EFFECTS OF SPLENECTOMY ON RED-CELL PRODUCTION IN MYELOFIBROSIS

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It has often been stated that in myelofibrosis the spleen becomes an important site of extramedullary erythropoiesis, and that splenectomy or splenic irradiation is harmful (Donhauser, 1908; Hickling, 1937; Jackson, Parker, and Lemon, 1940; Reich and Rumsey, 1942; *Lancet*, 1949; Sanneman, McIlvanie, and Beard, 1950; Learmonth, 1951). However, successful splenectomy has been reported by several authors, some of whom state that there was no evidence of diminished erythropoiesis after splenectomy (Edwards, 1951; Claman and Collier, 1952; Franks and Richardson, 1952; Green, Conley, Ashburn, and Peters, 1953; Hutt, Pinniger, and Wetherley-Mein, 1953; Panels in Therapy, 1955; Videbaek, 1956; Shinton, 1957; Andreasen, 1958).

Despite these observations the view that splenectomy is contraindicated is still widely held, and a recent review stated: "The treatment of myelosclerosis is based on the recognition that the haemopoiesis in the spleen is responsible for an increasing proportion of the patient's supply of blood cells. Splenectomy is therefore not proper treatment" (*Brit. med. J.*, 1960). We report two cases of myelofibrosis in which the course and findings after splenectomy throw doubt on the universal validity of this last conclusion. Evidence was obtained that in these two cases splenectomy was followed by increased red-cell production.

Methods

Plasma Iron.—The method of Bothwell and Mallett (1955) was used.

Isotope Techniques

^{59}Fe Utilization and Surface Counting Pattern.—10 μC of $^{59}\text{FeCl}_3$ buffered with sodium citrate was injected intravenously. A ^{59}Fe surface counting pattern was then obtained, using a directional scintillation counter, and counts were made over praecordium, sacrum, liver and spleen. The counting rate over the praecordium was taken to represent blood ^{59}Fe activity and that over the sacrum to represent marrow ^{59}Fe activity. The counting rates over each organ were plotted arithmetically against the time after the injection of ^{59}Fe plotted logarithmically (Fig. 1). The technique used is described in detail by Wetherley-Mein, Hutt, Langmead, and Hill (1956). Blood samples were taken and the percentage of the administered dose of ^{59}Fe which appeared in the circulating red-cell volume was calculated from the activity per ml. of blood and the blood volume. This percentage is referred to as the ^{59}Fe utilization. Normal subjects have a ^{59}Fe utilization of at least 70% by the seventh day.

^{51}Cr Red-cell Survival.—20 ml. of the patient's blood was withdrawn into heparin, centrifuged, and the

supernatant plasma removed. To the red cells was added 100 μC of ^{51}Cr as $\text{Na}_2^{51}\text{CrO}_4$, and the mixture was allowed to stand at room temperature for 30 minutes. Excess ^{51}Cr was removed by washing in normal saline, and the tagged red cells were reinjected

FIG. 1.—Normal ^{59}Fe surface-counting pattern.

into the patient. The total red-cell volume was calculated from the dilution of these cells in the circulation at 20 minutes. The apparent ^{51}Cr red-cell survival was calculated from the decline in specific activity of ^{51}Cr per ml. of whole blood.

Since the clinical situation before splenectomy precluded a long-term ^{51}Cr study, a short-term ^{51}Cr technique over 10 days was used and a comparable study performed after operation. The brevity of these studies did not allow an estimate of mean red-cell life to be made with any accuracy, and $T_{1/2}$ ^{51}Cr could be determined only after considerable extrapolation. The values obtained for ^{51}Cr activity on successive days were therefore plotted on semi-logarithmic paper and the best-fitting straight line through the points was drawn. From the slope of this was calculated the rate of ^{51}Cr loss from the circulation (expressed as percentage loss of ^{51}Cr per day). No correction was made for ^{51}Cr elution from intact red cells.

