Chronic disease can cause anaemia in a number of ways, such as poor nutrition, chronic blood loss and as a result of drug therapy. Leaving aside these factors, however, there is a specific type of anaemia associated with chronic infection, chronic inflammatory diseases and malignancy. This anaemia is characterised by decreased plasma iron and iron-binding capacity in the presence of normal or increased reticulo-endothelial iron stores, and has been termed the anaemia of chronic disorders (Cartwright and Lee, 1971). Although the anaemia of chronic disorders is one of the most common anaemias encountered in medical practice, its aetiology remains unclear and treatment unsatisfactory.

Laboratory features and differential diagnosis

The anaemia of chronic disorders is usually of moderate severity with the haemoglobin rarely falling below 80 g/dl unless additional factors are present. The red cells tend to be microcytic with the mean corpuscular volume (MCV) in the range 70–85 fl (normal range 80–92 fl). An MCV below 70 fl is suggestive of iron deficiency, although an MCV as low as 60 fl may be seen in the presence of adequate marrow iron stores; children with juvenile chronic arthritis tend to have particularly low MCVs (Koepker, Stempel and Dallman, 1978; personal observation). A value for MCV at the upper end of the normal range, or just above it, is extremely unusual in uncomplicated anaemia of chronic disorders but does occasionally occur. The morphology of the red cells is unremarkable, with varying degrees of anisocytosis and sometimes mild hypochromia. An elevated neutrophil count may accompany inflammation or malignancy, and high platelet counts may also be seen in malignancy and more particularly in chronic inflammatory diseases such as rheumatoid arthritis (RA) and especially in juvenile chronic arthritis. The erythrocyte sedimentation rate (ESR) is always elevated and, in general, there is an inverse relation between the ESR (and other indices of disease activity) and the haemoglobin level. The reticulocyte count is normal, i.e. low for the degree of the anaemia. The bone marrow in the anaemia of chronic disorders shows no specific diagnostic features. Iron stores are normal but the percentage of erythroblasts with siderotic granules is reduced suggesting a failure to take up iron. The erythroblasts often show minor dyserythropoietic features such as ragged cytoplasm and indistinct nuclear outline. There is often a modest increase in plasma cells and in chronic infections such as tuberculosis monocellular cells may be prominent.

Serum iron and total iron binding capacity (TIBC) are both low in the anaemia of chronic disorders in contrast to simple iron deficiency anaemia where the TIBC is always elevated. If iron deficiency supervenes on the anaemia of chronic disorders, the TIBC will rise, although not to supranormal levels. In a recent series of patients with RA studied by the author (Williams et al., 1982), those with absent marrow iron stores had TIBC values significantly higher (74·2±5·2 μmol/litre) than those with adequate marrow iron stores (51·6±9·1 μmol/litre). However, other authors have observed no correlation of TIBC with iron stores (Bentley and Williams, 1974; Smith et al., 1977; Blake et al., 1980) and while a TIBC of over 60 μmol/litre in an anaemic patient with the anaemia of chronic disorders is strongly suggestive of iron deficiency, it is often difficult to be certain whether such a patient is iron deficient without obtaining a sample of bone marrow to assess stainable iron.

When ferritin assays became available, it was hoped that measurement of serum ferritin would help solve this problem. Serum ferritin is in equilibrium with tissue ferritin, and has been found to give an accurate indication of tissue iron stores in normal subjects and in patients with iron deficiency and iron...
overload, patients with simple iron deficiency having serum ferritin values below 12 μg/litre (Jacobs et al., 1972). However, ferritin levels are known to be raised by inflammation (Lipschitz, Cook and Finch, 1974) so this value is inappropriate for patients with many chronic disorders; for example, serum ferritin has been found to be raised and to correlate closely with disease activity in children with juvenile chronic arthritis (Craft et al., 1977). Bentley and Williams (1974) studied a large series of patients with anaemia of RA and although they found a close correlation between serum ferritin and storable marrow iron, the mean ferritin in the 13 patients with absent marrow iron stores was 38 μg/litre and only 3 had values below 12 μg/litre. On the other hand, all those with adequate iron stores had ferritin values of over 20 μg/litre. Similar results in adults were obtained by Smith et al. (1977) while Koerper et al. (1978) found that, in children with juvenile chronic arthritis (JCA), those with serum ferritins below 25 μg/litre all responded to iron therapy. Thus, a value of below about 25 μg/litre in RA or JCA probably indicates iron deficiency, but values between 25 and 50 μg/litre may be found in patients with or without iron stores. Unfortunately many patients have values in this 'grey area', and bone marrow aspiration is still often necessary to establish iron deficiency with certainty. It is important to do this because many patients with RA receive unnecessary iron therapy (Blake et al., 1980).

