The Use of Positron-emitting Radioisotopes for the Localization of Brain Tumors[1]

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The preoperative detection and localization of intracranial neoplasms with radioactive isotopes from without the intact skull show promise of becoming an integral part of the neurosurgeon's armamentarium. In general, the technique is dependent upon the detection of relatively greater concentrations of isotope in neoplastic tissue as compared to that noted or found in normal structures. This, in turn, is dependent upon some biological property of the lesion which will favor concentration of the isotope or its carrier compound in the lesion, and upon the ability of a detection device to delimit differences in isotope concentrations in normal and in pathological areas. Up to the present, the isotope employed preoperatively has been the predominantly γ-emitting I^{131} contained in the dye diiodofluorescein (*1–6*).

To accurately locate a point source, or delimit an extended source, the system employed must be capable of sharply resolving the limits of the area of isotope concentration with reference to a suitable coordinate system. This requires that either the radioactivity or the detector be directional, and if the source is situated in a mass such as the human brain, scattering must be minimized.

Earlier workers have employed Geiger-Mueller counters as detectors, with suitable lead shielding to give directional collimation and protection from backscattered radiation. Such shielding effectively combines with the inherently low γ-ray detection efficiency of the Geiger-Mueller tube to lower counting rates materially.

The application of the recently developed scintillation counters should partially obviate the problem of low counting rates (*7–10*). These devices offer high detection efficiencies in a small volume. Crystal efficiencies of from 10% to a theoretical 100% may be obtained, depending on the total γ-ray cross section of the crystal, which, in turn, is a function of crystal thickness and the energy of the radiation being detected. At a given efficiency, counting rates are dependent upon the area of the effective counting surface of the crystal and the size of the pulse from the detector accepted for counting (the operating bias). With proper care, perfectly linear systems, in terms of pulse energy, can be constructed, thus enabling one to select for counting only those pulses of greater than a given energy. In principle, this should make possible the elimination of the more widely scattered radiation and effectively augment shielding.

[1] This work was done under contract AT(40-1)-289 between Duke University and the Atomic Energy Commission.

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In surveying the above facts, which obtain for single directional γ-ray detection systems, it seemed that an additional method of delimiting areas of concentrated radioactivity from without the intact skull might be possible. It is known that the 2 γ-quanta resulting from positron annihilation emerge simultaneously and oppositely directed, with a precision of 1/137 radian (*11*). From a consideration of this angular correlation, it appeared that if one were to count these 2 γ-rays in coincidence, the source of activity must then lie somewhere on a straight line joining the 2 counters. In the absence of scattering, no lead collimator should be required, since the directional characteristic of the system is inherent in the radiation itself and independent of the detector.

Accordingly, we have tested this hypothesis, and have performed the experiments to be described in order to compare the geometrical resolution so obtained with that using single directional γ-ray techniques.

We have constructed scintillation counters designed to operate singly or for coincidence counting of oppositely directed annihilation quanta. In the detector used in this work 1-in. crystals of thallium-activated sodium iodide yield light pulses which are amplified by RCA-5819 photomultiplier tubes. The pulses are then fed to the *X*- and *Y*-axis amplifiers of a commercial oscilloscope operated without a sweep. The amplifier gains are set equal by viewing their output on a synchroscope. Pulses arriving simultaneously appear on the oscilloscope screen as an oblique deflection. An L-shaped shield obliterates the vertical and horizontal pulses present, and, by adjusting the oblique pulse origin a minimum acceptable pulse size may be selected. The oblique screen deflection is used to trigger a 931-A photomultiplier, which, in turn, drives a standard scaling circuit without further amplification. All high voltage is furnished by the power supply of the scaler. Complete details of the apparatus and experiments will appear elsewhere.

The performance of this apparatus as a *single* directional γ-ray detector was tested. Point sources of radioactivity of strength suitable for convenient counting rates were prepared. Data were obtained in air and in a fixed brain contained in a bare skull. Results are shown in Fig. 1.

Curve *A* (Fig. 1) represents results obtained with a Zn^{65} ($E_\gamma = 1.12$ mev) source suspended in air 9 in. away from the center of the crystal, and with only the lead collimator number *I* of *C* (Fig. 1) in place. This collimator is a tapered cone of 3-in. maximum diameter, with a 1-in. square opening aligned with the 1-in. square crystal. The shape of the counting rate curve to be expected from this arrangement in the absence of scattering is depicted in *C* (Fig. 1). In position 1 the source "sees" all of the crystal, in position 2 it "sees" a portion, and in position 3 it "sees" none of the crystal. The width of the curve can never be less than the width of the collimating slit, a situation analogous to the umbral and penumbral shadows cast by a sheet with a square hole. The minimum pulse

