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USE OF RADIOACTIVE PHOSPHORUS IN MAPPING BRAIN TUMOURS AT OPERATION

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During the last thirty years or so new and mechanical techniques have been introduced into neurosurgery to amplify or verify the information obtained by classical clinical procedures. They were needed because, however excellent the observations, there were often doubts in interpretation. First came ventriculography, which helped greatly in location but which often brought important dangers into the management of a case that a surgeon would have preferred to avoid had alternatives existed. Next came angiography, which when successful gave not only the tumour site but often clues to its histological nature.

Attempts have recently been made to improve on both of these diagnostic aids—by the use, for instance, of the reflection or attenuation of ultrasonic waves passed through the head in the hope that the pattern of the ventricles would emerge (Ballantine *et al.*, 1950). But the most useful of the new techniques lies in the field of the isotopes, a subject well summarized in a recent annotation in the *British Medical Journal* (1952). Brain tumours pick up chemical substances in much greater quantity than does the normal grey or white matter, and some isotopes penetrate in only the smallest quantities into the cerebrospinal fluid. This affinity for chemical substances seems to depend on the cellularity of the tumour rather than on the immaturity or number of the tumour's blood vessels. The substances used so far have been radioactive phosphorus (P^{32}), potassium (K^{42}), di-iodofluorescein (I^{131}), and manganese ($_{25}Mn^{52}$ and $_{25}Mn^{54}$). After injecting radioactive iodine compounds or a manganese salt (the latter a positron-emitter) it has been found possible to pick up the emanations through the intact skull by means of scintillators which are fifty times as efficient as the standard Geiger-Müller counter. Davis *et al.* (1950), Moore and his co-workers (1950), and Brownell and Sweet (1952, personal communication) have all had some success with this method. The advantages of such procedures over ventriculography and angiography are self-evident, though neither of these older methods is at all likely to become obsolete. Midline tumours, those of the third ventricle and thalamus, and tumours of the pineal region and brain-stem are not such as can be satisfactorily demonstrated by these

newer means, while some sparse-celled tumours may give ambiguous results. But certainly it would be an advance if we could tell by a bloodless and harmless method that a tumour is present, even though the details had still to be worked out by other ways.

The use that we have made of P^{32} is quite different and would not lose its usefulness even if the gross location of the tumour had already been made by means of radioactivity. We have followed closely the plan laid down by Selverstone, Sweet, and Robinson (1949) and Selverstone, Solomon, and Sweet (1949). The object is to map the extent of tumour, subcortical or otherwise, after its site has been exposed, or to pin-point its location in order that a successful biopsy may be made.

Technique

One millicurie of P^{32} is injected intravenously the evening before operation—a period of approximately 12 hours. The dose of P^{32} and the time of injection are immaterial provided that the concentration of beta emissions from normal brain is great enough to be recorded and that the dose of P^{32} is not so large as to harm the patient. We have tried to keep the dose and time interval between injection and recording standard so that the readings of the rate of beta emission taken at operation are comparable in all cases. Lately, however, we have found that P^{32} is concentrated in a significant amount in tumour within minutes of the injection. In three such cases the tumours had been exposed before the injections were made. This is in line with similar findings by Easson and Gilbert (1951, personal communication), who studied the rate of uptake of the isotope in different tissues, including breast cancer. At operation the modified Geiger-Müller probe counter—designed by Selverstone and Robinson and described by Robinson and Peterson (1948) (Fig. 1)—is used to detect the tumour by picking up the beta particles emanating from it when the probe is inserted into or very close to the tumour.

The detailed description of the apparatus is beyond the scope of this article, but it is necessary to mention its essential features. P^{32} is a pure beta-emitter, and this is why it was originally chosen by Selverstone in this work, for its emission is uncontaminated by gamma radiation. The range of the beta particles of phosphorus in normal white matter is only 5 to 8 mm. This short range is an essential factor for the accurate recognition of the position of a tumour. The probe is made of thin stainless steel (cathode) and is marked

in centimetres, but the part of the tube that contains within it the "active" anode is situated near the probe's tip, and it is therefore only from this point that beta emissions are picked up and recorded. The probe is connected by a plastic insulated flexible attachment to a combined amplifier and count-rate meter that records by both dial and loudspeaker. The latter is an important addition to the instrument, for it enables the surgeon to be aware of the activity of the tissue he is probing without taking his eye off the field of operation. We cannot agree with Davis (1951) in the criticism he levelled at the Selverstone probe counter on the

FIG. 1.—Line drawing of the counter. The dark area near the tip represents the sensitive part of the probe. The probe is marked in centimetres. The method of attachment of the leads is shown.

grounds that its fragility and instability make it impracticable for routine theatre work. It will not withstand rough handling, but there is no reason why it should receive it. The life of this probe model is limited to about ten million counts. Owing to the difficulty of replacement the counter was used only when it had a definite role in the management of a case.