We have studied with this short ^{51}Cr technique 10 normal subjects and 11 patients having normal ^{51}Cr red-cell survival curves (Jones, Wetherley-Mein, Ingram, and Langmead, 1960). From an analysis of the results it appears that only 1 in 20 normal subjects would be expected to show rates of ^{51}Cr loss greater than 5.1% a day over the first 10 days of the study, and rates exceeding 5.1% a day may therefore be regarded as abnormal. It is not legitimate to infer normal red-cell survival from rates of ^{51}Cr loss less than 5.1% a day, but it may then be inferred that haemolysis is not contributing greatly to an anaemia.

Case 1

Summary of Haematological Findings (Fig. 2).—This patient maintained a haemoglobin level of between 8.3 and 12 g./100 ml. for five years after the diagnosis of myelofibrosis. The haemoglobin level then fell to 5 g./100 ml. and could hardly be raised by transfusion. Isotope studies showed greatly reduced red-cell production and there was evidence of shortened red-cell life. Prednisone therapy had

no effect on the haemoglobin level. Splenectomy was therefore performed and the haemoglobin was subsequently maintained at about 11 g./100 ml. without further therapy. Isotope studies now showed a very considerable increase in red-cell production compared with the pre-operative findings. There was now no evidence of shortened red-cell life.

FIG. 2.—Case 1. Course and findings after splenectomy.

History and Findings Before Splenectomy

In 1953 myelofibrosis was diagnosed in this 57-year-old man on the basis of splenomegaly, leuco-erythroblastic anaemia, dry sternal puncture, and the histology of a rib biopsy taken at another hospital.

He was first admitted to St. Thomas's Hospital in November, 1955, when investigations showed: Hb, 12 g./100 ml.; P.C.V., 39%; M.C.V., 118 cubic microns; M.C.H.C., 30.75%; reticulocytes, 3.1%; direct Coombs test negative; W.B.C., 4,500/c.mm. (segmented neutrophils 70%, lymphocytes 20%, monocytes 6%, metamyelocytes 3%, neutrophil myelocytes 1%); platelets, 368,000/c.mm. Microscopy of the original rib-biopsy material showed a considerable increase in reticulin fibrils throughout the marrow with, in some areas, extensive collagen formation. There was appreciable haemopoietic activity in the less densely fibrotic areas, the predominant cells being mature granulocytes, although erythropoietic foci could be identified. Megakaryocyte-like giant cells were enormously increased in numbers throughout. There was no evidence of active bone formation. A ^{59}Fe study was performed, and this suggested a partial failure of red-cell production (see Results, Case 1 (a)).

The patient was next admitted in April, 1957, on account of abdominal discomfort due to enlargement of the spleen, which extended to the left iliac fossa. Investigations: Hb, 8.3 g./100 ml.; W.B.C., 2,600/c.mm. (neutrophils 64%, lymphocytes 33%, monocytes 2%, eosinophils 1%); platelets, 198,000/c.mm. After a course of busulphan the spleen diminished slightly in size.

In May, 1958, the patient became increasingly tired and breathless on exertion. On his admission to another hospital the haemoglobin was found to be 4.9 g./100 ml. and a blood transfusion was given. A month later on readmission to St. Thomas's Hospital he was found to be extremely pale but not jaundiced. There was oedema of ankles and sacrum, and the jugular venous pressure was raised 1 in. (2.5 cm.). A soft systolic murmur was audible over the whole praecordium, but the heart was not enlarged radiologically. The spleen was grossly enlarged, reaching to the left iliac crest and extending across the midline into the right iliac fossa: it was very tender. The liver was palpable 1 in. (2.5 cm.) below the right costal margin. No enlarged lymph nodes were detected. Investigations: Hb, 3.5 g./100 ml.; P.C.V., 12%; reticulocytes, 5%; direct Coombs test nega-

tive; W.B.C., 600/c.mm. (neutrophils 73%, lymphocytes 23%, plasma cells 4%); platelets, 70,000/c.mm.; plasma iron, 246 $\mu\text{g.}/100\text{ ml.}$; serum bilirubin, 0.65 mg./100 ml. The stools contained no occult blood.

