Britain; while the specialists at the top have undergone a training as long and detailed as their counterparts in the West.

A second feature peculiar to the Chinese system is the vast amount of primary care provided by traditional doctors. Even from our few hospital visits it was clear that traditional doctors are found more often in country areas than in the cities; probably in the heart of the country they form the majority of trained medical personnel. The training of a traditional doctor is designed to fit him for primary care—surgery has no place in the system, nor have complex investigations. The traditional physicians provide China with huge numbers of doctors with no ambition for urban practice.

Both of these situations are changing, however. Each year barefoot doctors acquire more knowledge, as do the qualified doctors working in commune and county hospitals. In other countries experience has shown that as medical auxiliaries add to their experience and competence they want to enlarge the scope of their work: whether this will happen in China remains to be seen. The proportion of traditional doctors in the medical

work force is also changing—only 10% of new medical graduates have been educated in traditional medical colleges. At present the formal medical course in China lasts for only three years, and a medical graduate who wishes to specialize has a long post-graduate apprenticeship to serve before he can hope to get an appointment at a specialist hospital in Peking or Shanghai: but again the experience of other countries is that young medical graduates wish to work in academic centres rather than provide primary care in country areas.

One all-pervading impression in our travels in China was the cheerful enthusiasm of workers, doctors, and indeed everyone. The pioneering spirit, the sense of building a new society, is very apparent: people accept that the needs of the State rather than personal choice determine the sort of work they do and the place that they do it—and at present the emphasis is on the rural areas. It remains to be seen whether, with increasing material prosperity and improved communications, most of the new generation of Chinese doctors will be content to work in small hospitals in the country.

Today's Treatment

Blood and Neoplastic Diseases

Acquired Aplastic Anaemia

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British Medical Journal, 1974, 2, 432-435

The term "aplastic anaemia" is applied to a group of disorders having in common pancytopenia, hypocellularity of the bone marrow, and prolonged clearance of iron from the plasma. Patients with a similar clinical picture, in whom the marrow is cellular, are excluded by this diagnostic triad, though it is doubtful whether the distinction should be rigid. Aplastic anaemia can be a qualitative as well as a quantitative disorder: islands of cellular marrow, often with morphological features of dyshaemopoiesis, are frequently found in patients with a predominantly hypoplastic picture.¹ Moreover, some agents which usually cause aplasia may occasionally produce pancytopenia with a cellular marrow. The pathogenesis of acquired aplastic anaemia is poorly understood, but the disease is probably due to factors, exogenous or endogenous, which injure or inhibit haemopoietic stem cells and impair their ability to replicate, and thus fulfil their dual role of self-maintenance and of providing cells for the maturation pathway.

Classification

About half of cases of acquired aplastic anaemia have an identifiable cause. Industrial and pharmacological chemicals are the most commonly implicated, while viral infections account for an

unknown proportion. The remaining cases are usually classified as "idiopathic," but, because of the bewildering variety of potentially toxic agents to which an industrial population is exposed, the true incidence of idiopathic cases is probably lower. Chemical agents causing marrow damage are broadly divided into two groups: those in which the frequency and severity of marrow damage is proportional to the dose, and those in which there is no dose relationship (the onset of aplasia being unpredictable and depending on an unusual reaction by the patient to

*Drugs and Other Substances Producing Marrow Aplasia**

	Definite Association	Possible Association
	<i>Class 2</i>	
Antimicrobials, etc.	Chloramphenicol Sulphonamides Organic arsenicals	Penicillin Streptomycin Amphotericin
Pyrazalones	Phenylbutazone Oxyphenbutazone	
Hydantoins	Aminopyrine Mesantoin Tridione	Primidone and possibly others
Sulphonylureas	Dilantin Tolbutamide Chlorpropamide	
Metals Miscellaneous	Gold	Bismuth, Mercury Aspirin, Chloroquin, Potassium chlorate, Phenothiazines, Thiocarbamates, Sulphamyl compounds, etc.
	<i>Industrial Chemicals</i>	
Aromatic hydrocarbons	Benzene, TNT, Solvents	?Hair dyes
Insecticides	DDT Parathion	

*For non-phase specific and s-phase specific cytotoxic agents see text.

the drug). Most cytotoxic drugs fall into the first group; the table shows the commonly-used drugs of the second in which an association with aplastic anaemia is well established. A few substances—for instance, benzene and gold—occupy an intermediate position: marrow depression is partly dose-dependent, but there is considerable variation in patient sensitivity. In addition, there are a large number of drugs in which there is strong circumstantial evidence, from anecdotal reports, that they may rarely cause aplasia.

