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COMMUNICATIONS

A HISTOLOGICAL STUDY ON THE ACTION OF SHORT-WAVED LIGHT UPON THE EYE, WITH A NOTE ON "INCLUSION BODIES"

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(FOR THE MEDICAL RESEARCH COUNCIL)*

A CONSIDERABLE amount of work has already been done upon the action of ultra-violet light upon the eye, but it was considered expedient to undertake the present research since in some respects prior investigations are contradictory and require amplification. The object in view was two-fold: it was hoped to elucidate further the local therapeutic action of short-waved light in diseases of the anterior segment of the eye (see Duke-Elder, 1926-8) and to provide some criterion with regard to dosage, and the results are to be taken in correlation with the physico-chemical studies upon which we are at present engaged on the pathogenesis of cataract.

The first work of scientific value which was done upon this question was that of Widmark (1889-1903). Using a powerful carbon arc (1,200 c.p.) in the experimental radiation of the eyes of

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rabbits, he got a typical photophthalmic reaction, an acute conjunctivitis with chemosis and purulent secretion, a desquamation of the corneal epithelium, and, with strong doses, the formation of a corneal opacity, and a miosis and discolouration of the iris. With long exposures (2 to 4 hours) to more powerful arcs (4,000 c.p.) he obtained opacities in the lens when the animal was atropinized; with mild doses he noted karyokinesis and cellular proliferation in the capsular epithelium, changes which developed into swelling and partial destruction of the epithelium and of the anterior lens fibres, with the transudation of fluid between the lens capsule and the cortex. He further showed that the ultra-violet portion of the spectrum was responsible for these changes, since none were observed if these rays were cut off by glass or quinine solution. Following this pioneer work similar changes were recorded in the cornea and conjunctiva of experimentally radiated animals by Bresse (1891), Ogneff (1896), and Strebel (1901), but none of these obtained lenticular opacities. Presumably these were difficult to produce; it is to be noted that Widmark employed very much stronger doses of light, and even thus obtained them in four only out of eleven cases. Herzog (1903), on the other hand, again using rabbits, obtained some definite cataractous changes, in the production of which, however, heat was not altogether excluded.

In the same year, Hertel (1903), attracted by the therapeutic value of light, carried out more detailed microscopic observations. In the cornea he found considerable changes in the epithelium: karyokinesis, vacuole-formation, with swelling and proliferation of the corneal corpuscles. Birch-Hirschfeld (1903-10) corroborated and amplified these observations, and, in addition, described an iritis with the deposition of fibrin in the anterior chamber and widespread changes in the retina. These last involved chromatolysis and vacuole-formation in the ganglion cells, and changes involving essentially a loss of chromatin in the nuclear layers; they were observed to be very much more marked in the aphakic rabbit than in the intact one. In one experiment, in an aphakic rabbit, he described myelin degeneration in the optic nerve. Changes of a somewhat analogous nature in the optic nerve were reported by Mettey (1903).

None of these investigators detected any pathological alterations in the lens, even though they had been looked for. Hess (1907), however, experimenting on frogs, guinea-pigs, and rabbits with the mercury vapour lamp, obtained definite changes in the anterior sub-capsular cells. In a region corresponding to the pupillary aperture these were found to be swollen, and their nuclei were represented by scattered chromatin granules extruded from the still visible nuclear membrane. Suróunding this area Hess described a ring of heaped-up deeply staining cells, which he described as an epithelial "wall." Parsons (1909-10) and Martin (1912) repeated these experiments, and one rabbit showed appearances resembling those described by Hess. Birch-Hirschfeld (1909) also, in a later experiment, after exposing a rabbit's eye on three successive days for five minutes to the light from an arc lamp which traversed first a "euphos glass," obtained somewhat similar changes in the lens capsule; he accordingly concluded that the longer ultra-violet rays (about 4,000 A.U.) and probably the shorter blue and violet, were responsible for the reaction. The whole question was thoroughly gone into again by Verhoeff and Bell (1916). They showed that the characteristic effects were produced by light of wave-length shorter than 3,050 A.U.; they demonstrated the corneal changes and suggested that the most characteristic of these was the breaking up of the cytoplasm into eosinophilic and basophilic granules; they produced widespread effects on the lens capsule, again involving the formation of eosinophilic and basophilic granules, and, with intense exposures, superficial damage to the substance of the lens; they found considerable congestion of the iris; but they were quite unable to produce any ill-effects upon the retina.

In 1918, Chotzen and Kutznitzky again investigated the question, radiating rabbits in five minute doses with a quartz mercury vapour lamp; they obtained marked changes only in the conjunctiva and cornea; there was depigmentation of the iris, but no evidence of actual inflammation here or in the uveal tract, and retinal damage could not be detected. Politzer and Alberti (1924), on investigating the effect of ultra-violet on salamander larvae, observed lesions of the corneal epithelium, and noted a diminution of mitosis with pigmentary changes and subsequent increase of melanophores. Finally, Toulant (1926) carried out a histological research on radiated rabbits' eyes, and although he found corneal and conjunctival changes, he observed no reaction in the iris or the lens.

EXPERIMENTAL TECHNIQUE

Rabbits were employed throughout the experiments; they were radiated with a quartz mercury vapour lamp (K.B.B., 240 volts, 2/3 amps.) at a uniform distance of one foot for a period of ten minutes. The spectrum of the lamp did not extend beyond 6,000 A.U., so that only ultra-violet and visible light were in question, without any contamination with infra-red rays. The dose was based upon the results of some preliminary experiments (Duke-Elder, 1926), as one which gives a marked, but not an excessive reaction to ultra-violet rays. The dose of light, therefore, while considerably above that which may be used clinically (Duke-Elder, 1928), was not greatly in excess of it. Cocaine was instilled into the eye before radiation, and if the animal closed the eye or moved during radiation, the lids were kept open by hand. Throughout the course of the experiment the cornea was kept moist by a saline drip. Sixty-four animals in all were employed, one eye in each case being used as a control, and they were killed at periods varying from two hours to ten days after the experiment. Immediately after death the eyes were excised, placed in Zenker's solution, imbedded in celloidin, cut in serial sections, and stained, some by haematoxylin and eosin, some by Mann's stain, and some by van Gieson's method. The changes observed are detailed below. As a control, excised eyes (dead) were radiated, which on subsequent section showed no change. In a few experiments dogs were employed, and these showed changes comparable with those observed in rabbits.