Treatment with prednisone was started and ^{59}Fe and ^{51}Cr studies were begun. The ^{59}Fe study showed an almost complete failure of erythropoiesis (see Results, Case 1 (b)). ^{51}Cr -survival studies were interrupted by blood transfusion, but the rate of fall of haemoglobin—6% (Haldane) a day in the absence of haemorrhage—indicated considerable haemolysis.

It was now difficult to raise the haemoglobin by transfusion; the patient became critically ill, and splenectomy was undertaken in June as an emergency procedure. The spleen weighed 2,670 g., and microscopy showed disruption of the normal architecture, diffuse proliferation of reticulum cells with collagen formation, and occasional megakaryocyte-like giant cells. Red-cell precursors were abundant and scattered diffusely throughout. Granulocyte precursors were present but less numerous.

Course and Findings After Splenectomy (Fig. 2)

Post-operatively there was a remarkable clinical improvement. The haemoglobin level became steady at 11.1 g./100 ml., the W.B.C. rose rapidly from 700 to 9,000/c.mm. and the platelet count from 68,000 to 300,000. Four weeks later isotope studies showed a striking increase in red-cell production (see Results, Case 1 (c)). Five weeks after operation the patient left hospital.

In August, 1958, a small haematemesis occurred, and he was transfused. At this time the platelet count was 3,200,000/c.mm. and the W.B.C. 28,000/c.mm. He remained well until July, 1959, when he developed pain in the lower thoracic and upper lumbar spine. He became breathless on exertion, and was readmitted in August. The outstanding findings on examination were pallor, and enlargement of the liver, which was now palpable 4 in. (10 cm.) below the right costal margin and contained several prominent lumps, the largest of which was about 7 cm. in diameter. Investigations: Hb, 5.9 g./100 ml.; M.C.H.C., 25%; reticulocytes, 7.2%; direct Coombs test negative; W.B.C. 19,700/c.mm. (neutrophils 86%, lymphocytes 6%, monocytes 1%, eosinophils, 1%, basophils 1%, metamyelocytes 3%, blast cells 2%); 74 normoblasts per 100 white cells; platelets, 888,000/c.mm. Plasma iron 22 $\mu\text{g.}/100\text{ ml.}$ Tests for occult blood in the stools were positive. A ^{59}Fe surface counting pattern was obtained (see Results, Case 1 (d)). The absolute values, low plasma iron, and the presence of blood in the stools indicated an iron-deficiency anaemia due to gastro-intestinal blood loss.

Chest x-ray examination showed a round shadow in the left mid-zone which tomography indicated was situated posteriorly in the left upper lobe. No tubercle bacilli or neoplastic cells were found on examination of the sputum. A provisional diagnosis of carcinoma of the bronchus with liver metastases was made. X-ray examination of the painful areas of the spine revealed no evidence of metastases.

Two days after admission the patient had two haematemeses, and was transfused. A barium-meal examination showed a small projection of barium on the lesser curve of the stomach. The patient's general condition deteriorated steadily, and he died on September 9, 1959.

Post-mortem Examination

The bronchus to the apical segment of the left upper lobe was stenosed by tumour. Purulent tracheobronchitis and a small recent pulmonary infarct in the right lower lobe were also noted.

The liver was greatly enlarged and contained many deposits of tumour tissue. The anterior wall of the stomach was adherent to a large liver metastasis, and this had caused tethering of the gastric mucosa. Metastases were also present in the right adrenal gland, the right kidney, parietal peritoneum, retroperitoneal lymph nodes, and right cerebral

hemisphere. No macroscopic evidence of skeletal metastases was found.

Histological examination of the primary neoplasm in the lung and of the metastases revealed a spheroidal-cell carcinoma. Microscopy of the liver showed a slight increase in connective tissue with occasional megakaryocyte-like giant cells but no evidence of extramedullary erythropoiesis.

The marrow was cellular and contained numerous megakaryocyte-like giant cells. Many foci of red-cell precursors were present and granulocyte precursors were diffusely distributed throughout. Increased proliferation of reticulum cells was noted, but collagen formation was slight except in one area adjacent to a small nest of carcinoma cells.

