Today's Treatment

Drug-induced diseases

Drug-induced haematological disease

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The taunt about yesterday's remedies was that they were largely ineffectual. Today's treatment is often extremely effective but unfortunately has frequent bad effects, and much of modern therapeutic effort has to be directed at recognising and preventing morbidity from useful drugs.

One group of organs that suffers much from drug-induced ills is the blood and the blood-forming tissues. In many haematological textbooks there is a chapter on drug-induced blood diseases. It is unfortunately often true that in the ill effects produced by drugs on the blood, "the evil that men do lives after them; the good is oft interred with their bones." The effects may be predictable or unpredictable, and, indeed, drug-induced blood changes may be the first sign of unnoticed hereditary blood disorder, such as glucose-6-phosphate-dehydrogenase (G6PD) deficiency.

Marrow hypoplasia

Drug-induced mild hypoplasia of the blood cells is used clinically as the guide to the maximum safe dosage of cytotoxic drugs in treating many forms of malignant disease; the blood cells are a convenient tissue to biopsy at frequent intervals. Such drugs will always cause marrow depression, although the dose required to do so will show enormous variation among people, and is modified considerably by such factors as previous radiotherapy and the presence of infection and malnutrition. Sometimes the nadir of the blood count is delayed, as with melphalan, and sometimes one element of the blood cells is depressed more than the others—for instance, the nitrosoureas affect particularly the platelet count. Long-continued bone marrow damage by cytotoxic agents can produce more subtle effects—for instance, in patients having adjuvant chemotherapy for breast carcinoma a late effect is persistent depression of the neutrophil polymorph precursors, without a fall in the total white cell count. In fact, marrow aspirate in patients on cytotoxic chemotherapy with only modest depression of the peripheral blood count is often surprisingly hypocellular and fatty.

Some drugs, harmless to most people in the normal therapeutic

dose, will occasionally at that dose cause aplastic anaemia. The best-known example is chloramphenicol, where the risk is to about 1 in 60 000 people exposed to it, and the same odds are probably true of phenylbutazone. There is no way of identifying before use people with such a susceptibility; the defect may be in the marrow cells, at different phases of cell development, or be a defect of detoxification or excretion of that drug.

THROMBOCYTOPENIA

Aplasia (or, much more commonly, hypoplasia) may affect all three elements of the blood—red cells, white cells, and platelets—or may affect one element mainly or alone. When only one element is affected an immune-complex process is probably concerned—for instance, in drug-induced thrombocytopenia, where antibody production can be shown in some cases and where abundant megakaryocytes can usually be found in the marrow. This was first noted with the hypnotic apronal (Sedormid); hence the old name "Sedormid purpura." Of the present-day drugs producing this immune thrombocytopenia, the antituberculosis antibiotic rifampicin is an important occasional cause, and the thrombocytopenia of the thiazide diuretics, sulphonamides, digitoxin, quinidine, quinine, and parenteral penicillin probably has the same mechanism.

NEUTROPENIA

Neutropenia may be caused by a direct toxic effect on the marrow as with cytotoxic drugs, or be an occasional finding in sensitive people. "Immune" neutropenia is less easy to prove than is thrombocytopenia, and many drugs have been incriminated. These include the anti-inflammatory drugs, especially phenylbutazone; antihistamines—for instance, chlorpheniramine; antithyroid drugs, such as methylthiouracil and carbimazole; antidiabetic drugs, such as tolbutamide and chlorpropamide; phenothiazines—for example, chlorpromazine; various antibiotics, metronidazole, aminosalicylic acid, isoniazid, and the thiazides. The onset of neutropenia may be sudden, even in a patient who is well established taking the drug, and total agranulocytosis (absence of all mature cells of myeloid series from the blood) may occur, but is fairly rare, so that the old system of monitoring the white cell count of all patients taking, for example, antithyroid drugs, is probably not worth while. Chronic neutropenia, however, is not an uncommon cause of reference to a blood clinic, and drug-induced neutropenia must be among the commonest causes.

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ACUTE MYELOID LEUKAEMIA

Other effects of drugs on the white blood cells are less easy to measure. Depression of the normal functions of chemotaxis and phagocytosis by anti-inflammatory drugs has been shown. There is also considerable evidence that a marrow, once rendered hypoplastic after insult by a drug, is much more liable than normal to develop acute myeloid leukaemia. The major problem here is the impossibility of ascertaining how totally normal and stable the marrow was before the insult. There is a high index of suspicion about melphalan (an alkylating agent often used in myeloma) in inducing acute myeloid leukaemia, but in myeloma the marrow is already grossly abnormal, and several cases of simultaneous appearance of myeloma and acute leukaemia have been recorded. Similarly, the immunosuppressant drugs used during renal transplantation have been incriminated in the subsequent high risk of developing lymphomas; and the drugs used in Hodgkin's disease may have some part in the later risk of acute leukaemia, which is higher than expected.

DYSERYTHROPOIESIS

Red cell hypoplasia alone is rare, but the red blood cell may show evidence of other forms of drug-induced marrow upset in the form of dyserythropoiesis. This may take several forms.

