Experimental radiofrequency telethermohypophysectomy

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A new means of producing well-delineated lesions of the pituitary gland by the heating of implanted electroseeds with electromagnetic radiation has been tested in a series of eight adult baboons (Papio anubis). The technique shows promise as a future simple and safe means of depressing anterior or posterior pituitary function in a controlled fashion over a period of time. In addition, possible fallacies relating to the rationale justifying total sellar hypophysectomy are considered. The authors believe that progressive depression of pituitary function may represent a more logical therapeutic approach to patients requiring hypophysectomy for the palliation of malignant disease, diabetic retinopathy, or eosinophilic pituitary adenomas.

KEY WORDS pituitary telethermohypophysectomy electroseeds electromagnetic radiation baboon

Although hypophysectomy is an important neurological procedure in the management of pituitary tumors, diabetic retinopathy, and the palliation of malignant disease, it is also, unfortunately, one in which a practical, simple, safe, and controllable surgical method has not yet been attained.

A similar difficulty also exists in the many techniques being used for lesion production in nervous tissue. The disadvantages of the methods currently used involve one or more of the following complications:

1. Transient and residual diabetes insipidus
2. Panhypopituitarism
3. Cranial nerve palsies
4. Damage to normal brain
5. Inability to control or monitor lesion production
6. Significant morbidity and/or mortality
7. Inability to increase the lesion size temporally without additional morbidity
8. Complex or expensive instrumentation.

In the hope of mitigating these shortcomings, the principles of radio frequency telethermocoagulation were applied in a pilot telethermohypophysectomy study on baboons. Telethermocoagulation involves the implantation of a small metallic target ("electroseed") into biological tissue and the heating of this implant by means of an electromagnetic field whose frequency and power are innocuous to the tissues involved. A 10-year program of basic research and development has indicated the feasibility of the telethermocoagulation technique in certain neurosurgical applications.4,10-12

Method

Preliminary comparative anatomical studies revealed that of the many laboratory animals available, including the cat, dog, pig, and rhesus monkey, the baboon was the
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smallest primate in which the infundibulum, pituitary, and sella turcica were similar to those of the human. Following 60 days of isolation and inoculation at the University of Washington Regional Primate Research Center, eight young adult male baboons (Papio anubis), with an average weight of 16.2 kg (range 11.9 to 29.6 kg) were selected. They were anesthetized with 1 mg/kg intramuscular Sernylan (1-phenyl-cyclohexyl piperidine hydrochloride, Parke Davis) and intravenous 17 mg/kg Nembutal (pentobarbital sodium, Abbott), and an electroseed composed of grade 430 stainless steel was passed through a No. 17 Stub's gauge needle and implanted in the anterior (seven animals) or posterior (one animal) lobe of the pituitary gland. The animals were then observed for 1 month during which time baseline blood samples were taken (under Sernylan anesthesia) to assay growth hormone, thyroid stimulating hormone, follicular stimulating hormone, and luteinizing hormone.*

Serial blood samples for these hormones were also taken following each exposure to electromagnetic radiation. Serial skull films were obtained in each animal at the time of implantation, at the end of the post-implantation observation period, which averaged 125 days (range 118 to 148 days), and before each radiation exposure.

The heating of the implanted electroseed was performed by a specially constructed 5 kilowatt (kW) output radiofrequency generator† tuned to 0.098, 1.13, and 1.40 MHz. The electromagnetic energy from this generator was coupled to the electroseed by placing the animal's head within a 6½ in. diameter, 5-turn, insulated, water-cooled coil with the head oriented to achieve maximum coupling with the electroseed (Fig. 1). This orientation was confirmed by x-rays taken at the time of each radiation.

Initial in-air calibration of the electroseed to the electromagnetic flux density within the coil was done by using temperature indica-

* Immunoassay was performed at the Pediatric Endocrinology Laboratory, Johns Hopkins Hospital, Baltimore, Maryland.
† The radiofrequency generator was supplied by Lepel High Frequency Laboratories, Inc., Maspeth, New York.

FIG. 1. Baboon's head within 5-turn Teflon insulated coil. Arrow points to intrasellar electroseed implanted by a transcerebral route. Head is positioned so that the electroseed is at right angles to the plane of the coil.

† Color coded temperature indicators are available from Tempilaq, Tempil Corporation, New York, New York.
Representative cortical sections and the whole pituitary gland were imbedded in paraffin. Consecutive serial sections 7 μ thick were prepared of the lesions produced, and representative sections 7 μ thick were taken at intervals through the remaining gland. Slides were alternately stained with hematoxylin and eosin, and Nissl stain.