CLINICAL SYMPTOMS

The majority of the clinical symptoms which appear after radiation of the rabbit's eye with ultra-violet rays are already well known, and they will therefore be recapitulated briefly. Initially there is a latent period during which no effects are visible; this applies both to clinical signs and to histological changes; its significance will be commented upon later. It varies in length inversely as the severity of the exposure; with the exposures used it averages from four to six hours. Thereafter the conjunctiva becomes pink and hyperaemic, the inflammation gradually increasing in intensity until it involves oedema and chemosis, with the appearance of a varying amount of secretion which eventually may become frankly purulent. Meantime, in the early stages, the cornea shows a slight irregularity of its reflex and stippling of the surface which takes on a stain with fluorescein. The staining area gradually increases centrally, due to desquamation of the epithelium, but the edges of the area involved rarely show a well-defined margin. Examination with the ultra-violet slit-lamp in the fluorescent light obtained with the stain shows that this tailing off of the staining effect is due to a loss of the superficial cells in the neighbouring area producing a region of partial desquamation surrounding the central area of complete exfoliation. Meantime the central part of the cornea becomes somewhat hazy and oedematous, definite vesicles being occasionally formed under the epithelium. The clinical picture is at its height between thirty-six to fifty-four hours after radiation; thereafter it gradually clears up, until, four or five days later, the cornea becomes clear again, the conjunctival injection dies down, and the eye becomes normal in eight to ten days' time.

With the cornea hazy and oedematous, examination of the interior of the eye is difficult. The iris, however, obviously shows a considerable inflammatory reaction. The pupil is contracted, and the anterior surface of the iris loses its characteristic pattern and becomes muddy; a considerable amount of vascular congestion is seen with occasional large vessels, and very occasionally, actual haemorrhages may appear. These changes tend to clear up rapidly, about the fourth or fifth day. Examination with the loupe in no case revealed any changes in the lens; but occasionally the slit-lamp revealed slight changes in the anterior part of the lens with the formation of fluid clefts and vacuoles.

Lesser exposures than those employed as a routine produced, after a long latent period, similar but less severe changes in the cornea and conjunctiva, which cleared up in a correspondingly short space of time. More intense and prolonged exposures shortened the latent period, and produced an early and widespread desquamation of the corneal epithelium, accompanied by much opacity and thickening of the substantia propria, which became sodden and soft. In about a week the reaction had died down, leaving a highly vascularised interstitial opacity, which, in the course of three or four weeks cleared up to a surprising extent. These severe exposures are accompanied by a correspondingly severe conjunctivitis with chemosis and profuse discharge; but the structures inside the eye remain relatively unaffected. This immunity of the inner eye in these cases is probably due to the intensity of the corneal reaction cutting off the greater part of the shorter abiotic rays and thus protecting the structures behind.

The subjective symptoms would seem to correspond closely with those characterising the photophthalmic reaction in the human subject (see Duke-Elder, 1926). There appears to be no reaction during the latent period, while the commencement of corneal trouble is accompanied by all the signs of photophobia. This is evidently due to exposure of the free nerve endings in the cornea: if the cornea is protected during radiation the violent conjunctivitis is apparently accompanied by no distress, a circumstance seen in the human subject; and in the more severe exposures, where the whole central cornea has been destroyed, the evidences of subjective irritation are correspondingly less. It is interesting that between the latent period and the commencement of acute symptoms, at the time when corneal oedema is very obvious, and when in the human subject typical halos are most evident (Duke-Elder, 1927), the cornea becomes practically anaesthetic.

Although no concentrating lenses were used in these experiments, the central portion of the cornea was always that most affected. This is due to the greater direct absorption of the rays here; towards the periphery there is a considerable loss of energy owing to reflection, since the cornea is normal to the incident light in its central area, but is inclined at a considerable angle near the margin. The amount of energy absorbed will therefore follow Lambert's law, which states that the energy absorbed is in direct proportion to the cosine of the angle of incidence of the light.

It is this condition which is seen clinically in the solar photophthalmia met with in snow fields (snow blindness, keratitis nivalis), on deserts, and on the tropical seas, when the direct ultra-violet light from the sun is reinforced by reflection from extensive surfaces. It is also seen in the industrial photophthalmia (photophthalmia

electrica) met with in welders, workers with arc lamps, cinema artists, and others who are exposed to excessive short-waved light, or is met with after accidents, such as the short-circuiting of a high-tension current, or exposure to a flash of lightning.

HISTOLOGICAL CHANGES

1. THE CORNEA.

There is no observable histological change after radiation until four hours have elapsed. At this time the arrangement of the epithelial cells remains unaltered, and their regular stratification is unimpaired, but here and there, both in the superficial and basal cells, some spacing out and swelling are evident. The nuclei of some of the more superficial cells contain some acidophil granules which take on a sharply defined eosin

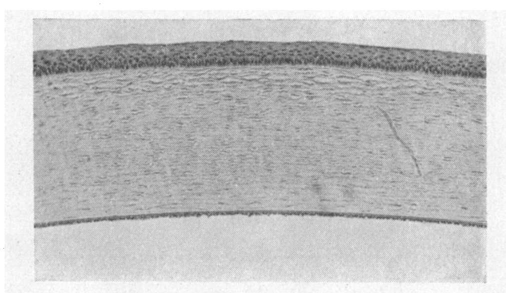

FIG. 1.
The normal cornea of the rabbit
(Haematoxylin and eosin.)

stain, while most of the cell nuclei are normally coloured blue. Some nuclei contain partly red granules and partly blue, and some few are uniformly red; some of the red staining nuclei become swollen, the contour of the nucleus being bulged irregularly outwards. On the other hand, other nuclei contain basophil granules, which are occasionally heaped up together to form nucleolar-like structures in the substance of the nucleus, which are frequently surrounded by a clear area resembling a vacuole. At this stage the changes are limited to the epithelium, and while the substantia propria and the endothelium appear normal; there is no sign of infiltration round the limbus, nor have any subjective signs of irritation become evident. Clinically, the latent period is still present.

