been reported by Hutt *et al.* (1953) and Richardson and Pinniger (1953).

Richardson and Pinniger (1953), Croft (1956), and Asher (personal communication) describe cases where the features of myelosclerosis, polycythaemia vera, and leukaemia have occurred in the same patient at different times, as has also megaloblastic anaemia in the case described by Croft (1956). According to this myeloproliferative theory, the myeloid

metaplasia in the spleen is not a compensatory mechanism, and in fact splenic hyperactivity may contribute to the pancytopenia, neutropenia, thrombocytopenia, and haemolytic anaemia which may develop in this condition. Splenectomy, by this hypothesis, is not contraindicated, and has now been reported in at least 23 histologically proved cases of acquired generalized myelosclerosis (Hirschfeld, 1914; Mettier and Rusk, 1937; Waitz and Warter, 1938; Carpenter and Flory, 1941; Reich and Rumsey, 1942; Dustin, 1947; Engell, 1947; Heller, Lewisohn, and Palin, 1947; Edwards, 1951, 1955; Andersen and Sorensen, 1952; Franks and Richardson, 1952, and personal communication; Green, Conley, Ashburn, and Peters, 1953; Merskey and Budz-Olsen, 1953; Nelson, 1954; Asher, 1955, and personal communication; Croft, 1956; Linman and Bethell, 1957).

Against this background four further cases of acquired myelosclerosis are reported in which splenectomy was performed.

Case 1

A 59-year-old man was admitted to hospital in March, 1951, with dyspnoea and hepato-splenomegaly. Haematological examination showed a normocytic normochromic anaemia with erythroblast-

FIG. 1.—Rib marrow from Case 1 showing fibrosis (reticulin). ($\times 230$.)

aemia, neutropenia, and thrombocytopenia (red cells, 3,260,000 per c.mm.; Hb, 8.5 g. per 100 ml.; M.C.V., 83 cubic microns; M.C.H.C., 30%; reticulocytes, 2.6%; normoblasts, 500 per c.mm.; white cells, 1,850 per c.mm. (700 neutrophil polymorphs, 15 eosinophils, 15 basophils,

250 myelocytes, 700 lymphocytes, and 170 monocytes); platelets, 73,000 per c.mm.). Radiographs revealed no bone changes. On sternal puncture no marrow was obtained, but on histological examination a rib biopsy showed osseous trabeculae in the medullary cavity, between which were numerous collagen and reticulin fibres (Fig. 1); cells of the erythroid and myeloid series and megakaryocytes were present in normal or possibly increased numbers. The patient was treated by blood transfusions, but after 12 months these failed to maintain his haemoglobin above 7 g. per 100 ml. (Fig. 2). During this time his serum bilirubin was always less than 0.5 mg. per 100 ml., and the direct Coombs test was negative. In September, 1952, a course of corticotrophin (20–40 mg. a day intravenously) was administered over 22 days (total 680 mg.) without benefit.

In view of the persistent pancytopenia and failure of repeated blood transfusions it was decided in October, 1952, to perform a splenectomy. At operation the spleen was found to be grossly enlarged, weighing 2,000 g., and on histological examination showed foci of erythroid and myeloid haemopoiesis but very few megakaryocytes; macrophages in the pulp contained a moderate amount of haemosiderin. A rib biopsy taken at the operation showed changes similar to those seen 18 months before. After splenectomy there was a marked erythroblastemia, a rapid rise of platelets to 200,000 per c.mm. and of neutrophil polymorphs to 3,300 per c.mm.; the haemoglobin level became stationary around 10 g. per 100 ml. Two months later the patient returned to work, continuing until May, 1953, when he developed haemorrhagic pericarditis, the cause of which was never satisfactorily explained. In view of the fall in haemoglobin at this time a further transfusion was given.

He remained well until April, 1954, when he developed epigastric pain followed by recurrent haematemesis. A barium study showed the presence of a duodenal ulcer. This did not respond to medical treatment, and further severe haematemeses necessitated partial gastrectomy in October, 1954. Shortly after the operation he developed cardiac failure and died.