Apart from the information this method can give in locating a tumour, it is a simple and practicable technique that can be used in any operating theatre. No extra assistant is required, and the precautions to be taken in handling the P^{32} are little different from familiar aseptic practice. No special knowledge of electronics is needed in the interpretation of the results. The equipment uses the mains supply of electricity. It is portable and unobtrusive, and, by modern standards, cheap (the whole outfit costs about £150). The probe can be sterilized by immersion in lysol or by autoclaving at 120° C. for five minutes, and the leads suffer no harm from boiling. The probe has an external diameter of slightly more than 2 mm., which is the dimension of brain cannulae in everyday use.

Discussion

Even with the help of P^{32} the surgery of the gliomas remains disappointing because of their tendency to invade basal structures and because such invasion is already present in many patients by the time they become aware that something is wrong. This is not universally true, but it is very often the case. It is possible to see the place where gliomas fade into normal brain, but sometimes the observer cannot define the boundary very narrowly. It would be an advantage if the absolute boundary could be detected by the radioactivity of a narrow fringe containing but few cells. This would call for a degree of sensitivity beyond anything yet available. The objection may be made that even if one knew to a millimetre it would make no practical difference for the reason already mentioned—invasion of functionally vital areas. But everything that gives greater precision and immediate knowledge of tumour extent must be welcomed. Future probe counters may fulfil this demand. The present type will detect a cellular piece of tumour but will not make known the few scattered cells sufficient to ensure recurrence. It might do that service better with larger doses of P^{32} (up to 2 or 3 mc.), but we have been content as a rule with recognition of the main tumour mass, and with the naked eye to define the boundary. We should add that in one case in which a meningioma of the inner and middle thirds of the sphenoidal wing had been removed the counter discovered an unsuspected nubbin of tumour that had been left behind under the frontal lobe. Our uses of P^{32} can best be summarized as follows.

(1) *Recognition of Tumour Tissue for Biopsy.*—Perhaps the most useful application of the method is in the taking of biopsy specimens by puncture and aspiration along a cannula introduced through a burr-hole. Every experienced neurosurgeon knows how uncertain the burr-hole biopsy can be, yet by confirmation of histological structure a tedious and useless operation can be avoided. This is particularly true, as everyone knows, of malignant gliomas and secondary tumours, especially in aphasic and hemiplegic patients. Such a tumour can often be felt with the cannula, but sometimes it is far from certain that a satisfactory specimen has been obtained. By exploring with the probe counter one can make sure that a cellular part of the tumour has been found.

The brain cannula can then be passed to the same depth and in the same direction as the probe with confidence that tissue extracted from that situation will contain tumour cells. Even more gratifying confirmation is obtained when the radioactivity of the tiny fragment removed confirms the fact immediately that a specimen of tumour has indeed been secured. Out of 15 burr-hole biopsies conducted in this way 14 gave the information sought.

In Fig. 2 the findings in one such case have been graphically recorded. The fall in count rate as the probe enters the white matter is well shown. The fall may not occur until a depth of 2 cm. or so has been reached if the probe is in contact with the buried grey matter surrounding a sulcus or fissure. The cortical counts are relatively low and are in marked contrast with the rise that occurs when a cellular tumour is penetrated.

(2) *Mapping the Lay-out of a Subcortical Tumour.*—When a direct attack is to be made on a tumour lying subcortically it is valuable in planning the incision into the brain if one can discover the exact depth at which the tumour begins to influence the counter. The operator knows that the probe is touching it, and by sinking the counter at several points he can map out the lie of the tumour. Further, it can be discovered, by probing before excision is attempted, whether the tumour is accessible (Fig. 3) or extends into regions that cannot be removed—for instance, the motor area—or whether, again, in frontal lesions, tumour activity can be recognized in the opposite hemisphere, rendering a unilateral lobectomy fruitless. Such steps as these are helpful in the surgical attack. Selverstone and White (1951) have shown by comparison between isotope maps at operation and the verified extent of the tumour at post-mortem examination how closely the prediction tallies with the facts.

We have spoken of tracing a tumour in terms of large extent. There is another side to it; the discovery that a tumour is smaller than had been thought. Thus, by passing

FIG. 2.—Detection through a burr-hole of active tumour situated at considerable depth. Biopsy: secondary carcinoma. Cortex invariably shows a slightly greater activity than white matter. The stippled blocks represent the activity of biopsy fragments of normal brain and tumour.

FIG. 3.—Deep left frontal tumour suspected. Probing with the counter revealed active tumour filling the third ventricle. Operation terminated.

