Of the 10 untreated patients—excluding one who survived for some two months—the survival time ranged from 4 to 20 days, with a mean of 12 days. The 40 treated patients survived from 2 days to 32 months, with a mean of 9.1 months. This figure compares unfavourably with that of Lightwood et al. (1960), whose cases had an average survival time of 13.3 months. This untreated cases, however, survived for three months, which would suggest that there was a higher proportion of very ill children in the present series. Zuelzer and Flatz (1960) also report a mean survival of 13 months in their cases of acute lymphoblastic leukaemia.

Factors Influencing the Response

In 12 children the predominant cell type was clearly granulocytic—this includes the case of mononuclear leukaemia. Six of these were treated, but in only one was there a remission; this followed some 10 weeks of treatment with 6-mercaptopurine and multiple blood transfusions. When the remission became established treatment had been stopped because the outlook appeared hopeless. The mean survival time of the six cases was two months; one child survived for 90 days, but there was no clinical or haematological remission. Of the six undifferentiated cases only three were treated; in one there was a good remission with a 12-months survival; the other two did not respond, and died within two weeks.

Of the children thought to be suffering from acute lymphoblastic leukaemia—30 in all—the mean survival time was 11 months and there were full remissions in 24 patients (80%). As the survival time of the whole series was 9.1 months, it would appear that the lymphoblastic cases did better. The chances of a worthwhile remission would seem to be much poorer if the cell type is granulocytic. This conclusion was also reached by Fessas et al. (1954).

It has been suggested that there might be an inverse relationship between the initial leucocyte values and the prognosis (Haut et al., 1959; Zuelzer and Flatz, 1960). In the present series the survival time was approximately 20 weeks in those children with leucocyte counts of 5,000/c.mm. or less, whereas in those with counts of 5,000 to 50,000/c.mm. the mean survival time was 43 weeks. This difference is highly significant (P<0.002 vs 0.1). The eight children with leucocyte counts of over 50,000/c.mm. survived a mean period of 31 weeks, but there was such a great individual variation in this small group that the significance cannot be assessed. This finding of a poorer prognosis in the leucopenic patients does not agree with the finding of the authors mentioned above.

There was no obvious relationship between prognosis and any other clinical or haematological finding.

Summary

A series of 50 cases of childhood leukaemia have been studied. Nearly all these children were treated initially with steroids, after which the antimetabolites 6-mercaptopurine and aminopterin or methotrexate were used successively after steroid withdrawal. Steroids were also used to cover changes of therapy and in the terminal illness. Of 10 untreated cases (excluding one which survived for two months) the mean survival time was 12 days. Of the 40 treated cases the overall survival time was 9.1 months. Cases of lymphoblastic leukaemia survived for 11 months, but with one doubtful exception.

No case of acute granulocytic leukaemia responded to treatment. Case summaries are given of four children who developed cerebral complications during treatment.

References


ANAEMIA IN THE RETICULOSES

BY

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Among the diverse features of the reticuloses, one of the most constant is the appearance at some stage of anaemia, and in many patients there will be phases of the disease in which this is the principal cause of disability. The severity and rapidity of development of the anaemia is very variable, but, in general terms, a rapidly worsening anaemia, as in acute leukaemia, produces a much more profound disturbance and more marked symptoms than a slowly developing anaemia of similar degree. In chronic myeloid leukaemia the anaemia is early to develop but usually only very slowly progressive, so that patients may be found performing a normal range of daily tasks despite a well-marked reduction in their circulating haemoglobin level. In chronic lymphatic leukaemia, however, the anaemia is often delayed to a comparatively late stage of the disease and is more rapid in development once it has appeared, with the consequence that its effects are more insistent and its prognostic significance may be worse. The frequency with which anaemia is found in these conditions has been emphasized by studies such as those of Samuels and Bierman (1956), in which haemoglobin levels of under 10.3 g./100 ml. were demonstrated at some stage in 97% of series of acute leukaemia, 95% of chronic myeloid leukaemia, and 75% of chronic lymphatic leukaemia.

