Aplastic anaemia: an analysis of 174 patients

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Summary
The authors summarize their experience with 174 patients with aplastic anaemia (AA) with particular reference to course, prognostic factors, conversion to other blood disorders, treatment and outcome. Aplastic anaemia was defined as pancytopenia and a hypocellular marrow at some time during the illness. Seven patients terminated with acute leukaemia, 8 developed haematological features of sideroblastic anaemia and 5 showed a red cell membrane defect commonly found in paroxysmal nocturnal haemoglobinuria.

Complete recovery occurred in only 4 patients; 70 others showed a partial remission with some residual haematological abnormality in peripheral blood. Eighteen of these had spontaneous remission. Remission was brief in 27 patients who died; only 32 patients remained in partial remission. Twenty-five per cent. of the patients with AA run an acute course and die within 6 months of the time of diagnosis. The remainder run a subacute or chronic course, punctuated in some cases by a transient remission, but in others by a conversion to other related haematological disorders. An acute course is suggested by a rapid onset of symptoms, a falling neutrophil count, a haemoglobin level less than 5 g/dl and a very low platelet count. A chronic course is likely in those patients who have a slow onset of symptoms, a stable neutrophil count and a Hb level in excess of 5 g/dl. The authors' experience shows that the disease runs either of the 2 courses irrespective of the supportive therapy.

Introduction
Since Ehrlich's (1888) description of a case of aplastic anaemia (AA) with a fulminating course, the natural history of this disease and its haematological features have become recognized as being extremely diverse. Its relationship to paroxysmal nocturnal haemoglobinuria and leukaemia (Dameshek, 1967), the occurrence of chromosomal abnormalities in

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Fanconi's anaemia (Dosik et al., 1970), and the clinical remission which follows bone marrow transplantation all support the concept of a defective haemopoietic stem cell arising after an episode of marrow damage. It is difficult to understand how drugs can influence a disorder in which the basic defect is stem cell damage.

The introduction of androgen therapy by Shahidi and Diamond (1959) stimulated a great deal of enthusiasm but widely different results have been reported by various workers (Sanchez-Medal et al., 1964; Mir and Delamore, 1974; Williams, Lynch and Cartwright, 1973; Davis and Rubin, 1972). Variations in diagnostic criteria may account for some of these differences. The purpose of this paper is to review the authors' experience with 174 patients with AA with particular regard to course, prognostic factors and the success of therapy.

Patients
All of the patients in this study were seen at the Department of Clinical Haematology, Manchester Royal Infirmary, between the years 1940 and 1973. All had pancytopenia (i.e. Hb <11·7 g/dl; neutrophil count <1·8 x 10^9/µl) and a hypocellular bone marrow some time during the course of the illness. Patients with myelophthisic anaemia, those with Fanconi's anaemia and patients with AA secondary to radiation or cytotoxic therapy were excluded. Haematological investigations were performed by standard methods (Dacie and Lewis, 1968). Using these criteria the clinical and laboratory details of 174 patients (76 male, 98 female) were analysed. Other workers have also noted a female over male predominance (Vincent and De Gruchy, 1967; Bomford and Rhoads, 1941).

A definite history of exposure to a drug considered to be related to marrow aplasia was obtained in 38 patients. Eleven patients had exposure to a variety of drugs not usually associated with AA (i.e. chlor Diazepoxide, diazepam, amitriptyline and various phenothiazine derivatives).
**Aplastic anaemia**

**Haematological studies**

All but 7 of the patients had a low Hb level (<11.7 g/dl) when they were first seen. On first examination the leucocyte count was more than 10 000/μl in 3 patients and between 5000 and 10 000/μl in 20 but these values subsequently fell to below 5000/μl in all patients. Table 1 shows the distribution of the initial and the lowest neutrophil counts in all patients. In 91 patients the neutrophil count fell below 5000/μl during the course of their illness.

The platelet count was less than 15 000/μl in all but 9 patients on presentation. During the course of their illness the count fell further and 98 patients had values below 10 000/μl (Table 2).