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the counter through a tumour, a sudden fall in registration of beta particles indicates that the probe is out into normal white matter on the far side (Fig. 4). This is very valuable information, and an encouragement to radical surgery.

FIG. 4.—At operation a tumour (astrocytoma) was seen on the surface of the convexity of the brain. Its deep extent was mapped with the counter; radical removal was undertaken

(3) *Scanning the Bed from which a Tumour has been Removed.*—We are doubtful of the value of the counter for this purpose in its present degree of sensitiveness. We have had only one case of glioma in which completely negative responses were obtained after radical excision. It is too soon yet to say how reliable the information was, since the operation was done only a year ago. We have not used the counter for cerebellar gliomas, as the extent of these tumours can usually be accurately recognized by vision, and when they do fade out it is usually because they are invading the medulla oblongata or pons, where they could not be pursued in any case.

(4) *Negative Information.*—In only four cases did we obtain no reply on puncture. One of these was a diffuse and very slow-growing basal ganglion glioma. It is probable that owing to the existence of a large hydrocephalus the probe never entered into tumour tissue. In another, proof was obtained at necropsy that the lesion was a vascular one in spite of a history strongly suggesting neoplasm. In two others, although tough resistance indicated that the probe was certainly in a tumour, the counts were lower than even in the neighbouring white matter. Biopsy proved that the tissue was neoplastic; both were fibrillary astrocytomas.

Material

Our series is a small one. We have used the probe in 37 cases out of a total of over 200 tumours operated on during the same period. But the method had already proved its value, and we used it only when we thought that the information it could give was unobtainable by any other means. "True-negative" responses have already been alluded to. "False-negative" recordings are obtained when the probe is not directed into or near the tumour. Small deeply situated tumours may be missed in this way, and it is plain that good location is required by other means before the probe is used. A small tumour situated at a depth of, say, 6 cm. may escape detection by the probe passing to either side of it. At that depth a small change of direction of the probe will result in a considerable change of position of its tip, and there is obviously a limit to the number of times the probe may be passed before the brain suffers damage. With some tumours, particularly astrocytomas, the radioactivity may not be high. We assumed that the lowest significant count rate was twice that produced by probing normal cortex, and that such a difference indicated pathological activity; the difference was usually very much greater—up to 50 times more. A "false-positive"

recording may be encountered when the cavity left after removal of a tumour is scanned. There may be no tumour remaining except at one point, yet the emissions from that piece may be picked up on the far wall of the cavity because the particles travel a considerable distance in air. The tip of the probe must be buried in brain before a positive reading is accepted as the true one.

It is not possible to make a pathological diagnosis from the activity of the tumour. Meningiomas, glioblastomas, and secondary carcinomas emit beta particles at comparable rates and the differences in a small series are not significant. Reduced activity is found in areas of gross central necrosis in malignant tumours. The less vascular and better-differentiated astrocytomas, however, appear not to take up the isotope with such facility. In this respect astrocytomas behave in the same way when di-iodofluorescein is presented to them in the blood stream. The figures for the tumours in our series are set out in the Table. Counts in normal

	No. of Cases	Range of Differential Counts	Average Differential Count
Meningiomas	7	10-40	22
Secondary carcinomas ..	5	6-50	18
Glioblastomas	8	6-50	17
Astrocytomas	11	1-12	6

brain vary within a narrow range from one person to another. The count of normal white matter must be taken in each case in order to compare it with the count obtained from tumour. The ratio between the two figures gives the "differential count."

Much discussion has taken place on the subject of which component in a tumour is responsible for the uptake of the isotope—the tumour cells or the newly formed capillaries. One thing is certain: increased activity is not due simply to increased blood supply, for then the highest recordings would be found in blood alone, and that is not so. It seems that activity increases with the metabolism of the tissue, and in this all cell elements share. Nor is this increased activity peculiar to brain tumours, for those in other parts of the body have the same property. A cerebral inflammatory lesion may occasionally show it: one case in our series is of particular interest. Exploration of a suspected frontal tumour with the probe indicated an area low in the frontal pole of very greatly increased radioactivity. A circumscribed reddish mass some 4 cm. in diameter was removed, and was proved histologically to be an old abscess. The inflammatory focus had not reached the final stage of scarring and gliosis, but was in effect a small pyogenic granuloma with an active thick wall.

The term "blood-brain barrier" can be misleading in so far as it suggests that there is some unique property of the capillary endothelium in the brain: it is the chemical nature of the brain tissue in which the capillary lies that determines what shall go through the vessel wall. Certainly the isotope is concentrated in abnormally large amounts in cerebral tumour and in inflammatory lesions, but this is a property not confined to such conditions in the brain alone. A rich endowment with blood vessels offers a quantitatively greater opportunity for the tumour cells to exchange phosphorus.