When compared with the histological appearances of the rib biopsy taken in 1953, erythropoietic tissue was much more evident in the post-mortem specimen. The granulopoietic cells contained proportionately greater numbers of immature forms. Megakaryocyte-like giant cells were still present in excess but were less abundant than in the original sections. Reticulum-cell proliferation was less evident in the post-mortem sections and there appeared to be less collagen formation, although it was difficult to be certain about this.

Case 2

Summary of Haematological Findings (Fig. 3).—For one year after a diagnosis of myelofibrosis had been made in this patient, regular blood transfusions were needed to maintain the haemoglobin level. The rate of fall of haemoglobin was about 1% (Haldane) a day, and isotope studies showed greatly reduced red-cell production without increased red-cell destruction. It became progressively more difficult to raise the haemoglobin level by transfusion, and isotope studies then showed a shortened red-cell life. Splenectomy was performed, and after operation the haemoglobin level was maintained at about 12 g./100 ml. without further therapy. Isotope studies now showed a considerable rise in red-cell production and no evidence of shortened red-cell life. The patient later developed obstructive jaundice and died three and a half months after splenectomy. During this latter period the haemoglobin level fell slowly to 10 g./100 ml., and there became steady.

FIG. 3.—Case 2. Haematological findings.

History and Findings Before Splenectomy

In April, 1957, splenomegaly was discovered in this 56-year-old woman at laparotomy performed at another hospital on account of abdominal pain. A post-operative diagnosis of myelofibrosis was made on the basis of a leuco-erythroblastic anaemia and the histology of a rib biopsy taken after a dry sternal puncture.

On the first admission to St. Thomas's Hospital in June, 1957, the spleen reached the left iliac fossa, and anaemia and purpura were noted. The liver was not palpable. Investigations: Hb, 10 g./100 ml.; P.C.V., 36.5%; M.C.H., 31 μ g.; M.C.H.C., 30%; reticulocytes, 3%; 2 normoblasts per 100 white cells; W.B.C., 4,100/c.mm. (segmented neutrophils 61%, lymphocytes 34%, monocytes 3%, eosinophils 2%); platelets, 67,000/c.mm.; direct Coombs test negative; E.S.R., 7 mm. in 1 hour (Westergren). Examination of the original rib-biopsy material showed a considerable increase in reticulin fibrils throughout the marrow, with widespread collagen formation. Granulocyte precursors were evident throughout, but only occasional foci of erythropoietic cells were seen. There was a moderate increase in megakaryocyte-like giant cells. Active bone formation was not observed. ^{59}Fe and ^{51}Cr studies suggested considerably reduced red-cell production with no evidence of increased red-cell destruction (described under Results, Case 2 (a)).

For the next 10 months the haemoglobin level fell about 1% (Haldane) a day, necessitating regular blood transfusion. Increasing difficulty in maintaining the haemoglobin level led to readmission in May, 1958. The spleen was greatly enlarged and reached the right iliac fossa, but the liver was palpable. Investigations: Hb, 10.4 g./100 ml.; reticulocytes, 6.3%; direct Coombs test negative; W.B.C., 6,200/c.mm. (segmented neutrophils 69%, band neutrophils 3%, neutrophil metamyelocytes 2%, lymphocytes 22%, monocytes 3%, basophils 1%); platelets, 221,000/c.mm. Plasma iron 289 μ g./100 ml.

^{59}Fe and ^{51}Cr studies indicated a severe failure of erythropoiesis with evidence of shortened red-cell life (described under Results, Case 2 (b)). The haemoglobin level was now falling about 2% (Haldane) a day, and the reticulocyte count varied between 4.5% and 7.1%.

In view of these findings and the steady deterioration of the patient's condition splenectomy was performed. The spleen weighed 4,490 g. There was loss of the normal architecture with proliferation of reticulum cells and megakaryocyte-like giant cells. Throughout there were numerous foci of red-cell precursors with a more diffuse distribution of granulocyte precursors. A liver biopsy showed considerable proliferation of reticulum cells in the portal tracts. Accumulations of normoblasts, granulocytes, and occasional megakaryocyte-like giant cells were present in the liver sinusoids.