After six hours the same changes are much more evident. A large number of nuclei take on the red stain, but it is noticeable that side by side with these are many apparently normally staining cells. The basal cells appear more widely spaced out and show evidences of oedema, and the arrangement of the superficial layers becomes somewhat irregular (Fig. 2). At the eight hour stage the more superficial cells in the central area begin to be cast off. The pathological changes are most noticeable after twelve hours. A large number of the nuclei of the epithelial cells take on the red stain markedly; some remain granular, in others the granules appear to have coalesced to form amorphous red bodies in the interior of the

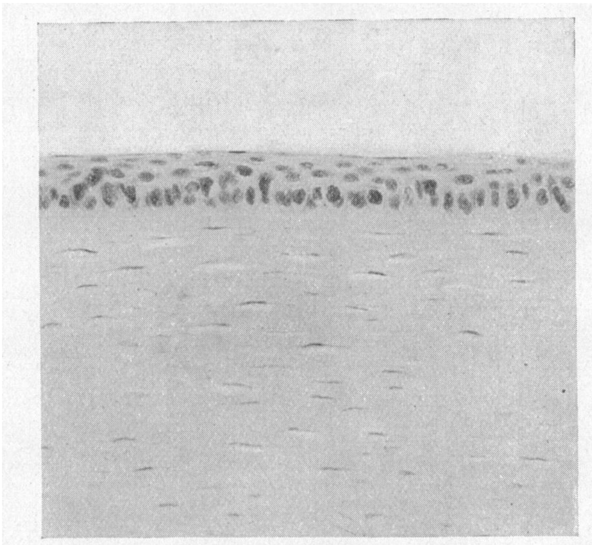

FIG. 2.

The cornea 8 hours after radiation. The basal cells of the epithelium are swollen, and many nuclei are taking on the altered staining reaction. There is as yet no evidence of desquamation.

nucleus (Plate I, Fig. 2). These are of varying sizes; sometimes they fill the entire nucleus, sometimes one or two small granules are present inside the nucleus, in which case they usually appear surrounded by a vacuole-like space; sometimes they bulge out of the nucleus, deforming it; and occasionally they escape from the nuclear membrane altogether (Figs. 3 and 4). Occasionally a cluster of these bodies of various sizes lies in a position where a nucleus has apparently disintegrated, leaving the remains of its nuclear membrane. In other cells the changes are less marked: the nucleus may stain a purplish colour, and may contain one or two isolated red granules, or perhaps none at all. On the other hand, many nuclei retain their blue staining. Of these some show a granular appearance; in others the granules are aggregated into masses; while in others the general basophil staining is relieved by one or more highly refractile red granules. Other cells, frequently in close proximity to those showing the most marked changes, remain to all appearances quite normal. In the cytoplasm both basophil and eosinophil granules are frequently found, but, although it is not possible to say so definitely, it is probable that these are largely derived from the nuclei: certainly these last are the site of the most pronounced changes. At the stage of sixteen hours these red bodies are very numerous, large numbers of them being included within the nuclear membrane or extruded into the cytoplasm (Plate I, Fig. 1).

Meantime in the central area desquamation is proceeding. Round the desquamating area there is frequently, but not invariably, a heaped-up region of the epithelium, where layers of cells without any appearance of regular stratification, and showing marked staining changes and nuclear disintegration, are arranged indiscriminately eight or ten thick. Such a proliferated area of the epithelium usually tails off gradually to a single layer of malformed cells, which itself ultimately disappears leaving the cornea completely denuded of epithelium. At other times the epithelium appears to have been more or less abruptly cast off leaving the normal stratification, as it were, in mid-air. There are one or two mitotic figures, but, even where the cells appear to have proliferated, mitosis is very rare indeed (Plate 1, Fig. 3).

Meantime the substantia propria shows somewhat similar changes which gradually decrease in intensity in the deeper layers. The nuclei stain deeply with methylene blue, and then begin to fragment. About the sixteen hour stage there is a large number

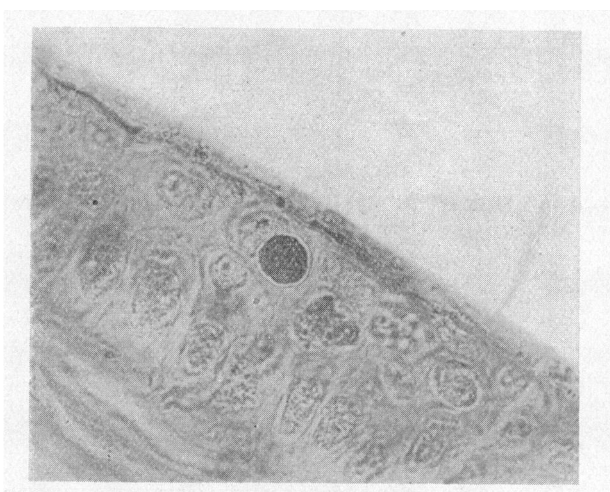

FIG. 3.

A typical "inclusion body" enclosed in a vacuole-like space. Some of the other nuclei show early changes (12 hours after radiation).

PLATE I.

