Recent Advances in the Treatment of Blood Diseases.

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During the past few years there has been considerable research activity in the therapy of blood diseases and success has been recorded in many instances.

Polycythaemia rubra vera: Polycythaemia rubra vera has been satisfactorily treated with *radio-phosphorus* ($P.^{32}$). This is a radio-active isotope, with a half-life of 14.5 days, capable of emitting negative B-rays; it may be obtained by bombarding ordinary phosphorus by slow neutrons in cyclotron and is used in the form of disodium phosphate in isotonic glucose solution, being given intravenously in doses of 5-10 millicuries and repeated when the R.B.C. count rises to abnormally high figures again, usually at intervals of about three months, but remissions lasting as long as two years are on record. $P.^{32}$ is considered to be the best drug at present available against this condition.

Macrocytic anaemias: Since the discovery by Minot and Murphy in 1926 of the value of liver treatment by mouth in Pernicious Anaemia, and the subsequent elaboration of an extract suitable for parenteral therapy, as well as the introduction of oral treatment with desiccated hog's stomach, there has been no major advance in the therapy of macrocytic anaemias until quite recently.

In an attempt to increase the concentration of liver extract and to minimize the allergic side-effects, which occasionally develop in some patients, liver extracts were progressively more refined, until it was realised that the highly refined extracts were potent in true pernicious anaemia, but often valueless in other non-addisonian nutritional macrocytic anaemias (notably those occurring in tropical countries especially in association with defective diets, with pregnancy or Sprue); whilst satisfactory remissions, in these, could still be induced by feeding whole liver or injecting its crude extracts. It was thus obvious that whole liver contained at least two haemopoietic factors, one essential for the cure of pernicious anaemia (present also in very refined liver extracts), the other essential for the treatment of tropical and some other macrocytic anaemias (and found in the cruder forms of liver extracts but not in the very refined ones).

Recent work by Rickes et al. has led to the isolation of the active principle in liver extract, effective against pernicious anaemia; this is a red crystalline substance designated by the above workers "*Vitamin B12*"; it is identical with the Lactobacillus Lactis Dorner's essential growth-factor, known to be present in commercial liver extracts. It has been found to be clinically and haematologically active in pernicious anaemia in a single intramuscular injection of 3ug. (West).

The active principle effective against tropical macrocytic anaemia (Wills' factor) has not been finally isolated in the pure state; but it is expected that the discovery of the anti-P.A. factor would help in the disentangling of the other haemopoietic factors in liver.

Davidson in 1945 tried, with gratifying results, the haemopoietic activity of a papain digest of liver at PH 5.6 (*proteolised liver*) by mouth and found that a number of megaloblastic anaemias, previously refractory to treatment with adequate, potent, liver extract by injection, responded satisfactorily to this preparation. Professor Davidson believes that these results may be

explained either by a potentiation of the haemopoietic factors in the gastro-intestinal tract, or more probably, by the presence of haemopoietic factors (including Folic acid and factors of the B2 complex), normally destroyed in the chemical processes used in the manufacture of liver extracts for parenteral injection. Whatever the explanation the fact remains that refractory macrocytic anaemias, occurring in association with pregnancy, sprue or idiopathically, can often be cured by this method.

Folic Acid (Pteroyl-glutamic acid, vitamin B11, Lactobacillus casei factor), introduced by Spies in 1945, and synthesized by Waller in 1946, is effective in doses of 5-10 mgm. per day by mouth, against macrocytic anaemias with megaloblastic bone marrows, including Addisonian Pernicious Anaemia; but recent clinical experience shows that its use should be limited to non-addisonian macrocytic megaloblastic anaemias, as in pernicious anaemia it is very liable to precipitate Subacute Combined Degeneration of the spinal cord.

