NEW METHODS

RADIOGRAPH — UNIVERSAL NON-LINEAR INTEGRATOR FOR IN VIVO INVESTIGATIONS BY MEANS OF RADIOACTIVE ISOTOPES

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(Received September 13, 1955)

The trend of modern experimental medicine is away from "single-moment" investigations (often only in refined experimentation) towards prolonged "in vivo" observations, carried out with minimum disturbance of the natural course of live processes.

The utilization of methods involving radioactive indicators, i.e., labeled atoms, is of utmost importance in investigations of this type.

However, most of the investigations carried out by means of radioactive indicators are not "in vivo" in the strict sense of the word. As a rule, in physiological and biochemical investigations the animal into which the labeled preparation is introduced is killed and then the radioactivity of various tissues and chemical fractions is determined. In studying the dynamics of the "behavior" of the labeled preparation in the organism, experiments are carried out on a large number of animals, which are killed at different periods of time after the preparation was introduced.

It is quite natural that the diagnostic application of isotopic indicators is limited, in these cases, to the measurement of the radioactivity of secretions, excreta and of various blood-sample fractions.

The utilization of γ-emitting isotopes offers substantially different perspectives. It seems, at first glance, that this penetrating radiation would readily permit long-range observation of the transfer and concentration of substances in various organs and tissues without taking of blood samples, biopsies etc. However, such long-range investigations are associated with difficulties — "kinks" — such as the gross γ-radiation of the entire organism into which the indicator was introduced. Therefore, almost the sole field of application of radioactive isotopes in which the method in in vivo investigation is widely used is the investigation of the functions of the thyroid gland by means of radioactive iodine. The selectivity of the thyroid gland in absorbing iodine, coupled with its superficial anatomical location, permits ready "in vivo" observation of the accumulation of radioactive iodine in it. During such investigations the thyroid gland captures iodine so rapidly from the blood that the intensity of the gross γ-radiation of the entire body is many times less than that of the radiation emanating from the thyroid gland.

It is precisely this characteristic of the thyroid gland that permits the most common standard radiation counter (type B-2,etc.) to be used for "in vivo" measurements.

However, when the investigator attempts to use radioactive isotopes for other types of investigations, he inevitably encounters a host of difficulties which seem insurmountable when the common type of radiation counter is employed.

Even when faced with such a seemingly simple problem as the determination of the rate of flow of blood by means of radioactive indicators, these difficulties are very marked. In principle, the tracer method is ideally suited for the determination of the rate at which the blood moves. It seems necessary only to introduce the radioactive substance in the blood and to observe through its radiation, determined by means of a counter that is placed at some definite region of the body, how this substance moves in the organism as it is carried by the blood stream.

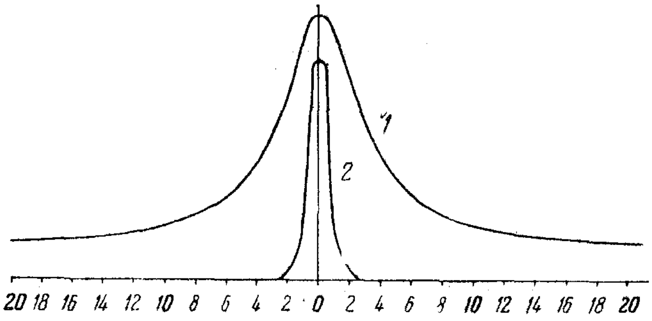

Fig. 1. Readings of the usual radiation counting apparatus (1) and of the radiograph (2) after moving a point source of γ-radiation relative to the counter;