The anaemia of chronic disorders usually presents as a complicating problem in a patient known to have a particular disease. Occasionally, however, anaemia may be the presenting feature and, when shown to fulfils the criteria of the anaemia of chronic disorders, should stimulate the search for an underlying cause, such as occult malignancy.

The aetiology of the anaemia of chronic disorders

Anaemia can, of course, result either from accelerated red cell destruction or from failure of production. Early work using the Ashby (differential agglutination) technique suggested that there was a modest decrease in red cell survival in patients with the anaemia of RA (Freireich et al., 1957a), but later studies using 51Cr labelling failed to show any significant alteration in red cell survival (Lewis and Porter, 1960; Mongan and Jacox, 1964). More recently, calculations of mean cell life have been made from ferrokinetic data using a computer assisted technique (Ricketts, Jacobs and Cavill, 1975). Studies in patients with chronic inflammatory disease (Cavill, Ricketts and Napier, 1977a), RA (Dinant and de Maat, 1978; Cavill and Bentley, 1982) and Hodgkin's disease (Al-Ismail et al., 1979) have indicated that red cell life-span is normal in the majority of these patients. Some have modest reductions in mean cell life but significant haemolysis is rare; thus the main factor in the anaemia of chronic disorders is failure of production of red cells. Factors which may be implicated in this inadequate response include failure of erythropoietin to increase in response to the anaemia, inadequate supply of iron from the reticulo-endothelial cells to the developing erythroblasts, humoral or cell-mediated suppression of erythroid progenitor cells and an increase in ineffective erythropoiesis (the proportion of erythroblasts which die before maturing into red cells). All these aspects have been studied but unfortunately the results are often conflicting. The disease which has most often been studied is rheumatoid arthritis but some investigations have been carried out in patients with malignant disease and with chronic infections, and there is some evidence that different aetiological factors may be important in different diseases.

Erythropoietin

In most forms of anaemia apart from the anaemia of chronic disorders, plasma erythropoietin (Epo) becomes progressively elevated as the haemoglobin falls below 9–10 g/dl. Various studies have been carried out comparing serum Epo levels in patients with the anaemia of chronic disorders with those of patients with anaemia due to iron deficiency or primary haemopoietic disease. The majority of these studies have used bioassay methods which are not very reliable and which are not sensitive enough to measure levels of Epo within the normal range.

Levels of Epo lower than expected for the degree of anaemia have been observed in several studies in patients with RA (Ward, Gordon and Pickett, 1969; Zucker, Friedman and Lysik, 1974; Douglas and Adamson, 1975; Mahmood et al., 1977; Pavlovsky-Kentera et al., 1979). In contrast, Cotes et al. (1980) using a sensitive radioimmunoassay method capable of measuring levels of Epo within the normal range found that Epo levels in 23 patients with RA did not differ significantly from those in patients with other types of anaemia. However, a more extensive study suggests that some patients with RA do have inadequate rises in immunoreactive Epo (Cotes, Evans and Samson, 1983). There is no evidence for any serum inhibitor of erythropoietin in patients with RA (Ward et al., 1969; Zucker, Friedman and Lysik, 1974).

Results in patients with infection and malignancy are also conflicting. Low levels of Epo have been observed both in patients with infection or inflammation (Ward, Kurnick and Pisarczyk, 1971; Zucker et al., 1974; Douglas and Adamson, 1975; Mahmood et al., 1977; Wallner et al., 1977) and in experimental
inflammation in animals (Lukens, 1973). In some studies, patients with malignancy have also been found to have inadequate Epo levels (Ward et al., 1971; Firat and Banzon, 1971; Douglas and Adamson, 1975), but Zucker et al. (1974) found that Epo was appropriately raised in 18 patients with anaemia caused by advanced malignancy.

