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EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

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CELL REGULATION

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SVMMARIVM — Generalia delineantur principia, quibus cellulae aptantur, et quibus haec earum accomodatio stabilitur et firmatur.

Unicellular organisms such as bacteria can be taken as prototypes displaying many of the essential characters of living things in general. In the use of nutrient materials from their environment they show an apparent power of choosing the most advantageous and ignoring the less advantageous: they can develop resistance to toxic substances, and they gradually improve their capacity for utilising new sources of growth material by a process sometimes referred to as 'training'.

One school of thought has attributed all such phenomena to shifts in the balance of populations containing different types of individual, these types themselves having arisen by chance errors or mutations in the operation of normal hereditary mechanisms. But others have felt that nature, and the processes of natural selection will have endowed cells with the means

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for a considerable degree of automatic regulation of their internal economy, so that they can in fact respond individually to many of the challenges of a varying environment.

My colleagues and I have for a long time studied these problems both experimentally and theoretically, and Dr. A.C.R. DEAN and I have recently attempted to formulate some simple and general theoretical principles describing the processes of cell regulation ([1]).

We start from the fact that cells synthesize from very simple starting materials, for which endless alternatives exist, highly complex proteins, nucleic acids, polysaccharides and other compounds. This must occur in a vast sequence of relatively simple chemical steps, with many alternatives, branchings, and cyclical internal connexions. This may be called the reaction pattern. The next step in the argument is that the major cell components are related in an intricate system of mutual dependences: nucleic acids contain the information necessary for the building up of proteins, proteins constitute the enzymes by whose operation the nucleic acids themselves are built up. Both these types require material from outside the cell, and the supply is controlled by the nature of the cell wall, partly polysaccharide, which in its turn can only be made by the action of protein-containing enzymes. Thus we have a great system of mutual dependences, bifurcating and rejoining in an elaborate network.

Further consideration shows that the network meshes are closed. No nutrient material can be brought into action except by an enzyme, whose protein must be made under the influence of a nucleic acid, in the formation of which many enzymes have been involved. No train of such dependences followed out in thought comes to an end but closes in on itself. One can set up simplified mathematical models of such mutually dependent

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([1]) « Nature » 1963, *199*, 7; 1964, *201*, 232; 1964, *202*, 1046.

systems and examine their properties which prove to bear a strong resemblance to the cellular properties which were referred to in the introductory paragraph.

According to what we have called the network theorem, the proportions of the cell components will change in any given medium to those which allow an optimum rate of growth in that particular environment: enzymes which are not of use in that medium will diminish in amount (compare the phenomenon known as enzyme repression) and when a steady state in a constant medium has been reached, each individual component will increase with time according to the exponential law of autocatalysis. While no individual component of the cell is in fact autosynthetic in its own right, the cell as a whole in virtue of this system of total integration has the power of autosynthesis.

The orderly exponential increase in total mass is punctuated by the occurrence of cell division. As a cell increases in size the surface/volume relations change and so the constants of the various processes involved in the network relations cease to be optimal: they are restored to optimum values when rearrangement to smaller masses restoring the original conditions has occurred.

The cell is not only organised in respect of the mutual dependence of its reactions, that is to say possesses an organisation in time; it has also a spatial organisation. The various macromolecular components are disposed according to some kind of spatial map. This will also present its own problems of mechanical stability and geometrical conformity. When cells are transferred to a new environment the network theorem predicts a rapid establishment of a new reaction pattern. This, however, may well correspond to a non-optimum spatial map, so that a complex sequence of secondary adjustments is initiated. The detailed study of these throws light upon the great variation which is observed in practice in the stability of adaptive changes of cells. In particular it leads to an understanding of one of the most striking phenomena observed experimentally, namely that adaptive adjustments when first called forth are unstable, but when they have been in existence for a long time acquire a considerable degree of stability.