Multiplicity of Pituitary Hormones

THE large number of pituitary (anterior as well as posterior lobe) hormones postulated has for some time caused uneasiness to workers in that field. The reasons for this seem to be mainly the following: (1) It appears inconceivable that an organ of the size of the pituitary gland which has in the anterior lobe three and in the case of the neural lobe only one type of cell which may be secretory should elaborate so many individual substances. In answer to this it can be said that neither size nor cytological differentiation of an organ or organism has so far been shown to limit the complexity of its chemical pattern. The number of substances present in or derived from liver cells or unicellular organisms serve as example. (2) It has been suggested that some or all of the supposedly existing hormones may be cleavage products of larger molecular compounds, that is, artefacts produced by the chemical and physical procedures used for their isolation. This concept seems originally to have been formed by J. J. Abel[1], who maintained that the secretion of the posterior pituitary lobe consisted of large molecules carrying all known post-pituitary activities. Riddle[2] and Collip[3] applied this concept to the secretion of the anterior pituitary lobe. Cameron[4] has recently endorsed their view. The experimental basis of Abel's theory has since been partly invalidated as it has been possible to separate the oxytocic and pressor-antidiuretic activities of posterior pituitary extracts by mild procedures (fractional adsorption, electrophoresis) which make an injury to an originally present large molecule unlikely.

Separation of certain anterior lobe factors by 'mild', non-chemical procedures like electrophoresis and fractional adsorption has also been reported. However, certain clinical and comparative physiological observations suggest rather that pituitary principles are not secreted singly but in groups. As Cameron has pointed out recently, tumours of the different anterior pituitary cells are associated with signs which suggest an abnormal secretion of well-defined and constant groups of anterior lobe factors. With the reservation that little is known about the specificity of the secretory stimulus, these clinical observations may be taken to mean that there is no abnormal production of a single pituitary activity. Similar conclusions evolve from observations which touch the fundamental concept of hormonal action, namely, that tissue reactions to hormones are apparently in large measure dependent on adaptation of the cellular protoplasm to pre-existing substances. Unless we accept this contention, which has been endorsed by recent experimental evidence[5], it would be difficult to explain why, for example, the lactogenic anterior pituitary hormone[6] and the oxytocic posterior pituitary hormone[7] are found in the glands of male animals. The distribution of the posterior pituitary 'water-balance' activity throughout the vertebrate series furnishes a similar example. It appears that comparatively large amounts of this factor are present in all classes of vertebrates[8]; but an action (temporary increase of body-water) has so far only been found in amphibians. It would be easier to understand its presence in the pituitary glands of those classes of vertebrates on which, to our present knowledge, it does not act if we assume that the water-balance activity constitutes one of several activities of a large molecule to each of which the tissues of any phyletic class must be specifically adapted if an effect is to be produced.

Such indirect evidence is clearly of very limited value. The question arises therefore how more direct experimental evidence for or against the multiplicity of the pituitary hormones could be obtained. Two ways may be suggested: (1) Is a physiological stimulus for the secretion of a pituitary principle which by chemical methods has been successfully isolated, invariably associated with the secretion of *all* activities produced by the same type of pituitary cell? For example, Gilman and Goodman[9] and others have shown that the urine of rats deprived of water contains abnormal amounts of an antidiuretic substance. The post-pituitary origin of this substance was strongly suggested by the observation that hypophysectomized animals failed to excrete it. It has been claimed, therefore, that dehydration constitutes the physiological stimulus for an increased secretion of the post-pituitary antidiuretic principle. A clear proof that the stimulus of dehydration leads to the excretion of larger amounts of oxytocic as well as the antidiuretic factor could be interpreted to mean that the oxytocic factor is by necessity secreted with the antidiuretic one because both are activities of the same large molecule. (2) Can it be shown that pituitary principles which have been successfully isolated *in vitro* are present in significantly different amounts in the gland and in body fluids *in vivo*? Several hints to that effect have already been published[10,11]. With the important reservation that the methods used for the estimation of the active principles should be known to be uninjurious to protein molecules, investigations of this nature seem to offer the most profitable approach to the problem of the multiplicity of the pituitary hormones.

The question whether the various types of anterior and posterior pituitary cells are able to secrete every activity singly, or whether their secretion consists of large molecules with multiple activity the action of which depends on the response of the effector tissues, would seem to be not only of theoretical but also of practical interest. It is easily conceivable that the same processes which lead to an artificial separation of a single factor produce a change in its pharmacological and therapeutic properties.

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Jan. 9.

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