Studies with tracer elements have shown that substances injected into the blood stream are distributed and concentrated in some normal organs—for example, liver, spleen, thyroid, bone marrow—with astonishing rapidity to serve their high metabolic requirements. It is for this reason that P^{32} could not be used in doses sufficient to kill a tumour, since it will damage the liver and other vital organs with equal or greater facility. Brownell and Sweet (1952, personal communication) have recently tried to make a different use, in a therapeutic sense, of the ability of malignant gliomas to concentrate boron. By exposing the patient to an atomic pile which explodes the intracellular concentrate, disappearance of the tumour is a possibility.

Summary

A method of locating and demarcating brain tumours, using P^{32} and a Geiger-Müller probe counter, is described. It is a valuable additional aid to the surgeon at operation in selected cases, particularly in the taking of a small biopsy specimen through a burr-hole.

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DYNAMICS OF HEART FAILURE*

BY

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LECTURE II

Mitral Stenosis

The evolution of mitral stenosis shows a variety of reactions of considerable diversity and interest. The relation of the varied haemodynamic responses to different degrees of valvular obstruction and of associated mitral incompetence is not yet fully understood. A great many facts, however, have been collected, and these can be seen to fall into various patterns (Bayliss *et al.*, 1950a). In discussing pressures in the pulmonary artery in mitral stenosis it should be kept in mind that in normal subjects the lung vessels dilate to accommodate the increased blood flow of moderate exercise without any significant increase in pressure (Hickam and Cargill, 1948).

Some mitral stenoses are so mild as to cause little in the way of radiological signs, and many of these show an absence of any rise in pulmonary vascular pressures, at least at rest. More than half the patients, however, show elevation of pulmonary vascular pressures at rest and in a few pulmonary hypertension is extreme.

There is a well-recognized group of mitral stenotics with some associated mitral incompetence who have massive dilatation of the left auricle. There is little or no detectable enlargement of the pulmonary artery. Daley and Franks (1949) have shown that these patients may be astonishingly comfortable for many years and even for decades. On the radiological evidence of absent pulmonary artery enlargement they surmised that there was little pulmonary hypertension. This surmise

seems to be correct. In one example the pulmonary systolic pressure was 36 mm. Hg at rest, and the patient was capable of increasing her cardiac output from 3.8 to 6.2 litres a minute on effort. Although the pulmonary pressure rose *pari passu* (36 to 63 mm. Hg) with the cardiac output, it subsided very rapidly to nearly normal in a minute or two after the exercise was over. This contrasts with the reaction to effort in other mitral stenotics (cf. Fig. 8). The relative mildness of symptoms in this group is presumably related to the absence or transient nature of pulmonary vascular engorgement.

The auricle must hold the blood which flows into it while the ventricle is contracting. Opdyke *et al.* (1948) have shown that the left auricle is normally less distensible than the right. If the auricle is small the normal volume inflow will cause a considerable rise of pressure during the later part of ventricular systole, but if the chamber is greatly enlarged the pressure will not rise nearly so much (Dock, 1949). The same volume of blood can be accommodated in a large chamber with less linear stretching of its walls. It seems possible, therefore, that a very large auricle may permit the maintenance of a reasonable blood flow through the lungs at a lower pressure than would otherwise be required.

In another group of mitral stenotics the pulmonary artery is enlarged radiologically: the pressure in the pulmonary artery is moderately elevated at rest but rises to very high levels during exercise. It is an interesting point that the rise in pulmonary artery pressure which takes place during exercise in mitral stenosis in such patients is not associated with any significant increase in the cardiac output (Fig. 8). During exercise,

FIG. 8.—A woman aged 37 with mitral stenosis. Exercise increased the pulmonary arterial systolic pressure from 33 to 85 mm. Hg without significant cardiac output change.

therefore, resistance to blood flow through the lungs is considerably increased. The resistance might conceivably develop as a result of shorter diastolic time from the resulting tachycardia. Where diastole is short there is less time for the left auricle to empty into the left ventricle, and blood could collect in the left auricle until pressure was high enough to restore flow through the narrow valve in the limited diastolic time. The second alternative is that a vasoconstrictive reaction develops in the pulmonary arterioles. In favour of the latter hypothesis are the following facts:

(a) Acceleration of the heart by atropine in a few instances of mitral stenosis has not in our experience been accompanied by any significant rise in pulmonary arterial pressure (unpublished).

(b) Studies with the dye method on pulmonary blood volume show that this is not greater than normal during exercise (Ball *et al.*, 1952). If elevation of pulmonary vascular pressures had resulted from a rise of pressure in the left auricle an increased blood content of the lungs might be expected.

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