favour of the other, has this finding any value? Certainly from the scientific point of view this is the case. We have shown that hypophysectomy achieves something that cannot be achieved by adrenalectomy and this is an important scientific fact. It will direct the attention of research workers in this field to the growth hormone and other hormones specific to the pituitary, and to the effect of adrenal tissue lying outside the confines of the adrenal gland. In this way research into the endocrine effects on hormone-dependent growths will be more distinctly focused and the image more brightly illuminated.

REFERENCE

ATKINS, H. J. B. (1959) *Guy's Hosp. Rep.*, **108**, 423.

Interstitial Irradiation of the Pituitary

By GORDON S. RAMSAY, F.R.C.S.

London

THE development of the technique of transnasal implantation of the pituitary at the Royal Marsden Hospital is entirely due to the efforts of Mr. Peter Greening who performed the first implant more than five years ago (Greening, 1956). I have been associated with him in this work since 1956.

The history of interstitial irradiation of the pituitary goes back thirty years or so. Cushing implanted radon seeds via a craniotomy, into patients with basophil adenoma, and there have been several reports since of the use of radon in this way for the treatment of pituitary tumours. In 1936 Lodge described an approach via the orbit and ethmoid sinus to the sella turcica in cases where the latter had become grossly expanded by a tumour. He removed as much of the growth as possible and then implanted radon seeds. This same route is used by Bauer (1956) to insert a cannula into the gland.

The demonstration by Luft and Olivecrona (1953) of the value of surgical hypophysectomy in patients with metastatic breast cancer led inevitably to the search for a simpler method of destroying the normal gland.

External irradiation with conventional X-rays produces little or no effect upon this extremely radioresistant structure (Kelly *et al.*, 1958). The effect of a high energy proton beam is being studied (Tobias *et al.*, 1958). Electrocoagulation (Bauer, 1956) has not proved satisfactory because the electrode becomes covered with an insulating layer of charred tissue and further destruction is thus prevented. The injection into the gland of solutions of corrosives or of radioactive materials is dangerous because of the impossibility of limiting the fluid to the confines of the sella; it always leaks out and may damage surrounding structures.

Radon seeds were an obvious choice but experience showed that their penetrating gamma rays caused serious damage to the optic nerve which led to total blindness in many cases (Forrest *et al.*, 1956; Westminster Hospital, 1956).

Radioactive gold grains (^{198}Au) were first inserted via a transnasal cannula by Greening in February 1955, and at the same time, Forrest started using a similar technique for the insertion of radon seeds.

In 1953 Rasmussen *et al.* suggested, from experimental evidence, that yttrium 90, a pure beta ray emitter, would be a suitable source for producing localized destruction of the pituitary without damage to surrounding structures. Their experimental findings were confirmed by Yuhl *et al.* (1955) who introduced yttrium pellets at craniotomy. Yttrium was first used at the Royal Marsden Hospital in July 1956. ^{198}Au emits mainly gamma rays which are less penetrating than those from radon. A small quantity of beta rays is also produced but these travel a very short distance. The half-life of the two isotopes is, for all practical purposes, the same. Isodose curves (Fig. 1) show the much more rapid fall off with distance of the radiation from yttrium compared with that from gold.

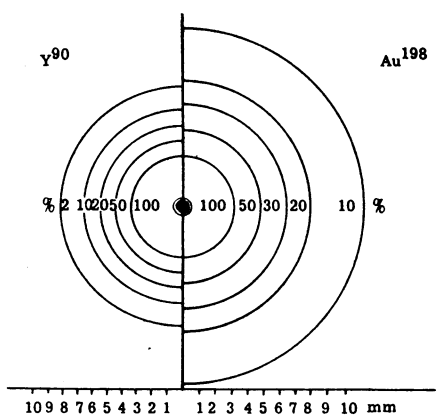

FIG. 1.—Isodose curves for ^{90}Y and ^{198}Au. (Doses equated at 3 mm from source.) Modified from Scheer *et al.* (1959) by kind permission.