Megaloblastosis

Megaloblastosis with or without the development of megaloblastic anaemia is one form. Many drugs interfere with the absorption of vitamin B₁₂ from the ileum, including neomycin, aminosalicylic acid, metformin, various anticonvulsants, and slow-K. Although this results in a low serum vitamin B₁₂ concentration, this rarely results in a definite megaloblastic anaemia. Nevertheless, a clinically important form of iatrogenic vitamin B₁₂ deficiency recently described occurs in patients being ventilated with a gaseous mixture containing 50% nitrous oxide, after cardiac bypass surgery, or in general intensive care. The picture, clinically and haematologically, is that of acute vitamin B₁₂ deficiency, probably from interference by the nitrous oxide with B₁₂ function due to oxidation.

Methotrexate and cytarabine are both powerful antifolates and cytotoxic agents. Many anticonvulsants, especially phenytoin, primidone, and barbiturates, produce folate deficiency, the incidence depending apparently on the dose and type of drug and the diet of the patient; relatively few patients develop severe megaloblastic anaemia. Trimethoprim, usually given as co-trimoxazole (Septrin), inhibits bacterial dihydrofolate reductase, and megaloblastic anaemia has been noted especially when co-trimoxazole has been used long term, and in patients with dietary folate deficiency. Pyrimethamine, related to trimethoprim chemically, may have the same effect. An important cause of acute megaloblastosis is hyperalimentation, usually using intravenous essential amino-acids, sorbitol, and ethanol. Postoperatively in a malnourished patient, often with gastrointestinal cancer, the condition is of considerable importance, because hypoplasia and disordered maturation affect all the marrow cells, and acute leucopenia and thrombocytopenia may result. This can be prevented by the simultaneous addition of daily intravenous folic acid.

Sideroblastic anaemia

Sideroblastic anaemia is another form of dyserythropoiesis that may be drug-induced. Here the biochemical lesion is not an abnormality of DNA synthesis in erythrocyte formation but a fundamental abnormality of haem development. In anti-tuberculosis treatment with isoniazid and cycloserine, after several months a small proportion of patients, perhaps with an

underlying genetic tendency, develop a rapid fall in haemoglobin, with the marrow showing characteristic ring sideroblasts. Alcohol used therapeutically in hyperalimentation may also produce sideroblastosis.

HAEMOLYTIC ANAEMIA

In megaloblastic and sideroblastic anaemias there is both reduced production and increased destruction of red cells, a mixture of hypoplasia and haemolysis. Certain drugs produce a pure haemolytic anaemia, however, and the number of drugs recognised as doing so is increasing.

Penicillin and many cephalosporins are small molecules, which produce IgG-type antibodies. The latter do not fix complement, and red blood cells that have been exposed to and coated with penicillin may lyse (modestly and extravascularly) when high doses of intravenous penicillin are given. These two groups of antibiotics are likely to cross-react in this as in other respects.

The more usual drug-induced haemolytic mechanism is: drug + serum protein + antibody + red blood cell reaction. When complement is added the red blood cells lyse, intravascularly, so that haemoglobinuria and sometimes renal failure occurs. Drugs in common use that occasionally produce this effect include quinine and quinidine, aminosalicylic acid, isoniazid, and the sulphonamides (including sulphasalazine).

One special form of drug-induced haemolytic anaemia is that associated with α -methyl dopa treatment. Around 20% of patients treated with this drug for three months or more develop a positive direct antiglobulin test (Coombs test) of IgG-type showing rhesus-specificity. About 0.5% of all patients on the drug will develop overt haemolytic anaemia; the more antibody present in the serum the more likely is the patient to develop anaemia. Haemolysis may be severe enough to require blood transfusion and temporary use of corticosteroids. The drug should never be used again, even though haemolysis stops within a few weeks and the direct antiglobulin test reverts to negative in six to 18 months after cessation of the drug. Other drugs incriminated in producing the same effect are chlorthalidopoxide, mefenamic acid, flufenamic acid, and indomethacin; levodopa may produce the positive Coombs test.

Drug-induced haemolysis may occur when the red cell is already abnormal—for instance, in G6PD deficiency, which accounts for about 95% of all hereditary red cell metabolic defects. The incidence of this deficiency is widespread, being found in natives of China and Western Europe, as well as around the Mediterranean littoral and in negroes, so that, in multiracial Britain, it is a condition to be borne in mind. There are many different isoenzymes of G6PD (which is carried on the X chromosome, and has, thus, sex-linked inheritance), and different clinical features result from different isoenzyme deficiencies. The characteristic, however, of a G6PD-deficient red cell is that it haemolyses on exposure to oxidising stress, and the oxidant is often a drug.