Folic Acid is not the active principle in liver extract responsible for the cure of pernicious anaemia, as was originally suspected; in fact the amount of it present in liver extract is too small for that to be true; this was recently proved by the isolation of Vitamin B12, which is about 7000 to 8000 times more active in that direction, and which is present in liver in amounts running parallel with its therapeutic activity in pernicious anaemia. The exact relationship of liver extract to folic acid has not been definitely established, though it has been suggested that liver extract (or Vitamin B12) restores normal pteroyl glutamic acid metabolism, possibly by freeing it from the conjugated form in which it normally occurs in foodstuffs; folic acid being ultimately responsible for the full maturation of the R.P.C. series brought about by liver extract.

Hypochromic anaemias: There has recently been found that the addition of small amounts of *Molybdenum* to Ferrous Sulphate (1/20gr. to 3grs.) markedly enhanced the assimilation and efficiency of iron therapy, so that the haemoglobin percentage was raised to normal in a shorter period and with approximately half the total amount of iron usually required; it is also claimed to lead to diminished incidence of gastro-intestinal side-effects.

A note of warning was recently sounded against the indiscriminate use of *blood transfusions*, especially in women before the menopause, without previous testing for Rh. incompatibility. Besides reactions known to be liable to occur in the pregnant, in the parous and in those being transfused a second time, there is also the danger of causing a permanent Rh.-immunization, of such a degree and permanency, as to be frequently the cause of haemolytic disease of the new born. This explains the recent finding that while 2 per cent of unselected mothers at an antenatal clinic had had a transfusion, 36 per cent of mothers of babies with haemolytic disease had been transfused.

The Leukaemias: No notable advance has recently been made in the treatment of the *acute* cases, but considerable symptomatic relief and prolongation of life can now often be brought about in the *chronic* cases.

Chronic Myeloid Leukaemia often responds strikingly, both clinically and haematologically, to *urethane* (Igm., t.d.s., in keratin-coated capsules, or parenterally in 50 per cent solution, until the W.B.C. count has been brought under check; subsequently reducing to a maintenance dose). Urethane is a nuclear poison, acting selectively on cells in rapid division. It is liable to cause somnolence, anorexia, nausea, and vomiting; but its advantages (efficiency, cheapness, availability, ease of administration, etc.) far outweigh its disadvantages.

Chronic lymphatic leukaemia also responds to urethane, but less constantly.

Radio-phosphorus (P^{32}) has also given good results in the treatment of Chronic Leukaemia, especially in the myeloid type; but it probably has no advantages over deep X-rays as a form of treatment, except for

those suffering unduly from radiation sickness.

The *Alkyl-amines or Nitrogen-Mustards* (Methyl-bis-(B-Chloro-ethyl) amine hydrochloride and tris-(B-Chloro-ethyl) amine hydrochloride) at a dosage of .1—.2 mgm. per Kg. of body weight, given intravenously for 3—6 successive or alternate days, have also proved capable of inducing remissions in Chronic Leukaemia especially in the myeloid type. They are chromosomal poisons, notably on cells undergoing rapid division. They have however proved more useful in promoting a remission, occasionally of several months' duration, in the terminal cachexia of Hodgkin's Disease. Side-effects to be expected are nausea and vomiting, 3 — 4 hrs after injection; and anorexia and headache during 3 — 6 days administration of the drug; leakage into the subcutaneous tissues is liable to result in a severe inflammatory reaction with vesication; agranulocytosis is rare, occurring in less than one per cent of treated cases.

Agranulocytosis: A notable advance was made in the treatment of this condition when it was realised that the essential part of the treatment, after stopping the toxic agent, was the prevention and treatment, with *penicillin* of the invariable infection which often killed the patient, thus tiding him over for a sufficient period to allow of the resumption of normal granulocytic maturation. *Pyridox* (Vitamin B6) and *Folic Acid* have each been claimed to restore the maturation of the myeloid series of cells earlier.

Purpura: Toxic purpura associated with arsenic or gold therapy has been successfully checked by the administration of *British anti-Lewisite* (B.A.L. or 2-3 dimercapto-propanol) therapy.

