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The pathogenesis of aplastic anaemia

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The association of fatty atrophy of haemopoietic marrow with multiple cytopenias in the blood was first noted by Ehrlich in 1888. He described the case of a young pregnant woman whose disease ran a particularly fulminating course, but the term aplastic anaemia was probably not introduced until 1904 when Chauffard used it to describe the syndrome. Although these early accounts. based on autopsy findings, emphasized hypoplasia of the marrow as a cardinal diagnostic feature, the terminology later became confused because, for some time, "aplastic anaemia" was virtually synonymous with blood pancytopenia.

Benzene, the first substance found to cause marrow damage, is indeed unusual in producing pancytopenia with both hypocellular and hypercellular marrow pictures, but it was not until marrow aspiration became a routine clinical investigation that the morphology of the marrow in pancytopenic patients was studied in detail. Patients whose marrow was cellular or hypercellular were subsequently recognized as cases of hypersplenism, or classified somewhat unsatisfactorily as having achrestic anaemia, refractory anaemia with cellular mamw. or (in kinetic terms) functional aplasia. The paper by Bomford and, Rhoads (1941) which correlated the histological appearances of the marrow with blood film appearances was a notable landmark. Later the importance of trephine biopsy for assessing marrow cellularity was realized, while the recent introduction of plastic embedding for processing these histological sections permits detailed scrutiny of residual haemopoietic cells and their relationship to the stroma.

It is now realized that patients with aplastic anaemia frequently show islands of cellular. although abnormal. haemopoiesis known as "hot pockets" (Kansu and Erslev, 1976): indeed complete aplasia would be incompatible with life. However. there still seem to be reasonable clinical grounds for distinguishing between cytopenic patients with predominantly hypocellular and those with hypercellular marrows. Thus. isolated cytopenias are more frequent in the latter group and the natural history is different: leukaemia may be a commoner sequel (Vilter et al, 1967) while others respond to splenectomy or immunosuppressants. *Also,* the aetiology is probably different. Apart from benzene and possibly X-irradiation, no substance is known to cause chronic marrow failure with both hypercellular and hypocellular marrow pictures. Butazolidin has been suspected of causing a picture indistinguishable from preleukaemia, but this remains unproved, although there is no doubt as to the association between this drug and marrow aplasia. Drugs known to cause panhypoplasia may also cause selective hypoplasia of one or more cell lines, but the latter is more often reversible when treatment is stopped.

On the other hand there *are* undoubted similarities between the two syndromes. The cultural characteristics of marrow from both groups of patients are often indistinguishable (see below). The same qualitative abnormalities of erythropoiesis and granulopoiesis are found in patients with predominantly hypoplastic marrows as in those with hyperplastic ineffective marrows. Occasionally patients presenting with isolated cytopenias (such as red cell aplasia) later develop panhypoplasia, and children with constitutional marrow failure (such as Fanconi's anaemia) *are* sometimes found to have cellular marrows at diagnosis but later progress to profound hypoplasia.

Normal haemopoiesis

The daily production of differentiated blood cells is maintained by the proliferation of stem cells in the marrow. These occur in all rapidly dividing tissues and are defined as cells that both maintain their own numbers and give rise to differentiated cells. The haemopoietic system is in fact a cell renewal system in which a continuous supply of highly specialized non-dividing blood cells is sustained by the proliferation and differentiation of *such* ancestral pluripotent cells. The attribute of "stemness" is not lost abruptly and there is at least one other major stratum of stem cells that fulfils the criteria defined above but is committed to a particular line of differentiation (for example, erythroid stem cells produce only erythrocytes under the influence of erythropoietin). Subsequent repeated divisions in the more differentiated progeny of these committed cells — sometimes called the transit compartment — produces an amplifying effect, so that except under conditions of stress, stem cells need only divide intermittently. Moreover it can be shown experimentally that comparatively normal production of mature blood cells can be achieved with a stem cell compartment that has undergone serious depletion. The long resting phase that characterizes the kinetics of the individual stem cell has biological advantages: it permits a period for "genetic housekeeping" (Lajtha, 1978) and reduces the risks of propagation of abnormal clones.

