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Target Organs

The Blood*

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Introduction

The blood volume in a person of average build is about 70 ml kg body weight, of which the plasma accounts for 40 ml/kg. All the blood cells are derived from the haemopoietic organs which include the bone marrow, spleen, liver and thymus and the lymph nodes.

In the embryo, blood cells are first formed in the area vasculosa of the yolk sac. At a later stage of development they arise from the body stalk and the placental site. then from the liver, spleen and thymus and finally from the bone marrow. After birth, the bone marrow is normally the only site at which the red cells and granular leucocytes are formed, but the liver and spleen may resume their blood-forming role following massive blood loss or in severe anaemias, especially in infants,

The cells of the blood have a common origin from reticulo-endothelial (RE) cells which give rise to the primitive haemocytoblast. From this cell, precursors of all the cell lines, red, white and platelets are formed, which, after varying stages of maturation, form the cells which circulate in the peripheral blood.

The Red Cell

The formation of the mature red cell is represented diagramatically in *Fig.* 1. Each stage may be affected by toxic agents as will be discussed below. Erythropoiesis is controlled through the mediation of erythropoietin, a hormone with a molecular weight of about 46 000, which is produced in the kidney in response to hypoxia. Erythropoietin production may be severely impaired following damage to the renal tubules, including the type which can be induced experimentally in animals by mercuric chloride (Reissman et al., 1960), the possibility that this may also follow occupational exposure does not appear to have been investigated.

The red cell has a life span of about 120 days and, in health, senescent cells are removed by the phagocytic action of RE cells in the spleen and liver. The normal ranges for haemoglobin concentration, red cell numbers and red cell indices are shown in *Table I*.

Table I. **Normal red cell values**

Haemoglobin (g/dl)	13·5–18·0 (men) 11·5–16·5 (women)
Red cells (10^{12}/l)	4·5–6·5 (men) 3.9–5·6 (women)
MCV (femto litres)	76–96
MCH (picograms)	27–32
MCHC (g/dl)	30–35

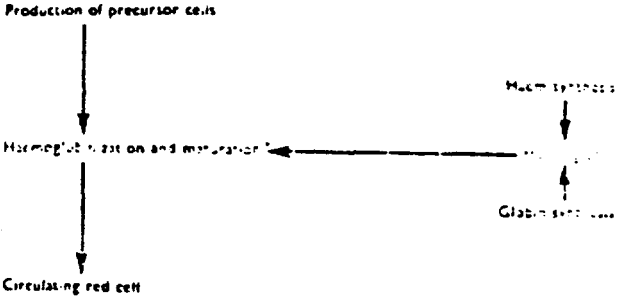

Fig. 1. Stages in red cell maturation.

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Table II. Major functions of the white cells

Neutrophil	Phagocytosis of small particles of foreign material; bacterial phagocytosis greatly facilitated by the presence of specific antibodies
Eosinophil	Phagocytosis of antigen-antibody complexes, rheumatoid factor complexes and red cells (in the presence of immune sera)
Basop.	Release of histamine
Monocyte	Production of tissue macrophages; phagocytosis (including that of large particles); pinocytosis of proteins and colloids
Lymphocytes	Mediation of specific immune responses

Table III. Normal white cell values

Total white cells	Absolute level	
Neutrophils	2500–7500 × 10⁶/l	(40–75%)
Lymphocytes	1500–3500	(20–45%)
Monocytes	200–800	(2–10%)
Eosinophils	40–440	(1–6%)
Basophils	0–100	(0–1%)

The White Cell

The white cells are formed in the bone marrow and the mature forms are released into the blood where their life span is generally short. Following their release from the marrow, the lymphocytes undergo further modification in the lymphoid tissues, some in the thymus (the T-cells) and some (the B-cells) elsewhere, probably in Peyer's patches in the small bowel. The T-cells and B-cells can be distinguished under the scanning electron microscope since the B-cells have a ragged appearance whilst the T-cells are smooth. The prime function of the 13-cellsis to divide in response to contact with *antigen* to produce plasma cells which in turn produce specific antibodies. The T-cells help the B-cells in initiating primary immune responses and are themselves involved in cell-mediated responses, including rejection phenomena.

The most important functions of the white cells are outlined in *Table II;* normial values appear in *Table III.*

Effects of Toxic Agents

A convenient way to begin the discussion of the effects of toxic agents on the blood is by considering each of the cell lines shown in *Fig. 1*, remembering that some agents exert their

Production

Bone marrow damage is rarely sustained in industry and the number of agents which are known *to* induce aplastic anaemia as the result of occupational exposure is small. The best known are benzene, tri-nitro toluene (TNT) and irradiation, but a few cases have been reported following exposure to organic insecticides (Friberg and Martensson, 1953), whilst exposure to cadmium has also been associated with changes in the bone marrow (Cotter and Cotter, 1951; Berlin and Friberg, 1960).

