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The Differential Action of X-Rays on Tissue, Growth and Vitality.—Part IV.—*The Biological Reaction to X-Radiation in Relation to Time.**

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Preliminary Experiments.

In the investigation of a selective action of homogeneous X-radiation on the allantoic membrane of the chick (Moppett, 1929), a constant time of exposure was adopted since one cannot assume that the "time factor" is expressed by a linear function. It was observed at an early stage that a considerable fluctuation in current supply did not materially alter the biological reaction if the normal time of exposure were given. An experimental investigation was carried out using a wave-length of 0·5 Å. which produces a hypertrophic reaction with an exposure of $\frac{1}{2}$ hour and an atrophic reaction in $1\frac{1}{4}$ hours, when other conditions are similar. The reaction shows up abruptly when the above values are exceeded, suggesting the breakdown of a process of repair and the phenomenon is aptly described by the term threshold dose.

Typical experiments are given in the following table (I) and the results are represented by the letter A for atrophy, H for hypertrophy, and HA for an intermediate stage. Experiment 147 may be taken as a standard in which a certain quantity of energy is given over a period of 1 hour, the reaction being HA. In experiment 135, approximately the same dose was given over a period of 2 hours and the reaction was increased to A+. The reliability factor 5/5 indicates that five consistent pairs of experiments showed an increased reaction in association with a longer time of exposure. Experiment 142 illustrates the fact that an increased reaction is obtained even if the exposure is given intermittently over a long period of time.

The above variation is opposite in sign to what may be termed a repair factor which is illustrated by experiments 306 and 308. A reaction to homo-

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geneous radiation may be prevented by an adequate dose of non-effective mixed radiation given immediately before the effective radiation (Moppett, 1930.) If an interval of 48 hours is made between the two applications a normal reaction results, indicating that the protecting action of the mixed radiation has been annulled.

Table I.

Number of experiment.	Wave-length.	Slit width.	Time of exposure.	Milli-amps.	Incidence on specimen.	Remarks.	Result.	Reliability.
	Å.	mm.	hours		°			
147	0·5	1	1	4	60	—	HA	5/5
135	0·5	1	2	2	60	—	A+	
142	0·5	1	2	4	60	Interrupted 10 min. on, 10 min. off	A+	—
306	0·5	1	2	4	60	Prior dose 10 min. direct rays	No reaction	7/8
308	0·5	1	2	4	60	Prior dose 15 min. direct rays 48 hrs. before homogeneous rays	A+	2/2

Confirmatory Experiments.

In order to confirm the above indications, a series of experiments was made with a constant potential apparatus by Gaiffe Gallot on the assumption that the output of any frequency should be roughly proportional to the milliammeter reading. A wave-length of 0·27 Å. and a potential of 65 KV. were used throughout and the results are expressed graphically in fig. 1 where the open circles represent no reaction and the shaded circles a hypertrophic reaction. The product of milliamperage and time is plotted in a vertical direction and time along the baseline and the results for $\frac{1}{2}$ hour exposure shown by double circles represent an accurate determination of the threshold dose in connection with another investigation (Part II). The milliamperage could not be reduced sufficiently to obtain no reaction when the exposure exceeded 1 hour, so a filter of aluminium 12 mm. thick was used to give a $\frac{1}{4}$-value intensity and the product of time and milliamperage was divided by 4 in plotting these results.

The threshold dose is represented on the graph by a line which passes between the open and shaded circles and in this region one obtains an equal number of reactions and blanks owing to variations covered by the term idiosyncrasy. It may be assumed that a greater dose will give a reaction and

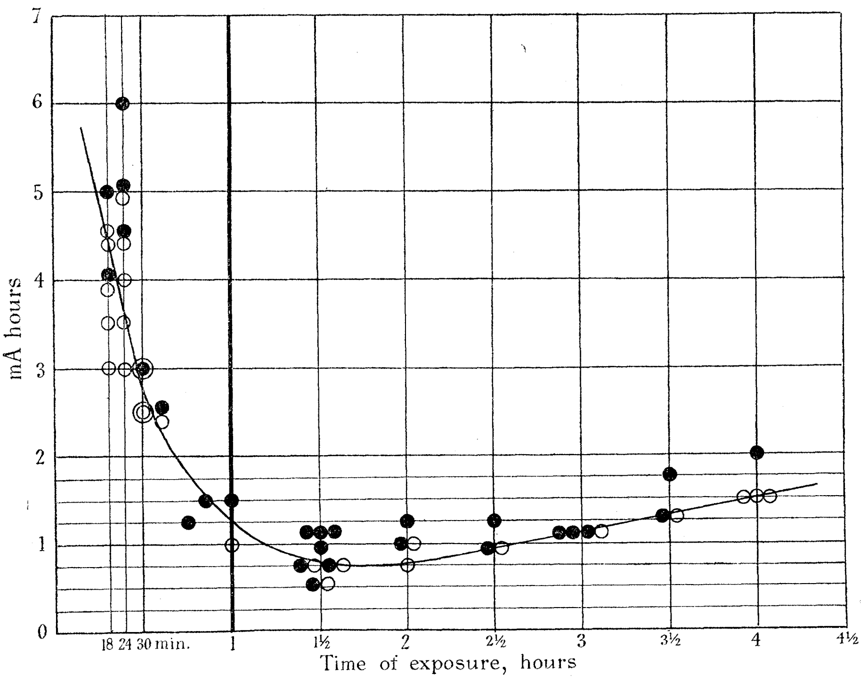

Fig. 1.

a smaller dose no reaction, for example on the right-hand portion of the smooth curve.