**Table 1. Initial and the lowest neutrophil count**

<table>
<thead>
<tr>
<th>Cells/μl</th>
<th>Initial</th>
<th>Lowest</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–499</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td>500–999</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>1000–1499</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>1500–1999</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>2000–2499</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>2500+</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Initial and the lowest platelet count**

<table>
<thead>
<tr>
<th>Cells x 10⁹/μl</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>64</td>
</tr>
<tr>
<td>10–50</td>
<td>51</td>
</tr>
<tr>
<td>50–100</td>
<td>30</td>
</tr>
<tr>
<td>100–150</td>
<td>20</td>
</tr>
<tr>
<td>&gt;150</td>
<td>9</td>
</tr>
</tbody>
</table>

**Bone marrow**

The trephine marrow biopsy was not a routine procedure in the Manchester Royal Infirmary laboratory before the year 1963. All trephine biopsies performed since 1964 were examined and the patients with hypocellular marrow were included in this group. A decision regarding the marrow cellularity of patients seen before 1963 was established by a careful survey of the aspiration reports and of marrow sections taken at post-mortem. Only those patients known to have had unequivocal hypocellularity were included.

**Outcome**

Of the 174 patients, 44 were alive at the time of writing this report (1979); 27 patients were lost to follow-up; 19 of these had not achieved remission, 6 had partially remitted and did not require blood transfusions and 2 others were still in need of fortnightly blood transfusions.

**Deaths**

One hundred and three patients died and post-mortem was performed on 64 of these. Infection, haemorrhage or a combination of the two was the usual terminal event. At post-mortem, infection was considered to be the main cause of death in 16 patients; 7 of these had sepsicaemia, 2 infective endocarditis and one had fibrocaseous pulmonary tuberculosis. Haemorrhage was the sole cause of death in 26 of the 64 patients. Seven of these had cerebral haemorrhage: one patient died with asphyxia due to sudden pharyngeal haemorrhage, while 18 others had generalized haemorrhage. Sepsicaemia and infection both contributed to death in 8 patients; 6 of these had developed acute leukaemia as the terminal event (see below). The cause of death in these 64 patients is given in Table 3.

**Table 3. Cause of death at post-mortem**

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Septicaemia</td>
<td>7</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2</td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Others (e.g. urinary tract, upper respiratory tract)</td>
<td>4</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>18</td>
</tr>
<tr>
<td>In the central nervous system</td>
<td>7</td>
</tr>
<tr>
<td>In the epiglottis</td>
<td>1</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
</tr>
<tr>
<td>Sepsicaemia and haemorrhage</td>
<td>8</td>
</tr>
<tr>
<td>Other causes</td>
<td></td>
</tr>
<tr>
<td>Haemosiderosis</td>
<td>5</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Necrosis of the liver</td>
<td>1</td>
</tr>
<tr>
<td>Alveolar proteinosis</td>
<td>1</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>2</td>
</tr>
</tbody>
</table>

**Remission**

Four patients (2%) achieved complete remission as judged by a normal bone marrow and peripheral blood picture. A fifth patient (case 75) was in full clinical remission for 5 years during which all her haematological data were normal. The appearance of ring sideroblasts in her bone marrow preceded the recurrence of the anaemia 7 years after the initial diagnosis. She died 3 years later.
Partial remission
Some improvement in haematological picture occurred in 70 patients: their haemoglobin level improved and they did not require blood transfusions but their Hb, white cell and platelet counts did not reach normal levels. Twenty-seven of these patients died. The reasons for relapse were not obvious in every patient: 4 patients terminated with leukaemia, 6 had a massive cerebral haemorrhage, 2 terminated with sideroblastic anaemia, one died with acute myocardial infarction, 2 died with haemosiderosis and, in 5, infection was the terminal event. In 7 patients the cause of death could not be ascertained. Eleven patients were lost to follow-up.

Continuing aplasia
Eight patients showed a stabilization of the haemoglobin level, albeit at a low level, and they still required periodic transfusions.

Surviving patients
Four of the 44 surviving patients have achieved complete clinical and haematological remission; their peripheral blood picture is normal and the bone marrow examined in 3 patients showed adequate cellularity with no features of dyshaemopoiesis. A toxic agent was implicated in 2 of these (cases 42 and 106). Of the remaining 40 surviving patients, 32 showed a partial haematological recovery with some abnormality in their peripheral blood picture. A low platelet count was the commonest haematological abnormality in patients with partial remission and was present in all these and in the other 8 who were maintained by periodic blood transfusion. Bone marrow was hypocellular in 22 of the 32 patients in partial remission, and in all the 8 patients with continuing aplasia who required transfusions. A completely normal peripheral blood and marrow picture was found in only 2 of the 44 surviving patients; others showed some evidence of marrow damage (hypocellularity neutropenia, thrombocytopenia) and stressed haemopoiesis (i.e. high mean corpuscular volume [MCV], raised Hb F) after 2 to 18 years of clinical remission. It seems that after the initial episode of aplasia some abnormality remains even though it may be masked by clinical remission. For example, cases 75 and 112 enjoyed 5 and 20 years of clinical remission before they developed sideroblastic anaemia.