Cure of these diseases remains unattainable, and their treatment is most often reduced to the management of their anaemia and the symptomatic treatment of lymphomatous masses. It is our purpose here to consider the former, which to us often appears to be a neglected aspect of these diseases.

Investigation of Anaemia

The cause of anaemia is only occasionally apparent in the individual patient, and the underlying processes are only now being defined with any certainty.

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Haemorrhage, usually external, is the major factor in only a minority of patients and is often associated with low platelet levels in the peripheral blood.

In general the accompanying anaemia may be said to be due either to reduced production or to diminished survival of red cells, and it has for long been accepted that the main cause is a reduction in the rate of production due to the “crowding out” of the bone-marrow with abnormal cells. However, for many years occasional cases have been described in which haemolysis appears to be present (Hirschfeld, 1906); and Jaffé (1935) was able to demonstrate haemaphagocytosis and erythrophagocytosis in necropsy material, which he regarded as suggestive of excessive red-cell destruction. Much of the difficulty encountered in the acceptance of haemolysis as a factor in the production of anaemia in these conditions undoubtly derived from the relatively insensitive methods, such as the reticulocyte count and serum bilirubin level, which were available for its detection; but with the wider use of tracer studies, at first with the Ashby technique and later with isotope labelling, its importance was more firmly established. More recent studies (Berlin, Lawrence, and Lee, 1951; Brown, Elliott, and Young, 1951; Wetherley-Mein, Epstein, Foster, and Grimes, 1958) have emphasized the occurrence of haemolysis in these diseases.

Gray and Sterling (1950) described the radiochromium method for labelling the red cell, and this has provided an acceptable method for estimating the red-cell life-span, suitable corrections being applied for loss of the isotope by elution from the cell. The main advantages of $^{51}$Cr labelling are that the subject’s cells can be studied in his own circulation, and, secondly, it is possible to assess the most important sites of destruction by estimating the changes in the radioactivity at the body surface over various organs (Jandl, Greenberg, Yonemoto, and Castle, 1956; Schloesser, Korst, Clatanoff, and Schilling, 1957). Provided that it is reasonably certain that changes in the haematocrit value are reflecting changes in the red-cell mass, and are not secondary to abnormalities in plasma volume, the level of marrow activity may be inferred from the red-cell life-span, as suggested by Chaplin and Mollison (1953). In a review of this problem Price and Greenfield (1958) concluded that there was no satisfactory evidence that blood volumes were abnormal in neoplastic disease provided that comparisons were made on the basis of the lean body mass, and that haemoglobin concentrations and haematocrit values were reasonable criteria of anaemia in neoplastic disease.

It is possible to obtain independent evidence of marrow activity, and this may be given by radioiron studies, performed if necessary simultaneously with the radiochromium technique. Useful information may be gained by the determination of the percentage of iron utilized in haemoglobin formation after the intravenous injection of a dose of $^{59}$Fe bound to the patient’s $\beta$-globulin, accompanied by serial surface estimations of activity over the lumbar or sacral bone-marrow, liver, and spleen. These may be compared empirically with normal patterns, and give information concerning marrow erythropoietic activity, organ accumulation of iron in stores, destruction of newly formed cells, and extramedullary haemopoiesis. The rate of disappearance of iron from the plasma has also been used as an index of marrow erythropoietic activity (Huff, Hennessey, Austin, Garcia, Roberts, and Lawrence, 1950; Bothwell, Hurtado, Donohue, and Finch, 1957). But the interpretation of the results has been criticized and the method is doubtfully valid as a measure of erythropoiesis when a significant fraction of the injected iron enters the body stores (Price and Greenfield, 1958; Joske, McAlister, and Pranker, 1956).

