THE EFFECT OF PITUITARY-STALK SECTION ON THYROID FUNCTION AND GONADOTROPIC-HORMONE EXCRETION IN WOMEN WITH MAMMARY CARCINOMA*

GORDON S. DUGGER, M.D., JUDSON J. VAN WYK, M.D., AND JAMES F. NEWSOME, M.D.

Department of Surgery, Division of Neurosurgery, and Endocrine Division, Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, North Carolina

(Received for publication February 23, 1962)

The rationale of attempting to modify the course of advanced mammary carcinoma by transecting the pituitary stalk has been discussed in a previous publication.\(^5\) Preliminary observations on the small group of patients reported previously were sufficiently encouraging to warrant an extension of these studies in a larger group of women. Studies have been carried out to compare the known effects of hypophysectomy with the physiological alterations that occur in humans when the pituitary gland is isolated surgically from its normal anatomical connections with the hypothalamus. A detailed study of adrenal function in these patients has revealed that the ACTH feedback mechanism virtually is abolished following section of the stalk, although the ability of the adrenal glands to secrete cortical hormones in response to "stress" is diminished only in proportion to the adrenal atrophy that occurs.\(^5\) Additional studies of adrenal function and the course of mammary carcinoma following section of the stalk will be reported subsequently. The present paper will report the effect of pituitary-stalk section on thyroid function and gonadotropin-hormone excretion.

MATERIALS AND METHODS

Thirty-four women between the ages of 32 and 69 years were selected for operation. All of them had advanced mammary carcinoma. Many had been treated previously by mastectomy and oophorectomy or with exogenous hormones such as androgens and estrogens. The pituitary stalk was visualized through a right frontal craniotomy and divided. In the early cases a plate of tantalum was placed between the divided ends of the stalk. Autopsy material in some instances showed that revascularization of the pituitary body by the hypophyseal-portal vessel system had occurred in some patients around the margins of the plate. For this reason in later cases the entire pituitary fossa was covered by a sheet of polyethylene in addition to the metal plate.

The 24-hour uptake of I\(^{131}\) was measured after the oral administration of carrier-free N\(^{131}\)I using formula No. 2 as described by the Oak Ridge Institute for Nuclear Studies.\(^4\) When serial counts were obtained correction was made for radioactivity remaining in the gland from previous studies.

The protein-bound iodine was measured by a modification of the method described by Barker.\(^2\)\(^†\)

The gonadotropin assay was carried out on 24-hour collections of urine which were stored in a refrigerated container without preservatives. Aliquots were shipped promptly by air to another laboratory for assay.\(^†\) The gonadotropin content was

\(^*\) These investigations were supported by research grants from the National Institutes of Health, Grants CY 3348(C4S1) and A 1022, The Elza U. Pardee Foundation, The United Fund, and by an Institutional Grant from the American Cancer Society.

\(^†\) The PBI values and gonadotropin assays were performed by Bio-Science Laboratories, Los Angeles, California.
assayed by the immature-mouse uterine-weight method after preliminary concentration of the urine on kaolin.

RESULTS

The effect of section of the stalk on the I\textsuperscript{131} uptake is charted in Fig. 1. In this hospital a 24-hour uptake of 15 per cent is considered to be the lower limit of the normal range. Twelve patients had a normal uptake of I\textsuperscript{131} before operation and in all of these individuals the postoperative uptakes were reduced sharply. In 11 of them the postoperative values fell within the hypothyroid range and in 1 the postoperative values were within the low euthyroid range. The fall in I\textsuperscript{131} uptake occurred as early as the second postoperative day (the earliest that it was measured).

The I\textsuperscript{131} uptake values of 7 patients were abnormally low before operation. Many of the patients previously had been subjected to multiple diagnostic and surgical procedures and it is possible that some of the low uptake values resulted from exposure to iodine in either inorganic or organic form. In 2 of these individuals the uptake tended to rise in subsequent determinations and in 1 instance it reached the euthyroid range. Because of technical difficulties the pituitary stalk of this patient could not be severed and other parameters of her endocrine function remained normal. None of the other patients regained uptake levels above 15 per cent during the period of observation although upward trends were noted in some patients.

Effect on PBI. Data are available on 17 patients before and after operation. These data are plotted in Fig. 2. The two elevated values were obtained in individuals who were clinically euthyroid. One of them was known to have had bronchography many months previously. All but 1 patient exhibited a postoperative fall in her protein-bound iodine level. An additional patient had a postoperative rise in PBI level but later became hypothyroid with a PBI of 3.2 μg per 100 ml. of plasma. In 9 patients one or more values fell below 4μg per cent. Symptoms of hypothyroidism which were judged to be sufficiently severe to require substitution therapy were encountered in only 4 patients. Late postoperative rises in PBI levels occurred in 4 patients after an initial fall. One of the 3 patients whose postoperative values fell to the hypothyroid range regained a normal level after many months.