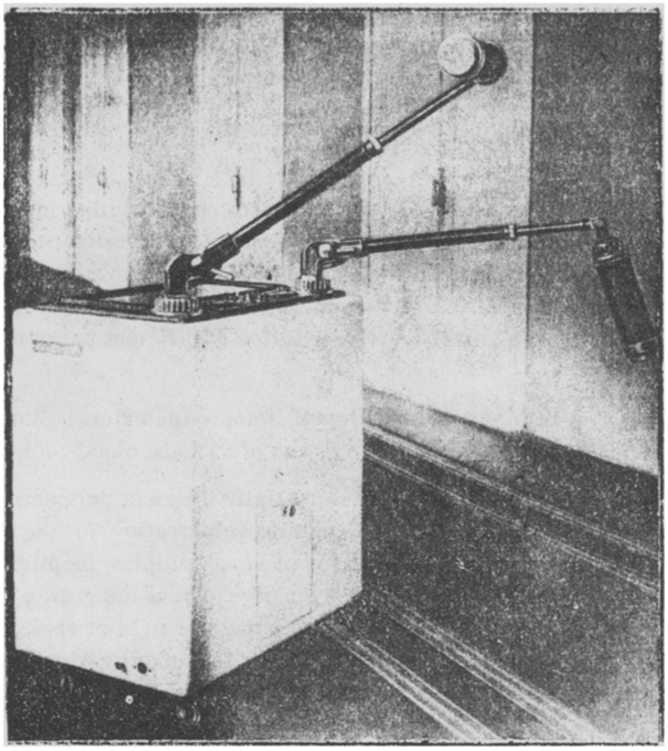

Fig. 2. External appearance of the first model of the two-channel radiograph.

Wide use of such a method of determining the rate of blood flow would eliminate a number of defects in the usual clinical methods [2, 5].

However, utilization of the common radiation counting apparatus does not achieve the desired results. In order to determine the rate of blood flow, it is necessary, as we know, to fix the moment at which the labeled portion of blood passes through that region of the body to which the counter is applied. This moment corresponds to the maximum rate of count (maximum number of pulses per second). However, when the usual apparatus is used, the increase in the number of pulses registered due to radiation, still "from afar" so to speak takes place so slowly and the maximum obtained is so "diffuse" that it is impossible to determine the moment the indicator passes under the counter accurately.

One of us, previously , attempted to overcome these difficulties by designing an instrument that registers the so-called "chance coincidences" in two counters [3, 4]. Later, the same principle of change coincidences, however now in one counter, was utilized in the construction of an instrument, "radiometer", which our industry mass-produced.

The designing of instruments that register chance coincidences may be considered the start of the development of the so-called "non-linear" radiation counting apparatus. While the readings of the usual radiation counting apparatus must be strictly proportional to the intensity of the measured γ-radiation, the so-called "non-linear" instruments give modified non-proportional readings. This means that γ-radiation of weak (for the given working range of the apparatus) intensity causes the non-linear apparatus to give a greatly reduced reading and radiation of relatively high intensity causes the apparatus to give large magnified readings.

This principle of non-linear registering of γ-radiation permits the detection, with considerable contrast, of even minute and brief variations in radiation intensity which are virtually undetectable by the usual methods.

It should be noted that the development of the method of chance coincidences [3, 4] was preceded by the attempt to apply the scheme of genuine coincidences, widely employed in nuclear physics, to in vivo observations.

However, in determining the γ-emission, the relative number of genuine coincidences in the two counters is suprisingly low, even if the beam of γ-ray passes through both counters. Therefore, the suggestion of A. Babenko and E. Karputkin [1], who described an electronic circuit designed to integrate coincident pulses in two counters during biological investigations,can hardly be considered of value.

Moreover, continuous recording of the process in the form of integral-current registration has, undoubtedly, a great advantage over automatic registration of each chance coincidence in the form of a discrete point on a paper ribbon, as was done in the "radiometer" [3, 4].

In searching for a solution to the given problem it was necessary to discard the idea of coincidence as the non-linear element.

In the new non-linear integrating apparatus, which was named "radiograph", we used a different principle which permits non-linear summation of all the pulses of the counter. The non-linearity is obtained by means of a specially developed electronic circuit in which the amplitude of the pulses coming from the counter is transformed in such a manner that the impulses that follow each other at infrequent intervals have a small amplitude,while the impulses that come with great frequency have an amplitude that is increased proportionally to the frequency of the succession of the impulses. Then the charges of the impulses are collected in an accumulator. Since all the pulses are of the same duration, the total charge per unit time, i.e. the charge current, is proportional to the product of the mean amplitude times the mean frequency of the pulses. However, since the amplitude itself is proportional to the frequency of the pulses, a current is obtained which is proportional to the square of the frequency of the impulses from the counter. In other words, the output current of the apparatus is proportional to the square of the intensity of γ-emission that penetrates the counter. This means that when the radiation intensity changes by a factor of 3, the current changes by a factor of 9; a 4-fold increase of intensity increases the current 16-fold,etc. This relationship has the general form

$$R = kI^2 \qquad (1)$$

where R is the reading of the "radiograph", I is the intensity of γ-emission and $\underline{k}$ is the coefficient of proportionality (constant magnitude).