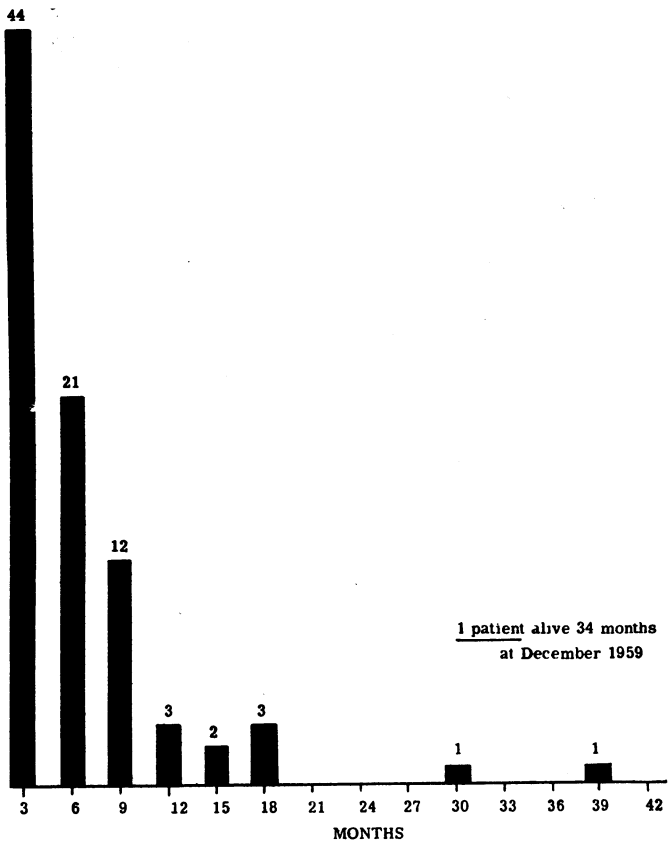

FIG. 2.—Survival after implant (non-responders) = 88 patients.

From February 1955 to March 1958, 100 patients with metastatic carcinoma of the breast were treated by implantation of the pituitary. Gold was used in 54 cases and yttrium in 36. The remaining 10 patients had first one and later the other isotope implanted. Screened gold grains, 2·5 mm long, 0·8 mm in diameter and with a sheath of platinum 0·15 mm thick were used at first, but later we changed to unscreened rods 5·0 mm long and 0·8 mm in diameter.

The operation is carried out under antibiotic cover, and cortisone 50 mg daily is started on the day before operation for those patients not already receiving it. It was withheld from some of the early cases and the onset of signs of adrenal insufficiency (usually within the first week after operation) was taken as an indication that the pituitary had been destroyed. This practice has been abandoned because it imposes unnecessary discomfort and risk to the patient.

Results

2 patients only are alive. 12 (11 ^{198}Au, 1 ^{90}Y), had objective evidence of regression and one of these survives forty-four months after implant. The remainder lived for periods ranging from seven to forty months with an average survival of 19·4 months. The length of survival of the 88 non-responders is shown in Fig. 2. 65 were dead in six months, and 13 lived for less than one month. The few who lived for a long time serve only to remind us how chronic this disease can be.

These patients were specially selected for the trial of a new method of treatment and most of them had very advanced disease which all other forms of treatment had failed to control. In 5 only was pituitary implant done as the first planned treatment. 37 had had previous endocrine surgery, either oophorectomy alone or combined with adrenalectomy. None of them showed improvement after pituitary implant no matter what their response to the previous operation had been. This is not surprising in those cases treated by adrenalectomy, as response to pituitary ablation is rare after this operation. There was only one patient who relapsed after successful oophorectomy, and pituitary implant failed to induce further regression. It is obvious that no fair comparison can be made of the

results in this series with those obtained by other methods of treatment.

The extent of destruction of the pituitary was estimated in 39 specimens obtained at post-mortem and examined histologically. In 4, the gland was totally destroyed, 3 by ^{90}Y (11·9, 12·8 and 8·6 mc) and one by ^{198}Au (80 mc). In a further 7 cases the extent of destruction was estimated to be between 90% and 95% and the activity of the rods ranged from 34 to 115 mc of gold and from 5·4 to 11·7 mc of yttrium. The smallest amount of ^{90}Y known to have destroyed the pituitary was 8·6 mc and the largest amount that was proved not to have destroyed all the gland was 11·7 mc. Thus about 10 mc of ^{90}Y should be sufficient to produce total necrosis in most cases. In common with other workers, we have found that gold is not efficient in producing total necrosis and in one case 125 mc still left between 10% and 20% of apparently viable cells.