Thus the value of radioisotope studies of these conditions lies mainly in their ability to distinguish anaemia due to deficient production of red cells from that due to reduced red-cell survival. Further, in cases showing haemolysis they may indicate the principal sites of destruction. Their main disadvantage is that they are time-consuming, taking at a minimum five to ten days, and cannot provide immediate solutions; generally speaking, they need to be used in special situations to complement information obtained from the more orthodox methods of investigation available.

The Haemolytic Component

There is now ample evidence that the red-cell life may be shortened in patients suffering from many of the reticuloses. This may be evident by an obvious haemolytic clinical picture very similar to that found in acquired idiopathic haemolytic anaemia with evidence of autoimmunity, but more commonly the haemolysis is “latent” or “occult” and requires estimation of the R.B.C. life-span for its detection.

Frank Haemolytic Anaemia

The commonest of these diseases to be associated with autoimmune haemolysis is chronic lymphatic leukaemia, but the association has also been described in lymphosarcoma (Troup, Swisher, and Young, 1960), Hodgkin’s disease (Dacie and deGruchy, 1951; Rosenfield, Vogel, and Rosenthal, 1951; Sulzer, 1952), reticulosarcoma (Dacie, 1954), and giant follicular lymphoblastoma (Rosenthal, Pisciotta, Komninos, Goldenberg, and Dameshek, 1955). In contrast to haemolytic states without demonstrable antibodies, the autoimmune anaemia is often rapidly progressive and may occur at any stage in the progress of the underlying disease, and may indeed herald the onset of more frankly leukemiac features. There is considerable reduction in the red-cell life-span, which is usually of the order of 5 to 15 days.

Case 1. Chronic Lymphatic Leukaemia with Autoimmune Haemolytic Anaemia

A housewife aged 65 complained of increasing lassitude and swelling of both legs for the previous five weeks. On examination she showed marked pallor, the spleen was palpable 5 cm. below the umbilicus, and the liver was felt 3 cm. below the right costal margin. There was no significant lymphadenopathy. A blood count showed haemoglobin 6.4% of the cells; the white cell count was 6,000/mcL, white cells 3% lymphocytes, neutrophils 60%, and eosinophils 2%. The reticulocyte count 4.8%. The direct antiglobulin test was positive to a titre of 1 in 2,048. There was no excess of urinary urobilinogen. A differential marrow count showed 73% lymphocytes and 1% blast cells.

For the first few days after admission the patient’s condition continued to deteriorate, she became afebrile and the haemoglobin fell further. Steroid therapy with prednisone 60 mg. daily led to a prompt fall in the fever and a rise in the haemoglobin. There was a slight decrease in the size of the spleen, the serum bilirubin fell to 0.5 mg./100 ml. and the reticulocytes to 1.2%. but the direct antiglobulin test was still positive one year later. The subsequent
haematological findings in relation to treatment are shown in Fig. 1. It can be seen that there has been a sustained remission of the anaemia for over three years while steroid therapy has been continued.

Fig. 1.—Case 1. Effect of steroid therapy on autoimmune haemolytic anaemia due to chronic lymphatic leukaemia.

The mechanism of haemolysis in this group of disorders appears to be due to agglutination of cells in the peripheral circulation. According to the coarseness of the agglutinates red cells may be trapped in the liver, the spleen, or the bone-marrow. In the case of the finest agglutinates, only the spleen appears to show a trapping action (Jandl, Jones, and Castle, 1957).

Latent Haemolytic Anaemia

"Latent" haemolysis is less dramatic in its onset and course and is not detectable by the commonly used indirect criteria of haemolysis. It has now been described in a substantial number of cases of the more common reticuloses (Brown, 1950; Berlin, Lawrence, and Lee, 1951; Weinstein and LeRoy, 1953; Wetherley-Mein et al., 1958; Ulmann, 1958; Desforges, Ross, and Moloney, 1960), and varies considerably in its severity, the red-cell life-span being commonly between one-fifth and one-half of the normal. Some cases show abnormalities in the appearance of the red cells, with anisocytosis and polikilocytosis, suggestive of an intracorpuscular defect, while cross-transfusion studies have demonstrated shortening of the life of normal red cells in the circulation of patients with leukaemia, indicating an extracorpuscular cause (Berlin, 1951; Brown et al., 1951; Ross, Crockett, and Emerson, 1951). It is probable, in fact, that more than one mechanism may be responsible, a view supported by the recent demonstration of random destruction in patients with myeloid leukaemia and Hodgkin's disease, and finite shortening of red-cell life in two patients with lymphatic leukaemia by Eernisse and van Rood (1961) using $^{32}$P as the red-cell label.