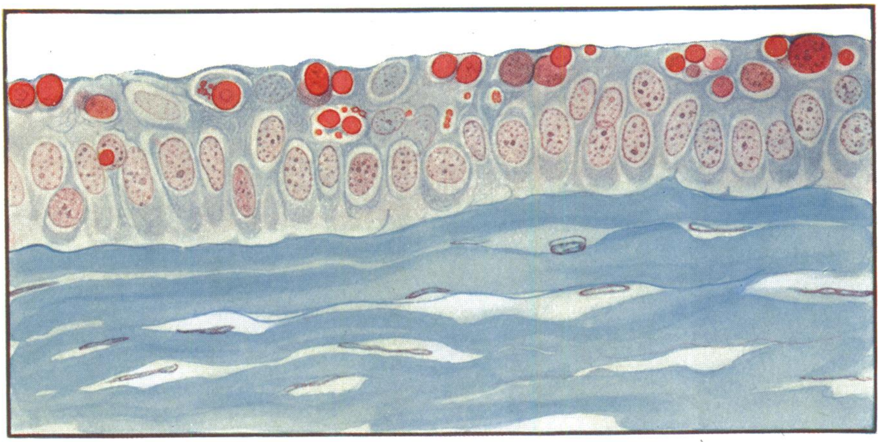

FIG. 1.
The corneal epithelium 16 hours after radiation showing well-marked nuclear changes.

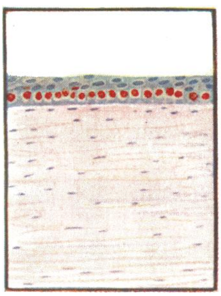

FIG. 2.
The epithelium 8 hrs. after radiation.

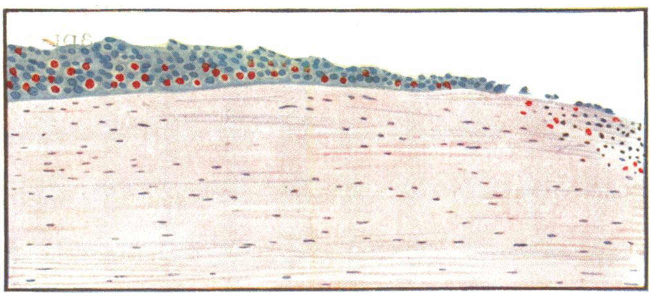

FIG. 3.
The epithelium 24 hours after radiation showing a heaped-up "wall" and a central desquamated area.

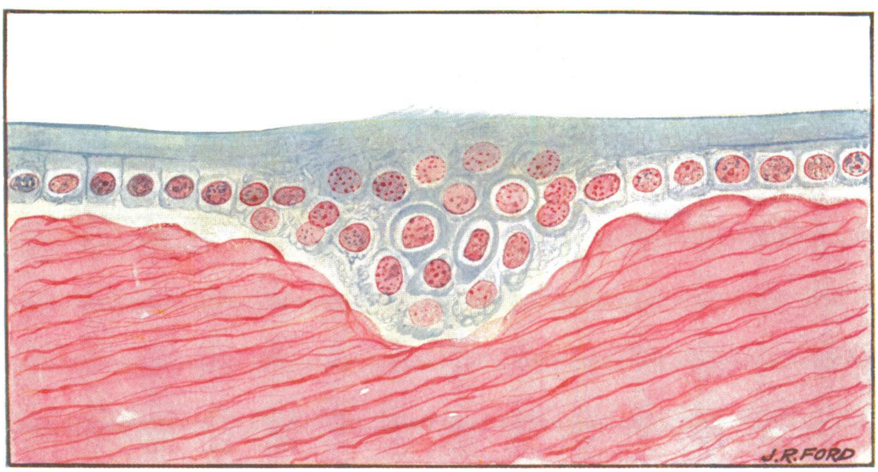

FIG. 4.
The lens capsule 20 hours after radiation, showing traumatization of the capsule, nuclear changes in the cells, and the formation of an epithelial "wall" at the pupillary margin.

which has become definitely acidophil, and ultimately a number of basophil and eosinophil granules becomes extruded. The lamellae become swollen, and in the more affected central area appear spaced apart. From the periphery, about twelve hours after radiation, that is, some time after there are widespread changes established in the corneal epithelium, an infiltration appears at the limbus, which, while it shows some polymorphonuclear cells, is very largely composed of eosinophils. Travelling towards the most severely traumatized parts of the cornea, these become broken up and disintegrated, adding to the granular debris from the nuclei. The

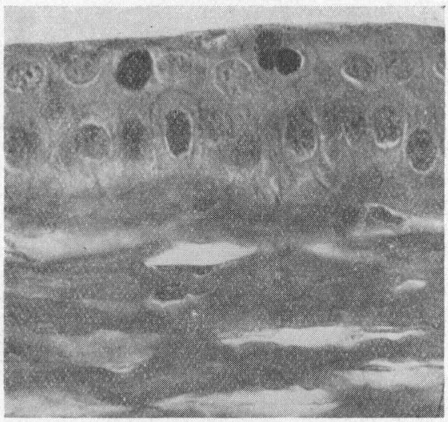

FIG. 4.

A more advanced stage than Fig. 3, showing several altered nuclei. One shows disintegration into three eosin-staining masses (14 hours after radiation).

greatest number of these granules are usually segregated near the desquamating margin of the epithelium. Directly underneath the radiated area, at the twenty-four hour stage, the substantia propria shows few granules and practically no corpuscles, but merely feebly staining swollen lamellae separated here and there by fluid clefts (Fig. 5). The endothelium shows a similar red staining in many of the nuclei of its cells; but it is rare that any exfoliation occurs.

From this time onwards until thirty-six hours after radiation little or no change is histologically evident. The red bodies included in the nuclei remain distinctly seen, and they always tend to break through the confines of the nuclear membrane and scatter themselves in the cytoplasm, which now contains large numbers of minute red and blue granules. Round the desquamated area there is usually a heaped up "wall" of cells which still show few or no evidences of mitosis. Meantime in the region of the limbus there is a very marked infiltration; blood spaces of considerable size are seen, and the eosinophils are largely replaced by a massive invasion by polymorphs. In places the endothelium has disappeared, and in the regions denuded of cells there are quantities of eosinophilic and basophilic granules adhering to Descemet's membrane.