Course and Findings After Splenectomy (Fig. 3)

After splenectomy the haemoglobin level became steady at about 12 g./100 ml. The ^{59}Fe utilization was much higher than before splenectomy, while the ^{51}Cr study now provided no evidence of shortened red-cell survival (see Results, Case 2 (c)). There was a considerable rise in W.B.C. but a slight and short-lived fall in platelet count (Fig. 3). The general condition of the patient was strikingly improved, and she left hospital five weeks after operation.

She remained well for the next two months but then gradually became jaundiced and was readmitted. The liver was now palpable 5 in. (12.5 cm.) below the right costal margin. The urine contained bile and an excess of urobilinogen, but the latter disappeared after two or three weeks. Investigations: serum bilirubin, 3.8 g./100 ml.; thymol turbidity, 2 units; alkaline phosphatase, 232 King-Armstrong units; plasma albumin, 3.1 g./100 ml.; plasma globulin, 2.2 g./100 ml.; serum electrophoresis showed a slight increase in the gamma-globulin fraction; serum cholesterol, 845 mg./100 ml.; serum calcium, 7.7 mg./100 ml.; serum phosphorus, 3.7

mg./100 ml.; prothrombin time, 16 secs. (control, 14 secs.); blood urea, 42 mg./100 ml. On a normal ward diet the stool contained 47 g. of fat a day, and when ^{131}I triolein was given by mouth 71% of the dose appeared in the stools during the next five days (normal 0 to 5%). Thus there was evidence of obstructive jaundice with gross steatorrhoea. Haematological investigations showed: Hb, 10 g./100 ml.; reticulocytes, 2.6%; direct Coombs test negative; W.B.C., 63,000/c.mm. (segmented neutrophils 87%, band neutrophils 1%, lymphocytes 9%, atypical mononuclears 3%); platelets, 157,000/c.mm. A ^{59}Fe study was performed (see Results, Case 2 (d)).

Six weeks later the patient died. During this period there was no further haematological deterioration. Permission for necropsy was not granted.

Results of ^{59}Fe and ^{51}Cr Studies

Case 1

(a) November, 1955.— ^{59}Fe utilization, 48% by the seventh day. The ^{59}Fe surface counting pattern obtained is shown in Fig. 4. When compared with the normal pattern (Fig. 1)

FIG. 4.—Case 1. ^{59}Fe surface-counting pattern in November, 1955 (pre-splenectomy).

FIG. 5.—Case 1. ^{59}Fe surface-counting pattern in August, 1959 (post-splenectomy).

the major differences are: the rise in counting rate over the sacrum was much reduced; the counting rate over the spleen was initially high and rose to a peak at about four hours.

(b) June, 1958.— ^{59}Fe utilization, 5% by the fifth day, when the study was abandoned as transfusion was necessary. The shape of the curve relating ^{59}Fe utilization to time is such that the above measurement would indicate a seventh-day utilization of about 10%. Plasma iron, 246 $\mu\text{g.}/100$ ml. Surface pattern: the rise in counting rate over the sacrum was again much reduced; the counting rate over the spleen was again raised and reached a peak at 72 hours, but this rise was less pronounced than in the previous study; the counting rate over the liver rose slightly during the first 24 hours.

(c) July, 1958 (Post-splenectomy).—Performed at a time when the haemoglobin level had become steady. ^{59}Fe utilization, 91% (the seventh day). Plasma iron, 200 $\mu\text{g.}/100$ ml. Surface pattern, unsatisfactory owing to technical difficulties.

(d) August, 1959.—Surface pattern (Fig. 5) shows a peak in the counting rate over the sacrum of almost normal height and contour. There was no abnormal increase in counting rate over the liver. The study was abandoned (owing to transfusion) before a satisfactory measure of ^{59}Fe utilization could be obtained. Plasma iron, 22 $\mu\text{g.}/100$ ml.