Case 2. Latent Haemolytic Anaemia Complicating Myelomatosis

A consulting engineer aged 65 was first seen six weeks after the onset of severe lower lumbar pain radiating to the lower limbs. Flexion of the spine was limited by pain, and radiography showed collapse of the third lumbar vertebra. Investigation showed haemoglobin 13.9 g./100 ml, white cells 7,000/c.mm., E.S.R. 54 mm. in one hour, total serum proteins 10.5 g./100 ml, and electrophoresis revealed the typical increase in the $\gamma$-globulin of myelomatosis. The urine contained Bence Jones protein, and a marrow smear showed 27% of abnormal plasma cells. Local radiotherapy to the lumbar spine and $^{32}$P to a total dose of 10.2 mc. was followed by considerable improvement in the pain.

A steadily progressive anaemia later supervened and eight months from the onset of symptoms the haemoglobin had fallen to 10.7 g./100 ml, and six months later to 6.3 g./100 ml. The serum bilirubin was 0.5 mg./100 ml, and the direct antiglobulin reaction was negative. Extensive multiple transluencies were present in the x-ray films of many bones with partial collapse of the second lumbar vertebra. Radioisotope studies at this time indicated a mean red-cell life-span of 15 days, but there was no significant accumulation of the $^{51}$Cr tracer in the liver or spleen. Iron utilization ($^{59}$Fe) corrected for haemolysis was 62%. Blood transfusion raised the haemoglobin level to 7.7 g./100 ml, but no further improvement followed treatment with prednisone 60 mg. daily. Shortly afterwards the patient died from a myocardial infarction complicated by pneumonia. Necropsy confirmed the extensive myelomatous deposits in bone. The spleen was small and atrophic (weight 90 g) with very prominent fibrous trabeculae.

At the present time little is known of the mechanisms by which the red-cell life is shortened in this group, although one possible system has been partially defined by Crosby and Benjamin (1957), who found that cells from patients with leukaemia and other malignant diseases showed greater in vitro haemolysis than normal cells, and that this was inhibited by a low pH, added glucose, or removal of calcium. The most useful division of cases, in the absence of more fundamental criteria, is into those in which there is no dominant organ responsible for destruction and those in which one organ, usually the spleen, is playing a significant part, since in the latter there is the therapeutic possibility of splenectomy. Fig. 2 shows the results of a $^{51}$Cr study in a patient aged 55 with chronic myeloid leukaemia and gross splenomegaly, in whom the tracer showed accumulation in the spleen. This may be compared with Fig. 3 from a study in a patient with reticulo-sarcoma, who also showed considerable shortening of the red-cell life but without significant organ accumulation of $^{51}$Cr.

Impaired Erythropoiesis

Impairment of the production of red cells is clearly present in cases showing anaemia in the presence of a normal red-cell survival; two instances are shown in the Table, one with chronic lymphatic leukaemia and the other with myelomatosis. Evidence of reduced unit activity of the bone-marrow may also be inferred from surface counting over the lumbar spine or sacrum after administration of a dose of radioiron; the significance of the patterns found has been discussed by Harris, McAlister, Prankerd, and Singh (1957) and Bowdler.

