respect in which the operation has great advantage over transfrontal interstitial irradiation hypophysectomies (*Lancet*, 1960).

Comparison of the Two Operations

The two groups of cases, those submitted to hypophysectomy and those to bilateral adrenalectomy and oophorectomy, when analysed were approximately similar in composition as regards age distribution, site and extent of metastases, and previous experience of other forms of treatment, as one would expect when cases are chosen by random selection. Counting all deaths from whatever cause within twenty days of operation as operative deaths, the operative mortality following hypophysectomy was 3 deaths (4%) and following adrenalectomy was 7 deaths (9%). It is perhaps noteworthy that all 7 patients who died after adrenalectomy had a pulmonary metastasis, whereas only 1 of the 3 who died after hypophysectomy had such a lesion. This appears to indicate that patients with pulmonary lesions should for preference be treated by hypophysectomy which involves only one anæsthetic and not by adrenalectomy which involves a two-stage operative procedure.

All the remaining patients have since been followed up at regular one- or two-monthly intervals, and their progress checked at each examination by the method known as the Mean Clinical Value (M.C.V.) of Walpole and Paterson (1949). This method assigns a scale of values such that, if all the lesions are improving the M.C.V. is 12, if on balance the lesions are stationary, the M.C.V. is 6, and if all are deteriorating the M.C.V. is 0. The appearance of this latter value is usually followed shortly by death.

There are several ways in which a statistical comparison can be made between the two groups. The principal way in which we have done it is to average out the M.C.V. for all patients at regular four-weekly intervals after operation. In compiling these averages all surviving patients and also all patients who, had they not died, could have completed each follow-up period are included, the deceased patients each being assigned an M.C.V. of zero. We found that whereas after hypophysectomy the average M.C.V. improved, reaching an average level of 7·2 at about the third month, and then declined, after bilateral adrenalectomy the average M.C.V. fell steadily from an initial level of 6 at a rate which at first sight appeared to parallel the decline in the hypophysectomy series after the third month. The longest time of survival after bilateral adrenalectomy was fifty-three months and after hypophysectomy seventy-five months.

It might be argued, however, that hypophysectomy, although superior in its results during the first two or three months after operation, subsequently loses its efficacy at a rate proportionate to that after bilateral adrenalectomy. However, the proportions of patients surviving after hypophysectomy at three months and at twelve months were 0·812 and 0·567 respectively, compared with figures after bilateral adrenalectomy of 0·666 and 0·405 respectively. These figures give a statistical probability that hypophysectomy is a superior operation of 0·04 at the third month and of 0·05 at the twelfth month, both of which come within the conventionally accepted figure of probability of 0·05.

REFERENCES

ATKINS, H. J. B. (1957) *Proc. R. Soc. Med.*, **50**, 859.
——, FALCONER, M. A., HAYWARD, J. L., and MACLEAN, K. S. (1957) *Lancet*, i, 489.
——, ——, ——, ——, SCHURR, P. H., and ARMITAGE, P. (1960) *Lancet*, i, 1148.
FALCONER, M. A. (1957) *Proc. R. Soc. Med.*, **50**, 861.
Lancet (1960) i, 489.
LUFT, R., and OLIVECRONA, H. (1953) *J. Neurosurg.*, **10**, 301.
WALPOLE, A. L., and PATERSON, E. (1949) *Lancet*, ii, 783.

A Comparison of Adrenalectomy and Oophorectomy with Hypophysectomy in the Treatment of Advanced Cancer of the Breast

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MR. MURRAY FALCONER has stated that after five years' work we have been able to demonstrate that hypophysectomy is better than bilateral adrenalectomy with oophorectomy in the treatment of advanced cancer of the breast. It is my task to answer two questions: What do we mean by "better" and, How much better?

What Do We Mean by "Better"?

In order to answer the first question it is necessary to examine the criteria by which we assess these treatments. A properly controlled trial, from the purely scientific point of view, would have demanded that we divide our population into three groups by random selection. One group would have been left untreated, one group would have been treated by hypophysectomy and one group by bilateral adrenalectomy with oophorectomy. However, the fact that occasionally miraculous and often satisfactory alleviation can be procured by either of these operations, made this procedure unethical and we had to be content with two groups, one treated by hypophysectomy and the other by adrenalectomy with oophorectomy.

