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COMMUNICATIONS

SOME EFFECTS OF GAMMA RADIATION ON THE
DEVELOPING RAT RETINA*

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Introduction

GAMMA rays from radium even in very small doses have a profound effect on the development of the immature rat retina. Irradiation quickly causes a disturbance of the normal cell division which is followed by widespread degeneration among the undifferentiated cells of the retina, a diminution in the size of the eyeball and the formation of typical retinal rosettes. A new fibre layer dividing the inner nuclear layer may also appear if the retina is subjected to the radiation at a particular stage of development.

The present paper is primarily concerned with the production of rosettes and of the new fibre layer. Although perhaps the most striking result of radiation, these new formations are probably the least fundamental of the effects observed, in that they are only the consequence of an extensive degeneration of cells. The underlying processes which concern alterations in cell division and the production of cell degeneration will be dealt with in a later publication.

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PREVIOUS WORK.

Rosettes consist of complicated infoldings of the outer part of the retina so that their lumina are bounded by the external limiting membrane through which project the rods and cones. Their appearance is essentially a feature of the developing retina and they only occur in eyes in which there has been some interference with normal development of the immature retina. They are always found in tissue cultures of the retina and can be produced by trephining the undeveloped eye. They are also a well-known feature in glioma retinae (Flexner, 1891; Wintersteiner, 1897). In a previous paper by one of us (Tansley, 1933) the formation of rosettes was discussed in relation to intra-ocular pressure and on the evidence then available it seemed probable that there was some relationship between them.

Rosettes have several times been observed in the retinae of human foetuses which have been aborted after irradiation of the pregnant uterus by X-rays (Goldstein and Wexlar, 1931; Lindenfeld, 1931). They have also been produced experimentally in the rabbit by both X-ray and radium treatment "in utero" (Law, 1934; Pagenstecher, 1916) and in the newborn cat and dog by subjecting the head to X-rays (Demel, 1936; Desjardins, 1931; Tribondeau and Belley, 1907; *a* and *b*, Tribondeau and Récamier, 1905).

The appearance of rosettes in the retina after irradiation was explained by Fuchs, in the discussion on Pagenstecher's paper, as an increased growth of the outer nuclear layer and by Desjardins as due to an inhibition of the growth of the inner nuclear layer. Neither suggestion has any experimental evidence to support it and still leaves unexplained the occurrence of rosettes in unirradiated eyes where a lowering of pressure during development seems to be the important factor. On the other hand there is no evidence that short exposure of the eye to gamma and X-rays has any effect on the intra-ocular pressure.

The experiments to be described here were undertaken in an attempt to discover the precise effect of radiation on the developing retina. Gamma rays were chosen for the irradiation because accurate data on some of the biological effects of given doses were available (Spear, 1935) together with the apparatus with which these data were collected.

METHOD.

Rats were selected for the investigation because the rat retina is not fully developed at birth. Individual animals can therefore be irradiated with precision and then be returned to the mother until required for histological examination. Serial experiments were done on 2-day old rats, and the left eye of each animal irradiated

and then examined. A few rats of other ages up to 11 days were exposed and examined for purposes of comparison.

The source of radiation was 302.1 mgm. radium element, in the form of sulphate, put up in a cylindrical container, 13 mm. in diameter and 2.5 mm. deep. This was mounted for ease of manipulation in a flattened brass ring to form a plaque 4.75 cm. in diameter. The total filtration was 0.5 mm. platinum plus a thin sheet of mica and the distance between the plaque and the eye (left) was about 0.75 cms. The eye thus received only γ rays at an intensity on the skin surface of approximately 280 Sievert units.* The exposures varied from 2 minutes up to 60 minutes, the smallest dose used (2×280 Sievert-minutes) being of the order of 1/33 of the human skin erythema dose.