Table of Red-cell Survival and Marrow Activity in Patients with Reticuloses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean</th>
<th>Index of Marrow Activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Red-cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Life</td>
<td></td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
<td>26%</td>
<td>24 days</td>
</tr>
<tr>
<td>&quot;</td>
<td>23%</td>
<td>27 days</td>
</tr>
<tr>
<td>&quot;</td>
<td>27%</td>
<td>30 days</td>
</tr>
<tr>
<td>&quot;</td>
<td>34%</td>
<td>28 days</td>
</tr>
<tr>
<td>&quot;</td>
<td>38%</td>
<td>30 days</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>34%</td>
<td>28 days</td>
</tr>
<tr>
<td>Reticulosarcoma</td>
<td>33%</td>
<td>15 days</td>
</tr>
<tr>
<td>Myelomatosis</td>
<td>19%</td>
<td>15 days</td>
</tr>
</tbody>
</table>

*Index of marrow activity = Normal R.R.C. life-span

Patient's haematocrit = Normal haematocrit

Fig. 4 illustrates a virtually normal pattern from a patient with reticulosarcoma (A), impairment of iron uptake in a patient with chronic lymphatic leukaemia (B), and an almost complete suppression of iron uptake and release in a subject with chronic myeloid leukaemia (C). Further evidence of impaired marrow activity is the inadequate response made by many of these patients to the stress imposed by shortening of the red-cell life. The index devised by Chaplin and Mollison (1953) expresses red-cell production as a fraction or multiple of the normal by the product of the ratio of the observed to the normal haematocrit and the ratio of the normal to the observed red-cell life-span. Despite the assumptions made concerning the significance of the haematocrit value, this provides a useful guide to the net erythropoietic activity, and in long-standing haemolytic anaemias indices of 6 or more are commonly found. It can be seen from the Table that such a marked increase does not occur, and the best response we have found is approximately three times the normal output of red cells.

It has commonly been held that the reduced activity of the marrow is due to marrow replacement by abnormal cells, but there are extensive sites for the expansion of the erythropoietic cells both within and outside the marrow cavities, and on marrow biopsy many cases appear to have adequate numbers of red-cell precursors. Secondly, red-cell production may be increased above normal in the presence of haemolysis, although not to the extent which would be provided by a normal marrow. It thus appears that the impairment of red-cell production is relative rather than necessarily absolute, in that there is an inadequate response to the demands of the usual controlling factors. Whether this is due to humoral inhibition, to some form of metabolic competition, or to insufficiency of a regulating hormone is not yet clear.

The estimation of urinary erythropoietin in eight patients with this type of anaemia by the method of Cotes and Bangham (1961) revealed elevated levels in three, while in five they were not elevated, and it is impossible to say at present what part erythropoietin may play in the development of these anaemias.
Associated and Secondary Forms of Anaemia

The forms of anaemia so far considered are usually normochromic and normocytic. It must be remembered that occasionally other forms of anaemia are to be found in association with reticuloses (sometimes incidentally, such as idiopathic hypochromic anaemia) or, as shown in the following case, arising from the effects of the reticulosis itself.

Case 3. Folic-acid Deficiency Complicating Hodgkin's Disease

A male cashier, aged 43, when first seen was complaining of generalized pruritus of six weeks' duration. He showed a widespread erythematous rash and enlarged mobile lymph nodes in the groins, axillae, and neck; the spleen was just palpable and the liver slightly enlarged. Investigation showed haemoglobin 10.6 g./100 ml., white cells 5,600/ c.mm. (differential normal), and E.S.R. 28 mm. in one hour. Chest radiography showed a fine diffuse pulmonary reticulosis. Biopsy of an axillary lymph node showed typical Hodgkin's lymphoma, but a skin biopsy revealed no specific changes in the papillary and reticular nodes regressed after radiotherapy and the rash improved. Four months later he complained of increasing lassitude and failure of concentration, and the haemoglobin level was found to have dropped to 7.8 g./100 ml. Two weeks later the haemoglobin was 3.8 g./100 ml., white cells 800/c.mm., platelets 50,000/ c.mm., and serum bilirubin 0.6 mg./100 ml.; the direct antiglobulin reaction was negative. Marrow aspiration showed well-marked megaloblastic changes and no megalakaryocytes or blast cells. Transfusion of 1 litre of blood raised the haemoglobin to 4.7 g./100 ml.