Normally, the rate of haem biosynthesis by erythroblasts increases in response to anaemia as the result of stimulation by Epo of the rate limiting enzyme δ- amino-laevulinic acid synthase (ALA-S). The rate of haem synthesis in marrow from patients with the anaemia of chronic infection was, however, found to be significantly reduced compared with normal controls (Kumar, 1979b) and this was not due to a reduction in the uptake of iron. Campbell et al. (1978) measured the major enzymes of the haem biosynthetic pathway in the anaemia of RA, and found that although there was no specific defect, there was a failure of ALA-S to rise in response to the anaemia. This would account for the failure of haem synthesis to increase and could be due either to a failure of Epo secretion or a primary marrow defect.

An attempt to distinguish between these possibilities was made by Zucker et al. (1974) who assessed the ability of the bone marrow in RA, infection and malignancy to respond to Epo by measuring haem synthesis in marrow cultured with and without Epo. They found that in the patients with RA and infection who had serum Epo levels which were consistently lower than expected for the degree of anaemia, the response of the marrow to Epo was normal. In contrast, the patients with malignancy had appropriately raised serum Epo levels but the response of the marrow to Epo was markedly reduced. This suggested to them that inadequate Epo production was a major factor in anaemia associated with RA and infection, but that in malignancy the main factor was marrow unresponsiveness to Epo. This hypothesis has not been proven and it is likely, at least in RA, that if Epo production is inadequate it is only one of a number of factors contributing to the anaemia.

**Inadequate iron supply**

The combination of a low plasma iron with normal iron stores in the anaemia of chronic disorders has suggested that failure of release of iron from stores may be important in limiting red cell production. The vast majority of the iron used for haemoglobin synthesis is derived from the breakdown of senescent red cells by the reticulo-endothelial (RE) system. This iron is then either stored as ferritin or released onto plasma transferrin which delivers it to the developing erythroblasts. It is possible that a small amount of iron is directly transferred from RE cells to erythroblasts as ferritin but the majority of the iron has to be released from the RE cell onto transferrin before it can be used (Aisen, 1982). Conventional ferrokinetic studies with 59Fe-labelled transferrin in patients with the anaemia of RA have shown normal incorporation of the label into red cells (Freireich et al., 1957a; Roberts et al., 1963). These observations are contrary to what would be expected from other indications that red cell production is depressed and may be an artefact resulting from a reduction in the miscible iron pool (Kumar, 1979a). However, if the 59Fe is administered in the form of labelled haemoglobin solution or labelled damaged red cells, then the iron has to be removed by RE cells and released on to plasma transferrin before it can be used, thus more accurately reflecting the in vivo situation.

Studies of this nature have shown defective re-utilisation of iron in dogs with turopoline abscesses (Freireich et al., 1957b) and in patients with anaemia associated with malignancy or chronic inflammation (Haurani, Young and Tocantins, 1963; Haurani, Burke and Martinez, 1965).

Subsequently, Beamish et al. (1971) developed a method of calculating RE iron release using a double isotope technique in which 59Fe-labelled dextran replaced labelled haemoglobin for measurement of iron re-utilisation and 59Fe-labelled transferrin was used to measure plasma iron utilisation. Comparison of the utilisation of the two isotopes indicated reduced RE iron release in patients with lymphoma, renal failure and some cases of RA. In one patient with RA, for example, transferrin iron utilisation was 71% but iron dextran utilisation was only 40%, from which it was calculated that only 53% of the iron given as dextran was released onto plasma transferrin for subsequent utilisation. Several further studies demonstrated reduced utilisation of iron-dextran in patients with anaemia associated with inflammation, infection and lymphoma (Davies, Beamish and Jacobs, 1971; Beamish et al., 1972; Bennett, Holt and Lewis, 1974). All this work supported the concept of failure of release of iron by the RE cells, and this has become widely accepted as an important aetiological factor in the anaemia of chronic disorders.