Survival curve
A survival graph was constructed to show the fate of 147 patients on whom all the follow-up data were available. Twenty-nine per cent. of these patients died within the first 6 months and 60% died within the first 3 years; thereafter the death rate was slow and only 8% more died within the next 3 years (Fig. 1).

A further 8% died within the next 10 years but the data on long-term survival are incomplete because some patients were lost to follow-up.

Prognostic factors
Various clinical and haematological factors were examined to explore their prognostic significance in relation to survival of patients.

Duration of symptoms before diagnosis. The shorter the duration of symptoms before diagnosis, the higher was the 5-year death rate. Thus, of the 22 patients who had symptoms for one month or less, only 7 (32%) were alive at the end of 5 years. On the other hand, the 5-year survival rate was 47% in 40 patients who had symptoms for longer than 6 months before the diagnosis.

Age and sex. The outcome did not relate to the age of patients at diagnosis. Females had a better outlook with a 45% 5-year survival rate as compared with 32% in males.

Haematological factors
A low Hb level was associated with a bad prognosis since 40% of the patients with a haemoglobin level of <5 g/dl at diagnosis died during the first year. The long-term outlook was still poorer in these patients, as only 18% of those who presented with an Hb level below 5 g/dl were alive after 12 years. Similarly, a platelet count of <10 000/μl was ominous as regards survival. The absolute neutrophil count on presentation did not appear to be significant as regards the death rate. There was a 38% 5-year survival in patients with <500 neutrophils/μl. However, a falling neutrophil count emerged as an important factor. Of the 18 patients with a neutrophil count of <500/μl, in whom the count fell further, 16 died during the first month. The degree of marrow hypoplasia and the initial
Reticulocyte count were also considered because patients with mild marrow hypoplasia and reticulocytosis responded better to oxymetholone than those with severe hypoplasia (Mir and Delamore, 1974). However, the overall significance of these 2 factors was negligible. The mean corpuscular volume (MCV) data on admission were available on 31 patients. Of these, 18 had a MCV of >100 fl, and 9 died. Of the 13 patients with normal MCV, 9 died. Finally, the 6-year survival curve (Fig. 1) showed a steeper decline during the first year than the subsequent years. Any patient alive 3 years after diagnosis had a 70% chance of survival as compared with 25% during the first year.

It thus seems that the duration of symptoms before diagnosis, the platelet count and the Hb level at diagnosis have prognostic significance. As AA can either manifest as an acute disease with a rapidly downhill course, or as a chronic smouldering disorder, the authors considered whether these 3 factors would help one decide the likely course in a patient. For this purpose, one mark was allotted for each of the 3 favourable factors; one if the speed of onset was longer than 6 months, and one each for the presenting Hb level of more than 5 g/dl and for the platelet count of >10,000/ul. The survival curve shown in Fig. 1 was replotted for the 2 populations; one curve represented the patients who had 2 or more marks (92 patients) and the other curve represented those (55 patients) who had one or less (Fig. 2). The death rate was significantly (P<0.001) faster in the patients who scored one or less marks; only 7% of the 55 patients were alive at the end of 6 years. On the other hand, patients with 2 or more marks as a group had a much slower death rate, and most of these patients had probably a more chronic form of aplastic anaemia.

**Therapy**

Supportive therapy was given to all patients. This consisted of blood transfusion, antibiotics and, in recent years, included platelet and white cell transfusions. Various therapeutic agents have enjoyed a short lived popularity but it seems clear that, with the exception of immunosuppressants in pure red cell aplasia (Krantz and Kao, 1969) and the possible value of antilymphocytic serum in some cases of AA there are no drugs at present which could reverse marrow aplasia in AA. The drugs used in this series are listed in Table 4.