Case 2

(a) June, 1957.— ^{59}Fe utilization, 26%. Surface pattern (Fig. 6) shows little rise in counting rate over the sacrum, a high counting rate over the spleen reaching a peak at about six hours, and a raised counting rate over the liver which did not greatly alter. ^{51}Cr red-cell loss, 4% a day.

FIG. 6.—Case 2. ^{59}Fe surface-counting in June, 1957 (pre-splenectomy).

(b) May, 1958.— ^{59}Fe utilization, 19%. Plasma iron, 289 $\mu\text{g.}/100$ ml. The counting rate over the sacrum did not rise at all. The initial counting rates over spleen and liver were higher than normal, but neither changed significantly until the spleen counting rate started to rise after 48 hours, and continued rising until the study ended at 100 hours. ^{51}Cr red-cell loss, 5.5% a day.

(c) June, 1958 (Post-splenectomy).—Performed when the haemoglobin level had become steady. ^{59}Fe utilization, 73%. Plasma iron, 287 $\mu\text{g.}/100$ ml. ^{51}Cr red-cell loss, 3.3% a day. Surface pattern unsatisfactory for technical reasons.

(d) September, 1958.— ^{59}Fe utilization, 57%. Surface pattern (Fig. 7) shows a greater rise in counting rate over

the sacrum than in previous studies, but this was still sub-normal. The initial counting rate over the liver was raised and showed a peak at about 24 hours.

FIG. 7.—Case 2. ^{59}Fe surface-counting pattern in September, 1958 (post-splenectomy).

Discussion

In both patients there had been great difficulty in raising the haemoglobin level before splenectomy, even with frequent transfusions. The main haematological value of splenectomy lay in its effect on the haemoglobin, which was maintained at a reasonable level without therapy for 12 months in Case 1 (apart from one transfusion after a haematemesis) and for three and a half months in Case 2. Fourteen months after splenectomy the first patient again became anaemic. Although in the peripheral blood there was still evidence of the underlying myeloproliferative disorder in the shape of immature leucocytes and red cells, the anaemia was of iron-deficiency type with a low plasma iron and could be predominantly ascribed to the gastro-intestinal bleeding.

Conventional haematological investigations often fail to establish the relative importance of impaired erythropoiesis and increased red-cell destruction in the pathogenesis of anaemia in myelofibrosis. It is not therefore usually possible to decide if improvement after splenectomy is due solely to lengthening of the effective red-cell life. In the cases here reported there was evidence that after splenectomy not only was red-cell destruction decreased but red-cell production was strikingly increased.

The use of ^{59}Fe in the assessment of erythropoiesis is well established, although the sources of error in the interpretation of the results are not always considered (Wetherley-Mein and Hutt, 1960). An important source of difficulty is the effect of variations in the size of the plasma iron pool immediately labelled with the isotope. In the above cases there were only small changes in the size of the plasma iron pool when the ^{59}Fe utilizations

were determined immediately before and four weeks after splenectomy. In each case the large increase in ^{59}Fe utilization may be taken to indicate increased erythropoiesis, unless some as yet unknown factor was operating to depress utilization before splenectomy.

The ^{59}Fe surface-counting patterns shown originally in both patients (Figs. 4 and 6) are commonly seen in myelofibrosis, and their interpretation has been discussed elsewhere (Hutt, Jones, and Wetherley-Mein, 1959). They are not adequately explained by variations in the size of the liver and spleen, the degree of anaemia, or the level of red-cell production. Variations in the size of the iron pool labelled affect the rate of removal of ^{59}Fe by various organs, but do not determine the differential distribution of the isotope. The flattened sacral marrow curve and splenic peak in myelofibrosis do not necessarily vary with the level of red-cell production. It is of interest that in both these cases the marrow curve tended to return towards normal after splenectomy (Figs. 5 and 7), although in neither case was a normal pattern fully established. This change further supports the view that the improved ability of these patients to maintain their haemoglobin levels resulted from increased erythropoiesis as well as from lengthened red-cell life.