However, the development of a method of measuring 59Fe-transferrin in the presence of 59Fe-dextran made it possible to look more directly at RE iron release. Following the injection of 59Fe-dextran, the labelled dextran is cleared from the blood and over the next 16–20 hr 59Fe reappears in the plasma as 59Fe-transferrin (Kanakakorn, Cavill and Jacobs, 1973). Williams, Cavill and Kanakakorn (1974) used this method to study RE iron release in the anaemia of RA and found no differences from normal subjects in the rate of clearance of the iron dextran, the proportion of the label which reappeared bound to transferrin, or the time taken to reach the peak 59Fe-
Iron absorption

Roberts et al. (1963) in their study of the anaemia of RA found that iron absorption was reduced unless the patients were also iron deficient. They suggested that poor absorption contributed to the hypoferrae-mia. However, Boddy and Will (1969) found that the absorption of iron in RA measured by whole body counting did not differ significantly from that of controls, although RA patients who were iron deficient did not increase absorption to the same extent as did patients with simple iron deficiency anaemia.

Ineffective erythropoiesis

Although dyserythropoietic changes are commonly observed in bone marrows from patients with the anaemia of chronic disorders suggesting reduced viability of the erythroblasts, it is only recently that attention has been paid to the possibility that an increase in ineffective erythropoiesis might contribute to the anaemia. Samson, Halliday and Gumpel (1977), using a method of assessing ineffective erythropoiesis based on the production of labelled bilirubin from the breakdown of developing red cell precursors, observed a marked increase in ineffective erythropoiesis in a patient with the anaemia of RA which reverted to normal when the patient improved with gold therapy. When haemoglobin is broken down to bilirubin, carbon monoxide is released, and carbon monoxide production has also been used as a way of measuring haem breakdown. Cavallin-Stahl, Mercke and Lundh (1976a,b) found that in anaemic patients with Hodgkin’s disease and breast carcinoma, carbon monoxide production was significantly increased compared with non-anaemic patients. This increase could not be accounted for by a shortening of red cell survival and it was concluded that the excess carbon monoxide arose from ineffective erythropoiesis.

At about the same time, Ricketts et al. (1975) in Cardiff developed a different method of assessing ineffective erythropoiesis based on ferrokinetic studies, in which, by computer analysis of the disappearance curve of injected plasma 59Fe-transferrin, the reflux of labelled iron into the plasma between 1 and 14 days after injection could be detected and measured. This iron reflux was thought to be derived from ineffective erythropoiesis and was used to calculate ineffective iron turnover (IIT) while the incorporation into circulating red cells represented effective iron turnover (EIT) and the sum of the two was the total marrow iron turnover (MIT).

Using these ferrokinetic measurements the Cardiff group studied patients with the anaemia of RA and found no increase in IIT, whereas in patients with iron-deficiency anaemia, there was a significant increase in IIT (Cavill et al., 1977a,b). Using the same method, however, Dinant and de Maat (1978) found increased IIT in 6 of 14 patients with the anaemia of RA. They observed that the levels of IIT in these patients were similar to those seen by Cavill et al. (1977a,b) in their patients with iron deficiency anaemia, and suggested that functional iron deficiency might be the cause of increased ineffective erythropoiesis in RA. Recently, Cavill and Bentley (1982) have reported results of ferrokinetic studies on a larger series of patients with anaemia of rheumato-doid arthritis, some of whom were iron deficient (as defined by serum ferritin of less than 12 µg/litre), and compared results with those in normal subjects and in patients with simple iron-deficiency anaemia. They again found an increase in IIT in the patients with simple iron deficiency, while IIT in the patients with anaemia of chronic disorders was actually below normal. In the iron-deficient RA patients, IIT rose, though not to the level seen in simple iron deficiency. These results seem to indicate firstly that...
ineffective erythropoiesis (as judged by % IIT) is not increased in anaemia of RA, and secondly that the pathogenesis of the anaemia of RA is different to that of simple iron-deficiency anaemia. Apart from the study of Dinant and de Maat (1978) therefore, the ferrokinetic technique has provided no evidence for increased ineffective erythropoiesis in RA. The Cardiff group have also used the ferrokinetic technique to study erythropoiesis in Hodgkin’s disease (Al-Ismail et al., 1979). They found that total marrow iron turnover was markedly depressed but that the proportion of this which was ineffective was not increased. These observations are consistent with those of Zucker et al. (1974) (v.s) who felt that inability of the marrow to respond to erythropoietin was the chief cause of the anaemia associated with malignancy, but contradicted the evidence for increased ineffective erythropoiesis obtained by Cavalin-Stahl et al. (v.s).