Necropsy (Dr. J. G. Jackson).—Both lungs showed pulmonary oedema, and the heart (375 g.) had a pale friable myocardium with interstitial fibrosis, the coronary arteries and aorta showing slight atheroma. The liver (2,500 g.) was enlarged, and showed erythroid and myeloid metaplasia with occasional megakaryocytes. The femora contained soft red marrow throughout the length of each shaft, but the sternum, ribs, and vertebrae showed a moderate increase of laminated bony trabeculae in the medullary cavity with an increase of collagen and reticulin fibres. The bone marrow from each site showed many foci of erythroid and myeloid cells, but no increase in megakaryocytes.

Case 2

A 71-year-old housewife was admitted to hospital in September, 1955, with gross splenomegaly accompanied by severe abdominal pain. Haematological examination

FIG. 2.—Blood levels in Case 1.

showed: red cells, 4,460,000 per c.mm.; haemoglobin, 12.3 g. per 100 ml.; P.C.V., 38%; M.C.V., 84 cubic microns; M.C.H.C., 35%; reticulocytes, 8.6%; white cells, 32,000 per c.mm. (21,000 neutrophil polymorphs, 7,800 myelocytes, 2,300 lymphocytes, and 350 monocytes); platelets, 157,000 per c.mm. Puncture of the sternum and iliac crest was easily carried out, but no true marrow was obtained, a finding very suggestive of myelosclerosis.

In view of the patient's persistent pain and of her extreme difficulty in walking due to the abdominal swelling, it was decided to perform a splenectomy. The spleen was grossly enlarged, weighing 5,440 g. Histological examination showed the pulp to contain large numbers of erythroid and myeloid cells and megakaryocytes (Fig. 3). The evening following

FIG. 3.—Spleen from Case 2 showing erythroid and myeloid metaplasia with megakaryocytes. (H.E. $\times 560$.)

operation the patient became hypotensive, and an emergency laparotomy revealed bleeding from the small vessels under the diaphragm which could not be controlled. She died of peripheral circulatory failure 48 hours after splenectomy.

Necropsy.—There was a large blood clot beneath the left diaphragm but no other evidence of haemorrhage throughout the body. The liver (2,770 g.) was enlarged, showing scattered white nodules of erythroid and myeloid cells within the hepatic lobules and along the portal tracts. The ribs, sternum, and femora showed a general increase of laminated bony trabeculae and a patchy increase of collagen and reticulin fibres associated with foci of erythroid and myeloid cells, but without increase in megakaryocytes.

Case 3

A 58-year-old man was admitted in January, 1956, with a three-months history of pallor and dyspnoea on exertion. No abnormal physical signs were detected. His blood values were: red cells, 2,030,000 per c.mm.; haemoglobin, 5.3 g. per 100 ml.; M.C.V., 79 cubic microns; M.C.H.C., 33%; reticulocytes, 3.8%; white cells, 4,000 per c.mm. (3,500 neutrophil polymorphs); platelets, 182,000 per c.mm.; a small number of normoblasts; red cell osmotic fragility normal;

direct Coombs test negative; and serum bilirubin less than 0.5 mg. per 100 ml. Radiographs of the long bones showed no abnormality. Bone-marrow puncture at different sites on three separate occasions was carried out with difficulty and poor specimens of hypocellular marrow were obtained. A provisional diagnosis of myelosclerosis was made and the patient given monthly blood transfusions.

Over the next three months the spleen became palpable and gradually increased in size; myelocytes began to appear in the peripheral blood; urinary and faecal urobilinogen was raised, but the serum bilirubin was never above 0.6 mg. per 100 ml. By August blood transfusions failed to raise the haemoglobin above 6 g. per 100 ml. (Fig. 4), and it was therefore decided to perform a splenectomy. The spleen was enlarged, weighing 1,350 g., and showed marked hyperplasia of the sinusoids, the pulp containing large numbers of macrophages laden with haemosiderin. A very small number of erythroid and myeloid cells with a few megakaryocytes were present. A rib biopsy at the time of operation showed the marrow to be almost completely replaced by fibrous and osseous tissue; a few foci of erythroid and myeloid cells were present and megakaryocytes were increased.