Reticulocytes were plentiful in the peripheral blood of these patients at times when red-cell production was much reduced. This apparent discrepancy has been observed in myelofibrosis by others (Nathan and Berlin, 1959), and may be due to an alteration in the phase life of the reticulocyte in the circulation.

It is often held that in this disease the spleen is an important site of erythropoiesis and that splenectomy is therefore contraindicated. However, despite histological evidence of numerous red-cell precursors in the spleen, the results in the cases reported here suggest that in some cases not only may the splenic contribution to effective erythropoiesis be insignificant but that the spleen may itself inhibit red-cell production elsewhere. In one of their cases Nathan and Berlin (1959) obtained evidence that the spleen was producing red cells but failing to discharge them into the circulation. The presence of red-cell precursors in histological preparations of the spleen does not necessarily imply the efficient delivery to the circulation of normal red cells.

In reported cases of myelofibrosis where there has been benefit from splenectomy, the usual indications for operation have been uncontrollable haemolytic anaemia or persistent thrombocytopenia, but it seems that increasing difficulty in the management of an anaemia due to failure of red-cell production may be an additional indication for splenectomy. We have observed other cases of myelofibrosis subjected to splenectomy where the patient's ability to maintain his haemoglobin level after operation has been increased in some, unchanged in others, and occasionally diminished. A method of predicting the effects of splenectomy on red-cell production would be valuable. In one case of myelofibrosis in which ^{59}Fe and ^{51}Cr studies were made we observed no increase in red-cell production after splenectomy. In this patient's bone-marrow there was a total absence of red-cell precursors. In the marrow of the two cases reported above, scattered islands of red-cell precursors could be found. It may be that a failure to find in the marrow any evidence of active erythropoiesis, however slight, indicates that no increase in red-cell production can be expected after splenectomy.

Further work is necessary to define the indications for splenectomy, but we think it premature to conclude that it is never indicated in this condition.

Increasing hepatomegaly after splenectomy in myelofibrosis has been described, but has not necessarily been associated with either jaundice or rapid clinical deterioration—for example, Case J. G. of Nathan and Berlin (1959). We have observed this change after splenectomy in other myeloproliferative disorders in the absence of haematological deterioration. During the three months following operation in Case 2 reported here, the liver enlarged considerably and an obstructive-type jaundice was present for the last month of life. Necropsy was not allowed, and the pathology of this jaundice is unknown. It remains to be seen whether the possibility of subsequent liver damage should contraindicate splenectomy in this condition.

A brief consideration of the theoretical implications of our findings is appropriate. The relationship between the spleen and the bone-marrow remains obscure, and the relative roles of red-cell hypersequestration and marrow inhibition by the spleen are still debated (Doan, 1949; Dameshek, 1955). It is difficult to interpret the results obtained in these two patients wholly in terms of splenic hypersequestration of red cells. The increased red-cell production after splenectomy implies splenic inhibition of erythropoiesis. This finding lends support to the view that the spleen may not only be an important site of red-cell destruction, but may on occasion simultaneously limit effective red-cell production.

Summary

In two cases of myelofibrosis splenectomy was followed by considerable haematological improvement.

Evidence was obtained that erythropoiesis was increased after splenectomy in each case. The significance of this finding is discussed.

The indications for and against splenectomy in myelofibrosis are still uncertain, but it is premature to conclude that the operation is never indicated in this condition.

