

THE PRODUCTION OF PERSISTENT ALOPECIA IN RAB-
BITS BY ROENTGEN RADIATION; A STUDY OF THE
MINIMUM DOSE REQUIRED AND THE CON-
SISTENCY OF THE REACTION.

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Biological reactions to Roentgen rays exhibit, in general, fairly wide variations even under conditions which are assumed to remain constant. It is not easy in most cases to decide how much of the inconsistency is the result of inexact diagnosis, how much is caused by errors in dosage, and how much is referable to normal biological variation. Many commercial Roentgen ray plants function more or less erratically; and the complexities of Roentgen radiation, and of its behavior, render difficult, and in some cases impossible perhaps, the exact prediction or the measurement of dosage.

Skin reactions offer obvious advantages for experimental study of Roentgen ray effects since they may be followed in the living animal over long periods, and in particular, the alopecia reaction commends itself because it is so readily recognized. The authors are making a series of experiments on small animals in order to determine, if possible, the degree of normal biological variation to be expected in this particular reaction, under minimum radiation, after uncertainties of dosage have been eliminated in so far as is possible. This paper presents in some detail the study of a single series of fourteen rabbits treated on the abdomen with soft rays—the only series which has been under observation for a length of time sufficient to justify a statement of the results. The animals were carefully selected for reasonable uniformity of weight, absence of pigmentation on the abdomen, general health, and particularly for freedom from nose disease.

The Source of Radiation.

A standard broad-focus Coolidge tube is operated on 60 cycle current, the inverse part of which is suppressed by two kenetrons—one at either terminal of the transformer secondary. The current is kept constant by a modified Victor-Kearsley stabilizer. When the machine is in use, both the stabilizer control and the fine adjustment of the field current of the primary current generator are constantly under control of the operator. The milliammeter is connected between the halves of the transformer secondary, at which point the circuit is grounded.

The tube occupies the upper compartment of a large lead-lined cabinet, the lower compartment of which is fitted with an adjustable shelf, for supporting the board on which the animal is placed. The lead-covered partition, between the compartments, has an aperture under the tube, and is fitted with a filter slide and a lead shutter. A narrow vertical slot in the back of the cabinet permits the ionization chamber to be inserted at any desired height. All parts of the cabinet are ventilated by means of an external fan, which forces air through lead-protected channels.

The constancy of operation of this plant was checked by means of ionization measurements, made with a standard guard-plate chamber, during a period of more than a year before animal experiments were started. No variation in efficiency amounting to more than 2 per cent was found. During this time, the outfit was operated only for the purpose of testing. It is to be expected, of course, that, with prolonged use, the tube and the kenetrons will undergo slight changes. The tube becomes coated with tungsten vapor, which absorbs the soft rays to some extent. The tests proved only that the plant does not behave erratically. Measurements of the efficiency of the tube as a function of direction disclosed no lack of uniformity over the small angular field used in the present experiments.

In the experiments described in this paper, the tube was operated at 30 kilovolts (peak) and 22 milliamperes, at a target distance of about 27 cm. Much care was exercised to keep the target distance constant throughout the experiments. The care with which the animals were adjusted to proper position, as well as the slight eccentricity of those

parts of the radiation field which are of importance in the final result, makes it reasonable to suppose that the actual distance did not differ in any case from the mean value by more than about 1 per cent. The radiation was very nearly normal to the skin in all cases. The rays were filtered at a target distance of about 20 cm. through thin bristol board covered on one side with aluminium leaf for electrostatic protection.

Preparation and Exposure of the Animals.

The treatments were given through apertures in a shield of lead-filled sheet rubber. This shield, 40 cm. square, is 1.5 mm. thick except in the middle, where a rectangular portion 15 by 18 cm. is built up to a thickness of 3 mm. In this thick part are seven apertures—two parallel rows of three circular holes, each 1 cm. in diameter, and one elongated aperture at one end of the double row, for purposes of identification. All of the apertures lie within a rectangle 3 by 6 cm. The shield is prepared for use by coating the middle part on the under side with adhesive mixture, taken from surgeon's tape by applying the adhesive surface of the tape to the shield, dampening with xylol, and stripping off the fabric.