In Britain the drugs most commonly incriminated are pyrazalones, hydantoin, sulphonamides, sulphylureas, chloramphenicol, and gold. In the U.S.A. chloramphenicol heads the list.²

Pathogenesis

Cytotoxic agents injure rapidly replicating cells, and appreciable marrow depression is often found at therapeutic dosage. Nevertheless, since the vast majority of dividing cells in the normal marrow are found among the "committed" cells, the stem-cell compartment may be relatively spared. This is particularly true of "S-phase specific" drugs, such as methotrexate, cytosine arabinoside and 6-mercaptopurine. On the other hand α -irradiation, alkylating agents, and probably vinca alkaloids produce greater stem-cell depletion at therapeutic dosage. After ablation of the committed compartment, the rate of recovery of the marrow depends on the number of surviving stem cells and the speed with which they divide. For example, after ablation with cytosine arabinoside, recovery to normocellularity may take only a few days. In the elderly, however, those with severe toxæmia, uræmia, or marrow infiltration, this "functional reserve" is reduced, and recovery is slower. After treatment with alkylating agents (for instance, nitrogen mustard or busulphan) recovery may take longer and overdosage is more likely to produce permanent aplasia. Moreover, repeated courses appear to produce progressive depletion of the stem-cell compartment.

Obviously, the risks of aplasia must be seen in the context of the disease which is being treated: the treatment of acute myeloblastic leukaemia with cytosine arabinoside usually requires severe hypoplasia as the prelude to haematological remission. On the other hand, when the same drug is used to treat disseminated herpetic infections, the myelosuppressive effect is a limiting factor.

The manner in which drugs of the second group produce stem-cell damage is not known with certainty, and probably varies. Most of the hydrocarbons incriminated as causes of aplasia in man contain the benzene ring; benzene itself is probably toxic by virtue of the phenolic breakdown products which inhibit DNA synthesis. Chloramphenicol produces two distinct effects on the marrow: a transient, reversible suppression of erythropoiesis found in most individuals who take the drug, related to dosage, and believed due to inhibition of mitochondrial protein synthesis.³ A very few patients (1:30,000), however, develop an irreversible bone-marrow aplasia, not related to dosage, and possibly due to a permanent alteration in the genetic material of the stem cell, rendering it incapable of differentiation. This might, in turn, be due to an inability to detoxify the drug, or to a "hypersensitivity" reaction.

There is circumstantial evidence that patients who develop aplasia after butazolidine ingestion metabolize the drug abnormally slowly.⁴ On the other hand, chloramphenicol, and some other drugs causing aplasia, can act as haptens; combination of drug with stem-cell protein might lead to its rejection by cytotoxic lymphocytes or humoral antibodies. Drugs might produce minor antigenic changes in the cell membrane, or damage the microvasculature of the marrow. The lymphocytes of patients who develop aplastic anaemia following gold therapy may undergo blastogenesis *in vitro* in the presence of the metal, while antibodies to chloroquine have been demonstrated in patients suffering from aplastic anaemia believed to be due to that drug. Nevertheless, in general, skin testing with a suspected drug usually produces negative results.⁵

Diagnosis

Aplastic anaemia may be a fulminating illness or a chronic, indolent disorder lasting many years. The diagnosis rests on the three criteria mentioned above, but haemoglobin, granulocyte, and platelet counts do not always decline in accord, especially in chronic cases. Bone-marrow aspiration and trephine, preferably from more than one site, are mandatory before the diagnosis is accepted. Ferrokinetics, or better, marrow scanning with ⁵²Fe, are helpful in assessing the severity of marrow hypoplasia and in delineating foci of active marrow. Some younger patients have increased amounts of HbF in their blood, and this is said to be a favourable prognostic sign. The degree of red-cell macrocytosis, proportion of residual "myeloid" to "non-myeloid" cells in the marrow, and the corrected reticulocyte count are also possibly of some guidance.

