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Relation of Prolan to the Anterior Hypophyseal Hormones.*

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In our preceding paper we have shown the incapacity of the hormone found in the urine of pregnant women (Prolan) to affect sexual development and function in hypophysectomized animals. It is now well established that Prolan is also for some reason limited in its effect on the gonad development which can be produced within 100 hours in immature normal animals, as measured in terms of ovary weight.

We can, for example, state that no matter how frequently or how much Prolan is administered the average weight of the ovaries produced in 26-day-old rats at the close of 4 days of treatment is about 60-70 mg. and the maximum in several hundred of our experiments was 102 mg. We, and other investigators, have pointed out that in contrast with this the implantation of anterior hypophyseal tissue is very markedly more effective in the ovary weights produced in young rat hosts, and we have shown that increasing "doses" of the implants also give increasing weights of the young ovaries.

As will be detailed in another communication, similar very marked effects on the immature gonads can now be secured by certain fractions out of extracts of anterior hypophyseal tissue. Here also, in contrast to Prolan, increasing doses give increasing effects on the youthful gonads. With such preparations, we have, for instance, in 100 hours produced ovaries weighing 190 mg.

We searched for a point of view which would harmonize these 3 experiences. That Prolan is totally ineffective in hypophysectomized animals and that it is only partially effective in young animals when compared with cases to which actual hypophyseal substances were administered seemed to us best explained by regarding Prolan only as an activator to a substance in the hypophysis itself which we may call a pro-hormone, a substance totally absent, of course, in hypophysectomized animals and small in amount in very young normal animals. This idea seemed capable of simple test by the simul-

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taneous administration of Prolan and hypophyseal hormones, the effect of each of which alone was previously known. The following table and description of a single experiment will illustrate our results:

TABLE I.
Effects on the youthful ovary of Prolan and hypophyseal hormone given separately and in combination.

	Total Dosage During 3 Days mg. dry weight	Average Weight of Ovaries after 100 hours mg.
Prolan	54.2	62 (6-12 corpora lutea, a few large follicles)
Hypophyseal hormone	65.0	21.3 (1-6 small corpora, otherwise undeveloped)
Prolan combined with hypophyseal hormone	119.2	156.3 (Innumerable corpora and many large follicles)

We purposely chose a small dose level of an hypophyseal extract containing both growth and gonad-stimulating properties which, when given alone, either failed or barely provoked sexual maturity at the close of the 100-hour period in young animals. We selected a Prolan preparation which, when administered alone produced the normal maximal effect of Prolan preparations, that is, ovaries weighing about 60 mg. at the close of the test period. As the table shows, the mixture of these particular Prolan and hypophyseal extracts each given in the same dosage and same volume as when administered alone now produced ovaries averaging 156.3 mg.

We have confirmed this activation of hypophyseal extracts by Prolan in several hundred individual experiments. That Prolan thus activates a specific substance in hypophyseal extracts is shown by its failure to activate when the hypophyseal extracts have been heated to 100°C. for 10 minutes or to 70°C. for 30 minutes, in which procedure no noticeable changes in any of the physical properties of the extract could be detected.

Most surprisingly, it is not the gonad-stimulating hormone of the hypophyseal extracts which is activated by Prolan, for solutions rich in this hormone and almost devoid of the growth principle can not be activated, whereas growth hormone preparations free from gonad-stimulating properties are typically activated.

From preliminary quantitative work it would appear that the activation effect is dependent on the concentration of both constituents, the Prolan and the hypophyseal component.

Preliminary hypotheses must include at least 2 explanations of the

phenomena we have presented. The activator either converts an inactive pro-hormone in the hypophysis to an active form or else is able actually to convert the growth hormone into the gonad-stimulating one. It is attractive to strike an analogy here with the conditions found in the interaction of certain ferments and their co-ferments, for example the interaction of trypsinogen and enterokinase to produce tryptase, or again the cooperative action of the lactic-acid-forming enzyme with its co-ferment.

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Ionic Migration of Bismuth in Different Bismuth Products Under Different Conditions.

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Cerebral and spinal fluid penetration has not been established with certainty for all products of bismuth, and the efficacy of bismuth in cerebrospinal syphilis has been asserted and denied. It is conceivable that the variations here might be related to the amphoteric character of the metal which would vary with the product used. That is, penetration and activity might be favored by anionic bismuth, in accordance with the well-known composition of cerebrospinal fluid in which anions exist in relatively higher concentration than cations, and with the well-known appearance of the anions bromide, iodide and salicylate in this fluid. Correlated with these phenomena are the demonstrated penetration of the anionic bismuth compounds, sodium bismuthate and sodium iodobismuthite, and the negative or undependable penetration of the cationic bismuth products, bismuth metal, bismuth salicylate and potassium bismuth tartrate, previously reported from this laboratory.¹ Since the ionic character of bismuth in iodobismuthite only had been established in our previous work, the other products having been accepted on theoretical grounds, it appeared desirable to establish experimentally the ionic character of bismuth in various products under different conditions. Some of these products are claimed to penetrate the brain, and have been accepted for *New and Non-official Remedies* since our original work.

¹ Hanzlik, Mehrtens, Gurehot and Johnson, *J. Am. Med. Assn.*, 1931, in press; Gurehot, *Proc. Soc. Exp. Biol. and Med.*, 1930, **27**, 509.