We were able, in a few patients, to correlate the clinical response with the extent of necrosis found at autopsy and the pre- and post-implant urinary gonadotrophin levels. This was so in 2 of the 12 cases showing objective regression. The extent of destruction was 100% in one and 95% in the other and the gonadotrophin levels fell to zero in both. Among the non-responders there were 8 patients in whom this combination of circumstances occurred. In 6, the extent of destruction was between 80% and 100%, and in all these the gonadotrophin excretion fell to very low levels after implant. In the other 2 cases the amount of pituitary destroyed was small, 10% in one and 33% in the other, yet there was a similar dramatic fall in the amount of gonadotrophin excreted. We must therefore accept with caution a fall in urinary gonadotrophin excretion as evidence of complete histological destruction of the pituitary although it probably reflects loss of function.

Complications

All patients develop a headache but this is not usually severe and is easily controlled by simple analgesics. Diabetes insipidus occurred quite often in the early post-operative period but lasted only a short time in most cases. A few patients required injections of vasopressin tannate. Bleeding was common but was not often severe although 2 patients required transfusion. Optic atrophy occurred in 3 patients and must be assumed to be due to the implant; unfortunately we did not have the opportunity of confirming at post-mortem that the blindness was in fact the result of radiation damage to the optic nerve. Although this is the most probable explanation, there was one patient whose blindness was discovered at autopsy to be due to a metastasis.

The most disastrous complication was meningitis which caused 10 deaths. C.S.F. rhinorrhœa and meningitis, either separately or together, occurred in 21 patients. The material implanted was gold in 9 and yttrium in 12. 10 patients developed rhinorrhœa which sooner or later ceased spontaneously. 5 patients developed rhinorrhœa and subsequently meningitis and all died. 6 patients developed meningitis without previous rhinorrhœa and 5 of these died. A striking feature of this complication was the variation in the elapse of time after implant before meningitis occurred. The diagram (Fig. 3) illustrating this point includes 2 patients suffering from diseases other than carcinoma of the breast. Antibiotic cover as long as the leak persisted was the only treatment employed. We have no experience of operations to cure this condition although we have experimented recently with the insertion of a plug of wax to close the hole in the floor of the sella as the cannula is withdrawn. Meningitis was extremely resistant to treatment and the clinical course varied from acute fulminating to chronic. At post-mortem multiple adhesions with much fibrinous exudate were commonly found and it is not surprising that antibiotics have little effect in such cases. The cause of the C.S.F. leak provides scope for speculation and it seems that there are several possibilities. There was no correlation between the activity of the rods and the development of rhinorrhœa, but there is no doubt that it occurs if rods are placed high up anteriorly; in this position they lie just under the diaphragma sellæ and may cause it to necrose (Forrest *et al.*,

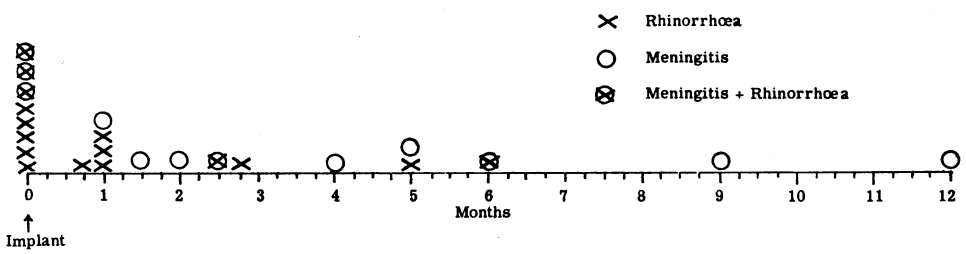

FIG. 3.—Onset of rhinorrhœa and meningitis following implant.

1959). Rhinorrhœa can, however, occur with properly placed rods and Forrest suggests that it is then due to overdosage, but this does not explain the immediate leak of C.S.F. which we have noted on several occasions on the introduction of the cannula low down near the floor of the fossa and we must seek another explanation. The cause, I believe, lies in abnormal anatomy and there are two variations from the normal which may be important. First, the depth of the fossa as shown radiologically does not necessarily indicate the depth of the gland which it contains. The pituitary may sometimes consist of no more than a flattened disc lying on the floor and in such a case the diaphragma is not stretched across the top but dips down to be closely applied to the upper surface of the gland. It is easy to see therefore, that a rod placed in the middle of the fossa and judged to be in the middle of the gland might in fact be lying above the diaphragma in the subarachnoid space. Secondly, the diaphragma sellæ is often deficient. Mahmoud (1958) found this to be so in 40 of 100 fossæ examined at autopsy. In some the deficiency is quite large and it is in such cases that I believe that the subarachnoid space may extend down into the fossa.