Treatment

Aplastic anaemia is a serious disorder, and, except in the reversible type due to cytotoxic drugs, complete clinical and haematological recovery may occur in as few as 10% of cases.² Mortality is still 50% during the first year, and 70% at five years. Late sequelae include paroxysmal nocturnal haemoglobinuria, acute leukaemia, and, possibly, sideroblastic anaemia.⁶ Supportive therapy is aimed at "buying time" during the period of marrow failure in the hope that remission will occur spontaneously or as a result of hormone therapy.

It is vital to identify and remove any environmental agent responsible, and the patient must be questioned about work, and hobbies, and the proverbial "search of the bathroom cupboard" made in every case. In hospital practice the patient has often taken several drugs, and, except where the disease is of abrupt onset and the relation with drug ingestion well defined, identification can only be an intelligent guess. There are, as yet, no reliable laboratory tests to indicate myelotoxicity and "provocative" tests with a suspected drug are never justifiable. The corollary is that every case of aplastic anaemia in which a drug aetiology is suspected should be reported; only in this way can low-risk drugs be identified.

ANAEMIA

Anaemia may be treated with infusions of packed red cells. Nevertheless, in acute cases, thrombocytopenic haemorrhage usually compounds the normochromic anaemia of marrow failure and infusions of fresh blood are more effective. The frequency of blood transfusions should otherwise be dictated entirely by the need to control symptoms and not aimed at maintaining the haemoglobin at any arbitrary figure. A conservative transfusion regimen reduces the incidence of isoimmunization, and haemolysis; moreover, red cells from which the "buffy-coat" has been removed help to reduce the incidence of reactions due to HL-A antibodies. In women, the contraceptive pill and anti-fibrinolytic drugs are useful in controlling menorrhagia.

THROMBOCYTOPENIA

Fatal haemorrhage is an ever-present risk in a patient with a platelet count of under 20,000/ μ l. Fresh blood can be given in an emergency, but platelet "concentrates" are now available in most centres, and are more effective. Four to six units are given, repeated 12 hours later if no clinical response is evident. Improvement may be monitored by the platelet count and shortening of the bleeding time. Ideally, the donor platelets should be HL-A as well as ABO compatible; platelets survive normally in untreated aplastics, but repeated transfusion of platelets leads, eventually, to the production of antibodies with diminishing clinical response. Infection often exacerbates thrombocytopenic bleeding and requires vigorous treatment.

NEUTROPENIA

Infections in aplastic anaemia are closely associated with the severity of the granulocytopenia. A neutrophil count of less than $250/\mu\text{l}$ is an ominous sign, though in chronic cases patients often seem to become "adapted" to neutropenia. Gram-positive coccal infections, particularly of the skin, bacterial pneumonia, and Gram-negative septicaemia are particular risks. The incidence of fungal infections is also increased. Blood cultures and nasopharyngeal, sputum, urine, and perianal swabs should be taken and the patient isolated. In patients with profound neutropenia, Gram-negative septicaemia is probably best treated with a combination of intravenous carbenicillin and cephaloridine: gentamicin is possibly less effective in the absence of functioning granulocytes. Bacteriological opinion inclines against casual antibiotic prophylaxis. However, a bowel sterilization programme, using broad-spectrum antibiotics and an antifungal agent, has been advocated in agranulocytosis; early reports indicate that this regimen is more effective if the patient is isolated in a plastic "life-island" or a laminar air flow system.⁷

Leucocyte infusions are now a practical proposition in centres where cell separators are in use, and may be of value in the presence of septicaemia or infections not responsive to antibiotics. Infection almost always leads to rapid deterioration in residual marrow function; in a patient with a partially compensated hypoplastic anaemia, an unexplained deterioration in the count should prompt a search for a focus of infection.

ANDROGENIC HORMONES

Androgenic steroids stimulate erythropoiesis by a mechanism which involves the erythropoietin system. In most cases of aplastic anaemia, however, plasma erythropoietin levels are already high; possibly androgens render the committed erythroid precursor cells more sensitive to its action, or (since the granulocyte and platelet counts also tend to rise) increases the mitotic index of the pluripotent stem cell. Though androgenic steroids have undoubtedly improved the prognosis in constitutional aplastic anaemia in children, their value in acquired disease in adults is still disputed.