The post-operative course was uneventful, but the haemoglobin level gradually fell during the next few weeks, becoming stationary around 7 g. per 100 ml. three months later when the patient again had some dyspnoea on exertion. Over the past year he has required blood transfusions on two occasions only, when the haemoglobin fell below 6 g. per 100 ml.

Case 4

A 62-year-old housewife was admitted to hospital in July, 1954, with gross splenomegaly and moderate hepatomegaly. The blood values were: red cells, 4,930,000 per c.mm.; haemoglobin, 11.1 g. per 100 ml.; M.C.V., 86 cubic microns; M.C.H.C., 26%; white cells, 17,900 per c.mm. (13,200 neutrophil polymorphs, 800 eosinophils, 400 basophils, 100 myelocytes, 900 metamyelocytes, 2,300 lymphocytes, and 200 monocytes); occasional myeloblasts and normoblasts were seen. Occult blood was present in the stools and a subsequent barium study showed a diaphragmatic hiatus hernia.

FIG. 4.—Blood levels in Case 3.

Radiographs of the chest and long bones showed no abnormality. On sternal puncture hypocellular marrow was obtained and a provisional diagnosis of myelosclerosis was made. No specific treatment, apart from ferrous sulphate, 6 gr. three times a day, for her anaemia, was considered advisable at this stage.

Twelve months later a count showed: red cells, 6,090,000 per c.mm.; haemoglobin, 17.6 g. per 100 ml.; white cells, 30,000 per c.mm. The spleen continued to enlarge with increasing abdominal discomfort, and two years after the first admission, in view of her distressing incapacity due to the splenomegaly, it was decided to attempt splenectomy. Immediately prior to the operation the clotting-time, prothrombin activity, and bleeding-time were normal. The spleen showed marked perisplenitis and weighed 7,650 g. The splenic vein and those in the splenic ligaments and retroperitoneal tissues were grossly dilated. A liver and tibial bone biopsy were made at the operation. Subsequent histological examination showed a marked erythroid and myeloid metaplasia of both spleen and liver with numerous megakaryocytes in both organs. The bone marrow showed evidence of myelosclerosis, particularly when stained for reticulin. Twelve hours after the operation the patient developed peripheral circulatory failure due to internal haemorrhage, probably from the splenic bed. The following day she died, but permission for a necropsy was not given.

Discussion

In none of the above cases was there any evidence of a specific aetiology. There was no history of exposure to toxic agents or any evidence of association with a neoplasm or tuberculosis. The concept of a compensatory extra-medullary haemopoiesis is difficult to accept in view of the improved blood values following splenectomy in Case 1 and the fact that the splenic enlargement in Case 3 was not due to myeloid metaplasia but to a hyperplasia of the sinusoids. The myeloproliferative theory receives support in all four cases.

In Case 1 the bone marrow showed increased cellularity of haemopoietic and fibrous tissue on all occasions examined over a period of three and a half years, and at necropsy the myelosclerosis was associated with a general marrow hyperplasia, a finding which could, on the other hand, be explained as an effect of the long-standing stimulus of chronic anaemia. The pancytopenia in this case, which greatly improved after splenectomy, was presumably the result of splenic hyperplasia leading to an inhibitory effect on the release of cells from the bone marrow or a diminution of their life span. The bone marrow of Case 2 showed focal areas of fibrosis with associated proliferation of erythroid and myeloid cells. In Case 3 the medullary cavity of the rib examined had been almost completely replaced by fibrous tissue; however, the spleen was considerably enlarged without much myeloid metaplasia; and, without postulating a primary splenic hyperactivity, it is difficult to explain the increased rate of red-cell destruction, in view of a normal red-cell fragility and a negative direct Coombs test. In Case 4 the myelosclerosis was for a time associated with polycythaemia vera.

