Letters to the Editor

[The Editor does not hold himself responsible for opinions expressed by his correspondents. Neither can he undertake to return, nor to correspond with the writers of, rejected manuscripts intended for this or any other part of NATURE. *No notice is taken of anonymous communications.]*

Gonad-Stimulating Hormones in Hypophysectomised Animals

EXPERIMENTS previously reported[1, 2, 5, 6] on the effect of gonad-stimulating hormones in hypophysectomised animals have yielded somewhat contradictory results, probably because the number of animals studied has never been large. One of us (H. S.) has recently hypophysectomised more than six hundred albino rats by a modification of the Smith technique, by means of which it has been possible to complete the operation within five minutes, with unusually low immediate mortality, and we wish to present here a preliminary report of our findings.

The testes of hypophysectomised male rats, whether immature or adult, undergo atrophy, with reduction both of germinal epithelium and of interstitial tissue; the epididymides, prostates, and seminal vesicles are also much reduced in size. Treatment with the anterior pituitary-like hormone of the human placenta ("A. P. L.")[3] does not prevent degeneration of the germinal epithelium, but the interstitial tissue displays marked over-development, and there is consequently no atrophy of the accessory sex organs.

Noguchi[4] says that, in the ovary of immature hypophysectomised rats under the influence of pregnancy urine or placental emulsions, the thecal cells proliferate, becoming in appearance like lutein cells, although no true corpora lutea are formed. He further states that in such cases sometimes continuous œstrus sets in. Evans[5], however, thinks that a pregnancy urine fraction (prolan) cannot work at all in the absence of the pituitary, and bases on this his theory of prolan action. It seems to us that our own extensive experimental material proves beyond doubt that A. P. L. does act on the ovary of the hypophysectomised rat, though this action is not the same as in the normal. Immature hypophysectomised females treated with A. P. L. fail to come into œstrus, whereas hypophysectomised adult females similarly treated show continuous œstrus (vaginal cornification) for days and even weeks. Immature females which have been injected for five days or more with A. P. L., in order to induce precocious puberty, and have then been hypophysectomised, also respond to continued A. P. L. treatment with continuous œstrus. It is clear that the response of the hypophysectomised female to A. P. L. is conditioned by the state of the ovary at the time of operation.

We have confirmed the finding of others that hypophysectomy leads to atrophy of the thyroid, adrenal cortex, and gonads, and to cessation of growth (which last, however, does not occur immediately in rats weighing less than 50 gm. at the time of operation); these processes are not checked by the administration of A. P. L. Nevertheless, A. P. L. does cause the appearance of pseudocorpora lutea in the ovaries of females hypophysectomised before puberty, and it evidently evokes a secretion of œstrin from the shrinking ovary of the adult hypophysectomised female, since ovariectomised hypophysectomised animals did not manifest an œstrus response.

We have also found that hypophysectomy of adult females, either immediately after parturition or later in lactation, leads very rapidly to retrogression of the mammary glands and failure of milk secretion; although maternal instinct is not impaired and the young still attempt to suckle until they perish. Neither control operations upon the sella turcica without removal of the hypophysis, nor ovariectomy, will lead to this failure of lactation.

We have also been able to confirm Smith's[1] finding that hypophyseal implants permit apparently complete replacement therapy; with alkaline extract of bovine hypophyses, we have obtained growth of hypophysectomised animals without checking the atrophy of the thyroid, adrenal cortex, and gonads.

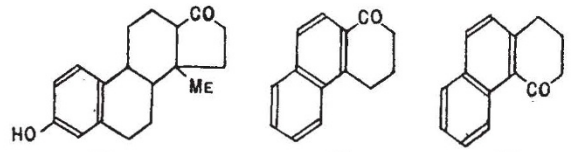
J. B. COLLIP.
H. SELYE.
D. L. THOMSON.

McGill University,
Montreal, Canada.
Dec. 9.

[1] Smith, *Amer. J. Anat.*, **45**, 205; 1930.
[2] Wallen-Lawrence and Van Dyke, *J. Pharmacol.*, **43**, 93; 1931.
[3] Collip, Thomson, McPhail and Williamson, *Can. Med. Assn. J.*, **24**, 201; 1931.
[4] Noguchi, *Jap. J. Med. Sci. Pharmacol.*, **5**, 104; 1931.
[5] Evans, *et. al.*, *Amer. J. Physiol.*, **100**, 141; 1932.
[6] Freud, *Deutsch. med. Woch.*, **58**, 974; 1932.

A Synthetic Oestrus-Exciting Compound

IN conformity with the hypothesis, for which there is at present no experimental basis, that the ovarian hormones are formed by degradation of sterols, and in the light of recent developments in the chemistry of the sterols, ketohydroxy-oestrin is possibly represented by formula (i).



(i) (ii) (iii)

This accords with all the facts supplied by the work of Butenandt[1], Marrian[2], and others, and we decided that the arguments in favour of this formula were sufficient to justify attempts to synthesise compounds of this nature. By analogy with other physiologically active compounds, it seems likely that a whole group of substances of related chemical constitution will be found to have oestrus-exciting properties, and the synthetic production of such substances would probably be of considerable clinical value.

We have found that 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene (ii), which we propose to utilise as a starting point in the synthesis of a substance of formula (i), has itself very definite oestrogenic action, although the dose required is very large in comparison with oestrin. The oestrus-producing activity of the substance was examined by the Allen and Doisy procedure. The technique followed was that described by Allan, Dickens and Dodds[3]. The material was dissolved first in olive oil, and later in sesame oil. It was found that the substances were not readily soluble in olive oil, with the result that large volumes had to be administered subcutaneously to the ovariectomised animals. This proved to be