**Table 4. Summary of therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive therapy alone</td>
<td>43</td>
</tr>
<tr>
<td>Corticosteroids alone</td>
<td>76</td>
</tr>
<tr>
<td>Androgens and corticosteroids:</td>
<td></td>
</tr>
<tr>
<td>Oxymetholone</td>
<td>25</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
<td>10</td>
</tr>
<tr>
<td>Testosterone</td>
<td>8</td>
</tr>
<tr>
<td>Androgens alone:</td>
<td></td>
</tr>
<tr>
<td>Oxymetholone</td>
<td>11</td>
</tr>
<tr>
<td>Testosterone</td>
<td>2</td>
</tr>
</tbody>
</table>

**Supportive therapy alone.** Forty-three patients were sustained with supportive therapy; 2 of these (patients 90 and 106), were given dimercaprol because heavy metals (gold, arsenic and bismuth) were implicated as the causative factors in these 2 patients. One patient (case 50) was given phytohaemagglutinin which enjoyed a short vogue in the treatment of AA (Humble, 1963). All these 3 patients achieved haematological remission. Sixteen other patients achieved partial remission and the total remission rate was 46% in this group.

**Corticosteroids.** Seventy-six patients were treated with corticosteroids alone and 26 (34%) of these achieved haematological remission. In 3 patients the haematological picture returned completely to normal.

**Oxymetholone with or without steroids.** Thirty-six patients received oxymetholone either in combination with steroids or alone and 18 patients (50%) showed some haematological improvement.

**Other androgens with steroids.** Eighteen patients were treated with various androgenic hormones (fluoxymesterone and testosterone) in combination with steroids. Eleven patients (61%) showed some haematological remission.
A haematological remission proved to be brief in some cases and did not influence the outcome. Thus, 9 patients in the Supportive Therapy group, 4 in the Steroids group, 7 in the Oxymetholone group, and 7 in the Other Androgens group died after a brief haematological remission. When survival figures are compared, there is no significant difference between the various groups (Figs 3 and 4).

**Fig. 3.** Survival curves showing comparison between treatment with corticosteroids (●—●), all androgens (O—O) and with supportive therapy alone (△—△).

**Fig. 4.** Survival curves showing comparison between treatment with oxymetholone (O—O) and other androgens (△—△). The number of patients is given in parentheses.

Conversion to other haematological disorders

Conversion to acute leukaemia. Aleukaemic leukaemia with a peripheral pancytopenic picture and aplastic anaemia are difficult to differentiate during their initial stages. When one disease is diagnosed and subsequently transforms to another it is difficult to agree on the significance of conversion particularly when fundamental differences exist on diagnostic criteria. If the criteria for AA are accepted as being pancytopenic with hypocellular marrow at some stage, and the transition to acute leukaemia is accepted when there are sheets of blast cells in the marrow and there is organ infiltration by abnormal cells, various reports in the literature show that such a transition does occur. In this series, 7 patients with features of AA eventually developed acute leukaemia; 6 terminated with acute myeloid leukaemia, and one with smouldering leukaemia. The length of time between the diagnosis of AA and the development of acute myeloid leukaemia was 10 months in 2 patients, 18 months in one, 22 months in one, 29 months in one and 46 months in the sixth patient. Case 112 developed smouldering leukaemia with features of sideroblastic anaemia 20 years after the initial diagnosis. The diagnosis was established by appropriate staining reactions. The previously hypoplastic marrow was replaced by sheets of blast cells in all but case 112, whose marrow showed features of sideroblastic anaemia and smouldering leukaemia. Except this patient, post-mortem was obtained in all and the diagnosis was confirmed by marrow sections and by visceral infiltration. In 4 of these, the change occurred after the administration of oxymetholone (Delamore and Geary, 1971). Whether this was a coincidence or due to the myelostimulatory effect of oxymetholone is difficult to say. It is worth pointing out that whereas 4 patients developed acute leukaemia in a group of 36 patients treated with oxymetholone, 3 others who developed acute leukaemia came from a group of 138 patients who did not receive oxymetholone.