The toxic effects of benzene on the bone marrow have been known since 1897 when they were first described by Santesson, and they have been studied extensively during the succeeding years. The changes which may be found in the peripheral blood of workers exposed to benzene depend upon which cell line, or lines, suffer the brunt of the injury. Anaemia is generally the first effect noted, followed sequentially by leucopenia, thrombocytopenia and finally, if the damage to the marrow is severe, by pancytopenia (Goldwater, 1940–1; Truhaut, 1968; Aksoy et al., 1971). These changes may follow from either acute or chronic exposure. and aplastic anaemia has been reported in those whose last known exposure took place 10 years before the onset of symptoms (Scott et al., 1959). All manner of abnormalities may occur in the bone marrow, from acellularity to hypercellularity, the latter occurring even though there is no evidence of cell formation in the peripheral blood (Aksoy et al., 1972). Aplastic anaemia following exposure to TNT is rare. but when it does occur. the bone marrow findings in living patients are similar to those in patients poisoned with benzene; marrow taken at autopsy is invariably hypocellular (Crawford, 1954; Scott et al., 1959). As with the aplastic anaemia following exposure to benzene, the onset of the disease may be delayed several years after the last known exposure (Hayhoe, 1953). The mechanism by which benzene produces damage to the marrow is still uncertain, although it has been shown to inhibit DNA synthesis in experimental animals, a fact which may be relevant to its leukaemic potential (Moeschlin and Speck, 1967). It is not entirely clear whether benzene itself, or a metabolite, is the toxic agent, although recent work is tending to favour the latter view (Andrews et al., 1977; Tinbrell and Mitchell, 1977; Uyeki et al., 1977).

The harmful effect of irradiation in the marrow

Table IV. Changes in' haem metabolism in lead poisoning

Blood	*Urine*
Erythrocyte protoporphyrin concentration elevated	Urinary ALA concentration raised
Red cell ALAd activity inhibited	Urinary coproporphyrin concentration raised
Serum ALA concentration raised	
Serum iron concentration raisd	

Heinecke (see Dunlap, 1942) and the time course of the [redacted] following massive doses of irradiation

[redacted]

atomic blasts in Japan. Severe leucopenia is the first abnormality to occur followed by thrombocytopenia and then by the production of anaemia; at this stage the bonc marrow shows an almost complete loss of cells!

Haemoglobinization and Maturation

Only one material likely to be encountered in the workplace affects haemoglobinization of the red cell to any significant degree, and that is lead. Benzene has been shown to inhibit the early stages of haem synthesis in experimental animals (Freedman et al., 1977; Greenblatt et al., 1977) and so has cobalt (de Matteis and Gibbs, 1977), but in neither case is the relevance of these findings to occupational exposure known.

Inorganic lead affects a number of the stages of haem synthesis by inhibiting the activity of the enzymes which control the progressive production of haem from glycine and succinyl Co-A (*Fig.* 2). Organic lead compounds in general have no effect on haem synthesis except to lower ALAd activity slightly (Waldron. 1975b). Many of the enzymes in this pathway contain essential sulphydryl (–SH) groups for which lead has a high affinity; by combining with these –SH groups, lead renders the enzyme inactive (Moore and Goldberg, 1974). As haem synthesis becomes progressively depressed by the action of lead, ALA synthesis is actually [redacted] probably as a result of an interference with the negative feedback loop shown in *Fig.* 2 (Strand et al., 1972). The complex impairment of [redacted] produces characteristic changes in the levels of haem precursors in the blood and

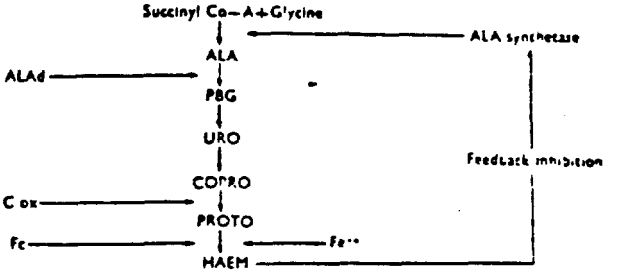

Fig. 2. Haem synthesis: the production of ALA by ALA synthetase is the rate-limiting step. Principal steps inhibited by lead are indicated by arrows on left. ALA, δ-aminolaevulinic acid; PBG, porphobilinogen; URO, uroporphyrinogen III; COPRO, coproporphyrinogen III; PROTO, protoporphyrin IX; ALAd, ALA dehydratase; C ox coproporphyrinogen oxidase; Fe, ferrochelatase.

urine which enable a definitive diagnosis of lead poisoning to he made (*Table IV*).