Stem cells or their progeny can be assayed both in vivo and in vitro. The mouse spleen assay uses the irradiated animal (Till and McCulloch, 1961) and

detects cells known as colony-forming units (CFU-S) which have the properties outlined above. They are capable of self-renewal and give rise to clonal colonies that contain cells of the granulocytic, erytiiroid, and megakaryocytic series (Siminovitch et al, 1963). For obvious reasons this assay system cannot be used in humans, but methods have been developed for growing haemopoietic cells in soft agar in the presence of a suitable conditioning medium. In the mouse it is now possible to grow mixed colonies of unicellular origin that give rise to all three cell types, as in the spleen assay (Johnson and Metcalf, 1977), but in man it has so far only been possible to estimate the pluripotent stem cell population indirectly by studying the numbers of their descendants.

These progeny of the CFU-S produce, only one type of differentiated cell line — erythroid, granulocytic/monocytic, or megakaryocytic. There are *two* types of erythroid colony: the burst-form unit (BFU-E) which is only slightly sensitive to erythropoietin (although it is probably under some other humoral control) and the CFU-E which is exquisitely sensitive to erythropoietin in culture. The CFU-C produce colonies containing cells exclusively of the granulocytic and monocytic series and are formed only when colony-stimulating activity is present in the conditioning medium. Assays of such colonies have shown that bone marrow from patients with aplastic anaemia possesses reduced or undetectable numbers of progenitor cells, both of CFU-C (Greenberg and Schrier, 1973; Kern et al, 1977) and of CFU-E (Hansi et al, 1977) lines.

Other in-vitro colony assays that detect progenitors of megakaryocytes, B lymphocytes, and T lymphocytes have been developed recently. Studies of genetic markers in patients with certain types of myeloproliferative disorder have ,provided tentative evidence that B lymphocytes. at least, are derived from an ancestral cell common to other haemopoietic cell lines. This may explain why some patients with Severe aplastic anaemia have lymphopenia involving B-cell populations and sometimes hypogammaglobulinaemia (Morley et al, 1974; Mir et al, 1977).

The marrow microenvironment

Haemopoietic stem cells do not exist in isolation and numerous observations testify to the importance of both cellular and humoral influences in the regulation of replication and differentiation. In a series of elegant experiments using graduated doses of irradiation Knospe and Crosby (1971) showed that an intact marrow vasculature is essential for haemopoiesis: stem cells could not repopulate fatty marrow unless the specialized sinusoidal matrix was present. and marrow transplantation was not possible in a heavily irradiated area unless this was curetted to promote vascularization.

Perhaps the most striking example of the importance of the marrow microenvironment is provided by the genetically anaemic $S1/S1^d$ (Steel) mouse. This animal possesses normal stem cells, as shown by the spleen colony assay and by the capacity of its marrow to reconstitute haemopoiesis in lethally irradiated mice, but has a defect in its haemopoietic environment that impairs the proliferation of normal stem cells. However, the anaemia can be cured by an implant of spleen tissue which provides a normal environment into which the animal's own stem cells can migrate and differentiate (Russell and Bernstein, 1966).

In the normal adult mouse the distribution of haemopoiesis in marrow and Spleen appears to depend on the presence of a specialized microenvironment that determines the growth and differentiation of blood cells; in this animal at least, bone marrow appears to be a highly organized tissue in which the distribution of granulocytic (CFU-C) and erythroid (CFU-E) precursor cells is not random (Lord et al, 1975). Thus there is evidence that environmental factors exert different regulatory influences on ancestral stem cells and may induce them to develop along one or other line of differentiation.