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REFERENCES

- Andreasen, A. P. (1958). *Myelofibrosis*. Munksgaard, Copenhagen.
 Bothwell, T. H., and Mallett, B. (1955). *Biochem. J.*, **59**, 599.
Brit. med. J., 1960, **1**, 625.
 Claman, M. A., and Collier, W. J. (1952). *Arch. intern. Med.*, **89**, 431.
 Dameshek, W. (1955). *Bull. N.Y. Acad. Med.*, **31**, 113.
 Doan, C. A. (1949). *Ibid.*, **25**, 625.
 Donhauser, J. L. (1908). *J. exp. Med.*, **10**, 559.
 Edwards, H. C. (1951). *Lancet*, **2**, 601.
 Franks, R. B., and Richardson, J. S. (1952). *Proc. roy. Soc. Med.*, **45**, 30.
 Green, T. W., Conley, C. L., Ashburn, L. L., and Peters, H. R. (1953). *New Engl. J. Med.*, **248**, 211.
 Hickling, R. A. (1937). *Quart. J. Med.*, **6**, 253.
 Hutt, M. S. R., Jones, N. F., and Wetherley-Mein, G. (1959). *Trans. 7th Congr. Europ. Soc. Haemat., London*.
 —, Pinniger, J. L., and Wetherley-Mein, G. (1953). *Blood*, **8**, 295.
 Jackson, H., Parker, F., and Lemon, H. M. (1940). *New Engl. J. Med.*, **222**, 985.
 Jones, N. F., Wetherley-Mein, G., Ingram, G. I. C., and Langmead, W. A. (1960). *J. clin. Path.*, **13**, 391.
Lancet, 1949, **2**, 756.
 Learmonth, J. (1951). *Brit. med. J.*, **2**, 67.
 Nathan, D. G., and Berlin, N. I. (1959). *Blood*, **14**, 668.
 Panels in Therapy (1955). *Ibid.*, **10**, 550.
 Reich, C., and Rumsey, W., jun. (1942). *J. Amer. med. Ass.*, **118**, 1200.

- Sanneman, E. H., McIlvanie, S. K., and Beard, M. F. (1950). *J. Kentucky med. Ass.*, **48**, 453.
 Shinton, N. K. (1957). *Brit. med. J.*, **2**, 1395.
 Videbaek, A. (1956). *Acta haemat. (Basel)*, **15**, 235.
 Wetherley-Mein, G., and Hutt, M. S. R. (1960). In *Recent Advances in Clinical Pathology*, series 3, p. 241, edited by S. C. Dyke. Churchill, London.
 —, Langmead, W. A., and Hill, M. J. (1956). *Brit. med. J.*, **1**, 1445.

EFFECT OF AN ANTIBACTERIAL NASAL CREAM ON NASAL COLONIZATION AND INFECTION IN THE NEWBORN

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The increasing incidence of staphylococcal infections in maternity hospitals has become a matter of some concern. Although most of the infections which occur in babies in hospitals are superficial and mild, severe infections—for example, pneumonia and pemphigus—may arise, and some may also develop after the baby has left hospital—for example, osteomyelitis. Similarly, severe staphylococcal infections are not common in parturient women while in hospital but may develop later—for example, breast abscess.

If the number of staphylococci in the environment could be lowered an appreciable reduction in the number of lesions due to these organisms might be found. A high proportion of babies' noses become colonized with staphylococci during the first few days of life (Cunliffe, 1949; Parker and Kennedy, 1949; Cook *et al.*, 1958; Gillespie *et al.*, 1958). Not only may this colonization lead to infections in hospital but a large proportion of babies may leave hospital carrying pathogenic staphylococci, which may give rise to serious sepsis in the baby or in the mother during the weeks after discharge. These staphylococci are often retained for many months (Ludlam, 1953; Hurst, 1957).

It has been shown that the use of an antibiotic nasal cream by the hospital staff reduces the incidence of staphylococcal cross-infection in a ward (Gould and Allan, 1954; Rountree *et al.*, 1956), but the routine use of a nasal cream by hospital staff presents considerable administrative difficulties. It was decided, therefore, to carry out a trial of the application of an antibacterial nasal cream ("naseptin") to the anterior nares of babies from birth and to study the effect on nasal colonization and on the incidence of infection.

Methods

The wards in which the investigation was carried out are large and old-fashioned, holding 14 to 16 beds; there are very few side-rooms, and the facility for isolation of mother and child is limited. The nurseries hold up to 15 cots, and the babies remain therein, apart from feeding-times and a period of five hours each day which they spend with their mothers. Masks are not worn by the paediatric nursing and medical staff nor by the mothers. The cord is tied with sterile ligatures, and