In Cases 1 and 3 the anaemia would appear to have had a haemolytic component, although no rise in the serum bilirubin was detected. Repeated blood transfusions failed to correct the anaemia, probably owing to the increased rate of destruction of red cells by the spleen. Following splenectomy, however, blood transfusions were required much less frequently in Case 3 and in Case 1 only when the patient developed haemorrhagic pericarditis and later haematemesis. A course of 680 mg. of corticotrophin in Case 1 produced no haematological improvement. In Case 3 the absence of leucocytosis or rise in platelets following splenectomy and the subsequent gradual fall in haemoglobin suggest a marked diminution of functional bone marrow and indicated a poor prognosis.

Of the 23 previously reported cases of splenectomy in acquired generalized myelosclerosis, 18 showed some benefit

following the operation, although four patients relapsed within a year and six died from other causes after one to 20 years. In 13 cases the indication for operation was relief of abdominal symptoms caused by the splenomegaly, some having an associated chronic anaemia and being diagnosed as Banti's syndrome. With the exception of one case in which the patient died from peripheral circulatory failure within three hours of the operation, all these cases received some symptomatic relief following the operation. Of 12 cases with chronic anaemia, with or without abdominal symptoms, only five improved, whereas all three regarded as having an overt haemolytic component showed benefit for up to two and a half years. Three of the four cases operated on for relief of pancytopenia had a good initial response, but two relapsed within three years. One patient with chronic anaemia which showed no haematological improvement lived for a further five years with frequent blood transfusions. Death following operation occurred only in the case of Hirschfeld (1914), but the largest spleen removed weighed 4,000 g., whereas in Cases 2 and 4, reported above, where death was due to post-operative haemorrhage, the weight of the spleen was respectively 5,440 and 7,600 g. Such large spleens have numerous diaphragmatic adhesions, leading to increased risk of reactionary haemorrhage from small vessels. In neither case was there evidence of a coagulation defect.

Neither in Cases 1 and 3 nor in any of those previously reported has there been evidence that splenectomy has altered the bone-marrow pathology or the natural history of the disease. However, there is no evidence, either in the present cases or in those reviewed, that, apart from the danger of immediate post-operative complications, the loss of the spleen *per se* is harmful. No form of curative therapy is known. Blood transfusion gives temporary relief of the anaemia, but haematinics, corticotrophin, cortisone, and testosterone have produced no marked beneficial effects. The removal of a grossly enlarged spleen carries with it the risk of uncontrollable reactionary haemorrhage and is therefore rarely justified for the relief of abdominal symptoms. The treatment of choice in these patients is probably irradiation of the spleen, as recommended by Hickling (1953). If pancytopenia, neutropenia, thrombocytopenia, or haemolytic anaemia develops, then splenectomy is indicated as a possible life-saving measure.

Summary

Four cases of acquired generalized myelosclerosis treated by splenectomy are reported; two of the patients died within 48 hours of operation from reactionary haemorrhage and two obtained some benefit from the operation.

Support is given to the hypothesis that acquired generalized myelosclerosis is part of a myeloproliferative disorder.

The literature is reviewed and the indications for splenectomy are discussed.

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THE PROBLEM OF RECURRING CYSTITIS IN WOMEN

BY

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The purpose of this paper is to draw attention to the fact that in many cases of cystitis the infection is of ascending rather than of descending origin. Below are presented 65 personal consecutive cases, compared in certain respects, in a series of charts, with the same number of cases of chronic frequency, which were also taken consecutively.