Although erythropoietin is the best understood of the humoral factors affecting blood cell development, granulopoiesis proceeds under the influence of an analogous glycoprotein, colony-stimulating factor, and thrombopoiesis and lymphopoiesis are also regulated by specific factors. Kegenerating marrow in the mouse produces a stimulatory factor that increases stem cell turnover, while normal marrow (in which the CFU-S are dividing only very slowly) specifically inhibits the proliferation of CFU-S obtained from regenerating marrow (Lord et al, 1977). It is possible that, in the intact animal, the rate of pluripotent stem cell turnover is adapted to satisfy different requirements by balancing the stimulatory and inhibitory substances.

Although little is known about the identity of the marrow stromal cells that regulate haemopoiesis, it is certain that macrophages and "epithelioid" cells (which may really be of endothelial origin) are essential for the propagation of CFU-S and CFU-C in culture (Allen and Dexter, 1976; Dexter et al, 1978) while the cooperation of a population of T lymphocytes is required to establish erythroid cell lines in the mouse (Jedrzejczak et al, 1977).

It is clear therefore that the control of normal haemopoiesis is extremely complex. Haemopoietic failure, that is aplastic anaemia, can arise as the result of a number of different lesions. In addition to direct damage to stem cells (Heimpel and Kubanek, 1975) defects in the marrow stroma (Knospe and Crosby, 1971), regulatory disturbances (Stohlman 1972), and autoimmune damage to the marrow (Ascensao et al, 1976) have been postulated. The subject has recently been reviewed by Alter et al (1978) and Geary and Testa (1979) among others. The possible pathogenetic mechanisms are summarized in *Table 1.*

Table 1. Possible lesions in aplastic anaemia

Pluripotent stem cell	reduced numbers
	defective (intrinsic) function
Committed stem cells*	
Environmental influences	defects in vascular or other 'stromal' cells
	abnormalities of short-range or long-range humoral factors influencing stem cell growth
	abnormal or excessive inhibitors

*A lesion acting on committed stem cells would need to damage all differentiating cell lines simultaneously if it were to produce panhypoplasia

Definition and classification of causes of aplastic anaemia

Aplastic anaemia can be defined as "a syndrome of peripheral blood .pancytopenia without dominant peripheral blood cell destruction, associated with hypocellularity of haemopoietic tissue in both intramedullary and extramedullary sites, and without bone marrow fibrosis or invasion by malignant cells" (Benestad, 1974; Heimpel and Kubanek, 1975). The absence of extramedullary haemopoiesis in aplastic anaemia is particularly significant and indicates an inability of surviving stem cells in the marrow to migrate and populate potentially fertile sites for haemopoiesis in the spleen and the liver.

It is possible for aplastic anaemia to occur as a result of an agent damaging simultaneously all cell lines in the transit compartment. However, this implies that the pathogenetic process is acting continuously, since the remarkable regenerative capacity of the pluripotent stem cell compartment would be expected to replenish the differentiating compartments following transient inhibition. Damage at this level results more frequently in isolated cytopenias such as red cell aplasia or agranulocytosis although, as already emphasized, these can occasionally progress into panhypoplasia. In such cases there is presumably less severe damage to stem cells and the production of one or more mature cell lines is maintained by physiological regulating mechanisms in the early stages of the disease. Patients presenting with incomplete pancytopenias may have a better prognosis than those who show complete pancytopenia from the outset (Heimpel, 1979).

Paroxysmal nocturnal haemoglobinuria and, less commonly, acute leukaemia occur as late manifestations of clonal instability in a proportion of cases, presumably as a result of the initial damage to the marrow. Those with acute leukaemia must be distinguished from patients (usually elderly) who have preleukaemia or smouldering leukaemia but in whom the marrow is also hypoplastic from the outset (Milner and Geary, 1979).

No classification of aplastic anaemia is completely satisfactory because the way in which bone marrow damage occurs is often uncertain, but that shown in *Table* 2 attempts a correlation of the known causes with possible pathophysiological mechanisms. Drugs and chemicals are the agents most commonly incriminated; although in most series 50 per cent of cases are labelled idiopathic, it is likely that many of these are due to exposure to environmental agents, such as small doses of benzene, or antibiotics in food, which may be difficult to identify.