Cyanocobalamin 1 mg. daily intramuscularly for 14 days produced no reticulocyte response and no further rise in the haemoglobin level, and megaloblasts were again demonstrated in the marrow at the end of this time. It was observed that the stools were bulky and greasy, and a fat balance showed impaired absorption (88%). Treatment was therefore started with folic acid 30 mg. intramuscularly weekly, which resulted in a prompt reticulocyte response and a rise in the haemoglobin level to 9.3 g./100 ml. within three weeks. No recurrence of the anaemia was observed during the next three years. It seems most probable that the steatorrhoea and folic-acid deficiency were due to malabsorption consequent upon lymphomatous infiltration of the small bowel or its lymphatic pathways.

Incidence

It is not possible to assess precisely the incidence of the different forms of anaemia, since this and other series have been made on selected patients. However, one estimate (Troup et al., 1960) has put the incidence of immune haemolytic anaemia in chronic lymphatic leukaemia at 14%, and the incidence of non-immune haemolytic processes at some stage in the disease will be higher. In chronic myeloid leukaemia, Hodgkin's disease, and myeloma immune haemolysis is rare, but the incidence of non-immune haemolysis may be as high as 40% towards the end of the course of the disease. Successful splenectomy for hypersplenism is a rare feature, while marrow depression accounts for anaemia in the remainder of patients.

Treatment

Satisfactory treatment of anaemia associated with the reticuloses depends first on correct diagnosis. In general, the anaemia resulting from haemolysis or marrow depression is normochromic and normocytic, although in cases showing autoimmune haemolysis spherocytosis may be marked. Chronic blood loss, on the other hand, classically produces the familiar hypochromic picture; but this is not found until the storage iron is depleted, and before this stage is reached the red cells will not be distinguishable from those found in the anaemias special to the reticuloses. It is thus essential in all such cases to investigate the possibility of blood loss, especially into the gastro-intestinal tract, since these cases will require further elucidation to determine whether the cause lies in a localized and possibly treatable condition or in a haemorrhagic tendency requiring appropriate correction.

The suppression of localized or generalized lymphomatous processes by means of radiotherapy or cytotoxic drugs may lead to the alleviation of an associated anaemia, especially during the initial course of treatment, but it is commonly found that on subsequent occasions the response is less satisfactory and a state of continuous anaemia may supervene. At this stage other forms of therapy directed more especially towards the anaemia must be considered.

Corticosteroids are probably the agents most widely useful in this respect, although their limitations remain to be more clearly defined. Their use in autoimmune haemolytic anaemia is illustrated by Case 1, in which a prolonged remission of the anaemia was induced, although the direct antiglobulin reaction was still positive for a long period. In these cases, although the red-cell life is not necessarily restored to normal it is sufficiently lengthened for the bone-marrow to provide more adequate replacement relative to the rate of red-cell destruction. In Case 1 it is most probable that the improvement in the anaemia resulted directly from the suppression of antibody production and not from an improvement in the leukaemic process, so far as this may be judged from the white-cell count, which did not vary with the dosage of the corticosteroid. In other cases, however, the effect of the steroid appears to be mediated by the depression of the leukaemic process, as may be seen in the following instance.

Case 4. Chronic Lymphatic Leukaemia Treated with Corticosteroids

A housewife first complained of fatigue, recurrent febrile episodes, and enlarged cervical lymph nodes at the age of 54. She was not anaemic, but the white-cell count was 24,000/c.mm., with 92% lymphocytes. The subsequent clinical course is outlined in Fig. 5. For two years she was...
treated with urethane without improvement. Early in 1956 she complained of ankle-swelling and exertional dyspnoea, which were not improved by intravenous mustine (HN2) given to a total dose of 24 mg. During the course of six months the haemoglobin level fell from 11.8 to 8.6 g./100 ml., where it was maintained only by transfusions of packed red cells, and the white-cell count rose.