Clinical Types of Cystitis

Broadly, the following clinical types of cystitis in which recovery occurs can be identified: (1) a single attack, which clears completely and has no recurrence after many years; (2) one or more attacks of cystitis, followed by frequency and other residual symptoms; (3) several attacks of cystitis, with no intermediate frequency; (4) recurring cystitis after intercourse; (5) honeymoon cystitis; and (6) cystitis associated with pyelitis of pregnancy. Chronic increased frequency of micturition is a feature that is common to most recurrent cases.

In 1956 I published the results of an investigation of 274 consecutive personal cases of chronic frequency of micturition which occurred in my practice. The inquiry embraced all ages and both sexes. In many there had been incidents of cystitis. If we examine the features of the frequency in the cases of cystitis and simple chronic frequency we find certain similar characteristics in both, as already set out (Winsbury-White, 1956).

In the past there have been two practical obstacles to the recognition of the posterior urethra as a common site of chronic infection: (1) the presence of a clear and sterile urine, in spite of persisting disturbances of micturition; and (2) the conventional disregard of the possibility that the posterior urethra could harbour a cause of chronic symptoms. It is only by a routine examination of the urethra in all cases of disturbances of micturition that a proper consideration can be given to this potential source of recurring symptoms. Some surgeons are practised in urethroscopy and others are not; therefore the medical attendant may or may not get a full report on the condition of the lower urinary tract.

Urethroscopy

I have the impression that many surgeons employ urethroscopy from time to time without seeing anything very convincing. With the inexperienced, especially, this is likely

to result in a second urethroscopy being carried out several weeks later, the first instrumentation having caused the more flimsy inflammatory vegetations to disappear completely. Thus the observer begins to doubt whether he really did see anything positive on the first occasion.

I cannot emphasize too strongly the need to use the best type of instrument. My personal experience is that this is the Geiringer pattern—in common use to-day, in slightly modified form, as the Swift Joly—which gives direct vision through a circular orifice at the distal end. I find that the oblique opening of the panendoscope pattern gives an important difference in magnification, according to whether the mucosa at the near or distal part of the oblique opening is being inspected. This requires regular rotatory movements of the instrument in order to see clearly the small inflammatory lesions that are sometimes present. Neglect to carry out these movements can give an incomplete impression of what one is seeing. I have had no success with other types of urethroscope in identifying inflammatory processes.

For more than 25 years it has been my regular practice to urethroscopically all women, children, and young men with disturbances of micturition. This has given me an experience of several thousand urethroscopies in women.

I have already described the differences in inflammatory changes to be observed urethroscopically in cases of frequency (Winsbury-White, 1956); the same groups exist in cases of cystitis, and these are referred to under the various decades of life to show how they broadly follow the same patterns both in urethral conditions and in clinical types.

We have only to remind ourselves of the difficulty of completely eradicating infection from the prostate to be aware that the same kind of gland structure in the female urethra probably provides us with the same kind of problem; so that it is not surprising that polypi and lesser signs of chronic inflammation are often to be seen in the posterior urethra of women. It is the regular experience of us all that chronic inflammatory changes are encountered on cystoscopy on the front of the trigone, and sometimes all round the internal urinary meatus, often when inflammation is to be found nowhere else in the bladder. When the investigation includes urethroscopy, posterior urethral inflammatory changes are inevitably found as well. By this routine, urethro-trigonitis is established as a frequent and somewhat concealed infective lesion. The combined bladder and urethral lesion is commonly found in young adult women.

Analysis of Cases in Decades

I find it difficult to discuss cystitis in women without considering chronic frequency in female children, because of a common urethral pathology. The cases of frequency in children inevitably include some with enuresis.

It is clear (Fig. 1) that there is a real spate of cases of chronic frequency in early childhood, and that these tend to tail off as childhood advances. Indeed, all disturbances

FIG. 1.—Comparison of frequency with cystitis in females. —, Incidence of cystitis. ---, Incidence of frequency.

of micturition, including enuresis, tend to disappear as adolescence advances. This clinical fact corresponds with the prevalence of non-vegetative forms of urethral inflammation and the rareness of urethral polypi in female children. Of the 29 cases of frequency in females in the