Table 2. Classification of aplastic anaemia (data from Benestad. 1974)

Ionizing radiation Cytotoxic chemicals	dose-deucndent
Chemicals and drugs (conditional or immunological)	largely dose-independent
Viral cytotoxicity (direct or immunological)	
Autoimmune cytotoxicity	
Hereditary defect	

Drug mechanisms: Only a few agents such as benzene, cytotoxic drugs, and X-irradiation have been clearly established as causes of marrow aplasia in experimental animals. In clinical practice the evidence of drug or chemical toxicity is usually circumstantial and there are no laboratory tests to prove a cause and effect relationship. Many patients are subjected to multiple exposures of several potentially toxic agents and a reliable exposure history is often difficult to obtain.

The incidence of drug-induced marrow aplasia clearly depends on the properties of the drugs as well as the frequency with which they are used. *Table* 3 shows the drugs most commonly incriminated in aplastic anaemia, but it must be remembered that as fashions in drugs change so do the patterns of exposure that may produce marrow damage. Chloramphenicol heads the list of known causes in most reviews but the incidence of cases due to this drug is slowly declining; for example in Sweden between 1966-70 the incidence of marrow apla caused by butazones was almost three times grea than that for chloramphenicol due to the m frequent use of the former drugs by that time (Botti and Westerholm, 1973). Penicillamine and Brufen among the newer drugs believed to cause aplas anaemia

Table 3. Some of the currently most important drugs associated with mamw aplasia

Antibiotics and chemotherapeutic drugs	chloramphenicol
	sulphonamides
Anti-inflammatory and antirheumatic drugs	phenylbutazone
	oxyphenbutazone
	gold compounds
	indomethacin
Anti-epileptic drugs	diphenylhydantoin
	troxidone
Antidiabetic drugs	chlorpropamide
Antithyroid drugs.	potassium perchlorate
	thiouracils
Tranquillizers	chlorpromazine

All cytotoxic drugs used in the treatment malignant disease, whether phase-specific (example cytosine arabinoside and methotrexate) cycle-active (alkylating agents and nitrosourea damage the rapidly dividing cells in the marrow tran compartment. However, resting pluripotent stem ce are largely unscathed by these drugs, so that recov occurs rapidly unless the patient has an intrin marrow disorder such as leukaemia. Nevertheless can be shown in both animals and man that repea doses of cycle-active drugs (such as nitrogen musta and its analogues) eventually produce depletion of stem cell compartment and perhaps also damage microenvironment. This may sometimes be of clini importance.

This type of inevitable, dose-related, and usua reversible marrow depression following the use cytotoxic agents must be sharply distinguished fr that occurring as a result of exposure to drugs chemicals that are noninjurious or slightly toxic the majority of individuals. The latter characteristically unpredictable, not related to do and often irreversible; it appears to be related tc single episode of cataclysmic damage. Although unl leukaemia aplastic anaemia is not a progress disorder, it appears that neither the microenvironm nor the damaged stem cells can be repaired. The ra of this type of damage is illustrated chloramphenicol with which it occurs in only ab one in 30 000 people taking the drug. while w Butazolidin the incidence may be as low as one 100 000 (Benestad. 1979).

Drug reactions producing marrow damage m thus be dose-dependent. conditional (or idiosyncrat or immunological. Conditional mechanisms im that either the target cells or drug metabolism abnormal; such a defect is most likely to be heredit and may render marrow cells susceptible to damage the drug or its metabolites. Although these conditio reactions are unexpected, increased doses usually g more marked effects which are closely related to int of the drug. In reactions having immunologi causes, however, the dose and time relationships much more erratic. Morley et al (1976) suggested t the apparently unpredictable and capricious onse aplasia after the use of chloramphenicol, and poss other agents that are normally only slightly myelotc might be explicable if the marrow stem compartment had already sustained damage from