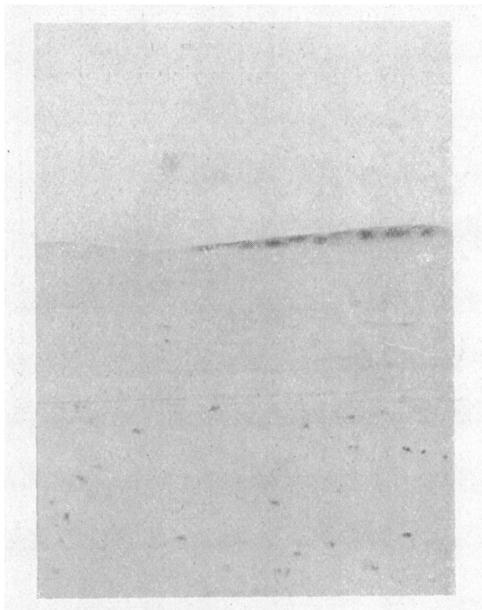

FIG. 5.

The cornea 36 hours after radiation. The epithelium has desquamated entirely in the central area, and the denuded portion is surrounded by one layer only of epithelial cells. The substantia propria shows marked changes, the lamellae being swollen and the corpuscles having to a large extent disappeared.

From about fifty to seventy hours after radiation, the red staining gradually fades; the epithelium near the periphery becomes more regularly arranged, and over the desquamated area a single layer of cells showing no acidophil properties begins to appear; it is particularly noticeable that these show few mitotic figures. The process of regeneration goes on with surprising rapidity and with little evidence of cellular activity. At seventy-six hours the epithelium is two or three layers thick; nuclei are appearing in the substantia propria, the corpuscles appearing somewhat irregularly arranged. At the limbus the vascular infiltration is at its height; large new blood vessels and blood spaces appear in great numbers. Frequently these are surrounded by young fibroblasts, of which the large egg-shaped nuclei and granules arranged in cart-wheel formation are peculiarly evident, while the whole tissue in this region and for some considerable distance into the cornea is infiltrated with polymorphs (Fig. 6).

One hundred and thirty hours after radiation the epithelial cells are beginning once more to take on an orderly arrangement, a palisade layer of basal cells being present, above which appear one

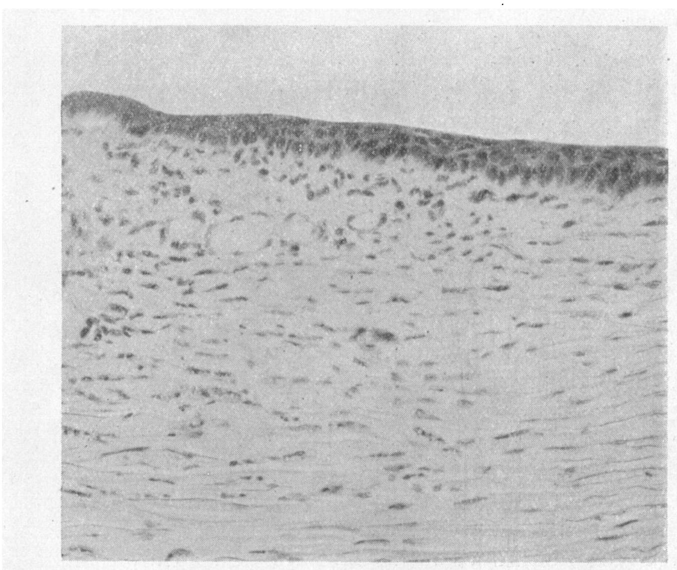

FIG. 6.

The limbal area of the cornea 60 hours after radiation, showing considerable infiltration and the formation of many new vessels surrounded by young fibroblasts.

or two irregular layers of horizontal cells: again, mitotic figures are few. Thereafter reparative changes progress slowly and without incident, until in seven days all the structures appear practically normal excepting the limbal infiltration, the greater part of which has cleared up at about the tenth day.

2. THE CONJUNCTIVA

Changes similar in kind, although less in degree, were observed in the conjunctiva. Many of the nuclei of the superficial cells take on the red staining, but in no case were definite inclusion bodies formed, nor were fragmentation of the nuclei and the extrusion of granules noticed. There was a complete absence of granules—eosinophilic and basophilic—in the cytoplasm. The superficial layers of the tissue became largely swollen, and many cells were desquamated, leaving a rough and irregular surface. Apart from the staining reaction and the presence of acidophil granules in quantity in some of the cells, the exfoliation appeared to be preceded by fewer pathological changes than in the corneal epithelium. The sub-epithelial tissue showed much congestion and some chemosis and oedema, while tiny interstitial haemorrhages and some considerable eosinophil and polymorphonuclear infiltration were evident.

3. THE IRIS

There is little observable change in the iris until about twelve to sixteen hours after radiation, when a very considerable degree of congestion begins to appear. The entire iris becomes rapidly filled with dilated blood vessels, and diapedesis and actual haemorrhages appear, especially towards the anterior surface; the presence of eosinophils is notable, and there are some polymorphs. Red staining is evident in the nuclei of some of the epithelial cells in the early stages of the reaction, and at a later stage there is a considerable disturbance of the iris pigment. Much of this appears to have escaped and lies as a somewhat loose powdery deposit at or near the surface. No posterior synechiae were ever observed or anything approaching thereto, but during the stage from forty to sixty hours after radiation a very large quantity of this pigment is deposited over the lens capsule. It is true that in the normal rabbit, iris pigment does adhere to the lens and adhesions can readily be produced as an artifact of fixation, but the deposit of pigment as a powdery layer over the lens and its accumulation in large masses opposite similar aggregations on the posterior surface of the iris during the later stages of the acute reaction is particularly obvious. After about eighty hours the congestion of the iris largely disappears, and the reaction resolves, leaving, however, some remaining traces up to about ten days' time.

