SPECIAL ARTICLES

CURE OF THE CACHEXIA FOLLOWING HYPOPHYSECTOMY BY ADMINISTRATION OF THE GROWTH HORMONE AND ITS RELATION TO THE RESULTING ADRENO-CORTICAL REPAIR[1]

IN 1927, Smith[2] demonstrated that daily intramuscular implants of fresh glandular substance (hypophysis) will repair most,[3] if not all, of the disabilities shown to characterize animals after complete hypophysectomy. The ground was thereby laid for adequate test as to whether extracts of the hypophysis contain one or all of the hormones present in fresh glands. In particular it could be seen, now, whether the growth and gonad-stimulating hormones originally detected by other tests (*i.e.*, their effect on normal mature and immature animals) made up the full complement of anterior hypophyseal hormones, and could therefore completely substitute for the missing gland, and, finally, it should be possible to discover in this way which of the known hormones was responsible for those other features of the syndrome from hypophysectomy besides the disturbance in growth and sex, the deficiency, for instance, in thyroid, parathyroid, and adrenal cortex.

While the administration of extracts, which Evans and Long (1922) had shown to contain the growth hormone, invoked growth in hypophysectomized rats in Smith's hands, he showed clearly that such extracts would not repair the gonadal deficiency, but in fact prevented its repair by implants. He stated that they also did not repair the subnormality of thyroid and adrenal cortex. The present paper reports that the latter result can be accomplished with satisfactory extracts of the growth hormone.

The resumption of growth in hypophysectomized animals following injections of extracts was confirmed by van Dyke. Furthermore, Reichert has shown that the prolonged administration of our growth hormone to completely hypophysectomized puppies produce dogs which exceed in weight and in skeletal dimensions their normal littermate controls. Striking results of this sort have been consistently secured by us. In a long series of experiments on hypophysectomized rats we have administered purified preparations of the growth hormone[4] free from gonad-stimulating effect. The growth rate of hypophysectomized rats receiving these preparations even exceeded that of normal animals receiving the same extracts.

Concerned for some years with the preparation of purified extracts of the growth hormone and more recently with the gonad-stimulating hormone of the hypophysis in order to distinguish their respective rôles or effects, we have applied such extracts to very considerable numbers of hypophysectomized rats. What we desire to place on record in the present communication is the remarkable, prompt and uniform relief from the cachectic state following administration of the growth hormone extracts. Not only is growth resumed, but a rapid and impressive change in the constitutional state of these animals results. This is indicated especially by the resumption of normal turgor to their tissues and above all of normal muscular strength and muscle tone. The myosthenia so characteristic of the hypophysectomized animals disappears within 10 days following the growth hormone therapy. In contrast with these results the administration of even large doses of gonad-stimulating hormone (growth-free) has no influence on the cachexia, even though these products provoke an extreme reaction in the gonads.

The animals injected with growth hormone are indistinguishable from normal animals. Only the genitalia retain the hypophysectomized condition, the glands and accessory organs being atrophic. Autopsy shows repair of both the thyroids and the adrenals. The reparation of the adrenals and thyroids under the influence of growth hormone is, however, not complete. The weights are consistently greater, but do not attain the weight of glands of normal animals. Under the conditions of dosage and time intervals studied thus far, the glands have never attained the weight of those of the normal controls, even when doses are given which stimulate normal or excessive body growth. The gonad-stimulating hormone free of growth hormone, which as stated before has no effect on the cachexia, also does not induce this repair of adrenals or thyroids.

The differences between the histological pictures of the adrenals of hypophysectomized animals and those receiving growth hormone are very striking. In the adrenals of the treated animals the cytoplasm of the cortical cells is restored and three zones become again distinguishable. The gonad-stimulating hormone, on the contrary, produces no such repair in adrenals, even though a dose is administered which causes excessive hypertrophy of the gonads.

The disappearance of the cachectic condition fol-

[1] From the Institute of Experimental Biology, University of California. Aided by grants from the Committee for Research in Problems of Sex of the National Research Council, and from the Rockefeller Foundation. These funds have been generously augmented by the Board of Research and the College of Agriculture of the University of California.

[2] Smith, P. E., *Jour. Amer. Med. Assn.*, 88, 158 (1927).

