LETTERS TO THE EDITORS

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Hormones and the Cytoskeleton

The object of this communication is to present the hypothesis that hormones modify the 'cytoskeleton' of the cell. Though I have held this view for some time, and have discussed it with others, I have not advanced it formally, because until now it did not appear to be useful. There are, it is true, subcellular actions which have been described for hormones; notably one may mention the interesting effects of thyroxine upon the oxidative phosphorylation of mitochondria which formed the basis of a recent lecture to the Third International Congress of Biochemistry by C. Martius. There are also conclusive observations upon the action of insulin in altering permeability to sugars[1,2]; and also, on the contrary, the widespread idea that insulin controls the formation of glucose 6-phosphate. Yet in spite of interest in these facts, there is a general feeling that hormones act upon the cell as a whole, and that their action is somewhat diverse rather than being upon one enzymic or other step (cf. A. Beloff-Chain *et al.*[3], and see particularly the discussion of this by O. Hechter[4]). It is from this aspect that I think the 'cytoskeletal' view may prove to be a useful working hypothesis.

Many years back I became impressed by the idea that to view the cell as a bag of enzymes, however specific these might be in their action, could not account for the integrated behaviour of cells, any more than disorientated carbon atoms could account for the reactions of the benzene ring; and I felt forced to postulate the presence of a fluid anatomy in the geography of the cell, being some tenuous network by the action of which the cell's enzymic activities were co-ordinated. (The term 'cytoskeleton' was given to this by J. Needham; it is a good description provided that it does not convey the idea of the rigidity of a bone.) Other biologists have felt the difficulties in accounting for the whole actions of cells, too, and a critical discussion of pros and cons may be found in the book "Cytology and Cell Physiology"[5]; see also ref. 6.

The 'cytoskeletal' hypothesis has met with some hostility, both from those who consider wrongly that it excludes the essential studies on isolated enzymes, and also from those who feared it might be a return to the long-discarded ideas of the giant molecule. Belief in the presence of intracellular structures has been made easier by recent electron microscopy of mitochondria (by Palade[7] especially and by other work); by the now known existence of nucleic acids in the cytoplasm, and by the recent report of the existence of cytoplasmic membranes seen by Palade. (I am indebted to Dr. E. F. Gale for telling me of these observations, reported to the Ford Enzyme Symposium on November 2, 1955.)

Whether the cytoskeleton consists of continuous thin membranes, or whether it is arranged like the bentonite gel by rapid re-formation of oriented particles, or by more classical chemical links or by hydrogen bonds—whichever way it takes place is immaterial from my present point of view. It has always been to me an obvious consequence of the 'cytoskeletal' idea that it was the cytoskeleton rather than individual enzymes which was the co-ordinating factor, as it were the master structure of the cell; this was pointed out by me some twenty-five years ago and is an essential emphasis in my point of view. Hence an agent which could change the cytoskeleton might be expected to modify several enzymic reactions simultaneously by giving a new direction to this fluid anatomy.

Hormones are active in small amounts, and it is definitely conceivable that very small amounts of peptide or steroid structures could enter the surface of cells and accomplish such an orientation. This is the reason why it is here advanced that a hormone re-orientates the cytoskeleton. From the point of view of this working hypothesis, the search for some one enzymic reaction which a hormone modifies is doomed to failure, and further efforts should be directed to clarifying the patterns of diverse reactions which may be modified by the actions of hormones upon whole cells.

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An Antigen determining Virulence in *Pasteurella pestis*

Despite assiduous search by many workers, the factor conferring the property of high virulence on strains of *P. pestis* has remained undetected. Virulent and protective avirulent strains have been studied comparatively by the methods of immunology, immunochemistry and biochemistry without yielding convincing evidence of a difference in their properties sufficient to account for their difference in virulence. This communication reports results showing that an important antigenic difference between virulent and protective avirulent strains does in fact exist.

It has been demonstrated that virulent and avirulent strains can be differentiated on the basis of ability of the former and inability of the latter to develop resistance to phagocytosis by mouse polymorphonuclear leucocytes under well-defined conditions *in vitro*[1]. Virulent organisms harvested from growths on nutrient agar incubated at 28° are highly sensitive to phagocytosis; I term these *V/S*. When they are incubated, with gentle rotation, for 3 hr. at 37° in tubes of tryptic-digest meat broth at *p*H 7·0, they become resistant to phagocytosis; virulent organisms so treated I term *V/R*. Avirulent cells similarly grown at 28° are also highly sensitive to phagocytosis (*AV/S*) and retain this sensitivity on similar incubation in broth at 37° (*AV/'R'*).