The animal with a posterior lobe electroseed was maintained in a metabolic cage where water intake, urine output, and urine specific gravity were followed from the time of the first radiation until sacrifice (4 weeks).

**Results**

**Implantation**

In the six baboons with an electroseed in the anterior pituitary and the one with an electroseed in the posterior pituitary (Fig. 2), there were no infections or neurological complications. Postmortem brain examinations showed that the route of the No. 17 gauge implant needle passed through the hypothalamus and optic tract, producing a very small diameter glia-lined tract. There was no evidence of local hemorrhage. All the electroseeds implanted were at the designated locations without evidence of operative complications.

**Serial Skull Films**

There was no detectable change in the electroseed position relative to the bone structures before or after irradiation. This finding is consistent with previous experience with intracerebral electroseeds. 4

**Electromagnetic Field Exposure**

Two complications were experienced during the electromagnetic radiation. The first 3-min exposure was 1.4 MHz, and this produced inductive and dielectric skin and subcutaneous tissue burns in areas of the head closest to the coil. Frequency was decreased to 1.13 MHz for the next baboon, and minimal areas of skin erythema were seen. All subsequent exposures were at 980 KHz without complications. One animal (No. 68207), the only baboon with a posterior pituitary implant, experienced generalized seizures during both of its 3-min electromagnetic field exposures (1.13 MHz and 0.980 MHz). These were controlled with intravenous Dilantin (diphenylhydantoin sodium, Parke-Davis). This animal was also remarkable in that it was exceptionally aggressive and bore numerous battle scars. Aside from the seizures, the animal was neurologically intact at all times.

![Fig. 2. Baboon skull films. A. A 4 x 1 mm cylindrical electroseed has been placed in the posterior lobe of the pituitary. B. The electroseed has been placed in the anterior lobe. Electroseeds are in the midline.](image)
Postmortem Findings

Figure 3 shows a whole pituitary specimen with implanted electroseed. In each animal, a well-defined and uniformly thermocoagulated lesion was produced about the electroseed and did not, in any case, extend beyond the lobe itself (Fig. 4). In animal No. 68207 with the posterior pituitary electroseed, there was almost complete destruction of the posterior lobe (Fig. 5) yet there was no clinical indication of diabetes insipidus. In animals with multiple radiation exposures, there appeared to be greater destruction of the gland although it was difficult to quantitate because of the marked individual variation of pituitary gland size and shape not related to body weight, the removal of coagulated tissue by macrophages, and the possible regrowth of intact residual pituitary gland.

In no case was complete destruction of a lobe produced, although nearly complete destruction from a single electroseed was produced in three animals. In all baboons there was a reactive meningeal thickening adjacent to the lesion. The pituitary gland was normal in the control baboons, and by 76 days after implantation there was no evidence of a foreign body reaction to the stainless steel electroseed.

Serum Immunoassay

Growth hormone levels were undetectable using an antihuman growth hormone. Thus, absence of growth hormone does not necessarily indicate that these baboons were not producing growth hormone, as the antiserum may not have cross-reacted with the baboon growth hormone. Low levels of luteinizing hormone follicular stimulating hormone, and thyroid stimulating hormone, were found. However, the values were at such a level that...
proportional dilutions could not be used to learn whether the values found actually measured baboon LSH, FSH, or TSH, or were artifact. The effect of the experimental procedure on the circulating levels of pituitary hormone, therefore, still remains questionable.

Discussion

This study supports our belief that radiofrequency telethermohypophysectomy is a means of producing well-delineated thermo-coagulative lesions in the pituitary gland. Lesions of the anterior and posterior lobes can be independently produced by electroseed placement. Incrementation of the lesions by additional exposure to electromagnetic radiation over a period of time was suggested but not clearly documented by this study. The difficulty in assessing this was due to significant intra-animal anatomic variation in the size and shape of the hypophysis, the progressive resorption of thermocoagulated tissue by macrophages, and uncertainty as to the extent of parenchymal regeneration present during the post-irradiation period. Earlier and more extensive studies on cat cerebral cortex have documented the phenomenon of lesion resorption,11 and the authors believe that the latter could also be shown in a study similar to this if a larger series of primates were used.