The animal, with abdomen shaved and washed, is placed on a board, and sandbags are arranged on either side to restrict its movements. The shield is then put in place, and the adhesive surface pressed into good contact with the skin. A frame of wires supports the free parts of the shield. With this arrangement, only a small part of the weight of the shield rests on the animal, and the apertures are maintained in a fixed relation to the skin during treatment. When the shield has been put in place, a lead-covered board, with aperture 12 by 15 cm., is placed over all, and supported at a fixed height above the first board on four pillars. The animal is adjusted vertically, until the surface of the abdomen is exactly flush with the lower surface of this board, in order to define the target distance.

Before treatment, each of the apertures of the shield save one, the large one, is covered with a little piece of leaded rubber. The lengths of exposure of the various areas are controlled by removing these patches, in a definite order, at proper intervals. After the treatment, the adhesive is removed from the skin with ether and alcohol.

Ionization Measurements.

Ionization measurements were made at intervals with apparatus previously described.¹ The small chamber (about 5 mm. in diameter), half imbedded in the surface of a wax phantom, which is used in place of the animals, is carefully adjusted to the skin-target distance. Two pieces of sheet lead laid on the wax, one on either side of the chamber, with their straight edges parallel to the chamber and equidistant from it, serve to define the width of the exposed portion of wax. In measurements made to follow up possible gradual changes in tube efficiency, an opening of 1.25 cm. was used.

In order to evaluate animal dosage in terms of ionization, it is necessary to estimate the variation of dose with aperture size caused by scattering. For this purpose, measurements were made with various widths of aperture between the lead plates. When the aperture was increased from 1.25 cm. to 3.75 cm., the ionization rate increased by 3 per cent. It appears, therefore, that measurements made with the smaller aperture should be decreased by about 1.5 per cent to correspond with the small apertures used with the animals. The proximity of the various rayed areas of the animal should introduce a slight scattering error. A consideration of all of the factors involved indicates, however, that it is negligible in the cases which have a bearing on the results of these experiments.

RESULTS.

Chart 1 contains the records of all of the animals treated, with the exception of one, No. 37, which developed multiple abscesses in the treated area after the 3rd week. There is no reason to suppose that these abscesses were caused by radiation, since they occur frequently in rabbits otherwise normal.

The black circles represent alopecia persisting at least 10 weeks after treatment. The white circles represent a definite regrowth of hair after an interval indicated, in weeks, by the numbers within.

Rabbits 1 to 8 (Group A) were rayed consecutively; that is, without allowing the plant to be used for other purposes. Likewise, the

¹ Clark, H., *Am. J. Roentgenol. and Radium Therap.*, 1924, xi, 445.