To the therapeutic armamentarium of thrombocytopoenic purpura, Allen and Jacobson have, in 1947, suggested the addition of intravenous *Protamine Sulphate* and of *Toludine Blue*, each of which, they found, had a dramatic effect on petechial formation: they believe that both these drugs act by diminishing physiological amounts of Heparin in the blood-stream, and in the case of the latter drug, possibly also by improving capillary permeability. These drugs are indicated as a temporary measure to control capillary haemorrhages and are not intended to take the place of fresh blood transfusions, or of splenectomy in the essential form. The value of the glycoside *Rutin* (obtained from the flowers of Buckwheat) in controlling the capillary fragility in Werlhoff's Disease is still "not proven", though there are definite claims for its use. None of the above drugs has yet passed the experimental stage.

Hypo-Prothrombinaemia: For the normal formation of prothrombin the healthy liver cell has to be adequately supplied with fat-soluble vitamin K. Apparently spontaneous or disproportionate traumatic ecchymoses, deeper haematomata, external or internal haemorrhages, referable to prothrombin deficiency from lack of Vitamin K., such as occur in a number of conditions (neonatal, obstructive jaundice, biliary fistula, steatorrhoea, ulcerative colitis, gastro-colic fistula, prolonged fevers, administration of toxic drugs e.g. salicylate, quinine, etc.) can be remedied by the administration of synthetic analogues of *Vitamin* K notably 2 — methyl 1—4 naphthoquinone. Neonatal haemorrhages can be prevented by the prophylactic administration of 10mgm per day to the mother during the last week of pregnancy. Where the bleeding is due to severe liver disease or causes other than K deficiency, Vitamin K. administration is useless.

Haemophilia: Haemophilia cannot so far be radically remedied, but as it notoriously affects males, though transmitted by healthy females, treatment with female sex hormones has empirically been tried and lately oestradiol implants have been favourably reported upon, by French workers, as preventing relapses. Haemophilic haemorrhage is best treated by the administration of fresh blood transfusions or of *Cohn's "Plasma-Fraction I"* found in the globulin fraction of plasma (freed from fibrinogen and

prothrombin). The accellerating effect of the latter on blood coagulation may last 48 hrs or more, but the effects seem to wear off with successive administration; haemostasis may also be brought about by the local application of a number of agents such as *Russel viper venom* (1/10000 solution), *Thrombin* concentrates from bovine plasma, with or without the use of *oxidised cellulose packs* each of which is capable of arresting haemorrhage in a few seconds.

Intravascular Clotting: In arterial (coronary, cerebral, retinal, limb, pulmonary, etc.) and venous (thrombophlebitis migrans, post-operative, retinal, portal, mesenteric, etc.) thromboses, anticoagulant therapy may prove useful in preventing the further spread of the thrombus thus allowing of its earlier reabsorption and canalization. Two drugs have been introduced for this purpose viz.: *Heparin* (or mucviton polysulphuric acid, prepared from mammalian liver or lung) and *Dicoumarol* (the anticoagulant principle in spoiled sweet-clover hay, now prepared synthetically), the former bringing about this effect immediately after injection, while with the latter, which is given by mouth, the anticoagulant effect is realized after a lag of 24 — 72 hours. Their use is not without hazard and both drugs are liable to cause spontaneous haemorrhages from delay in clotting, unless the prothrombin time is kept constantly under check; antidotes are respectively protamine sulphate and blood transfusion. Their use has, at least, made possible the recent advances in vascular and cardiac surgery, as well as the promising experiments of purification from urea and other metabolites of the circulating blood of patients suffering from renal failure, by permitting its dialysis through cellophane tubes, bathing in a suitably adjusted solution: "the artificial kidney".

To sum up, recent progress in the treatment of blood conditions and diseases has achieved, in most cases, striking remissions and relief from symptoms rather than effecting radical cures; but this notwithstanding, a definite step forward can be said to have been made in their rational treatment and new promising fields of investigation have been opened.

We acknowledge receipt of the following Journals; we apologise for any omissions:

"The British Medical Students' Journal".
"Melita Theologica".
"The Health Report of the Maltese Islands".
"British Medical Journal".