4. THE AQUEOUS HUMOUR

The anterior chamber showed no deposits of fibrinous exudate histologically, but chemical examination of the aqueous humour showed the usual type of plasmoid aqueous which follows a widespread dilatation of the blood vessels: the proteins are very considerably increased from the traces which are normally present to a considerable percentage, the sugar is slightly increased, and the chlorides are diminished. The following analysis was done eight hours after ten minutes' radiation at two feet distance from the mercury vapour lamp (water cooled). The proteins were estimated by the dipping refractometer, the "sugar" was taken as reducing substance estimated by the Hagedorn-Jensen method, and the chlorides by Ruszynák's method.

Rabbit	Left eye normal	Right eye radiated
Refractive Index	1.335168 (traces of protein)	1.340898 (approx. 3.0% protein)
"Sugar" - -	0.154 grm. per 100 c.c.	0.172 grm. per 100 c.c.
Chloride - -	0.693 grm. per 100 c.c.	0.520 grm. per 100 c.c.

It is to be noted that the reaction is not so pronounced as that produced by infra-red rays. This is shown by the following comparable analysis carried out after ten minutes' radiation at two feet distance from a carbon arc with the ultra-violet rays filtered off.

Rabbit	Left eye normal	Right eye radiated
Refractive Index	1.335247 (traces of protein)	1.431990 (approx. 3.5% protein)
"Sugar" - -	0.125 grm. per 100 c.c.	0.131 grm. per 100 c.c.
Chloride - -	0.661 grm. per 100 c.c.	0.501 grm. per 100 c.c.

It is probable that both sets of rays act in the same way, the radiant energy in each case being practically entirely absorbed by the pigment of the iris and there being converted into heat, any abiotic action being thus completely masked.

5. THE LENS

Despite many statements to the contrary, a reaction in the lens to ultra-violet radiation is markedly present. The most obvious changes affect the capsule, where the changes in general resemble those described by Hess (1907), Martin (1912), and Verhoeff and Bell (1916).

Immediately after radiation no change is observed in the capsule proper, and it is only in the stage of maximal response (about sixteen to thirty hours after radiation) that definite swelling and blurring of its outline is seen in a fairly circumscribed area near the pupillary margin situated over what will shortly be described as the "epithelial wall." As already noted, during the active stages of response, the capsule is thickly covered with large quantities of pigment derived from the iris.

The capsular epithelium shows the typical intracellular changes noted already in the corneal epithelium. Four hours after radiation the nuclei stain less deeply blue, and at the six hour stage several of them appear definitely red. The eosinophil staining shows up first as isolated granules in the nuclei, which gradually increase in number until in many cells in the pupillary area the entire nucleus is red (Fig. 7). The cells take up the red staining in a peculiarly indiscriminate and arbitrary manner, and throughout the entire pupillary area, intensely red nuclei appear side by side with cells, the nuclei of which are filled with basophil granules, or cells which appear to all intents and purposes normal. At the eight hour stage the epithelial cells become slightly swollen. In contradistinction to the appearances in the cornea, the nuclei rarely disintegrate, and the extrusion of granules into the cytoplasm is the exception.

About ten to twelve hours after radiation there appears round the pupillary margin a closely packed ring of cells arranged four to six

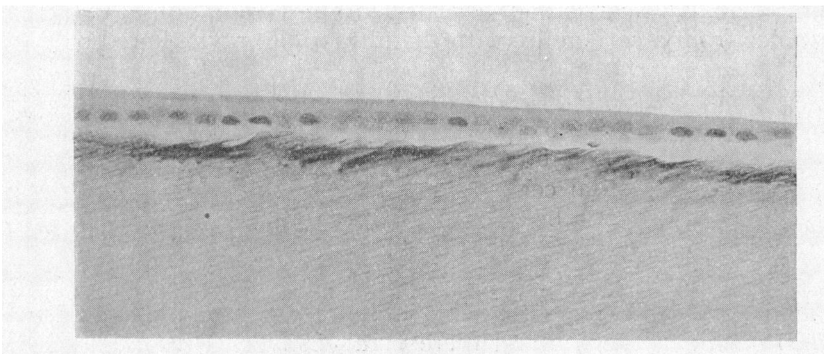

FIG. 7.

The anterior lens capsule 20 hours after radiation. In the sub-capsular epithelium a large number of cells show a deep eosinophil staining in their nuclei. Other cells, alongside these, appear normal. The lens fibres are altered only immediately underneath the epithelium.

layers deep. It starts abruptly and ends abruptly, being about eight to ten cells thick, and is heaped up, bulging the lens capsule on the one side and indenting the lens substance on the other. It is composed of large swollen cells, the nuclei of which all, without any apparent exception, take on a strongly eosinophil stain. About the stage of seventy hours, a considerable number of granules appear in the cytoplasm of the cells in the pupillary area, both eosinophilic and basophilic, the great majority of which appear to come from the nuclei. In the pupillary area itself mitosis is almost completely absent, and only a few mitotic figures are visible in the heaped up wall and in the unexposed area beyond this. At the end of ten days the cells are practically all normal: the only peculiarity at this stage is the disparity of the size of the nuclei, some of which are abnormally large, some of which are small, and some of which appear to be in the process of budding, occasionally producing a cell with a double nucleus.

The above appearances are those which are seen in transverse section of the lens capsule and the underlying epithelium. They were studied also in flat preparations of the lens capsule. When the animal was killed the eye was opened by an incision passing round the globe behind the ciliary body, and the lens carefully removed from behind after the zonule was cut round by scissors. Any adherent iris epithelium was removed and the lens was then placed in Zenker's solution for two hours. Thereafter it was washed in water and the capsule incised round the equator by a knife, whereupon the anterior capsule was easily floated off in water. The histological technique of Verhoeff and Bell (1916) was then followed. The usual treatment following fixation in Zenker was carried out, and radial incisions were made into the capsule, reaching to within a short distance of the centre. The capsule was then floated upon a cover glass so that the epithelium was in contact with the glass. The preparation was then blotted with filter paper, stained, and mounted.