"Androgen remissions" do not occur until three to nine months after therapy has started, when many of the "poor-risk" patients have already died; the survivors may, in any case, have a better chance of spontaneous remission. Nevertheless, patients treated with these hormones appear to have a better survival in the medium term (up to two years),⁸ and some can be shown to become androgen-dependent, relapse recurring on withdrawal of the drug. However, haematological remission is often incomplete. The disparate results obtained from various centres probably reflect the different criteria used for diagnosing aplastic anaemia. In one series where these criteria were carefully controlled, it was found that at five years there was little, if any, advantage in favour of androgen-treated patients.⁹ A controlled multicentre trial is at present in progress. The preparation most frequently used is oxymethalone (150-300 mg/day). Unpleasant side effects include fluid retention; a reversible, usually dose-related, cholestatic jaundice; diarrhoea and virilization; increased libido may be a distressing symptom in women.

CORTICOSTEROIDS

The value of corticosteroids is also not clear. Though occasional cases of aplastic anaemia appear to respond to prednisolone, they are the unpredictable exceptions, and glucocorticoids are not known to be stem-cell stimulators. Prednisolone is reputed to improve the haemorrhagic tendency by an ill-defined action on "capillary integrity," if not on the platelet count. Nevertheless, most haematologists believe that prednisolone should be avoided, at least in acute aplastic anaemia: its use increases the risk of infection in patients with agranulocytosis. A short trial, carefully monitored, may be justifiable in chronic cases not responding to androgenic steroids alone.

SPLENECTOMY

The role of splenectomy is controversial. Red cell survival is often reduced in aplastic anaemia and this haemolytic component may be compounded by hypersplenism in the chronic case. If ⁵¹Cr studies show increased sequestration of red cells, splenectomy may occasionally be of benefit, especially if there is evidence of residual marrow haemopoiesis. Hypersplenic thrombocytopenia also occurs and may be improved by splenectomy; adequate haemostatic "cover" for the operation is vital. Marrow function has occasionally improved after splenectomy.

MARROW TRANSPLANTATION

Successful marrow transplantation offers a hope of permanent restoration of haemopoietic function provided, of course, that the agent which originally caused the aplasia has been removed.

The few cases in which this has been successful are almost always those in which an identical twin has provided the donor marrow. Attempts to use marrow from non-identical siblings have usually failed, with a graft-versus-host reaction mounted by the lymphocytes in the engrafted marrow. Nevertheless, Thomas and his colleagues⁹ have described initially successful grafts in a number of patients with aplastic anaemia in whom the donors were non-identical siblings, but who matched the recipient in terms of the major HL-A loci. The recipients were prepared for the graft by large doses of cyclophosphamide, and immunosuppression was continued after the graft by the administration of methotrexate.

MARROW CURETTAGE

Knospe and Crosby¹⁰ have suggested that aplastic anaemia may sometimes be a disease of the marrow microcirculation (the "soil") rather than of the haemopoietic stem cell (the "seed"). Autologous marrow transplantation in rats, after x-irradiation of one limb, successful two weeks after the onset of aplasia, was unsuccessful two months later. This was interpreted as progressive failure of the sinusoidal microcirculation. However, if the marrow cavity was subjected to vigorous curettage before injection of the normal marrow, engraftment was successful. Whether this has any relevance to aplastic anaemia in man is unknown: marrow curettage in man has yielded equivocal results and the fact that spontaneous remissions do occur years after the diagnosis, and that marrow grafts have been achieved without previous curettage, suggest that in some cases, at least, the microcirculation is intact. Nevertheless, the micro-anatomy of the marrow sinusoid may render it peculiarly vulnerable to immunological damage.

The occasional case of aplastic anaemia which responds to prednisolone, or even splenectomy, and the marrow lymphocytosis found in some cases of aplastic anaemia, may support the hypothesis that aplastic anaemia is sometimes an immunological disorder. However, except in the case of pure red cell anaemia (which is rarely drug-related) cytotoxic immunosuppressive therapy cannot, in the present state of our knowledge, be advocated.