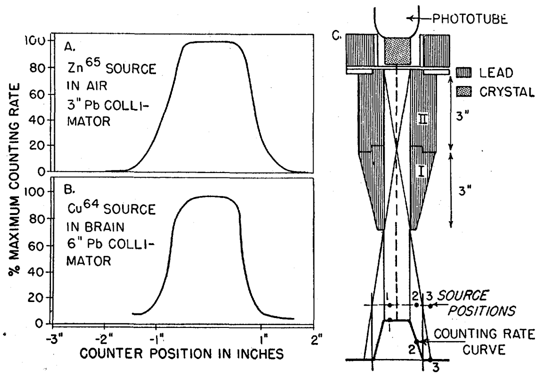

FIG. 1.

size accepted for counting was ¼ the size of the maximal pulse sizes present. Curve *A* (Fig. 1) may be seen to closely resemble the theoretical curve of *C* (Fig. 1).

Curve *B* (Fig. 1) reflects data obtained with a Cu^{64} source buried 1½ in. deep and ½ in. from the midline in the left occipital cortex of a fixed brain contained in its skull. Lead collimators I and II (of *C*, Fig. 1) were used. The center of the crystal was 7 in. away from the skull and approximately 9½ in. from the source. The decay scheme of Cu^{64} is said to be 54% K capture, 31% β-emission (0.571 mev), 15% positron emission (0.657 mev). A 1.35-mev γ-ray is mixed with the K capture radiation to the extent of 1.5% (*12*). Since the path of the positron is of the order of millimeters, in the matter used here, a strong point source of extranuclear γ-radiation resulted from the annihilation quanta. For this experiment the minimum acceptable pulse size was set at ¼ the size of the maximum annihilation pulses. With the exception of a persistent counting rate above room background at the ends of the curve, it may be seen that the shape of Curve *B* (Fig. 1) closely resembles Curve *A* (Fig. 1). This persistent elevation is thought due to scattering in the head. Counting rates obtained under the above conditions were increased by a factor of better than 47 over those obtainable with a shielded Geiger tube under the same conditions. Here again the width of the counting rate curve is commensurate with the effective crystal counting area. To decrease this width necessitates a sacrifice in counting rates.

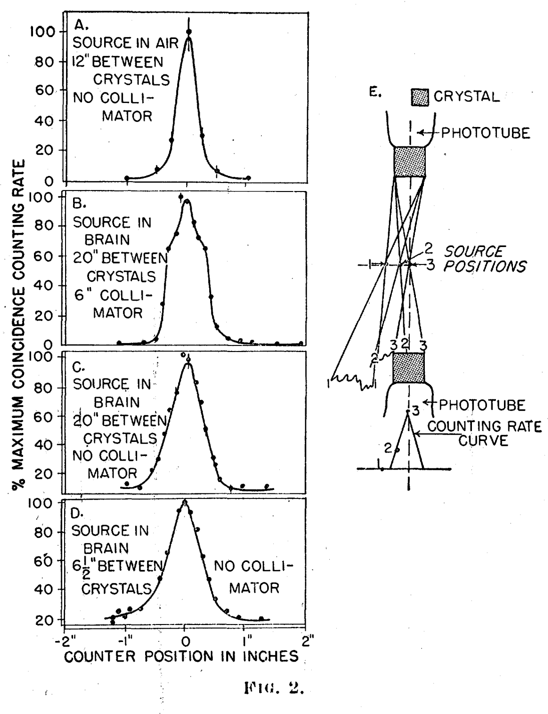

FIG. 2.

Data obtained by coincidence scintillation counting of annihilation pairs are shown in Fig. 2. Point sources of Cu^{64} were suspended in air or placed in fixed brain between directly opposing counters. Only those pulses greater than ¼ the maximum annihilation quanta pulse size were accepted for counting. Source strengths were suitable to give convenient counting rates.

Curve *A* (Fig. 2) was obtained with the Cu^{64} source suspended in air and encased in such a way that the positron ranges were short enough to enable consideration of the whole as a point annihilation quanta source. No collimator was used. It is obvious that the width of this curve is much smaller than the width of either of the curves of Fig. 1. Inspection of *E* (Fig. 2) reveals the reason. Consider those γ-rays which happen to strike the upper crystal in this diagram. With the source in position 1, the corresponding simultaneous and oppositely directed rays are confined to 1–1 and cannot strike the lower crystal. Thus, in the absence of scattering, no coincident counts will be recorded. With the source in position 2, some of the corresponding rays strike the lower crystals. With the source in position 3, all the corresponding rays strike and the coincidence counting rate is maximum. With a rectangularly shaped crystal, the counting rate should rise linearly in the region of which position 2 is typical, yielding a triangularly shaped curve. Curve *A* is a reasonable approximation of this expected shape.