Due to the various difficulties inherent in in vivo studies of ineffective erythropoiesis, Samson, Tikerpace and Crowne (1981) developed a simple in vitro method of assessing ineffective erythropoiesis, based on the release of $^{59}$Fe-haem from a cohort of erythroblasts labelled in short-term marrow culture. This method was used to study a large series of patients with RA, and a smaller number of patients with other chronic disorders (Williams et al., 1982). Haem release was significantly increased in the patients with anaemia of RA, but was normal in non-anaemic RA patients and also in those with anaemia associated with other chronic disorders or with simple iron deficiency anaemia. In two of the anaemic RA patients, haem release returned to normal when their anaemia responded to successful anti-rheumatic therapy, and in the group as a whole there was a significant correlation between haem release and disease activity. In contrast to the Cardiff group, therefore, these authors felt that ineffective erythropoiesis was a significant factor in anaemia of RA, though probably not in other chronic disorders.

It is obvious that methodological differences must account for the discrepant findings between the various studies of ineffective erythropoiesis; in particular, ferrokinetic studies appear to give contrary information to that obtained from studies of haem breakdown. However, at present, it is not possible to explain why this should be so.

**Abnormal development of erythroid progenitor cells**

The recent development of methods for culturing erythroid progenitor cells in methyl cellulose has opened up a new area of research into the anaemia of chronic disorders. Two types of erythroid cells can be cultured, the colony forming unit or CFU E, which develops into small colonies after 7 days of culture, and the more primitive burst forming unit or BFU E, which develops into a larger ‘burst’ of erythroblasts after 14 days of culture. The bone marrow contains both CFU E and BFU E and more primitive BFU E can also be cultured from peripheral blood. Growth of these cells is normally enhanced by T cells and macrophages (Nathan et al., 1978; Reid, Baptista and Chanarin, 1981).

Recently, Zanjani et al. (1982) showed that in some patients with systemic fungal infection, growth of CFU E and BFU E was decreased but returned to normal when macrophages were removed, in contrast to the normal situation where growth is depressed by removal of macrophages. Macrophages from these patients also suppressed growth of erythroid stem cells from normal donors. It is thought that the normal stimulatory activity of macrophages is mediated by a soluble factor and Zanjani et al. considered that the suppressive effect seen in the infected patients was also mediated via a soluble factor.

Similar techniques have been used to explore the effect of cancer cells immobilised in an agar under-layer on growth of CFU E from rat marrows (Zucker et al., 1980). The presence of the cancer cells suppressed growth of CFU E and this suppression was attenuated by antineoplastic drugs. Likewise, when cancer cells were added to suspension cultures of normal rat marrow, haem synthesis was markedly diminished. Although their experiments suggested that the cancer cells produced a soluble inhibitor of erythropoiesis, such a factor has not yet been isolated.

Studies of CFU E and BFU E growth from patients with RA, both anaemic and non-anaemic (Reid et al., 1983), showed no significant differences from normal. Depletion of macrophages resulted in significant reductions in BFU E growth in both groups, and re-addition of macrophages or co-culture with T cells restored growth in both groups. However, a profound difference was observed when human serum was added to the cultures. The stimulatory effect of macrophages was increased when 10% fresh normal serum was added, but, in contrast, autologous serum from anaemic patients produced significant suppression of BFU E in all cases studied. Serum from anaemic RA patients also suppressed the growth of BFU E from normal peripheral blood cells. It thus appears that in anaemia of RA, T cell and macrophage enhancement of erythropoiesis is preserved, but that there is a serum factor suppressing erythropoiesis. Humoral suppression of erythropoiesis had previously been demonstrated in 2 patients with RA as well as 10 with systemic lupus erythematosus by Dainiak et al. (1980) who cultured normal marrow in the presence of patient serum. They found the physical properties of the inhibitor to be compatible with those of an immunoglobulin. It is interesting
that serum from RA and other chronic disorders does not appear to inhibit haem biosynthesis (Wallner et al., 1976) or increase ineffective erythropoiesis (Williams et al., 1982).