Investigations of the Action of Mixed Radiation on Mouse Skin.

The investigation was extended to the skin of the mouse by the use of unfiltered mixed radiation, which was regarded as unbalanced radiation (Part II.) The hair was removed with sodium sulphide and the result was observed in 7 days and plotted in a similar manner in fig. 2, where the closed circles represent an erythema which is apparent as a region of slight desquamation in borderline cases. The skin was immobilised by four stitches beneath a lead shield with an aperture 0·4 cm. square, a value which was chosen so that the threshold dose, which varies with the area irradiated, should suit the characteristics of the apparatus (Moppett, 1930*a*).

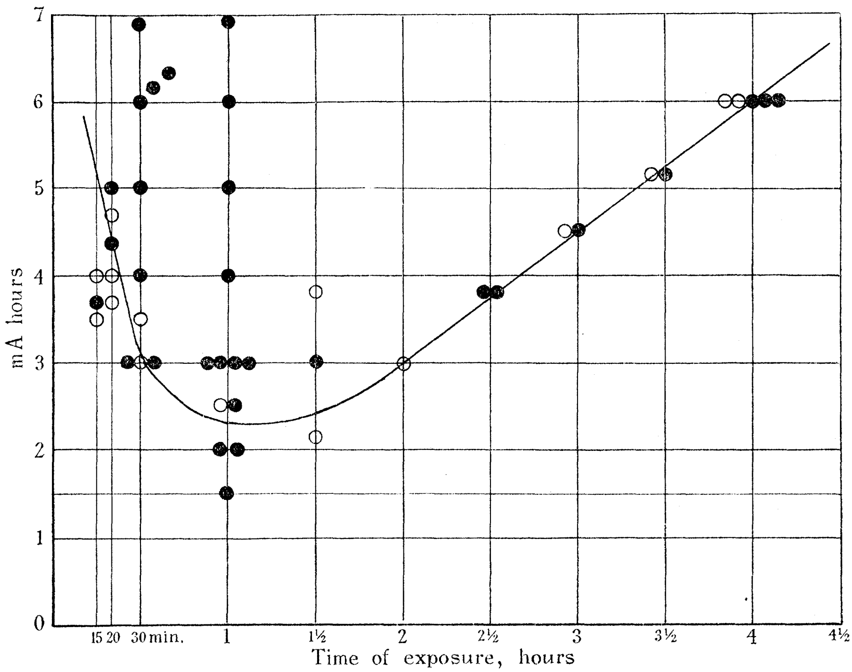

FIG. 2.

Discussion.

The "time" curve presents a minimum value at about 1 to $1\frac{1}{2}$ hours both when the allantoic membrane is exposed to homogeneous radiation and the skin of the mouse to mixed radiation. This confirms the experiments in Table I, but there a minimum is indicated at 2 hours or more, which may be a characteristic of the wave-length used. The two upward branches represent a "positive factor" when t is small and a "repair factor" when t is large. The explanation may be considered in terms of the mechanism of development of the reaction which was divided into a physical stage, a chemical stage, involving the ionised atoms and a final biological stage.

The positive factor may represent a physical phenomenon implying that when the rate of absorption of energy is small, the ordinary laws of probability do not hold and the atom can only absorb quanta when it is in a certain state which recurs cyclically. The form of the curves (fig. 4, Part II) suggest that the threshold dose approaches infinity as "t" approaches zero. The above phenomenon may be related to the biological stage implying a cyclical receptive state in the living cell, but this appears less likely. The repair factor is also capable of an explanation as a physical or biological phenomenon. In the case of the allantoic membrane, it may be expressed as the equivalent of a current of $-\frac{1}{4}$ milliamp. under the experimental conditions of this investigation (Parts I, II, III). The most likely explanation appears to be that of a return of the ionised atom to a normal state which must hold in experiments 306 and 308, since the mixed radiation produces no biological change.

In accordance with the supposition already made, one may assume that the ionisation is of some special or restricted nature, which is covered by the non-committal term "saturated receptor."

One may also assume a purely biological process of repair to exist which may complicate the interpretation of changes in the atom. The possibility of cumulative action for which there is much evidence in X-ray literature may be explained as an ultimate breakdown of the biological aspect of repair.

The curves may be approximately represented by the equation

$$y = k/t + (\alpha + \beta)t$$

where y is the threshold dose and t the time of exposure and k and $(\alpha + \beta)$ are constants.

The repair factor is represented as the sum of two constants of which α is related to the atom and β to a biological process of repair. The repair factor for mouse skin has a larger value than that for the allantoic membrane and where similar atoms are concerned one may assume that α has the same value, but β is larger representing a more effective repair in the more highly organised tissue. This would indicate that the resistance of mouse skin both to mixed and homogeneous radiation is much greater than that of the allantoic membrane although in all probability the ultimate phenomenon is similar.

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