The directional property of the radiation itself allows an approach to the problem of radiation widely scattered in the head. If 2 parallel lead collimators are employed, those scattered rays which deviate from parallelism will be unable to traverse the collimators and strike the crystals.

Using 6-in. lead collimators and the same Cu^{64} source located in fixed brain as described above, the counting rate data presented in *B* (Fig. 2) were obtained. Beyond the limits of the slit the rate rapidly approaches zero. The widening extending some 2/3 of the way up the curve is probably due to small-angle scattering from the collimator. Thus, it would appear that scattering can be practically eliminated.

With the collimators removed, Curve *C* (Fig. 2) was obtained. It may be seen that the effect of scattering is to slightly widen the curve and to give persistent background counts at both ends of the curve.

Curve *D* (Fig. 2) was obtained without collimators

TABLE 1

Method	Shield used	Relative peak counting rate
Geiger tube 9½″ from source	Shield and 6″ collimator with 1″ slit	1
Coincident scintillation counters, 6½″ crystal-to-crystal distance	None	23
Single directional scintillation counter 9½″ from source	6″ collimator with 1″ slit	47

and with the counters adjacent to the skull. It will be noted that the scattered counting rate increases more rapidly than the maximum coincidence counting rate. Spurious coincidences due to scattering are dependent upon the inverse square law, and the probability of their occurrence is greatest near the skull.

Maximum counting rates in the various experimental arrangements are in the approximate ratios shown in Table 1. With coincident scintillation counters and a 20-in. crystal-to-crystal distance, the rates were correspondingly lower than the 6½-in. crystal-to-crystal distance. Throughout this work, room background coincident counts were negligible, amounting to 0.11 cpm over a 72-hr period.

In coincidence work the counting rate is proportional to the square of the detection efficiency of the detectors used. The high detection efficiency offered by scintillation counters makes the counting rate loss in such work less serious than with Geiger tubes, where perhaps a hundredfold loss may be expected. Furthermore, with proper attention to the detection efficiency, and by operating close to the head, it is theoretically probable that a coincidence system could be made to yield counting rates comparable to those of the single directional γ-detection system.

Thus, it appears possible to more accurately delimit point sources and, hence, extended sources with the technique of coincidence counting of annihilation pairs. The width of the counting rate curve is again the width of the counter, but the sharp peaks are independent of counter size. Since scattering does not appear serious, and can be almost entirely eliminated, only the purely geometric factors of application of the counting rate curves to a suitable coordinate system would seem necessary to localize a radioactive source within the skull.

The Cu^{64} used in the work described is a readily available positron emitter.[3] To concentrate this isotope in a brain lesion the following facts were considered. Friedemann (*13*) has summarized the work leading to the principle that the blood vessels of the central nervous system are normally impermeable to anionic or negatively charged dyes or particles. If the tissue structure is altered, penetration of such agents into the altered areas may occur. In addition, Figge has reported the apparent affinity of certain carcinomata for the porphyrins (*14*). There is also some possibility of a specific affinity of brain lesions for organic dyes.

As a starting point in the localization of positron-emitting isotopes in brain lesions, preliminary studies, to be reported in detail elsewhere, have been performed with the anionic dye tetrasulfonated copper phthalocyanine (tetra-benzo-tetra-aza porphin).[4]

A simple method for the synthesis of Cu^{64} phthalocyanine has been developed. The preparation of sterile solutions of desired concentration can be accomplished in 2–3 hr, starting with metallic copper.

Doses up to 100 mg/kg have been given to a large number of rabbits, mice, guinea pigs, cats, and dogs, with apparent impunity.

The distribution and excretion of the injected dye have been followed in adult rabbits. Although the biological half-life exceeds the 12.8-hr physical half-life of the Cu^{64}, after 2 days only 6% of the injected radioactivity remains to injure tissue. The major route of excretion is via the biliary system.

Copper phthalocyanine will penetrate only those areas of the brain in which the tissue structure has been altered. Brain injury was experimentally produced in rabbits, mice, and cats by the intracarotid injection of radioopaque contrast media, needle punctures, and thermal coagulation (*14, 15*). Administration of the dye produced focal uptake in the damaged areas. Experimental tumors growing subcutaneously and intracranially in mice have been found to take up the dye in amounts considerably greater than the surrounding normal tissues.

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[3] Obtainable from Oak Ridge National Laboratories, Oak Ridge, Tenn.

[4] Suggested by Lester H. Corrsin, Molecular Spectroscopy Section, Department of Physics, Duke University.