The technique of exposure was as follows:—a litter of rats with their mother was brought in a cage to the radium room and one of the litter removed and killed as a control. The remaining young rats were then exposed in turn, each being suitably marked for purposes of subsequent identification. To restrict movement during irradiation the rat was wrapped in a blanket of cotton wool and then placed on its right side with its head on a pillow in a wooden cradle fitted with a heating device to prevent any chilling during the radiation. A sheet of mica, mounted on a stand, was then fixed over the cradle so that cross-lines marked on the mica lay over the centre of the left eye of the rat. The mica exercised a very slight pressure on the closed eyelids. The radium plaque, also centred with respect to the mica cross-lines, was then placed in position by hand and the exposure timed by stop-watch. After exposure the rats were returned to their mother and killed at intervals which varied from 20 minutes to 21 days. The left (irradiated) eye of each rat was fixed in Bouin's solution, sectioned and stained with haematoxylin and eosin. Some of the eyes were stained with de Castro's modification of Cajal's silver impregnation method to determine the nature of the new fibre layer which was formed.

Control rats subjected to the same pressure under the mica sheet but without radiation showed no recognisable changes in the eye.

RESULTS.

Fig. 1 shows a section of the normal rat retina 2 days after birth. It will be seen that the optic nerve fibres, the ganglion cell layer, and the inner fibre layer are clearly differentiated. Fixation in Flemming's solution without the acetic acid (F.W.A.) shows that

* One Sievert unit, or intensity millicurie (Imc.), is defined as the intensity due to a point source of 1 mgm. radium acting at a distance of 1 cm.; the rays being filtered through 0.5 mm. platinum.

the inner part of the inner nuclear layer is also differentiated at this age (Fig. 2).

The first recognisable effect of radiation was the diminution of cell division in the retina. This was observed as soon as 30 minutes after the end of a 2-minute exposure with a 2-day rat. If the dose was sufficient mitosis disappeared altogether but later on it returned and sometimes (*i.e.*, with exposures not exceeding 16 minutes) exceeded the normal. This wave of mitotic activity was accompanied by widespread cell degeneration scattered throughout but strictly limited to the outer, undifferentiated, part of the retina. For this reason degeneration was more marked in the periphery of those retinæ in which the central parts were already undergoing differentiation. A dose sufficient to destroy practically the whole of the outer part of the retina (30 minutes' exposure on a 2-day rat) was not able to affect those parts which were already differentiated at the time of radiation.

The younger the rat, the greater was the amount of degeneration seen after any given dose. An irradiation of 30 minutes destroyed nearly 90 per cent. of the undifferentiated cells in a 2-day rat but caused no degeneration in an 11-day rat. Table I shows, for 2-day rats, the relation between the amount of degeneration and the dose given.

TABLE I
Showing the relation between the dose of irradiation and the amount of degeneration in 2-day rats.

Duration of exposure in minutes (<i>t</i>)	Intensity of irradiation in Sievert units (<i>I</i>)	Dose (<i>Ixt.</i>) in Sievert minutes	Highest count of degenerate cells expressed as per cent. of total undifferentiated cells	
2	280	560	13	—
4	280	1120	25	Maximum reached in 12 hours
6	280	1680	35	—
10	280	2800	43	Maximum reached in 15 hours
12	280	3360	47	—
30	280	8400	89	Maximum reached in 39 hours

The degenerate cells were not scattered indiscriminately throughout the nuclear layers but tended to aggregate in columns between which lay apparently unaffected cells. The direction of these degenerate columns was at first radially, across the retina, but later their position changed so that they formed a band of degeneration within the inner nuclear layer at the junction of differentiated and undifferentiated cells. In this new position the alternation of normal and degenerate cells was still evident. Resorption of the degenerate cells followed and was associated with

- (1) a decrease in the size of the whole eye;
- (2) the appearance of a new nerve fibre layer on the inner side of the degenerate band;
- (3) the formation of rosettes on the outer side of the degenerate band.

(1) *Size of the eye*.—The left eye was always smaller than the right which was further from the radium and never received anything but a very small dose of radiation. Even two months after exposure this difference in size was quite noticeable (12 min. exposure to 280 Sievert units of intensity). The gross appearance showed the diminution in size to the naked eye. Microscopically the retina of the left eye was about the same thickness as that of the other and the number of ganglion and inner nuclear cells was practically equal on both sides but with this dose the visual cells in the left eye were reduced in number by about one-third as compared with the right eye.