Conclusions

Hence the current methods of treatment available for aplastic anaemia are unsatisfactory. Advances will depend on a better classification and understanding of the pathogenesis of the disorder, and the ability to distinguish those cases in which local factors are preventing repopulation of the marrow space by intrinsically normal stem cells from those in which the haemopoietic stem-cell compartment is irreversibly damaged.

The last group are unlikely to be helped by marrow-stimulating hormones, and the best hope at present is an improvement in marrow grafting techniques, such as the separation of donor haemopoietic cells from the unwanted immunological cells. For

the future, possibly techniques might be developed which would use the ability of certain undamaged non-haemopoietic cells in the marrow, such as fibroblasts, to undergo division, and to direct their maturation towards the erythroblast, granulocyte, and megakaryocyte pathways.¹¹

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For Debate

EB Virus and the Treatment of Lymphomas

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British Medical Journal, 1974, 2, 435-436

Summary

The high incidence of EB virus infections (and possibly of other viruses) in patients with African lymphoma and, to a lesser extent, in patients with lymphosarcoma in the temperate zones, is thought to be due to its being a passenger virus which persists in the human body and, since it is lymphotropic, presents an opportunistic infection of proliferating lymphoid cells. The thesis is put forward that by entering the cell nucleus, the virus renders malignant lymphoid cells more vulnerable to cytotoxic drugs. Hence a deliberate policy of EB virus inoculation before starting chemotherapy might achieve a more rapid response and longer remissions in indigenous lymphomas of the temperate zones, and might possibly render drug-resistant cases once more drug-sensitive.

The African lymphoma (Burkitt tumour) is characterized by the following four features: (1) a typical morbid anatomical distribution affecting the large viscera, deep abdominal lymph nodes, and the skeleton, without involvement of the peripheral lymph nodes, lungs or spleen; (2) the typical histological appearances of a uniform "starry sky" pattern; (3) cultural and serological evidence of an EB virus infection; and (4) a very definite, and sometimes dramatic, response to cytotoxic drugs.

These features merit a more detailed consideration.

Macroscopical Manifestations

A clear-cut distinction between African lymphoma and childhood lymphosarcoma in the temperate zones cannot be made as no single feature can be considered as diagnostic.¹ Nevertheless, in tropical Africa the combination of tumours of the major viscera associated with tumours of the skeleton—especially the disfiguring tumours of the jaws—constitute a diagnostic

clinical picture. The frequency of bone involvement of the clinical syndrome is impressive and is at present unexplained.

In contrast, the indigenous lymphosarcomas elsewhere tend to affect the peripheral lymph nodes and the spleen in a large proportion of cases.²⁻⁵ Neoplastic disease of the bones also does occur, but this presents either as diffuse lymphoid infiltrations or as nodular lymphomatous tumours of the cancellous bone; expansive and distorting tumours of the facial bones and adjacent soft tissues as seen in the African lymphoma are rare.

Histological Features

Microscopically the Burkitt tumour shows diffuse sheets of lymphoid cells with uniformly distributed cells of reticulum-cell type with much clear cytoplasm producing a "starry sky" pattern—a feature which is otherwise seen only in the reactive centres of lymph nodes.⁴ Nevertheless, occasional cases of African lymphoma may lack this characteristic feature.⁶

A similar histological variant of lymphosarcoma has been observed in many parts of the world, including the United States,⁶⁻⁹ in Papua and New Guinea,¹⁰ in South America,^{11,12} and in Southern India.¹³ Squire¹⁴ reported feline lymphomas with "starry sky" patterns. Among our own material 14 out of 78, or 18%, of lymphosarcomas showed similar histological features, though in most cases the distribution of the swollen reticulum-type of cells was less definite and was patchy rather than uniform. Moreover, in several cases the "starry sky" reaction was present exclusively in the subcapsular peripheral zones of the neoplastic lymph nodes, suggesting that this phagocytic reaction was of recent origin and represented a response to toxic stimuli reaching the lymph nodes via the afferent lymphatics.

In retrospect it would appear quite likely that a proportion of lymphomas, diagnosed in the past as Hodgkin's paraneoplasia, may have been lymph nodes reacting to a viral infection, such as an EB virus infection, which would explain the favourable clinical course of some cases in this group.

Evidence of Viral Infection

Cases of African lymphoma generally show evidence of an EB virus infection. This evidence is both direct and indirect. The