I-cad also inhibits the synthesis of the globin moiety of the haemoglobin molecule, impairing the production of both α and β chains in *vitro*; the former to a greater degree than the latter. In a study of lead workers, no alteration in α :β ratio was found. and, indccd, in some the ratio was increased. suggesting that thcrc may be a compensatory increase in a chain production in these men (Piddington and White, 1974). In other haem deficiency states, globin synthesis is impaired through the inhibition of the formation of the met-tRNA$_f$-40S ribosomal complex and it seems likely that this is also the mechanism in lead poisoning (White and Selhi, *1975).*

The incorporation of iron into the protoporphyrin molecule is prevented by the inhibition of ferrochelatase, but lead also interferes with iron metabolism in a numhcr of othcr ways which are discussed by Mahaffey (1974). Cadmium also seems to interact with iron, and, in experimental animals at least, the anaemia induced by cadmium is alleviated by the administration o i iron (Berlin and Friberg. 1960; Banis et al., 1969; Jacobs et at.. 1969).

The Circulating Red Cell

Arsine is the most notorious of the industrial haemolysins. It is used for doping in the manufacture of semi-conductors and it is also accidentally produced when nascent hydrogen comes into contact with compounds of arsenic. This may happen in a variety of different processes including electrolysis. the smelting of ores. the manufacture

of zinc sulphate and chloride, the wet treatment of scrap metal slags and where impure acids or metals are used. The intravascular haemolysis produced by exposure to arsine is often profound: for example, one of the cases described recently by Wilkinson and his colleagues (1975) had a PCV of zero! The mechanism of action is not yet fully established (de Palma, 1969; Hocken and Bradshaw, 1976; Ito, 1976), but amongst the possibilities which have been discussed are the production of elemental arsenic, or arsenic dihydride, the inhibition of catalase with a resultant production of hydrogen peroxide, and the formation of complexes with —SH groups which impair the sodium-potassium pump (Fowler and Weissberg, 1974). The multiplicity of explanations suggests that none is entirely correct. Likewise, the haemolytic action of TNT, one of the few other industrial haemolysins, has not been adequately explained (Stewart et al., 1945). It is interesting to note, however, that acute haemolytic episodes have occurred in TNT workers who have a deficiency of G6PD (Djerassi and Vitany, 1975) which suggests that, in these men, the lytic action is due to the oxidizing properties of the compound.

Lead is the other haemolytic agent which needs to be considered. It is the classic example of a toxic agent whose effects are due to a variety of mechanisms; for in the production of anaemia, not only does it inhibit the synthesis of haem, but it also exerts a weakly haemolytic effect on the circulating red cell. The haemolytic effects are thought to be due to abnormalities in membrane structure and function. Red cell Na^+ and K^+ ATP-ase is strongly inhibited by lead both *in vivo* and *in vitro* (Hasan and Hernberg, 1967) and this produces a great loss of potassium from the cell. This loss is much greater than would be expected from the inhibition of ATP-ase alone, and the conformational changes induced probably create a selective gate through which potassium (but not sodium) can leak (White and Selhi, 1975). Changes in the shape of the red cell are also in themselves likely to accelerate their rate of removal from the circulation by RE cells and perhaps to increase their mechanical fragility. It should be noted, however, that the haemolytic action of lead is of less importance in the production of anaemia than the alterations in haem synthesis and that frank haemolysis is a late manifestation of lead absorption (Chisolm, 1968).

Malignant Change

The malignant potential of ionizing radiation has been exemplified by the classic study of Court-Brown and Doll (1957) on patients with ankylosing spondylitis treated by X-irradiation and by the follow-up studies of the survivors of the atomic bomb blasts (Heyssel et al., 1960). In each of the groups observed, there was an excess of deaths from leukaemia, but there has also been an increase in other types of tumours amongst those Japanese who have survived the atom blasts for a sufficiently long time to allow for the development of malignancies with a long latent period. The peak incidence of leukaemia occurs about four years following irradiation and the acute non-lymphocytic types predominate.