Effect on Gonadotropic-Hormone Excretion.
Determination of urinary gonadotropic-hormone levels of excretion was carried out on 23 patients before and after section of the stalk. The results of these assays are plotted in Fig. 3. The patients are grouped according to the height of the preoperative determination. The figures in parentheses indicate the number of days after operation when the specimens were obtained.

Of the 15 patients with titers above 6 mouse units per 24 hours prior to operation, only 4 showed no decrease. One of these patients was A.S., whose pituitary stalk was not severed. In most patients the excretion of gonadotropic hormone was not abolished totally, since 22 patients had a measurable titer of gonadotropin in their urine after operation. Three patients with titers too low to measure before operation showed a low, but measurable, titer after section of the
stalk. There was no apparent correlation between the persistence of urinary gonadotropins and other parameters of pituitary function.

DISCUSSION

These studies demonstrate clearly that function of the thyroid is reduced following transection of the pituitary stalk, although not to the level that has been reported when hypophysectomy is complete. Our results are in essential agreement with those reported previously following section of the pituitary stalk with insertion of an impermeable barrier. A similar fall in uptake has been reported in patients treated by simple transections of the stalk without the insertion of a mechanical barrier, but in such patients a return of the iodine-concentrating mechanism often was observed by about the 10th week. A similar resurgence in function of the thyroid, after an initial drop, has been observed following incomplete hypophysectomy. The more permanent depression of thyroid function in the present cases would therefore seem to be related to the insertion of an impermeable barrier which retards or prevents regrowth of the portal system of veins.

The mechanism of the changes in function of the thyroid is not apparent from these studies. In other species, however, there is ample experimental evidence to support the belief that normal function of the thyroid-pituitary feedback mechanism is dependent upon specific centers located in the anterior basal hypothalamus and upon the integrity of vascular connections between the median eminence and the pituitary. Transplantation of the pituitary gland beneath the capsule of the kidney markedly reduces thyroid activity, whereas thyroid function is restored when the pituitary is re-implanted under the median eminence and is revascularized by the portal vessels. This occurs even though the pituitary volume is reduced sharply by the double vascular insult. The present studies suggest that the reduction of thyroid function in humans following section of the stalk likewise is the result of a more specific mechanism than simple reduction of pituitary mass from infarction of a portion of the gland. Histological sections of the pars distalis in 8 of our patients have revealed a substantial quantity of viable pituitary tissue surrounding the central zone of necrosis. There has been no direct correlation between the amount of surviving pituitary tissue and the degree of endocrine dysfunction that was produced.

The changes in gonadotropin excretion are more difficult to interpret. Excluding the patient whose stalk was not cut, only 1 of the 9 women with urinary gonadotropins over 50 mouse units failed to exhibit a postoperative decrease. The single postoperative observation on this patient was made only 5 days after section of the stalk and it is probable that insufficient time had elapsed for the titer to fall. It has been reported that following hypophysectomy gonadotropins may not disappear from the urine until 2 or 3 weeks after surgery, and in one series a number of patients who “subsequently were proved to have had complete removal of the pituitary” exhibited persistence of urinary gonadotropins for periods of 2 to 3 months before the titer dropped to an unmeasurable level.

Despite the difficulties in quantitating the secretion of gonadotropic hormones by these relatively crude methods, the data suggest that the excretion of urinary gonadotropins, although certainly not abolished, tends to be diminished following section of the pituitary stalk. In the 2 patients who were menstruating prior to section of the stalk there were no further menstrual periods in the 3- and 9-month intervals preceding their deaths. The effects of section of the stalk on gonadotropic function in other stalk-sectioned patients have been comparable to the results reported here.

The role of the hypothalamus and the hypothalamic-pituitary portal system has been less clearly defined in relation to FSH and LH secretion than has been the case with thyrotropin. Furthermore, there is considerable hazard in transferring physiologic data from lower forms to the human since the primate reproductive cycle differs in certain
important respects from that in other mammals. As with TSH, however, transplantation of the rat pituitary away from its normal location results in a diminished secretion of both FSH and LH and these effects are reversed when the pituitary is re-implanted under the median eminence.\textsuperscript{12,13,15} Contrariwise, the effect of removing the pituitary gland from its vascular connections with the median eminence does not diminish the secretion of prolactin (LTH), and, indeed, its secretion may be increased when the pituitary gland is transplanted to a distal site.\textsuperscript{1,7}

One of our patients was observed to lactate postoperatively. A similar observation was made in 4 of 17 stalk-sectioned patients in the series reported by Ehni and Eckles.\textsuperscript{6}

Thus, the observations in stalk-sectioned women tend to confirm that in the human, as in other species, the hypothalamus exerts an inhibitory effect on LTH secretion while its net effect on TSH, FSH, and LH secretion is stimulatory. Section of the stalk, by interfering with the normal vascular channels between the hypothalamus and pituitary gland, serves, at least in part, to abolish the normal influence of the hypothalamus on pituitary function. If precautions are taken to retard the re-establishment of the hypothalamic-hypophyseal portal system of veins, these functional alterations may persist for many months.

REFERENCES