(2) *The new fibre layer*.—The new fibre layer was obtained only if the retina was irradiated between 2 and 5 days after birth. When such rats were exposed to γ rays for 10 minutes or longer a new layer was found splitting the inner nuclear layer into two and separating the differentiated from the undifferentiated cells of this layer. This new fibre layer was fully developed about 3 days (72 hours) after radiation but a few fibres could often be detected as early as 24 hours after exposure.

An exposure of 6 minutes was followed by the appearance of a few fibres splitting the inner nuclear layer in the extreme periphery of the eye but this effect was only transitory.

Examination of a series of eyes of 2-day rats killed at intervals after a 12 minute exposure (to an intensity of 280 Sievert units) showed the sequence of events leading to the appearance of the new layer.*

* The normal migration of cells connected with the process of differentiation may be briefly summarised here. Up to the fifth day after birth there is great mitotic activity on the outer edge of the retina. The newly formed cells first migrate inwards. With the decrease of mitotic activity from the fifth day onwards there is an active migration of undifferentiated cells in the reverse direction from the inner to the outer nuclear layer accompanied by increase in thickness of the outer layer.

Twelve hours after exposure degeneration was widely scattered throughout the outer undifferentiated part of the retina (Fig. 3 and Diagram c). The tendency of degenerate cells to appear in columns was noticeable. About 24 hours after irradiation the recovery of cell division on the outer edge of the retina combined with the normal inward movement of cells caused a localisation of the necrotic cells in a band separating the outer, undifferentiated, from the inner, differentiated retina. (Fig. 4 and Diagram d.) Among the necrotic areas some unaffected cells were seen. Later the dead cells disappeared and their place was taken by a network of fibres which formed a new layer running horizontally along in the inner nuclear layer. This new fibre layer could be easily recognised 72 hours after the application of radium. (Fig. 5 and Diagram g.)

If rats whose retinæ contained this additional fibre layer were allowed to live for 18 days after the exposure before their eyes were examined it was found that there had been partial fusion of the new layer with the (normal) inner fibre layer. At the same time the inner part of the inner nuclear layer, though still present, was reduced to a single row of nuclei (Fig. 6). In still older eyes the fusion of the two fibre layers was more marked.

An exposure of 30 minutes destroyed so much of the outer retina that the whole histological picture was for a time completely distorted. Twenty-seven hours after irradiation practically the whole of the undifferentiated part of the retina appeared to be necrotic. Groups of unaffected cells were preserved like islands in the necrotic mass. In places the degeneration extended from the outer edge of the retina to the margin of the differentiated zone. At this margin a fine network of fibres could be detected adjacent to the irregularly arranged inner nuclear cells. A very few degenerate cells were seen in the cavity between the retina and pigment epithelium. The degenerate cells were resorbed by the epithelial cells in the vicinity.

Thirty-two hours after exposure (Fig. 7) great numbers of degenerate cells lay in this cavity. On the outer edge of the retina alternating groups of normal and degenerate cells were seen, while large, round epithelial cells filled with degenerate material were found near to the differentiated parts of the retina and in the cavity outside. The groups of intact cells of the outer retina linked up with the cells of the differentiated area. The network of fibres of the new layer was now slightly more pronounced.

Forty-eight hours after exposure nearly all the degenerate cells had passed into the cavity between the retina and pigment epithelium with consequent contraction of the undifferentiated zone. The fibre network was now very apparent as well as the alternations of intact and degenerate cells. Some of the large, round epithelial cells were free of inclusions, others were still full of them. The pigment epithelium also showed many inclusions.

Seventy-two hours after exposure only a few degenerate cells were present but the retina was considerably thinner than normal, due mainly to diminution in width of the outer nuclear layer and of the undifferentiated part of the inner nuclear layer. The outer nuclear layer was now "arched" (early stage of rosette formation) and where the arches met, the inner nuclear layer formed the outer edge of the retina. The large round epithelial cells were quite free from inclusions. The inner nuclear layer was definitely split into two zones by the new fibre layer.

Treatment of the eyes by silver impregnation showed that the new fibre layer consisted of nervous elements of the same nature as the normal inner fibre layer. There were found:

(a) Descending processes of the inner nuclear cells (outer zone) which connected with the ascending processes of the ganglion cells (Fig. 8). The descending processes of the inner nuclear cells (inner zone) were normal.