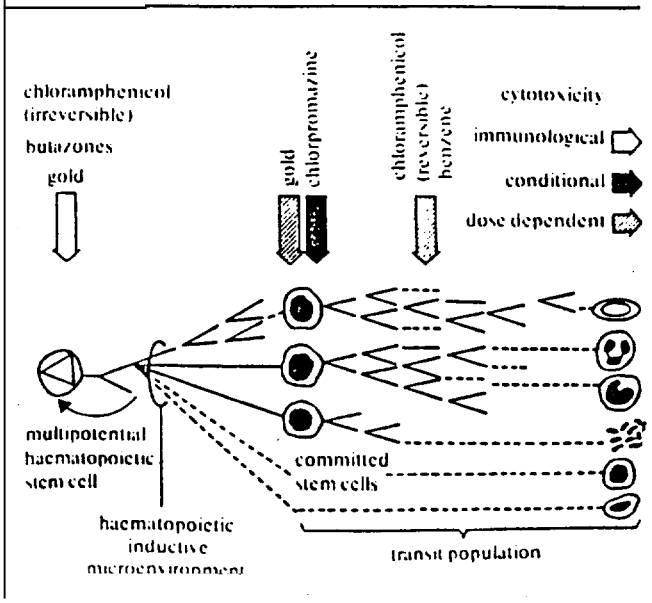
earlier insult which was unrecognized. It is also possible that a toxic agent kills only sensitive stem cells — some resistant cells survive but can only replicate more slowly. If there were a genetic predisposition to aplasia, the distinction between idiosyncratic and immune mechanisms would not be easier because the immune response to specific antigens is also influenced by genetic factors. *Fig.* 1 shows the stage in the haemopoietic cell system at which some of the drugs known to cause aplasia in man may act. It has to be admitted. however. that the evidence is often fragmentary and in some cases even conflicting (Benestad. 1979).

Some drugs that produce irreversible hypoplasia by damaging the stem cell compartment can also inhibit the transit compartment. presumably by a different mechanism. Thus in many individuals chloramphenicol also produces a temporary dose-related erythroid depression and sometimes a reversible par cytopenia, probably because the drug inhibits protein synthesis in mitochondria (Yunis, 1973). Dilantin causes reversible red cell aplasia in certain individuals as well as an idiosyncratic marrow hypoplasia. In one patient studied by Yunis et al (1969) the former syndrome was found to be due to an exaggerated depression of DNA synthesis in erythroid cells by the drug.

Gold may also produce marrow damage by different mechanisms. In some patients a progressive fall in blood leukocyte and platelet counts precedes marrow failure and this seems to be a dose-related effect (Kay. 1973). On the other hand, in a small group of individuals marrow aplasia occurs without warning after very small doses of gold salts (McCarty et al, 1962). Selective thrombocytopenia, agranulocytosis, and even red cell aplasia (Reid and Patterson, 1977) may occur as a result of damage to the transit compartment. Since gold persists for long periods in the body, these potentially reversible syndromes may remain after administration of the metal has ceased.

The bone marrow hypoplasia caused by chlorpromazine is fairly common in psychiatric patients (Pisciotta, 1971). It is a dose-dependent but unpredictable disorder, probably reflecting a constitutional defect in marrow cells which renders them

Fig. 1. ***Possible pathogenetic mechanisms involved in damage to bone marrow cells by certain drugs (from Benestad. 1979).***



unable to compensate for the depressing effect that this drug exerts on many tissues. It is usually rapidly reversible and the likelihood is that the marrow transit compartment, rather than the pluripotent stem cell, is affected. Other drugs that may act in this way include thiouracil and methicillin.