The complications encountered, seizures in one animal and inductive dielectric skin burns in two animals, were attributed to the application of higher frequencies and energies required to heat the relatively small electroseeds which were scaled down to size to accommodate the baboon pituitary gland. Another factor may be an unusual epileptogenic sensitivity seemingly specific to baboons.5,7,8 During previous experience in producing radiofrequency telethermo-coagulative brain lesions at lower frequencies (400 to 600 KHz) in over 200 experimental animals (cats, dogs, and rhesus monkeys) and 25 humans, these complications were not encountered. Human implantation requires larger electroseeds, which fortunately require less external field energy and lower frequency, thus minimizing complications.

In this study, transcerebral implantation as opposed to the transnasal-sphenoidal route was necessary because of the baboon's formidable snout and absence of a sphenoid sinus. Although the implant needle passed through the cortical mantle, hypophysis, optic tract, and diaphragma sella, there were no neurological or pathological complications relating to implantation. The small diameter needle (0.056 in.) may have prevented significant injury. For human application the implant needle diameter would be 0.083 in. and the transnasal-sphenoidal route would be used. The authors believe that the absence of damage to parasellar structures in these animals is related to the excellent heat sink effect of the adjacent cavernous sinus and internal carotid arteries. We also speculate that greater protection is afforded by producing heat lesions in this area, as vessel dilation is enhanced; cold lesions, on the other hand, would tend to enhance vasoconstriction and reduce the protective heat sink shield. A consistent finding was that the pituitary lesions produced never extended across the pars intermedia, suggesting some heat sink shield effect at this location.

The advantages of a simple technique in which lesion production can be controlled over months or years without additional morbidity seem most evident in the treatment of hormone-producing tumors such as eosinophilic granuloma (not extending beyond the diaphragma sella). In such a situation, the blood growth hormone levels could be used as feedback to determine the need for additional suppression of viable tumor while maintaining some normal pituitary function.

From this study it appears that a single implanted electroseed is not capable of producing total sellar hypophysectomy in the baboon when heated by radiofrequency electromagnetic radiation. It remains to be determined if this can be achieved by the implantation and heating of multiple electroseeds. Complete hypophysectomy appears to be the present neurosurgical goal in the palliation of malignant disease, diabetic retinopathy, and pituitary tumors. However, complete sellar hypophysectomy is probably attained only rarely on a true physiological basis. Moreover, if complete physiological hypophysectomy could be routinely attained, its clinical value would be less than a simple
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and safe means of progressive depression of pituitary function. There has never been a good correlation reported between the degree of pituitary destruction and subsequent clinical improvement. In some cases where good results were attributed to “total hypophysectomy,” residual functional islands of tissue were found within the sella at post-mortem examination. In addition, the ability of residual pituitary parenchyma to proliferate is not yet fully appreciated.

Another important consideration, so far unanswered, is related to the functional role of the pharyngeal pituitary when “activated.” This cluster of cells, which represents a remnant of Rathke’s pouch residing within the sphenoid bone, appears to be present in all persons.9 It receives a rich, direct innervation from the sphenopalatine ganglia and is well vascularized.2 Its usual composition is of small, poorly differentiated chromophobe cells which, with occasional acidophils,1 seem to have the capacity to “activate” in response to stimuli and differentiate into normal-appearing chromophobes and acidophils. Müller has examined the pharyngeal pituitary in a series of patients whose sellar hypophysis was destroyed by tumor or hypophysectomy. In all cases the pharyngeal pituitary resembled normal adenohypophysis, except for the absence of basophils.5 Besides “activation,” the pharyngeal pituitary can serve as the origin of extrasella chromophobe and acidophilic adenomas. Kepes and Fritzlen6 have documented such a case and reviewed other cases. Although the endocrinological complications of “activated” pharyngeal pituitary remain to be determined, a good case can now be made that the association of “total” sellar hypophysectomy with functional hypophysectomy may only represent a persistent myth as long as the pharyngeal pituitary remains intact.

Conclusions

Based on experimental studies in baboons, the authors suggest that telethermohypophysectomy may represent an approach by which pituitary function can be “depressed” by a simple and safe method of producing lesions using both clinical and biological data as feedback control. With this approach, the neuroendocrine axis would not be subject to the insult of sudden and complete anatomical hypophysectomy with attendant hormone replacement problems and usually transient but intense diabetes insipidus. In addition, recent technical advances in electroseed design have produced an implant (“thermoseed”) in which fine control of heat production can be achieved.3 The role of telethermohypophysectomy as clinical therapy is now being explored.

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References


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