Conversion to sideroblastic anaemia. AA has been included in the list of conditions associated with ring sideroblasts in the marrow (MacGibbon and Mollin, 1965). Eight patients (cases 9, 15, 57, 75, 102, 112, 149 and 153) developed haematological features characteristic of sideroblastic anaemia during the course of their illness. Sideroblastosis is, in this context, a morphological hall-mark of the dyserythropoiesis which is found in many cases of AA. The clinical and haematological details of 3 of these patients (cases 9, 112 and 153) have been reported by Geary et al. (1974). In 6 of these, the diagnosis of sideroblastic anaemia was made during a phase of partial recovery. In the other 2 (cases 75 and 112), periods of 5 and 20 years respectively separated the 2 diagnoses; case 75 has shown a complete haematological remission but in case 112 there was persistent thrombocytopenia with incomplete marrow recovery. The final marrow picture of this last patient was interesting because not only did it show ring sideroblasts, erythroid hyperplasia with megaloblastoid abnormalities, it also showed some features...
of smouldering leukaemia with maturation arrest in granulopoiesis and 7% blast cells. This patient died at home and no post-mortem was performed. His clinical details have been published elsewhere (Geary et al., 1974).

Conversion to paroxysmal nocturnal haemoglobinuria (PNH). PNH is a recognized complication of AA and may develop a long time after the initial marrow damage (Lewis and Dacie, 1967). There have been conflicting reports of the incidence of PNH in AA (Najean and Bernard, 1965; Heimpel, Rehbock and Von Eimeren, 1975). In the present series, 5 patients showed a PNH defect in their red cells.

Discussion

Difficulties will continue in comparison between various series as long as diagnostic criteria remain vague. The term aplastic anaemia was applied by Chauafford (1904) to a syndrome of pancytopenia with acellular marrow first described by Ehrlich (1888). In 1905 Blumer pointed out that hypoplasia of the marrow was not a constant feature. Bomford and Rhoads’ series (1941) had some patients with hypercellular marrow, and a recent study shows that most patients with aplastic anaemia do show residual islands of haemopoietic tissue (Kansu and Ersev, 1976). In this series, only those patients were included who had pancytopenia with hypoplastic marrow at some stage. These criteria would provide some basis for comparison between various series. Recently, there has been renewed support in favour of hypoplasia and pancytopenia as criteria for aplastic anaemia (Williams et al., 1973; Heimpel et al., 1975). The overall incidence of drug-induced AA in this series (28%) is much lower than 86% reported by Williams et al. (1973). However, Bottiger and Westerholm (1972) found that only 20% of their patients had antecedent drug or chemical exposure. The reasons for these discrepancies are not clear.

Prognostic factors

Since AA may terminate rapidly or may behave as a chronic smouldering disorder for many years, it is important to look for some clinical and haematological clues which might suggest the course of the disease in a particular patient (Williams, Lynch and Cartwright, 1978). Various authors have attempted to predict the likely course of the disease; some have found an increased reticulocyte count of favourable prognostic significance (Durate et al., 1972; Sanchez-Medal et al., 1969; Lewis, 1965). Bloom and Diamond (1968) regarded a raised alkali-resistant haemoglobin level as a hopeful prognostic sign. In this series, reticulocyte count and macrocytosis were not of any prognostic significance but the patients who responded to oxymetholone tended to have an increased reticulocyte count (Mir and Delamore, 1974). The reticulocyte count increased in these patients as the remission progressed. Macrocytosis would appear to reflect the presence of a greater number of reticulocytes, which in itself suggests an increased erythropoietic activity (Seno et al., 1964). In fact, macrocytosis with MCV of more than 110/µl persisted in most patients who survived long enough to achieve a stable Hb level. Similarly, alkali-resistant Hb appeared to be a sign of stressful erythropoiesis and reflected a response of the erythron to the insult causing hypoplasia. All the features considered to be of hopeful prognostic importance (i.e. raised MCV, reticulocytosis, fetal Hb) reflect dyserythropoiesis and indicate an increased and stressful erythropoiesis. A continuing increase in some of these indices would appear to show that the erythron is less damaged and more responsive. In that respect these features can be regarded as being of good prognostic importance. On the other hand a falling neutrophil count, falling Hb level and platelet count reflect the stem cell failure. In agreement with Vincent and De Gruchy (1967) it was found that all the 3 cell lines were depressed during infection. However, in 18 patients, the prognostic value of a falling neutrophil count (<500/µl) was well revealed since 16 of these died during the first 6 months. Of the 8 patients who had a neutrophil count of less than 100/µl on presentation, 6 died during the first 4 weeks.