Many drugs have been implicated in precipitating a haemolytic crisis in G6PD deficiency. Primaquin and the other anti-malarials were the first drugs noted, but sulphonamides (including sulphasalazine and sulphamethoxazole or co-trimoxazole), various antibiotics such as nitrofurantoin, aminosalicylic acid, and isoniazid, and vitamin K analogues such as Synkavit have the same effect. Infection, bacterial or viral, may also cause acute haemolysis in susceptible people, and it has proved difficult to sort out the role of infection from that of drugs, such as aspirin-containing analgesics taken for symptomatic relief, in causing haemolysis. In any one patient with a particular isoenzyme deficiency many drugs may cause no haemolysis at all. The characteristic of this form of drug-induced haemolysis is that it stops after a few days, despite continuing the drug, as young red cells are entering the circulation.

Heinz bodies can often be shown in acute haemolysis. They result from precipitation of the globin chain of haemoglobin, because of oxidant stress in vivo. Heinz bodies reduce

the ability of the red cell membrane to deform, so these red cells are delayed in the reticuloendothelial system, allowing them to be haemolysed and phagocytosed, usually in the spleen. Their presence makes an easy laboratory method of showing oxidant damage to haemoglobin by drugs.

CHRONIC POSTHAEMORRHAGIC ANAEMIA

Probably the most common drug-induced haematological condition is chronic posthaemorrhagic anaemia resulting from taking aspirin or aspirin-containing drugs, often self-prescribed, and causing occult peptic bleeding. Aspirin can produce such an anaemia in two ways—by local irritation of the gastric mucosa and by fundamental and life-long damage to circulating platelets. Thus the effect of two aspirin tablets may be shown by in-vitro platelet function tests for at least a week. Most of the anti-inflammatory agents used in chronic painful joint conditions may also produce gastric erosions or occult peptic blood loss. Many patients have indigestion or occult bleeding or both (and these two problems are often disassociated) with one anti-inflammatory drug, but none with another. Gastroduodenal blood loss may, of course, be much more overt and acute with any of these drugs.

HAEMOSTATIC DEFECTS

The production of haemostatic defects by drugs tends to be intentional and the main action, as with the oral anticoagulants (warfarin, coumarin, and the indanedione derivatives), the parenteral anticoagulants—for instance, heparin—and the drugs producing controlled defibrination, such as streptokinase and anicrod. Drugs such as aspirin and dipyrimadole are now being considered in the prophylaxis of further arterial thrombosis both after myocardial infarction and in transient ischaemic cerebral episodes. Thrombocytopenia has been mentioned earlier.

Lastly, some drugs will affect the blood in its role of monitor to the health of the body. Eosinophilia, and sometimes basophilia, may occur as indications of allergy, where perhaps the target organ of the drug is the skin. Similarly, the LE cell phenomenon can be shown in the blood of some patients having procaineamide and hydralazine, and these patients often develop the systemic features of systemic lupus erythematosus.

Drug-induced disease has been particularly well demonstrated with regard to the blood cells because of the ease in biopsying these cells. This has led to daunting lists of drugs that may upset blood cells, and since blood is such a complicated organ, the difficulty is often to unravel the mechanism of the damage.

Letter from . . . Chicago

Persian letter

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Usbek to his friend Rustan in Isfahan.

I came to this inhospitable climate towards the end of February, when icy blizzards were mercilessly pounding the city and more than 90 inches of snow had already fallen, covering the streets and sidewalks with an impenetrable frozen arctic layer. At least 100 people were said to have died from shovelling snow and pushing cars or snowblowers; hospitals reported numerous injuries from people falling off roofs while trying to clear the snow; and the incidence of frostbite injuries—aggravated by the cooling effects of the salt dumped on the roads—reached alarming proportions. Everybody was getting fed up, and psychiatrists were reporting an epidemic of "blizzard blues," with anxiety, depression, and irritability over being shut in, over fighting the snow and the traffic, over having one's car constantly stuck in the ice. Even getting to work and back was quite an accomplishment, and, with tempers growing short, arguments, slammed doors, and other outbursts were reported to be on the rise, while many people became depressed, sad, and preoccupied with the past, losing their appetite or eating, drinking, and smoking more, and feeling constantly worn out. Even watching TV or reading the

newspaper was exhausting, because when the news was not about the trouble in our dear homeland and how we would stop sending oil, it was about the cold and the wind and the snow, and also about the problems of the economy.

President's promises

The President, as usual, said that the state of the nation was sound; and both he and his vizier promised again that they would set up a health system as good as that in Britain, if not this year then the next, or may be in five years. They also promised once more to cut hospital costs and hoped the mullahs in Congress would go along with another draft of the by now legendary Cost Containment Bill. But the Ayatollah Kennedy did not think this was good enough and held a popular circus, in which he scientifically matched people who went broke from being ill in the US with people who came out ahead from having identical symptoms in Canada. The American Medical Association retorted by publishing accounts of many doctors who, disappointed with the Canadian system, have migrated to the US; and everybody now expects the ayatollah to publish lists of patients who, disappointed with American doctors, have emigrated to Canada.

The health-dervishes, meanwhile, were still busily writing about the catastrophic problems of American medicine and in particular about the need for controlling costs, preventing unnecessary surgery, beefing up peer review, etc, which at least gives them something to talk about, especially since, as Mr David Greenberg¹ recently pointed out, they invariably end up

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