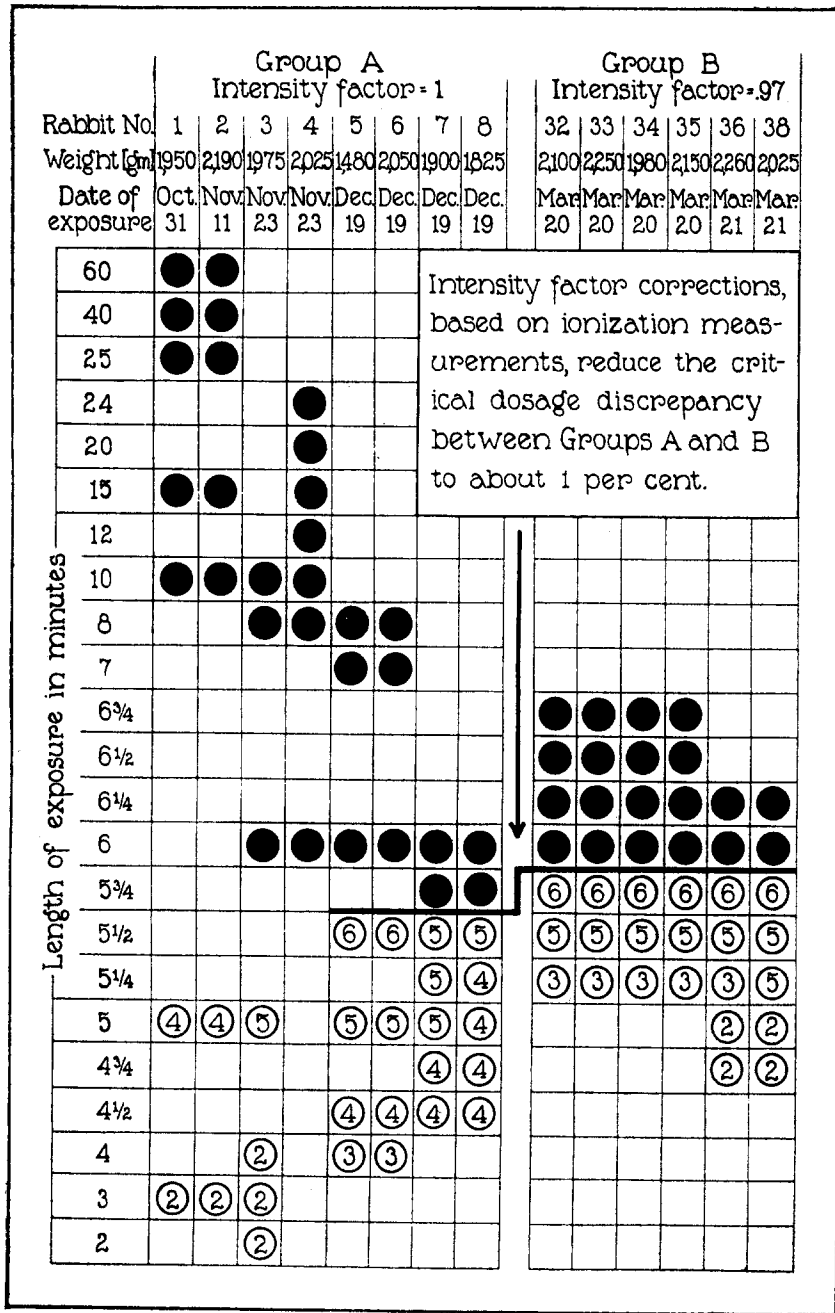


CHART 1.

animals of Group B were rayed consecutively. In the interval between the treatments of the two groups, the machine was almost constantly in use, and the ionization measurements indicated a consequent decrease of 3 per cent in the soft ray efficiency. The necessary correction is embodied in the intensity factors shown at the top of the chart.

When these factors are taken into account, the discrepancy in critical dosage between the groups, amounting to about 4 per cent on the exposure scale, is reduced to about 1 per cent. The experiments disclose, therefore, no evidence of any biological variation whatsoever. The weighted mean value of exposures, corresponding to all circles contiguous to the critical dose line on the chart, corresponds, for unit intensity factor, to an exposure of 340 seconds. The spacing of the exposures is such that this mean value may differ from the true critical exposure by about 2 per cent, which is just within the limits of accuracy assumed for the dosage.

This mean value corresponds, according to the ionization measurements, to the production of about 2.04×10^{15} ions (of either sign) per gm. of tissue. The correspondence entails, however, an additional chamber calibration error of perhaps 2 per cent, and it rests on the assumption that the method of phantom measurement is valid—an assumption not entirely free from objection.

In experiments of this kind, it is difficult to exclude unconscious personal bias in making diagnoses. In view of this fact, the work has been divided sharply into two parts. All treatments and ionization measurements were made by one of us (Clark) while all diagnoses were made by the other (Sturm, kindly assisted by Dr. James B. Murphy) without knowledge of the measurements.

This paper is presented as a record of the experiment without any conclusions as to the general validity of the results. Whether, in other circumstances, the reaction would have been less consistent, and whether, in the present ones, a larger number of animals would exhibit greater variations, are questions on which no opinion is ventured.

SUMMARY.

Seven areas on the abdomen of each of fourteen rabbits were exposed to soft Roentgen radiation of constant quality in doses

varying, in the region of the value critical for the production of persistent alopecia, by regular steps of about 4 per cent. Without exception the critical dose was found to lie between two such values, the upper limit being represented by exposures on eight of the animals and the lower on ten of them. With certain reservations, the critical dose corresponds to the production of 2.04×10^{15} ions of either sign per gm. of tissue.