These flat preparations confirmed in every way the appearance of the transverse sections. The most obvious phenomenon was the epithelial "wall" round the margin of the pupillary area: usually it extends all the way round in the form of a ring, sometimes it appears only in segments covering part of the distance. The presence of an abundance of granules of all kinds is peculiarly evident; this appears to be due to the fact that it is more difficult than in transverse sections to differentiate the pigment granules from the iris lying upon the surface of the capsule from the granules inside the sub-capsular cells, and in the case of these latter, it is much more difficult to be certain whether they arise in the cyto-

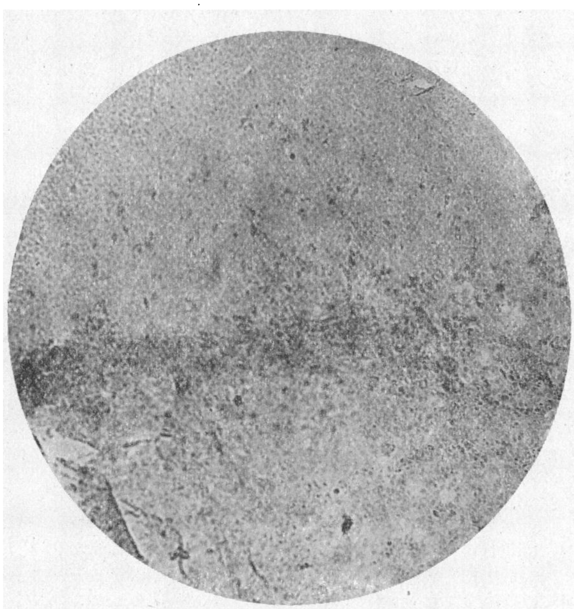

FIG. 8.

Flat preparation of the lens capsule, 24 hours after radiation. The epithelial "wall" round the pupillary margin is well seen.

plasm or have a nuclear origin. The nuclear changes can be confirmed: the basophil staining becomes less regular, and granules are formed, in some cells eosinophilic, in others basophilic. Mitotic figures are rare, and are more evident in the peripheral area than in the central radiated region of the capsule (Fig. 8).

The *lens substance* is markedly affected only in a narrow region immediately underneath the capsule. Here the staining is much less differentiated, the architecture of the fibres becomes blurred, and they themselves become swollen and tend to lose their orderly arrangement. These changes only affect a very thin sub-capsular zone. Some of the more superficial fibres are separated by clefts, and the capsule is frequently separated from the lens substance. In the interior of the lens nuclear changes are evident which seem to be confined to the radiated area: deeply staining basophilic granules are common, and from about twenty-four to thirty-six hours after radiation highly refractile eosinophil granules are seen. It is rare, however, for an entire nucleus to take on the eosinophil stain, and in no case was any fragmentation or disintegration of the nucleus observed.

6. THE RETINA

Although they seem to have almost invariably eluded the observation of previous workers, changes in the retina can be demonstrated after radiations with short-waved light in such intensities as were employed in these experiments. In the whole of the literature Birch-Hirschfeld (1904) seems to have been the only one to have described them, and his results and conclusions have never been confirmed, while they have frequently been denied. There is no doubt, however, that changes such as he described do actually occur. In the present series of experiments the most marked changes were evident from eight to twenty hours after radiation, and the retina was always normal fifty or sixty hours later. The retina was examined in vertical sections, and the greatest changes were always observed in the region of the posterior pole of the eye, that is, the area which was exposed to the greatest intensity of light. In the retina of the rabbit this region contains a much higher proportion of ganglion cells than any other part, and they always occur in one single row; they are similar in appearance to the ganglion cells of the human eye. This region, although large and not sharply defined, corresponds to the human macula. The changes, however, were not limited to this area, but occurred, to a minor degree, it is true, much more widely.

The most obvious changes affected the ganglion cells. Some cells showed a disintegration and bleaching of their chromatin, and the formation of vacuoles was noted. Other cells showed the presence of highly refractile acidophil granules; usually there were

PLATE II.

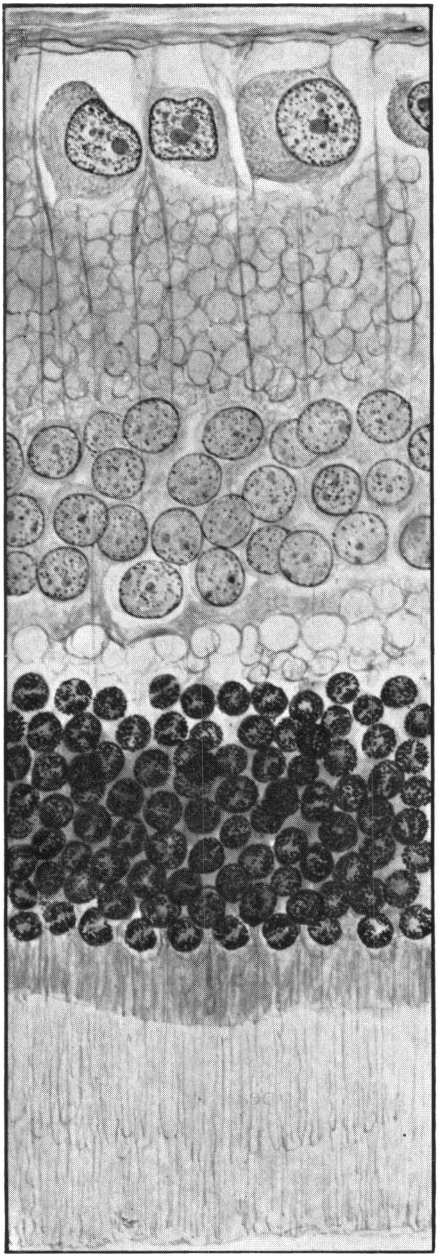

FIG. 1.

Retina from posterior pole of rabbit, 18 hours after radiation.