(b) Ascending processes of the inner nuclear cells (inner zone) which made contact with the descending processes of the visual cells in the outer fibre layer.

TABLE II

Showing the relation between effective dosage for producing rosettes and the age of the retina exposed to radiation.

Duration of exposure in minutes*	AGE OF RAT IN DAYS							
	2	5	6	7	8	9	10	11
10	0	—	—	—	—	—	—	—
12	++ in ciliary region only	—	—	0	—	0	—	0
15	—	++ in ciliary region only	++ in ciliary region only	—	—	—	—	0
20	—	+ in ciliary region only	—	+ in ciliary region only	—	0	—	—
30	+++ through-out retina	—	++ in ciliary region only	—	++ in ciliary region only	+ in ciliary region only	0	0
60	—	—	—	—	—	—	—	0

* Intensity of 280 Sievert units constant for all exposures.

(c) Processes connecting the horizontal cells with others in the same plane (Figs. 9 and 10).

(3) *Rosettes*.—Typical rosettes were observed in many of the irradiated eyes (Fig. 11). These only occurred in eyes under 9 days of age and with exposures of 12 minutes or more. Table II shows the relationship between effective dosage and age of rat exposed. It will be seen that the older the eye the greater is the dose necessary to produce retinal rosettes and that they cannot be obtained in rats over 9 days of age with any exposures of the range used.

In rats of any age between two and nine days where rosettes were found as a result of radiation they were confined to the ciliary area with the smaller doses, but might spread throughout the retina if the dose was large enough. It was usually found that rosettes would appear in some part of the retina if a minimum of about 50 per cent. of the undifferentiated cells were destroyed.

Rosettes were usually first observed about 48 hours after the exposure, but the early stages of their formation might appear as soon as 36 hours with the higher doses, *e.g.*, in a 2-day retina exposed for 30 minutes. (Fig. 7). The stages of their formation appeared to be as follows:

- (i) a degeneration of cells in the inner and outer nuclear layers forming columns separated by normal cells.
- (ii) a breaking of the continuity of the free margin of the retina by the resorption of groups of degenerate cells.
- (iii) the tendency of groups of normal cells on free margin of retina to curl up and form typical rosettes.

A number of 5-day old rats, irradiated for 20 minutes at an intensity of 280 Sievert units, were killed and their eyes fixed at daily intervals from one to seven days. At this age the outer fibre layer is already apparent in the central parts of the retina. Twenty-four hours after exposure many degenerate cells were found in the outer part of the inner nuclear layer near the optic disc, while the outer nuclear layer was practically free from them in this region. At the periphery of the eye the outer fibre layer is not yet apparent and here degenerate cells appeared both in the outer part of the inner nuclear layer and in the outer nuclear layer. After 48 hours the degenerations had disappeared except at the periphery of the eye. In some places a fine network of fibres marking the boundary between the differentiated and undifferentiated part of the inner nuclear layer was found, but this disappeared within 24 hours. Rosettes could be seen in all these eyes in the periphery of the retina in the region where degeneration occurred in both outer and inner nuclear layers.

By the fifth day after birth undifferentiated cells are restricted to the outer part of the whole inner nuclear layer, and peripherally to the outer nuclear layer as well. Since irradiation only affects undifferentiated cells it is impossible to reveal a continuous and permanent new fibre layer after this day. On the other hand as a consequence of degeneration in the outer nuclear layer (in the peripheral parts of the retina), rosettes can still be produced here. The differentiation in these parts is sufficiently advanced by the tenth day after birth to prevent any formation of rosettes by irradiation.