The high incidence of complications and the need to assess the results in the first 100 cases caused us to suspend the operation for a time. We have developed doubts about the superiority of yttrium over gold for the following reasons: (1) All but one of the 12 patients showing objective regression were implanted with gold. (2) The incidence of rhinorrhœa and meningitis was lower in the gold series (9 ^{198}Au, 12 ^{90}Y). We have also come to realize that the transnasal approach is not ideal. The only safe place to implant rods is low down near the floor of the fossa and the logical approach is a horizontal one. A horizontal approach via the nose is impossible in many cases and septal deviation and enlarged turbinates add to the difficulties of the operation. On the other hand, the transethmoidal route, which has been used by Bauer for twelve years, permits a horizontal approach to the fossa to be made in all cases and anatomical variations do not deflect the cannula. It also appears, theoretically at least, to be a more sterile route.

Finally, it is doubtful whether complete histological destruction of the pituitary is necessary to induce a remission. Bauer admits that he does not destroy the gland completely, in fact his patients do not need cortisone, and yet he obtains satisfactory results. These then are some of the problems yet to be solved before pituitary implantation can be established as a routine procedure.

REFERENCES

BAUER, K. H. (1956) *Arch. klin. Chir.*, **284**, 438.
——, and SCHWEITZER, L. A. (1958) In: Endocrine Aspects of Breast Cancer. Ed. A. R. Currie. Edinburgh; p. 56.
FORREST, A. P. M., BLAIR, D. W., PEEBLES BROWN, D. A., STEWART, H. J., SNADISON, A. T., HARRINGTON, R. W., VALENTINE, J. M., and CARTER, P. T. (1959) *Brit. J. Surg.*, **47**, 61.
——, BROWN, P. A., MORRIS, S. R., and ILLINGWORTH, G. P. W. (1956) *Lancet*, i, 399.
GREENING, W. P. (1956) *Lancet*, i, 728.
KELLY, W. A., EVANS, J. P., HARPER, P. V., and HUMPHREYS, E. M. (1958) *Surg. Gynec. Obstet.*, **106**, 600.
LODGE, W. O. (1936) *Brit. med. J.*, ii, 1257.
LUFT, R., and OLIVECRONA, H. (1953) *J. Neurosurg.*, **10**, 301.
MAHMOUD, M. E. S. (1958) *Brit. J. Radiol.*, Suppl. 8.
RASMUSSEN, T., HARPER, P. V., and KENNEDY, T. (1953) *Amer. Coll. Surg., surg. Forum*, **4**, 681.
SCHEER, K. E., GUDDEN, F., and BEKERUS, M. (1959) *Nuclear Med.*, **1**, 91.
TOBIAS, C. A., LAWRENCE, J. H., BORN, J. L., MCKOMBS, R. K., ROBERTS, J. E., ANGER, H. O., LOW-BEER, B. V. A., and HUGGINS, C. B. (1958) *Cancer Res.*, **18**, 121.
Westminster Hospital (1956) *Rep. Brit. Emp. Cancer Campgn.*, **34**, 173.
YUHL, E. T., HARPER, P. V., RASMUSSEN, T. B., and BERGENSTAL, D. M. (1955) *Amer. Coll. Surg., surg. Forum*, **6**, 489.

Localization of Radio-active Implants with Image Intensification and Television

By J. J. STEVENSON, M.D., D.M.R.

The Royal Marsden Hospital and The Institute of Urology

DURING the past five years we have carried out implantation of the pituitary gland with radio-active material in more than 200 patients.

At the beginning it was felt that the localization of the introducing needle and subsequent implant could be most conveniently done by means of fluoroscopy in two planes. However, it proved impossible to perceive adequate detail on the conventional fluorescent screen and moreover the use of very subdued room lighting with intermittent total darkness gravely handicapped the surgeons and anæsthetists concerned. For some time previously we had been making use of the image intensifier in the examination of the gastro-intestinal and urinary tracts at the Royal Marsden and St. Paul's Hospitals. This is an electron optical tube consisting essentially of two fluorescent screens with a high potential difference between them. When X-rays strike the front screen it fluoresces in the normal manner.