Benzene, which can be shown in rabbits to produce a dose-dependent pancytopenia with aplastic and hyperplastic marrow pictures and with disorderly maturation (Speck, 1975), is still used as a solvent in glue, cement, grease and insecticides, for example, and as a diluent for paint, varnish, and lacquer. It is interesting that toluene and xylol are free from myelotoxic activity. In an animal model the pluripotent stem cells (CFU-S) were unaffected by exposure to benzene and it is therefore possible that clinical aplasia in man is the result of an idiosyncratic reaction. The facts that chromosomal abnormalities have been seen in marrow cells after exposure to benzene and that it is undoubtedly leukaemogenic suggest a direct action on haemopoietic stem cells.

Virus-induced aplasia: Although it is possible that viral damage to the marrow accounts for a significant proportion of cases at present labelled idiopathic, the only well defined viral aplasia syndrome is that following infectious hepatitis. Transient inhibition of the marrow transit compartment Seems to be common, for example leukopenia is frequently found during the illness but the association with aplastic anaemia was not recognized until 1955 (Lorenz and Quaiser, 1955). In one series of 193 patients with aplastic anaemia following hepatitis 18 per cent had received chloramphenicol (Hagler et al, 1975) and it has been suggested that in some patients the aplasia is really due to chloramphenicol or other drugs, impaired detoxification of which might predispose to marrow damage. However. aplastic anaemia is not common in individuals with chronic liver disease and there are now sufficient recorded cases of aplastic anaemia resulting from hepatitis, with no known drug exposures, for a typical clinical picture to have emerged.

The age distribution is similar to that of uncomplicated infectious hepatitis and men are more commonly affected than women. The onset of aplasia is usually within 10 weeks of the hepatitis, which is often mild. However. the aplastic anaemia is particularly severe, especially in women: in one series the mortality rate was 88 per cent and the median survival only 10 weeks (Ajlouni and Doeblin, 1974). Patients with posthepatitis aplastic anaemia thus fall into that group with severe disease in whom bone marrow transplantation should be considered at an early stage. Williams et al (1973) suggested that hepatitis could cause aplasia by several mechanisms: direct viral damage to the marrow. damage to the microcirculation. an autoimmune response to the virus (see below). or failure by the liver to eliminate endogenous or exogenous bone marrow toxins.

Autoimmunity: Immune mechanisms involving both humoral antibodies and probably cell-mediated toxicity can injure proliferating haemopoietic cells in the marrow. Damage may be restricted to a single cell type or involve several simultaneously. The best recognized clinical syndrome of this type is pure red cell aplasia in which autoantibodies to erythroid precursor cells or erythropoietin are sometimes present, but autoantibodies to CFU-C as well as more differentiated myeloid precursor cells have been demonstrated in certain granulocytopenic patients (for a comprehensive review see Cline and Golde, 1978). The marrow lymphocytosis and plasmacytosis seen patients with aplastic anaemia resembles a chron inflammatory disorder, possibly of an autoimmu nature, and this may be triggered by unusual reactio to drugs such as chloramphenicol. On the other han aplastic anaemia is rarely seen in the clinical setting disorders known to have an autoimmune basis such . disseminated lupus erythematosus or Sjögren syndrome, whereas red cell aplasia and immu granulocytopenia are commonly found in such context. Moreover with the exception of posthepatit aplasia and those rare cases associated with thymom autoantibodies to blood cells are not seen in aplast anaemia. However, it has been suggested th autoantibodies in aplastic anaemia might be directe against a "private" antigen expressed only on t haemopoietic stem cell and not on its differentiat progeny (Benestad, 1974). Alternatively they may directed against vascular cells in the marrow.

An autoimmune basis for some cases of aplas received support from the recent work of Ascensao al (1976) who showed that some patients ha lymphocytes in marrow or blood that appeared suppress CFU-C or CFU-E growth from norm marrow. When these lymphocytes were removed fro the patient's marrow colony growth improve Although it is not yet certain whether the presence these suppressor cells is related to the cause of t aplasia or represents an epiphenomenon, perha following blood transfusions, it is worth recalling th thymic lymphocytes are essential cooperator cells f establishing erythropoiesis in mice (see above).