One criterion which we adopted and which has much to recommend it is length of survival measured in this instance appropriately in months. There is no argument about length of survival, which makes it an admirable criterion. There may, on the other hand, be plenty of argument as to whether this survival has been too dearly purchased or whether the quality of the life is worth preserving and these points will be considered later.

As Mr. Murray Falconer has shown, the mortality rates of the two operations expressed as a life table are different and, at three months after the operation, this difference is significant at the 0·04 level of probability. Survival rate therefore is helpful and has something to tell us about the effects of these operations.

Survival rate, however, is a crude measure in this condition because of the protean manifestations some of which, such as brain secondaries, may be lethal and others, such as skin secondaries, may be relatively innocuous. Thus, if treatment A is meted out to patient 1 with brain secondaries and this treatment is successful for three months after which a relapse occurs and the patient dies in nine months, then this treatment compares unfavourably with treatment B which is quite ineffective on patient 2 who has skin secondaries, but who lingers on for fifteen months.

If survival times were the only criteria, then treatment B, which was without effect, would be rated "better" than treatment A which at least had a temporary effect, and this would obscure the purpose of the trial which was to investigate the effect of the treatment on the cancer cell.

It is true that, if sufficiently large populations were contrasted, then these difficulties would be ironed out as there would be approximately the same number of skin and brain secondaries in each group. However, this is not practicable, so we have to be content with a possible maldistribution of such "deviants" as I have called them (Atkins, 1959) and see if there is not another criterion which we could use which obviates this difficulty.

The Mean Clinical Value, which Mr. Murray Falconer used to contrast the populations, is at once a more delicate and, in this context, a more appropriate index of response. In this method each lesion is examined at four-weekly intervals after treatment and a mark is given to it depending upon whether it has improved (2 marks), worsened (0 marks), or there is some doubt (1 mark). The marks are then added together and divided by the number of lesions to obtain an average, and this figure is multiplied by six, simply to bring it to a less unwieldy number. The effect, as we have seen, is to grade each patient at her four-weekly follow up with some mark between 12, which would indicate that all the lesions were getting better, and 0, which would indicate that all the lesions were getting worse. Some criticisms have been levelled at the method because it is asserted that it tries to be too exact, but assessment requires no more refined judgment than to say if a lesion is better or worse or that it is impossible to decide. Intermediate marks between 0 and 6, or between 6 and 12 occur because not all lesions respond to treatment to the same extent or at the same time. We have now used the M.C.V. method for many years at the Guy's Hospital Breast Clinic and we find it a most useful tool in the investigation of the response of these patients. It obviates the difficulty encountered in using the survival times as criteria in that, whatever the survival time, if the lesion responds the case will be given a high mark and if it fails to respond a low mark, irrespective of where the lesion is. Since therefore the principal aim is to find out the effect of treatment on the behaviour of the cancer cell, we regard this as the more important, as well as being the more delicate, index.

Mr. Murray Falconer has shown, using the M.C.V. as a standard, that the response to hypophysectomy is better than the response to adrenalectomy with oophorectomy. As befits a more elegant method, this difference is significant at the 0·03 level. By "better", therefore, we mean that patients survive longer after hypophysectomy than they do after adrenalectomy and that during the period of survival there is a more effective reduction in the volume of cancer tissue.

This, however, is not necessarily the whole story. We are dealing with what may be called heterogeneous populations. Apart, that is, from the natural heterogeneity of any sample population in respect of age, build, blood pressure and so on, there is a heterogeneity in regard to the type of lesions which are being investigated. All we have purported to show within the conventional limits of statistical acceptability is that when one such heterogeneous population is compared with another such heterogeneous population chosen by randomization, that population treated by hypophysectomy responds better than the population treated by adrenalectomy. Although the distribution of lesions and age groups in these two heterogeneous populations is approximately the same, we can make no statement about whether our findings are true at all ages or with all manifestations.

The fact that the bulk of our population is over 50 might, when the whole population is considered, mask the beneficial effect of adrenalectomy in the younger age group. In order to determine these matters, a great deal more detailed investigations of much larger populations will be necessary and it is for this reason, amongst others mentioned below, that it would be quite improper at this stage to give up adrenalectomy in favour of hypophysectomy when so little is known about the details of the behaviour of both these methods.

How Much Better?