DIAGRAMMATIC REPRESENTATION OF NORMAL AND IRRADIATED EYES

- (a) Normal 2-day rat eye. The optic nerve fibres, ganglion cell layer, inner fibre layer and inner part of the inner nuclear layer are differentiated. Mitosis (*m*) is only found on the outer edge of the retina.
- (b) Mitotic activity is absent 80 minutes after exposure of gamma rays (12 minutes exposure to 280 Sievert units).
- (c) 12 hours after exposure to the same dose of gamma rays mitosis has reappeared and degenerate cells (*dc*) are seen in the outer, undifferentiated part of the retina.
- (d) 24 hours after exposure to the same dose of gamma rays degenerate cells have collected into a necrotic band separating the differentiated from the undifferentiated part of the retina.
- (e) 36 hours after exposure to the same dose of gamma rays the continuity of the outer edge of the retina has been broken by degenerate cells. The new fibre layer has appeared on the outer margin of the differentiated area (central area of retina).
- (f) 36 hours after exposure to the same dose of gamma rays degenerate cells have invaded the cavity between retina and pigment epithelium and are being resorbed by the latter. Groups of intact cells on the outer edge of the retina have curled up into rosettes. The new fibre layer is clearly seen (peripheral area of retina).
- (g) 72 hours after exposure to the same dose of gamma rays degenerate cells have disappeared, the rosettes are being stretched and the continuity of the outer edge of the retina is re-established. The number of inner nuclear cells is normal but that of the outer nuclear cells is reduced. The outer fibre layer is differentiated.
- (h) Normal 5-day rat eye.

Discussion

The cell degeneration which follows exposure of the developing retina to γ rays is probably the significant factor responsible for the appearance both of the additional fibre layer and of rosettes. This degeneration is, in its turn, related to the mitotic activity of the tissue at the moment of irradiation. (Spear, 1935) has shown that the initial effect of small doses of γ rays is to prevent a certain percentage of cell division and (Cox, 1931) has demonstrated that the amount of degeneration following irradiation is proportional to the amount of cell division in the tissue exposed.

In the developing rat retina, cell division does not occur in those parts which are already differentiated and it has been impossible to detect any histological change in the cells in these areas, with the exposures so far used. On the other hand the undifferentiated outer part of the retina was found to be extremely sensitive, especially during the first 5 days after birth when many dividing cells can be seen along the outer edge of the retina. The number of dividing cells was always greater at the periphery of the retina where differentiation was less advanced than at the centre. As the area of differentiated cells extended peripherally, the number of dividing cells diminished.

After about 6 days from birth, mitosis was found to disappear from the central part of the retina but it persisted to some extent peripherally up to 11 days. The amount of degeneration produced by any given dose of radiation decreased with age and varied with the amount and distribution of mitosis present. Thus, an exposure of 30 minutes caused the death of approximately 90 per cent. of the undifferentiated cells in the central part and completely destroyed the ciliary region of the retina of a 2-day rat, but showed practically no effect on an 11-day retina. The fact that radiation was more destructive to younger eyes would seem to be explained by the relatively greater mitotic activity found in them.

The destruction of undifferentiated cells of the retina by radiation is followed by an aggregation of intact cells to fill the empty spaces caused by the resorption of the degenerate cells. This is accompanied by a renewed mitotic activity. With small doses no apparent disturbance of the normal differentiation is seen. With slightly higher doses a new fibre layer is temporarily formed together with rosettes peripherally. Both rosettes and fibre layer tend to disappear again quickly; the fibre layer by its fusion with the normal inner fibre layer and the rosettes by being stretched into a flattened outer nuclear layer. Only with high doses do these new formations persist for any length of time and even then the tendency is to ultimate disappearance. They are to be considered as transitory steps in the regeneration and organisation of the immature retina

effected in a remarkably short space of time by the neuro- and pigment-epithelium without the aid of vascularisation or connective tissue.

Conclusion

The formation of an additional nerve fibre layer and of rosettes as a result of exposure of the developing retina to γ rays does not appear to be due to any direct effect of the radiation on the tissue but is a sequel to a cellular degeneration which is not specific to radiation.

Summary

- (1) A method of exposing the eyes of young rats to γ radiation is described.
- (2) One result of radiation is degeneration of the undifferentiated cells of the retina. The amount of degeneration depends on the dose of γ rays and the age of the rat.
- (3) The size of the irradiated eye is reduced.
- (4) A new fibre layer is formed splitting the inner nuclear layer into two if the radiation is given under appropriate conditions.
- (5) Rosettes may also be produced in the retina after γ radiation.
- (6) The mechanism of the formation of the new fibre layer and the rosettes is secondary to the degeneration caused by the rays and not a direct effect of radiation.

