

Pardee, 1969; Holley, 1972), lectin agglutinability (Burger and Goldberg, 1967; Ozanne and Sambrook, 1971), cell surface components (Kijimoto and Hakamori, 1971; Hynes and Bye, 1974) and more recently, the leukaemia-associated nuclear antigen (Klein *et al.*, 1974).

In this talk, the variable expression of surface antigens with cell growth were illustrated and evidence presented for the occurrence of "division membrane antigens" in man. These antigens can only be detected at the cell surface during cell division and may therefore contribute to antigenic differences between tumour cells (dividing) and normal adult cells (resting).

Division membrane antigens specific for human lymphoid cells were first recognized using heteroantisera raised in rabbits against human thymocytes or Burkitt lymphoma cells (Thomas and Phillips, 1973). After absorptions with normal adult tissues, sera were specific for thymocytes and T lymphoblasts or B lymphoblasts and Ig-positive lymphoid cell lines. Recently, it was shown that cold agglutinin, anti-i sera recognize a determinant unique to dividing human cells, which has been designated the  $i^1$  antigen (Thomas, 1975). This antigen is present on the surface membrane of various cell types including lymphoblasts, fibroblasts, erythroblasts, and thymocytes and absent from normal adult tissues. Absorption studies have shown that the  $i^1$  determinant is distinct from the  $i^1$  antigens of erythrocytes.

To determine the temporal expression of division antigens during the life cycle, cultured lymphoblasts have been fractionated according to size, and therefore age, by velocity sedimentation in a zonal rotor. Rotor fractions were analyzed for the  $i^1$  antigen or blast-specific antigen and cells were assigned to a position in the cell cycle according to size and ability to incorporate  $^3\text{H}$ -thymidine into DNA. A majority of cell fractions from the rotor corresponding to the  $G_1$  (or  $G_0$ ) interval were negative for both specificities, whilst there was an enrichment of antigen-positive cells at the S and  $G_2$  interval. This indicates that surface markers exist which recognize cells "in cycle".

The above antigens are present on tumour cells, embryonic cells, and normal dividing cells; oncofoetal antigens have been demonstrated on tumour and embryonic cells, but as yet no attempt has been made to establish whether they are re-expressed on normal

dividing cells. Are division antigens oncofoetal antigens? There still remains a need for "comparison . . . between the cancer cell and a normal cell growing equally rapidly".

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#### ROLE OF TARGET CELLS IN DETERMINING LEUKAEMIC CHARACTERISTICS

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The bone marrow cell population may be described as a "three tier" structure of interrelated cell populations: (a) the pluripotent stem cells, (b) the "committed" precursor cells, and (c) the maturing "end line" cells. The inter-linking is in effect provided by the two differentiation steps which create populations (b) and (c) respectively, the rate of differentiation, in part at least, being controlled by the appropriate population sizes.

Both the "committed" precursor and the maturing "end line" populations are transit types of cell populations in the sense that while they possess proliferative capacity, this is limited to a varying number (4–10) of cell cycles. This enables a highly elastic amplification—depending on demand—in the transit populations, but only up to the limit of their proliferation capacity.

Both these transit populations undergo "age changes" *i.e.* maturation during their amplification transit and their rate of maturation—which thus limits their proliferation capacity—can be altered by physiological controlling factors.

Following leukaemogenic "transformation" the proliferation control is certainly affected—either directly (as is likely in the pluripotent stem cells), or indirectly (*e.g.* by interfering with the proliferation limiting maturation processes—the so-called "suicide maturation"—in the transit populations).

Differentiation control is also affected on leukaemic transformation but vestiges of differentiating capacity may be retained. Interference with the physiological rates of maturation processes *e.g.* slowing down maturation, also slows down the rate of loss of "pluripotentialities" (*e.g.* choice between granulocytic and monocytic direction).

This potential elasticity of the haemopoietic cell system makes the "pinning down" of the target cells difficult. The apparent properties of cells in the developed leukaemic clone(s) may be very misleading indicators of the precise position of the target cell in the developmental series. While it is possible that a relatively "late" cell develops autonomy, it is equally possible that very "early" cells retain some differentiation potential even after leukaemic changes. New *in vitro* culture methods, combined with specific cytotoxic manipulation are the necessary tools for the elucidation of the problem—including the possible role of intercell interactions in the leukaemogenic process.

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#### THE PATTERN OF MALIGNANT LYMPHORETICULAR CELL PROLIFERATION AND ITS RELEVANCE TO CHEMOTHERAPY\*

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One model for discussing this topic is the lymphoid cell population as found in the bone

marrow of children with acute lymphoid leukaemia (ALL). We use the term "lymphoid" to designate poorly differentiated cells larger than lymphocytes which may or may not have blast cell characteristics. In children with ALL usually more than 90% of the bone marrow cells are lymphoid at the time of diagnosis. Normal and leukaemic lymphoid cells cannot be differentiated by morphologic criteria.

The proliferative characteristics of lymphoid bone marrow cells (LBMC) have been investigated in patients with untreated and relapsing ALL (Mauer, Saunders and Lampkin, 1969; Killmann, 1972; Wagner, Cottier and Cronkite, 1972). The following observations were made: (i) only a small percentage of LBMC incorporated <sup>3</sup>H-thymidine after pulse-labelling; (ii) the percentage of LBMC varied from patient to patient and according to the stage of the disease; (iii) the median cell cycle phase transit times varied from patient to patient but were longer than those of myelocytes or red cell precursors; (iv) there was a reciprocal exchange of cells between the compartment of large, initially labelled, proliferating LBMC and the compartment of small, initially unlabelled LBMC; and (v) the majority of initially unlabelled small cells retained the capability to divide.

In patients with untreated ALL single drug injections produced the following effects (Lampkin, McWilliams and Mauer, 1972); (i) corticosteroids and L-asparaginase lysed proliferating and nonproliferating LBMC and inhibited the entry of surviving cells into S; (ii) methotrexate arrested and destroyed cells in S; (iii) cytosine arabinoside inhibited DNA synthesis, produced a partial synchronization of proliferating cells and apparently recruited resting cells; (iv) vincristine arrested cells in mitosis; (v) cyclophosphamide inhibited DNA synthesis, affected cells in mitosis and prevented the entrance of cells into S; and (vi) daunomycin lysed cells, particularly those in S. Based on these results attempts were made first to recruit and synchronize and then to kill LBMC with "cell cycle specific" agents. In view of the variability of the cell cycle phase transit times of LBMC in patients with untreated ALL and considering the inability to differentiate leukaemic and normal LBMC, these procedures risk

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