The fact that we have shown that hypophysectomy is better than adrenalectomy at the 0·03 level of statistical probability gives no indication of the degree of difference between these two measures. It does not imply that the difference is decisive, meaningful or worth while or indeed—in the colloquial sense of the term—significant! The term "significant", like the terms "confidence" and "fiducial limits", has been appropriated by the statisticians to define a mathematical parameter very much more restricted in its implications than its colloquial use would allow. This is a pity, because it has led to considerable misunderstanding on the part of those who have not had a statistical training and who are inclined to believe that if the difference between two populations is statistically very significant, that this difference must be very considerable, meaningful, worth while or what I have called "determinant", implying that it determines policy, and indeed what *they* would call "significant".

How much better is hypophysectomy than adrenalectomy, and is the difference determinant? The average survival for hypophysectomy is 10·8 months and for adrenalectomy 9·0 months. During this period of survival the average M.C.V. for hypophysectomy is 6·57 and for adrenalectomy 5·48. Furthermore there is a wide variation of individual figures about all four of these means.

If such considerations can be given mathematical precision, and I doubt this, these figures 10·8 : 9·0 and 6·57 : 5·48 do indicate roughly the order of the degree of difference between these two procedures. It is the sort of difference which, if the better method carried any specific disadvantages, would be immediately wiped out by practical considerations. In fact, of course, the two procedures are, from the patient's point of view, somewhat nicely balanced. Hypophysectomy has the advantage that it is a one-stage procedure (whereas bilateral adrenalectomy with oophorectomy is usually carried out in two stages) but it has the slight disadvantage that the sense of smell may be impaired, and there is a somewhat higher incidence of "cushingoid" features, which, however, can be controlled by giving thyroid extract. The mortalities of the operations, that is cases dying within twenty days of operation, have in our series been 7/79 for adrenalectomy, and 3/70 for hypophysectomy, the standard deviations being 12 and 10·8 respectively.

Hypophysectomy, however, is an operation which can be carried out safely by only a very few surgeons. Certainly it would be quite improper to read into our findings a recommendation that adrenalectomy should be discarded for hypophysectomy in the treatment of advanced cancer of the breast.

About 8,000 women die of cancer of the breast each year in England and Wales. Of these about 7,000 would be suitable for treatment by hypophysectomy at some stage in their illness, although this figure could be materially reduced by a method of preselection shortly to be published. Even if the number of adequately trained surgeons were doubled or preselection halved the number of suitable cases, the numbers would be unmanageably large. It may be urged that not quite such skill is demanded for stalk section or yttrium 90 implantation, though I would doubt this in regard to the latter, so that if these methods were allowed, there would be a sufficient number of qualified surgeons to deal with advanced breast cancer by destruction of the pituitary gland. We have, however, no evidence that stalk section or yttrium implantation is as good as surgical hypophysectomy or even adrenalectomy with oophorectomy, so that no statement can be made about this matter.

For a few years, therefore, no doubt, adrenalectomy will retain its place as a satisfactory and safe method of treatment for advanced cancer of the breast in the hands of any reasonably competent general surgeon. It is well that this should be so and, furthermore, that the most ethical way of choosing which patient should be subjected to which operation is still by randomization. Originally this method was ethical because we did not know which was the better procedure; it is now the most fair because not every patient can undergo what has been shown to be the slightly better procedure.

In this way it will be possible to continue our studies into the more detailed aspects of the effect of these operations. The series can be broken down according to age, type of manifestation and so on, so that additional evidence will be forthcoming on these points of detail.

Finally, if we have shown a significant difference in the effect of these two methods of treatment, but that the degree of difference is not such as to make it worth while to condemn one method in 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

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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.

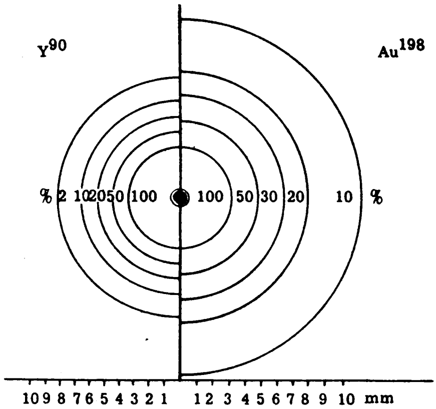

FIG. 1.—Isodose curves for ^{90}Y and ^{198}Au. (Doses equated at 3 mm from source.) Modified from Scheer *et al.* (1959) by kind permission.