The most compelling evidence for disturb immunity as a cause of aplastic anaemia derives fro the response of both drug-related and idiopathic cas to immunosuppressive therapy. Sometimes chem therapy has been given to prepare the patient for allogeneic marrow graft when, unexpectedly, regrow of his own marrow has been observed. Although o cannot exclude a transient "permissive" role of t transfused marrow which might supply cells humoral factors essential for haemopoiesis, such explanation would not be valid in cases whe remission has occurred after the use of antilymphocy serum alone (Speck et al, 1978). A particular instructive case of this type was that described by t Royal Marsden Hospital Bone Marrow Tran plantation Team (1977). A 15-year-old girl develop posthepatitis aplasia and rejected bone marrow tran plants from her identical twin. but after cyclopho phamide treatment a third graft was successful. Befo immunosuppressive therapy the patient's seru inhibited CFU-C growth in the twin's marrow. The was also evidence of a cellular inhibitor that w removed by co-culture with antithymocyte globulin.

Constitutional aplastic anaemia: This category includ patients with congenital. genetic, or familial disea who have an inherent disposition to bone marro failure. Sometimes the development of marrow hyp plasia appears to follow exposure to toxic extrins agents (already noted) so that patients with unrecognized propensity for aplastic anaemia will listed wrongly as having acquired disease. Howev the constitutional nature of the disease is more eas diagnosed when the child shows other stigmas.

Thus in Fanconi's anaemia, which is the best defin of these clinical syndromes and is inherited in an au somal recessive pattern, the child is often of sh stature and may show skin hyperpigmentatio skeletal or rend defects. and sometimes men

one manifestation of a generalized cellular defect. Most of these children show chromosomal abnormalities (cytogenetic analysis is an essential investigation in any child with bone marrow failure) and it has been postulated that the underlying biochemical lesion is a defect in DNA repair mechanisms. It is possible that some patients with constitutional marrow failure-who do not show the other nonhaematological features of Fanconi's syndrome represent formes frustes. In a recent review of 40 patients with constitutional aplastic anaemia diagnosed at the Children's Hospital Medical Center in Boston between 1958—77, 26 had the classic features of Fanconi's anaemia while 10 had bone marrow failure Without other stigmas and four had amegakaryocytic thrombocytopenia which eventually evolved into panhypoplasia (Alter et al. 1978). The incidence of leukaemia in these patients is much higher than in other forms of aplastic anaemia and an interesting feature held to be diagnostic of Fanconi's anaemia is the increased expression of the SV40T antigen when the skin fibroblasts from these children are incubated with this oncogenic virus in culture. This feature also occurs in first-degree relatives who do not show marrow failure (Dosik et al, 1979).

The defect in the marrow of children with Fanconi's anaemia is at the level of the pluripotent stem cell — both CFU-C and CFU-E are decreased (Saunders et al, 1974; Freedman and Saunders, 1975). By contrast, in congenital red cell aplasia (Diamond-Blackfan syndrome) the defect is at the level of the BFU-E which appears to be inhibited by abnormal T lymphocytes — this may be a disorder of cellular immunity (Steinberg et al, 1979).

Summary

Aplastic anaemia is thus a syndrome with a number of different causes. The fact that bone marrow transplantation restores haemopoietic function in a substantial number of cases (although there are still formidable immunological problems to be overcome) suggests that the disease is indeed often due to defective or deficient stem cells. However there is evidence to suggest that in some cases at least, stem cells are inhibited rather than completely destroyed. It must not be forgotten that only one in four patients has a suitable prospective donor, so the identification of a group in whom, for example, growth of haemopoietic cells was depressed by an autoimmune process would have important therapeutic implications. Although our understanding of the pathogenesis of this mysterious disease has advanced since 1919, when Smith concluded that the aetiology of aplastic anaemia was "nothing but speculation", much still remains to be learnt.

Figure 1 u reproduced by kind permission of the publishers Baillière Tindall

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