If a point source of γ-radiation is moved relative to the counter, the readings of the usual type of apparatus are inversely proportional to the square of the distance between the source and counter. Under the same conditions, the readings of the radiograph are inversely proportional to the fourth power of the distance. Thus, the increase and decrease of the "radiograph" readings as the source moves towards or away from the counter are considerably sharper than in the case of the usual apparatus (Figure 1).

The first model of the "radiograph" — UNIR-1 (universal non-linear integrating radiograph) consists of two independently operating instruments, which together with feed block and ink-writing apparatus are mounted in the general casing (Figure 2). Two massive arms,the upper portions of which possess 6 degrees of freedom, are mounted on the upper part of the casing. A luminescent counter, consisting of a photomultiplier and a luminescent crystal, is attached to the end of each arm. The crystal of each counter is encircled by a cylindrical lead shield to reduce the sensitivity of the counter to γ-radiation directed at a large angle to the axis of the photomultiplier crystal.

We also tried elongated crystals. When the height of the crystalline cylinder is three times the diameter of the crystal (which is approximately equal to the diameter of the photocathode) the luminescent counter selectively registers γ-radiation that falls toward the axis of the crystal. This selectivity is even further increased due to the lead shield.

The consequent non-linear electronic integration of the impulses makes the apparatus as a whole register the γ-radiation that emanates virtually exclusively from the region located directly under the counter.

If the counter contacts the body surface, the apparatus registers the γ-emission of only that radioisotope which is in the region located directly under the crystal; γ-radiation emanating from more distant regions of the body is virtually not registered by the apparatus.

The possibility of regulating the degree of non-linearity for various experimental conditions has been provided for: the ratio of the "radiograph" readings to the frequency of the pulses may be of a still greater order than the quadratic ratio expressed by equation (1).

Another characteristic of the "radiograph" is the possibility of "background" compensation. When it is necessary to carry out a repeated determination, for example, of the rate of blood flow or the rate of gastric absorption or another investigation associated with repeated introduction of a radioisotope into the organism, and also when working in a place with high background radiation, the apparatus may be adjusted so that the "radiograph" will register the increase of γ-radiation above the "background" created by previous introduction of the isotope or due to external causes.

The "radiograph" may be used in "in vivo" investigations and for any observations on the fate of a γ-emitting isotope introduced into the live organism for the purpose of studying hemodynamics, permeability, the process of adsorption, secretion and excretion of substances and their preferential accumulation in neoplastic tissue or in an organ, etc.

The apparatus may be used both in clinics and for various experimental investigations on animals.

The presence in the "radiograph" of two independent instruments with two counters permits simultaneous registration of γ-radiation from two arbitrarily selected points of the body.

This is especially important in determining the rate of blood flow since it permits measurement of not only the time required for a complete circuit of the blood but also of the rate of blood flow in any region, for example, in the extremities and separately in a small region of blood circulation.

The presence in the "radiograph" of two independent instruments is of considerable importance also in the diagnosis of malignant neoplasms. One luminescent counter is placed over the area in which the suspected tumor is located and the second is placed over known healthy tissue. If a radioactive substance is introduced, which accumulates, even with a slight degree of selectivity, in tumor tissue, than it is possible to gauge the localization of the malignant tumor by the difference between the two simultaneously registered radioisotope accumulation curves. By means of repeated measurements (without repeated introduction of isotope) it is also possible to establish the dimensions and location of the tumor more accurately.

When there is a pathologic process present in one of the kidneys, the excretion of labeled substance by the healty and affected kidneys can be compared; in order to do this, the first luminescent counter must be placed over the affected kidney and the second, over the unaffected one.

The "radiograph" can be of great assistance in studying the rate of absorption of labeled salt solutions in the stomach. The absorption curve is automatically registered as the radioactivity disappears from the stomach (first counter) and appears in the blood (second counter). This same method, without fluoroscopy and without the introduction of a contrast medium, cannot only permit evaluation but also recording of the dynamic curve of the passage of the stomach contents into the duodenum with the aid of the suitable labeled substances.

The distinguishing characteristic of the apparatus, which secures sharp localization of the measured radiation, makes possible the comparative study of the rate of lactation on separate lobes of the mamary gland which is of great importance not only for the experimental physiologist but for the veterinary as well.

In this article, devoted only to the principle of the method of non-linear and continuous registration of radiation possible with the apparatus "radiograph", it is impossible to encompass all applications of this apparatus; special communications will be devoted to this subject.

We may hope that the utilization of the "radiograph" will broaden the area of application of radioactive indicators for "in vivo" investigations carried out without disturbing the natural course of the physiological

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