The height and weight centiles of individual children are similar. In one child, growth in height was retarded compared with that expected from measurement of his parents and siblings. Despite long periods of malnutrition in early infancy, six of the eight children have normal intelligence as assessed by the 'draw a man' method and school progress.

10. INVESTIGATIONS OF NEUTROPENIA USING BONE MARROW CULTURE IN SEMI-SOLID AGAR

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Human myeloid precursor cells will proliferate in semi-solid agar to form discrete colonies of granulocytes, monocytes or macrophages. A glycoprotein found in human urine, serum, spleen and macrophages is required for colony formation. This colony stimulating factor (CSF) may form part of a hormonal mechanism controlling granulopoiesis in vivo, and studies with the 'cell-hormone' system in vitro provide clues to the pathogenesis of both spontaneous and drug-induced neutropenia.

Drugs such as methimazole and phenylbutazone, which probably cause neutropenia through a pathological immune response, do not inhibit colony formation at pharmacological concentrations, unlike chloramphenicol and 6-mercaptopurine (6MP) which are directly myelotoxic both in vivo and in vitro.

Sodium aurothiomalate, at concentrations within the range of therapeutic plasma levels, may inhibit the release of CSF from macrophages in vitro, whilst at much higher concentrations direct inhibition of colony formation is observed.

Minor changes in drug structure can alter apparent toxicity in the culture system. Chloramphenicol, for example, is more toxic than its sulphonyl derivative thiamphenicol although their bactericidal activity is similar, and 6-mercaptopurine is more toxic than 2-amino-6-mercaptopurine.

If culture conditions are standardized, the extent of colony formation depends upon the concentration of progenitor cells in the marrow specimen and their ability to divide. When neutropenia is associated with myeloma, aplastic anaemia, lymphocytic leukaemia and pre-leukaemia the rate of colony formation is subnormal. With some chronic neutropenias, the neutropenia associated with immune deficiency, and immune neutropenia colony formation is greater than normal. Marrow culture thus helps to differentiate neutropenia due to decreased survival of circulating granulocytes from that secondary to myeloid hypoplasia, a distinction often difficult on clinical and haematological grounds alone.

11. DRUG-INDUCED NEUTROPENIA — EFFECTS OF DRUGS ON GRANULOCYTE PROTEIN SYNTHESIS IN VITRO

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Idiosyncratic bone marrow depression is an important complication of therapy with many drugs in common use. Its sporadic occurrence, in the absence of a demonstrable pathological immune response, suggests the existence of a predisposing and possibly inherited biochemical abnormality to account for the abnormal drug sensitivity. In patients who have recovered from myelotoxic drug reactions Pisciotta (1971, Journal of Laboratory and Clinical Medicine, 78, 435) and Yunis (1969, Advances in Internal Medicine, 15, 357) demonstrated unique sensitivity of bone marrow nucleic acid biosynthesis to chlorpromazine and chloramphenicol in vitro, but the drug concentrations required to affect these short-term cultures of myeloid precursors were greater than blood levels usually reached during therapy. In view of the known inhibitory effects of chloramphenicol on protein synthesis by bacterial and mammalian mitochondrial ribosomes we have studied the effect of this and other myelotoxic drugs on the protein synthetic activity of intact human granulocytes in vitro.

Granulocytes isolated from venous blood (Blackburn, Andrews & Watts, 1973, Analytical Biochemistry, 51, 1) were incubated in buffered salt solution using the incorporation of [14C]-phenylalanine into tri-chloroacetic acid insoluble material as a marker of overall protein synthesis. Changes in intracellular precursor pool size and specific activity were monitored in parallel experiments. Antithyroid drugs, gold salts, phenylbutazone, chlorpromazine, co-trimoxazole and chloramphenicol were added to incubating granulocytes at concentrations within the range of therapeutic blood levels to determine their effects on both precursor pools and phenylalanine incorporation in molar terms. Apparent depression of protein synthesis was observed with therapeutic concentrations of chloramphenicol and chlorpromazine.