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Concluding Remarks

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At the end of this session, one cannot help but acknowledge with pleasure how nicely the different contributions complement each other and relate to the main subject of discussion.

The problem of the functions of pinocytosis came up, with different emphasis, in almost all presentations. Dr. Hancock discussed the possibility of relating the penetration of histones to their biological effect upon the nuclear metabolism. The failure to visualize fluorescein-labelled histones in nuclei of intact cells is perhaps given too much importance, since trace amounts of regulator substances that are not readily detected by morphological means may nevertheless suffice to elicit biological effects.

Dr. Cruchaud's contribution reminds us that most antigens are proteins which must be taken up in order to act. Whereas there may be some controversy about the real function of the RNA-antigen complexes isolated from sensitized macrophages, there is agreement in the postulate that both the pure and the complexed antigen are taken up by the cells responsible for initiating immune responses. It is noteworthy that the current views do not restrict this uptake to macrophages.

The new data of Dr. Fey and Dr. Kraehenbuhl relate to another function of pinocytosis, namely, the transcellular transport that carries immunoglobulin from the intestinal lumen across the epithelium into the blood. The comparative study of this process in newborns of four different species raises puzzling questions about transport regulation. It would appear that in the calf, the transport stops because proteins are no longer taken up at the luminal side of the cell, due perhaps to the loss of a specific receptor; by contrast, in the rabbit the transport never works very well because ingested proteins remain trapped in the cell. As we have seen, this trapping and intracellular digestion is a common event and is most efficient in the cells we have studied. One would like to know, therefore, how this destruction is prevented or temporarily inhibited in the intestine of the newborn calf, piglet, and rat. In our experimental system some inhibition can be achieved with drugs that act on lysosomes. There is a congenital disorder of the child called "granulomatous disease" due to abnormal leucocytes in which lysosomes fail to fuse with phagocytotic vacuoles. One might suggest as a working hypothesis that the intestinal cells of newborn mammals are characterized

by a comparable but temporary block in the fusion of lysosomes with pinocytotic vesicles. This could be tested experimentally.

The intriguing data on metabolic effects of immunoglobulins presented by Dr. McKENZIE raise a fundamental question, namely whether biologically active macromolecules must necessarily penetrate into cells in order to act. On the one hand there are clearcut instances in which they do: the nucleic acids in genetic transformation, and in malignant transformations; antigens in the immune process; interferon and other regulatory proteins. On the other hand, the current thinking in endocrinology assumes that protein hormones such as the thyroid-stimulating hormone, the luteotropic and melanotropic hormones and ACTH exert their action by interacting with specific membrane receptors, even though there is no doubt in my mind that they can get into cells. In view of its similarity of action to the thyroid-stimulating hormone, the thyroid-stimulating immunoglobulin described by Dr. McKENZIE may well belong to the latter group. Knowing how to inhibit and enhance protein uptake should make it possible to clarify this point, and decide whether this protein acts before or after penetration. The number of foreign proteins known to exert specific biological effects on cells and tissues is rapidly increasing and – as we just saw – the trend is continuing.

The messages of the papers presented at this meeting go beyond the scope of the main report. Dr. LÜSCHER's data, for instance, deal with the mechanisms of protein-membrane interaction that may trigger phagocytosis. Yet, it is likely that a better understanding of these mechanisms will throw light upon the molecular events that trigger pinocytosis. In turn, the binding of basic polyamino acids to membranes may show similarities to the binding of complement C′ to thrombocyte membranes and its effects. The specific mechanisms that operate in both cases probably rely upon the same parameters of membrane structure. It is a fact that phagocytosis also occurs in the cells we have studied. Monolayers of fibroblasts, for instance, readily take up the polystyrene particles used by Dr. LÜSCHER in his thrombocyte preparation. It would seem that with the possible exception of red blood cells, all mammalian cells are able to carry out both pinocytosis and phagocytosis. It appeared at first that these two processes differed only by the magnitude of the invaginations and resulting vacuoles. Recent data from our laboratory however, indicate that they differ markedly in their metabolic requirements. On the basis of Dr. LÜSCHER's data one would think that they also differ in their metabolic consequences in thrombocytes. A thorough study of these differences and their relations to primary events occurring at the cell surface cannot fail to broaden our knowledge of the structure and function of the plasma membrane.