[3] Normal gestation in the hypophysectomized female was not secured.

[4] These are essentially solutions of the acetone precipitate of the Evans-Simpson-Cornish Extract; see Evans-Simpson-Cornish, *Proc. Soc. Expt. Biol. and Med.*, 1930.

lowing the administration of the growth hormone parallels the repair of the adrenals. It is quite probable that the cachectic state and the atrophy of the adrenals are causally interrelated and that it is to the change in the adrenal following administration of the growth hormone that we must refer the remarkable general constitutional restoration. Experiments are now under way to see whether the cachectic symptoms following hypophysectomy can be relieved, although growth is not induced, by injections of adrenal cortical extracts.

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THE TRANSFORMATION OF SERUM ALBUMIN INTO SERUM GLOBULINS[1]

THE antiprothrombin (heparin of Howell) forms with protein complex compounds which show different properties according to the amount of heparin bound to the protein molecule.

The heparin combines with the organic complex of the protein and by means of its affinity for water (lyophil action) increases the solubility of the proteins. The antiprothrombin gives the protein an electronegative charge and moves its isoelectric point towards the acid side.

By adding heparin to pure globulin fraction in salt solution one is able to move the isoelectric point, which for globulins is normally around pH 5.0, towards the acid side; the range depends upon the concentration of the heparin. As is well known, the serum albumin does not flocculate at its isoelectric point. If heparin is added to serum albumin (at pH 5.0), which is freed from globulins by means of dialysis, a flocculation immediately takes place. The degree of flocculation depends only upon the amount of heparin added when excess albumin is present. Albumin-heparin compounds behave as genuine globulins, and we are justified in considering them as identical with the globulins. (Solubility, precipitation by means of weak acids, denaturation, precipitation by means of salts, solubility in heparin (in excess) dialysis, isoelectric point.)

Experiments on quantitative dialysis of whole serum show that the addition of small amounts of heparin results in an increased amount of globulin (determined by weighing).

The antiprothrombin is so far the only substance normally found in the body (the urea does not play any rôle in this connection), having the powerful action described, which is responsible for the formation of the globulins. We found that the amount of globulins present in blood serum is a direct expression of the amount of antiprothrombin. The coagulability of a plasma depends entirely upon the amount of globulins present. By means of the method to isolate the heparin as indicated by Howell, much greater amounts of heparin could be isolated from blood in which the amount of globulin was greater than from any other serums.

From the purified casein (*Hammarsten*) which behaves as a globulin and especially towards heparin, we were able to isolate a heparin-like principle of high activity, if not heparin itself.

Fibrinogen belongs to the globulins. According to the amount of heparin bound to the protein molecule, it is possible to place the various globulins in a certain system. When the various fractions of the serum proteins are precipitated in a buffer system of pH 5.0 as a function of the heparin concentration, the relative charge of heparin on the definite protein fraction may be determined. Heparin acts on the principle of the "unregelmässige Reihe," that is, greater amounts inhibit and smaller promote the flocculation.

The euglobulin goes into solution with a small amount of heparin; the pseudoglobulin needs a larger amount of heparin than the euglobulin for solution. The fibrinogen needs an even greater amount of heparin before it is dissolved. If we consider the serum albumin as heparin free, the other protein fractions of the plasma come as follows: fibrinogen, pseudoglobulin, euglobulin. Our experiments show that the euglobulin fraction is immediately formed when heparin is added to pure serum albumin. We suppose that there exist just as many protein compounds in blood as there are possibilities for heparin-albumin compounds. It is conceivable that the various compounds are dissociated according to the principle of the dissociation of the pluribasic acids. There are just as many dissociation steps as there are possibilities for heparin-albumin compounds, each with its own dissociation constant. This consideration agrees very well with the modern conception (*Sörensen*) which considers the proteins as reversible dissociable systems of components.

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PERIODICAL PROPERTIES OF ATOMIC NUCLEI

ACCORDING to our present knowledge of the structure of atoms, there is no reason to expect *a priori* the existence of a simple relation between the electron coverings of an atom and the internal constitution of the nucleus.

Therefore some experimental facts showing such a relation must be of interest. These facts have a statistical character. It is only possible after the investi-