Examination in December, 1956, showed a very pale dyspnoeic patient in mild cardiac failure and with generalized enlargement of superficial lymph nodes. The fundi showed several small haemorrhages, and purpura affected both lower limbs. The spleen was enlarged to 10 cm. and the liver to 8 cm. below the costal margins. A blood count showed haemoglobin 3.7 g./100 ml., M.C.H.C. 32%, white cells 180,000/c.mm. with 61% lymphocytes, platelets 29,000/c.mm., and reticulocytes 0.8%. The direct antiglobulin reaction was negative. Marrow biopsy showed a great excess of lymphocytes. No abnormal mediastinal shadows were seen in a chest radiograph. 91Cr studies showed a slight reduction in the red-cell life (T1/2Cr 20 days), but 4Fe-testing demonstrated a greatly diminished iron uptake by the lumbar marrow and no extramedullary sites of erythropoiesis. Transfusion raised the haemoglobin level transiently to about 8.5 g./100 ml., to be followed by a mild fall to the previous level within two weeks.

A further transfusion accompanied by prednisone 60 mg. daily led to a sustained rise in the haemoglobin level with a reticulocyte rise to a peak of 6%. Five weeks from the start of steroid therapy the haemoglobin had reached 10.7 g./100 ml., and, apart from a short course of radiotherapy to the lymph nodes of the neck, prednisone in a maintenance dose of about 20 mg. daily was continued as the only therapeutic agent. Eight weeks from the beginning of treatment the haemoglobin was 14.8 g./100 ml and the white cells 55,000/c.mm. The liver, spleen, and lymph nodes showed a marked reduction in size, the purpura had cleared, and the patient was symptom-free. Subsequently the white-cell and platelet levels returned to normal.

The satisfactory course was interrupted about two years later by the onset of persistent epigastric pain and intermittent vomiting. This was followed by the development of jaundice of obstructive type and the patient died shortly after, having failed to respond to a course of upper abdominal radiotherapy. Necropsy confirmed the cause of death as carcinoma of the head of the pancreas complicating chronic lymphatic leukaemia.

In other cases it has not infrequently been found that steroid therapy may relieve anaemia even when the primary disease appears to be unaffected and when autoantibodies cannot be demonstrated by the Coombs test. The response appears to be more common when the anaemia is dependent on accelerated red-cell destruction rather than on marrow depression alone, but a satisfactory means of selecting those patients likely to benefit from such treatment is still lacking and it is necessary to depend on a carefully observed individual trial. High initial dosage is frequently required, using up to 100 mg. of prednisone daily, or the equivalent of other steroids, reducing the dose, usually after about two weeks, when a response has been obtained. Maintenance dosage of about 20 mg. of prednisone is then needed to sustain the remission. Careful supervision must be possible before embarking on the use of steroids in this dosage, but the serious prognosis of the diseases in this group must be set against the possible complications of the therapy, which in many cases may be the only means of offering the patient some alleviation of symptoms. It is sometimes necessary to accept that the response to treatment may be limited to halting or slowing a progressive fall in the haemoglobin level, and that it may not be possible to maintain this at normal levels owing to limited power of the marrow; but this in itself may be of considerable benefit, especially when the patient has been committed to repeated transfusion.

Anabolic steroids have also been found by some (Gardner and Pringle, 1961) to be helpful in these cases, but we have not as yet seen an unequivocal response to these agents.

Occasional cases are found in which the spleen appears to play a significant part in the production of anaemia. Splenectomy must be carefully considered, since the value of a major operation in alleviating anaemia must be balanced against the probability that the effect at best will be only temporary. The finding of pancytopenia in the presence of an active bone-marrow on biopsy provides useful circumstantial evidence, but the best evidence of red-cell destruction by the spleen is given by tracer accumulation in the spleen in a 51Cr study as outlined previously (Fig. 2). Fig. 6 summarizes the clinical course of a patient with chronic myeloid leukaemia in whom the white-cell count was repeatedly lowered by radiotherapy to the spleen. Despite this there was a progressive anaemia requiring frequent transfusions. After splenectomy the haemoglobin level rose satisfactorily, although not to normal levels, and the patient received a considerable remission of his symptoms.