Conversion to other diseases

Various authors have observed a remarkable relationship of AA to PNH (Lewis and Dacie, 1967), to sideroblastic anaemia (MacGibbon and Mollin, 1965; Geary et al., 1974) and to leukaemia (Adams, 1951; Block, Jacobson and Bethard, 1953; Cohen and Creger, 1967; Delamore and Geary, 1971). Lewis and Dacie (1967) have suggested that PNH may represent a somatic mutation in a haemopoietic stem cell already damaged during the aplastic episode. Similarly, progressive changes in a damaged cell may lead to sideroblastic anaemia, at times many years after the original episode. It is of interest to note that sideroblastic anaemia developed 20 years after AA was diagnosed in case 112 and the final bone marrow picture showed dysmyelopoiesis associated with ring sideroblastosis. Such evolution might represent a clonal degeneration in an ‘unstable’ marrow. This problem is complicated by the fact that sideroblastic anaemia may develop soon after the aplastic episode, as happened in some of the patients in the present study. Both AA and acute leukaemia may occur in the same population exposed to a single toxic agent (Vigliani and Saita, 1964; Hamilton, 1931). Dameshek (1967) suggested that these might be different manifestations of the
same fundamental injury to the pluripotent stem cell, and the actual outcome may depend on the extent of the damage and the constitution of the patient. If this were the case one would expect a change from AA to acute leukaemia more frequently than has been reported.

The limitation in the way a cell can respond to trauma must be taken into consideration. The interrelationship of PNH, AA and acute leukaemia may be explained by the fact that the haemopoietic stem cell can respond to injury by these known manifestations and the actual end result depends on the type and the extent of the injury. At present it is reasonable to say that all 4 conditions (AA, PNH, primary sideroblastic anaemia and acute leukaemia) are irreversible disorders with grave prognosis, and these may all be 'clonal' diseases where after the initial damage the subsequent haematological picture may result from clonal evolution, degeneration or from a loss of genetic material required for production of enzymes concerned in haem synthesis as suggested by Catovsky and his colleagues (1971).

A 4% incidence of acute myeloid leukaemia in this series is higher than most other series. Although long follow-up and haematological surveillance are the probable reasons for the high incidence, 2 patients were diagnosed in 1956 when the diagnostic methods were less well developed. It is impossible to be certain that these patients had pure AA at the time of diagnosis. The incidence of PNH, on the other hand, is lower than reported by Lewis and Dacie (1967) but the figures for the present series are comparable with those published by other workers (Najean and Bernard, 1965; Heimpel et al., 1975).

Therapy and outcome

Since the prognosis of AA is poor, various therapeutic agents have been tried with the hope that these might influence the course of the disorder. Corticosteroids and androgenic steroids have been the commonest drugs used. This series dates back to the times when neither of these 2 therapies was available, and the authors have therefore attempted to compare the effects of these drugs on survival rate with the patients who received no drugs but were wholly sustained with supportive therapy. The survival rate is no different in the corticosteroid group from that of the 'supportive therapy' group; it is slightly better, but not significantly so, in the group of patients treated with oxymetholone with or without corticosteroids. Remission as found in this series may be brief and terminate in fatal relapse, acute leukaemia or in sideroblastic anaemia. The true efficacy of any therapeutic agent can be judged only after many years. An examination of a 30-year experience in this series shows that none of the drugs used influences significantly the 10-year survival rate.

It has been shown that no drug has any special advantage over the other. Disappointing results have also been reported after bone marrow transplantation (Davis and Rubin, 1972). There appear to be 2 different populations of patients with AA, one severely affected who have an acute course and deteriorate irrespective of any therapy. The other group runs a more chronic course; patients continue for many years with or without supportive therapy. Some of these patients live for many years with some haematological stigmata; some relapse and die with AA, while some develop one of the other haematological disorders (e.g. acute leukaemia, sideroblastic anaemia) and only very few show a complete clinical and haematological remission. It would seem that AA is the result of a permanent damage to the haemopoietic stem cell and the outcome is governed by the extent and the further progression of this damage. These findings nevertheless, support the thesis put forward by Williams et al., (1978) that there is a sub-population of patients with AA whose disease tends to lead a more indolent course, and in whom supportive measures are more likely to be effective.

References


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