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EXPLANATION OF FIGURES

- FIG. 1.—Section through the eye of a normal 2-day rat. The optic nerve fibres, ganglion cells and inner fibre layer are differentiated. Mitosis is found only on the outer edge of the retina.
(Bouin, Haematoxylin-Eosin H. and E.; $\times 160$.)
- FIG. 2.—Section through the eye of a normal 2-day rat, which was fixed in Flemming's solution without acetic acid. This shows that the inner part of the inner nuclear layer is also differentiated.
(Iron Haematoxylin; $\times 160$.)
- FIG. 3.—Section through the eye of a 2½-day rat, 12 hours after exposure to gamma rays (12 minutes exposure at 280 Sievert units of intensity) at 2 days old. In the outer undifferentiated part of the retina strands of intact cells (itc) alternate with columns of degenerate cells (dc).
(Bouin, H. and E.; $\times 160$.)
- FIG. 4.—Section through the eye of a 3-day rat, 24 hours after exposure to the same dose of gamma rays at 2 days old. The degenerate cells have collected roughly into a band separating the differentiated parts of the retina from the outer, undifferentiated part.
(Bouin, H. and E.; $\times 160$.)
- FIG. 5.—Section through the eye of a 5-day rat, 72 hours after exposure to the same dose of gamma rays at 2 days old. The band of degenerate cells has disappeared and its place is taken by a new fibre layer dividing the inner nuclear layer into two parts.
(Bouin, H. and E.; $\times 160$.)
- FIG. 6.—Section through the eye of a 20-day rat, 18 days after exposure to the same dose of gamma rays at 2 days old. A thinning of the inner part of the inner nuclear layer is seen together with a partial fusion of the inner fibre layer with the new fibre layer. The outer nuclear layer shows rosettes.
(Bouin, H. and E.; $\times 160$.)

FIG. 7.—Section through the eye of a 3½-day rat, 32 hours after exposure to gamma rays (*30 minutes exposure* at 280 Sievert units of intensity) at 2 days old. The continuity of the outer edge of the retina is broken by degenerate cells which have also invaded the cavity (ca) between retina and pigment epithelium. Groups of intact cells on the outer edge of the retina have curled up into rosettes and are linked by columns of intact cells with the cells of the differentiated area. At the margin of the differentiated part of the retina the network of fibres of the new fibre layer can be seen.
(Bouin, H. and E ; ×160.)

FIG. 8.—Section through the eye of a 5-day rat, 72 hours after exposure to gamma rays (*12 minutes exposure* at 280 Sievert units of intensity) at 2 days old. An ascending process of a ganglion cell passes through the inner fibre layer and the inner part of the inner nuclear layer and connects, in the new fibre layer, with a descending process of an inner nuclear cell of the outer zone.
(de Castro ; ×650.)

FIG. 9.—Section through the eye of a 5-day rat, 72 hours after exposure to the same dose of gamma rays at 2 days old. In the new fibre layer processes running horizontally connect cells of the inner zone of the inner nuclear layer. Owing to the impossibility of photographing all parts of the fibre in focus simultaneously, this figure has been retouched.
(de Castro ; ×650.)

FIG. 10.—The original photograph of Fig. 9.

FIG. 11.—Section through the eye of a 20-day rat, 18 days after exposure to the same dose of gamma rays at 2 days old. Typical rosettes (r) are seen in the outer nuclear layer.
(Bouin, H. and E. ; ×160.)

ABBREVIATIONS

<i>ca</i>	Cavity between retina and pigment epithelium.	<i>nfl</i>	new fibre layer.
<i>ch</i>	choroid.	<i>ofl</i>	outer fibre layer.
<i>d</i>	differentiated part of retina.	<i>opfl</i>	optic nerve fibres.
<i>dc</i>	degenerate cell.	<i>op</i>	outer part of inner nuclear layer.
<i>gcl</i>	ganglion cell layer.	<i>onl</i>	outer nuclear layer.
<i>inl</i>	inner nuclear layer.	<i>p</i>	pigment epithelium.
<i>ip</i>	inner part of inner nuclear layer.	<i>r</i>	rosettes.
<i>itc</i>	intact cell.	<i>sc</i>	sclera.
<i>ifl</i>	inner fibre layer.	<i>ud</i>	undifferentiated part of retina.
<i>m</i>	mitosis.	<i>f</i>	nerve fibre.