Blood transfusion presents many problems in these conditions, and in general is best regarded as a temporary measure for special purposes. In acute leukaemia it may be useful in providing time for a spontaneous or drug-induced remission to occur, but there inevitably follows a progressive lessening of the effectiveness of transfusion as the disease progresses and the survival of the donated red cells shortens. In more chronic conditions the patient frequently achieves a measure of equilibrium with a slight or moderate degree of anaemia, and is little impaired by it. In such cases there is little to be gained by transfusion, the effects of which can only be temporary, and which will transiently reduce the erythropoietic activity of the patient's own marrow. Committing a patient to a lifelong course of repeated transfusions carries its own special hazards, partly due to the possibility of transfusion reactions and incom-
patibility problems, but also to the secondary effects of excessive iron storage. In general, blood should be used sparingly, with the object of allowing other therapeutic measures to have their effect, or to counter acute haemorrhage or permit surgery.

Conclusions

Anaemia is a common accompaniment to the reticuloses, and, according to its severity and rate of development, it may be well or poorly tolerated, often proving a significant factor contributing to a fatal outcome. It arises from a variety of causes: in a few cases it is truly incidental, while in others it arises as a sequel to recognizable disorders resulting from the primary disease, such as haemorrhage or gastrointestinal infiltration. Least understood are the intrinsic anaemias, the pathogenesis of which remains largely obscure. These may be due to increased red-cell destruction, to marrow depression, or, perhaps most commonly, to a combination of both, and there is evidence that more than one mechanism may be responsible for each of these factors.

Apart from infections and the effects of tissue condition, anaemia is the commonest terminal condition encountered, and it is clear that its careful management can contribute much to the life and comfort of patients with these disorders, for which as yet there is no definitive treatment to be offered. The assessment of the individual case can be assisted by tracer procedures where these are practicable, and may suggest the most useful course to be followed within the relatively limited range of therapy at present available. As with other aspects of the treatment of these cases, the results of treating the anaemia are at best essentially temporary and the degree of improvement is often limited. Nevertheless, this constitutes an important facet of the total management of the patient with a reticulosis for which at the present time a more fundamental approach is not possible.

We are grateful to Dr. Gwen Hilton and Dr. E. W. Emery for their help and co-operation, and to the British Empire Cancer Campaign for providing assistance.

References


Isolation of Antibody-Like Gamma-Globulin from Lupus Glomeruli

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Gamma-globulin and complement have been demonstrated in the renal lesions of glomerulonephritis and systemic lupus (Freedman, 1960; Freedman and Markowitz, 1962). This report deals with an immunological property of globulins, eluted from a glomerulonephritic and a lupus kidney, which in the case of the lupus eluate manifested activity strongly suggesting that it was an antibody. A preliminary report of these experiments has already been made (Freedman and Markowitz, 1959).

Materials and Methods

Three kidneys were used: one normal (free from renal disease), one glomerulonephritic, and one from a patient with lupus nephritis. The kidneys were obtained within a few hours of death, packed in cold physiological saline, and stored at —20° C. until processed. By both clinical and histological data the designated category assigned to each kidney was felt to be correct.

Isolation and Elution of Glomeruli.—The glomeruli from approximately one whole kidney from each of the three necropsies were isolated by Greenspoon's method (Greenspoon and Krakower, 1950). The isolated glomeruli were suspended in 0.02 M citrate buffer, pH 3.2, and gently agitated by means of a magnetic stirrer for two hours at room temperature. At the end of this period the glomeruli were removed by cold centrifugation and the three eluates were neutralized. Evaluation of these eluates was conducted by filter-paper electrophoresis as well as immunologically with a rabbit antihuman gamma-globulin serum.