Aetiology—conclusions

It is difficult at the present time to draw together the conflicting evidence and provide a coherent account of the pathogenesis of the anaemia of chronic disorders. It is apparent from the above discussion, as outlined in Table 1, that methodological differences account for many of the discrepancies obtained. It also appears that different factors are involved in the different disease states. The general consensus of opinion is that Epo is not appropriately elevated in RA or infection, but it is unlikely that this is the chief cause of the anaemia. It is also clear that reduction in red cell survival and in iron absorption are unimportant in contributing to the anaemia. The idea of defective RE iron release is now losing favour but the ferrokinetic data have not yet been adequately explained and may require much more complex compartmental analysis than has yet been applied, and the role of ineffective erythropoiesis is also unclear. Recent work suggests that failure of the bone marrow due to humoral inhibition or abnormal T-cell and/or macrophage function may be important, but clearly very much work remains to be done in elucidating the pathogenesis of this common type of anaemia.

**Therapy**

Although patients with the anaemia of chronic disorders have adequate iron stores and do not respond to oral iron, a temporary improvement in haemoglobin and rise in MCV may follow intravenous or intramuscular injection of high doses of iron (Richmond et al., 1958; Bentley and Williams, 1982). However, the improvement is not maintained and continual parenteral iron therapy would result in iron overload, so that this is not a practical means of maintaining a normal haemoglobin. In experimental animals, the anaemia of chronic inflammation can be corrected by giving erythropoietin (Lukens, 1973), or cobalt which stimulates endogenous Epo production. However, cobalt is toxic and not suitable for use therapeutically. Unfortunately, the only current

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TABLE 1. Possible aetiologial factors in the anaemia of chronic disorders studied by different methods. See text for references and discussion

<table>
<thead>
<tr>
<th>Technique</th>
<th>Disease state</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cell life</td>
<td>Ashby</td>
<td>Moderate reduction, Normal</td>
</tr>
<tr>
<td></td>
<td>$^{51}$Cr</td>
<td></td>
</tr>
<tr>
<td>Ferrokinetic</td>
<td>RA</td>
<td>Normal (2/3) or moderate reduction (1/3)</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>Normal except in extensive disease</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Bioassay</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>RA, infection</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>?Appropriately elevated ?low</td>
</tr>
<tr>
<td></td>
<td>Radioimmunoassay</td>
<td>Appropriately elevated</td>
</tr>
<tr>
<td>RE iron release</td>
<td>Labelled red cells or Hb</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>$^{59}$Fe-dextran utilisation</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>$^{59}$Fe-colloid</td>
<td>Normal</td>
</tr>
<tr>
<td>Ineffective erythropoiesis</td>
<td>Early labelled bilirubin</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>CO-production</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>In vitro haem release</td>
<td>Increased in 50%</td>
</tr>
<tr>
<td></td>
<td>RA, other inflammatory disorders and lymphoma</td>
<td>Normal</td>
</tr>
<tr>
<td>Marrow activity</td>
<td>Growth of erythroid precursors</td>
<td>Inhibited by cancer cells</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>Inhibited by macrophages</td>
</tr>
<tr>
<td></td>
<td>Fungal infection</td>
<td>Inhibited by added RA serum</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>but not by macrophages</td>
</tr>
</tbody>
</table>
Anaemia of chronic disorders

means by which the anaemia can be permanently improved is by treatment of the underlying disorder. In future, it is to be hoped that better understanding of the pathogenesis of the anaemia may lead to the development of new therapeutic options.

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