The data from Japan indicated that there was a linear relationship between the radiation dose and the incidence of leukaemia above 100 rad, but below this dose the shape of the curve was uncertain. At Nagasaki no increase in incidence in leukaemia was observed when the dose was less than 100 rad but at Hiroshima, an increase was noted for doses down to 20 rad (Anderson, 1971; Miller, 1971). In recent years, and particularly in the wake of the debate concerning the use of plutonium as a fuel source, there has been considerable discussion as to the risks involved from exposure to doses of radiation which are currently considered acceptable. Mancuso and his colleagues (1977) have evinced epidemiological evidence that workers making plutonium at the Hansford Works in Washington State have an enhanced death rate from malignant disease (including leukaemia) although exposure has seldom exceeded 5 rads per annum. The study of Sajarian and Colton (1978) of deaths amongst workers at the Portsmouth Naval Shipyard where nuclear submarines are repaired appears to support this view since the observed number of deaths from leukaemia was 1·74 times that expected. No details of exposure were available, however, although it was assumed that lifetime exposure was less than 100 mSv (1 Sv = 100 rem), and the number of cases was small (12 observed deaths from leukaemia), deficiencies to which the authors themselves gave ample consideration. Mole (1978) was critical of Mancuso's work, in particular the suggestion that the doubling dose for bone marrow tumours (myeloid leukaemia plus myeloma) is only 0·8 rads. This dose seems impossibly low and Court-Brown and his co-workers (1960) concluded

from their studies relating the incidence of leukaemia with background exposure that a dose of 1 rad would produce only 1 case of leukaemia per million man-years of exposure. Bonnell and Harte (1978) suggest that the risk of a person exposed continuously to 10 mSv/yr (the maximum dose usually experienced by workers in the British nuclear power industry) from the age of 20 developing radiation induced leukaemia is between 1 in 100 000 and 1 in 50 000, but Lindop (1978) considers the risk to be much greater, 1 in 1400. Clearly, this is a sensitive area and one in which a great deal more epidemiological work is needed and, as the *Lancet* (1978) pointed out, there is probably enough data already buried in the records of employing authorities in this country and the United States to enable an adequate case-control study to be undertaken.

The only other significant risk of developing occupationally related leukaemia appears to arise from exposure to benzene and there is a considerable number of case reports, mostly of the acute non-lymphocytic type, although an unusually large number of cases of erythroleukaemia have also been reported (Vigliani and Saita, 1964; Girard and Revol, 1970; International Agency for Research on Cancer, 1974; Aksoy, Erdem and Dincol, 1974, 1976). Numerous chromosomal observations have been found in patients with leukaemia who have had chronic benzene exposure (Hartwich et al., 1969; Aksoy, Erdem, Erdogan et al., 1976), which is consistent with the impairment of DNA synthesis [illegible] animals (Moeschlin and Speck, 1967). Epidemiological studies (Ishimaru et al., 1971; Infante et al., 1977; Brandt et al., 1978) have confirmed that benzene may induce leukaemia, and, although not all authors would agree with this view (Thorpe, 1974), the case against benzene is generally held to have been proven.

Control and Supervision

When all that can be done has been done in the way of substitution, segregation and environmental and personal protection, the control of hazards likely to cause disorders of the blood depends upon a [illegible] of the toxic and site of action of the materials in question. Lead workers can be supervised by monitoring the excretion of haem [illegible] in the urine or by estimating erythrocyte [illegible] concentrations; the measurement [illegible] a technique [illegible] more valuable an indication of metabolic effect than the other tests. Anaemia is a late manifestation of lead poisoning and haemoglobin estimations, if used at all in routine screening programmes, must be supplemented by tests which will provide early warning of impaired haem synthesis. On the other hand, routine haemoglobin estimations and red cell counts will be helpful in the supervision of workers exposed to benzene or other haemolytic agents, since in their case anaemia is an early sign of their potentially harmful effects. With the present radiation doses in industry, there is little point in undertaking any form of haematological monitoring except following accidental exposure to high doses.

The occurrence of leukaemia will be prevented only by limiting exposure and nothing is to be gained by looking for leukaemic or pre-leukaemic changes in the blood of those potentially at risk. There is a very great need, however, for the initiation of soundly planned epidemiological studies to establish the degree of risk for men exposed to those agents already known (or suspected) to be leukaemogenic, and also to provide information on the malignant potential of other materials. For instance, it would be of great interest to know whether those engaged in the handling and manufacture of immunosuppressive drugs (including steroid hormones) are at risk in any way, or whether other sources of radiation are capable of inducing malignant change. This is an area which would be well worth further study.

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