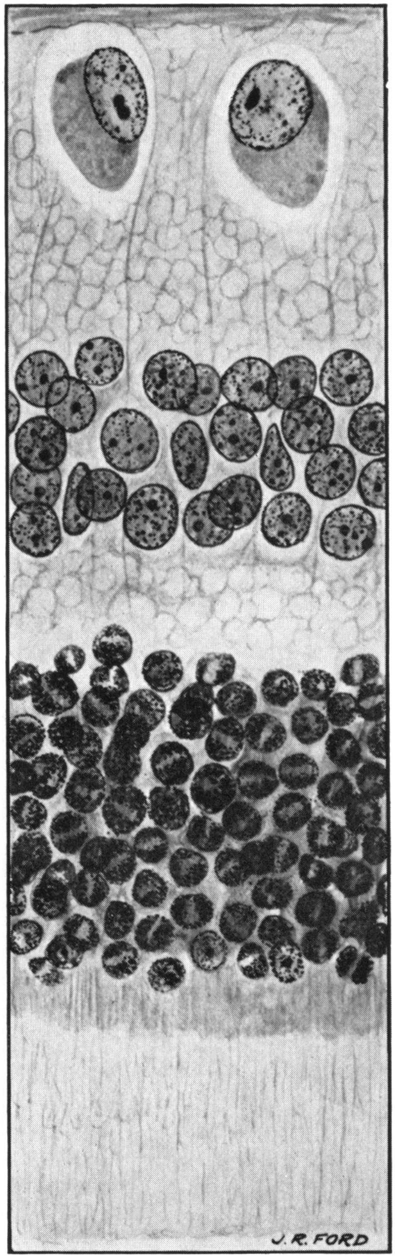

FIG. 2.

Normal retina from the other (non-radiated) eye in approximately the same region. For description see text.

only one or two present, but in some cases in the central region the whole cell took on a red stain. The inner nuclear layer showed swelling of the nuclei accompanied in places by a more or less widespread chromatolysis, while occasionally one or two red granules appeared. The outer nuclear layer appeared in some few

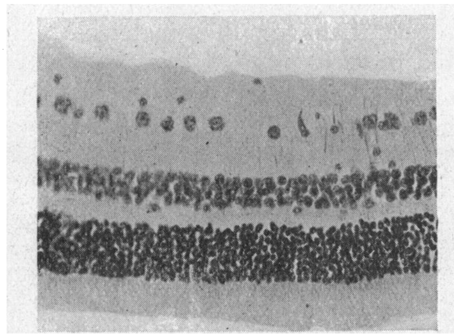

FIG. 9.

The normal retina of the rabbit near the posterior pole of the eye.

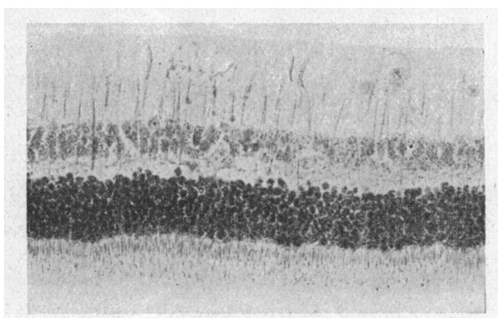

FIG. 10.

The retina from the same region as Fig. 9, 24 hours after radiation. The layer of ganglion cells has suffered most severely, and a considerable amount of chromatolysis is evident in the inner nuclear layer. The outer nuclear layer and the layer of rods and cones are to all intents and purposes normal.

cases to show a lessening of chromatin, but the changes here, if any, were always slight, while the rods and cones always appeared normal (Fig. 10).

In assessing the significance of these changes it must be remembered that there are great variations in the ganglion cells in the retina of the normal rabbit, and there are wide differences in the intensity with which the normal cells of the nuclear layers stain; but even considering these differences the occurrence of a definite change after radiation is undoubted (*cf.* Fig. 9).

The Abiotic Reaction

It is evident that very definite and characteristic changes are caused by short-waved light which distinguish it from other kinds of trauma. They are completely different from the thermal effects of infra-red rays (Duke-Elder, 1926, Bücklers, 1926). The most marked reaction is seen in the cornea, for it receives the whole of the incident energy and absorbs the greater part of it; considerably less is transmitted to the lens, and the pathological changes here do not proceed so far; a much smaller portion of the short-waved light is transmitted to the retina, and here the reaction is least of all. The reaction of all the tissues, however, seems identical in quality although it varies in degree. The ideal site to study a mild abiotic response is the epithelium of the lens capsule, while the corneal epithelium affords the best opportunity for observing a severe reaction.

Generally, the nuclei of the cells are affected in preference to the cytoplasm; indeed, with the exception of swelling, and in some cases the formation of granules, the latter appears to be relatively little affected. This conclusion is in opposition to the opinions of some investigators: Verhoeff and Bell (1916), for example, in discussing the corneal changes say that "the most characteristic change is the breaking up of cytoplasm into eosinophilic and basophilic granules," while "the nuclei are relatively unaffected." They describe the changes in the lens capsule similarly: they do not deny the possibility of a nuclear origin of these granules, but state that such cannot be traced, while "the impression is given that the cytoplasm first breaks up into, or is transformed into the eosinophilic granules, and that the basophilic granules are formed within these." Hess (1907), on the other hand, describing the lens capsule speaks of nuclei "being represented by scattered chromatin granules extruded into the cytoplasm from the still visible nuclear membrane." We subscribe to the latter opinion.

The sequence of events appears to be somewhat as follows. The first change is a lessening of the chromatin of the nucleus as is evident from the falling in intensity of the methylene blue staining. At this stage the cytoplasm swells somewhat, and usually the nuclei also appear larger. Thereafter an acidophil staining becomes evident in the nucleus: in the milder reactions the whole nucleus, or a portion of it, turns reddish, and some days later takes on the normal blue stain again. In more severe exposures highly refractile red granules appear. There may be one or two of these in the basophil nucleus, or the entire nucleus may take on the acidophil character. These granules then coalesce, sometimes into small aggregates, sometimes into large "inclusion bodies," and a nucleus may contain a very large number of the former or be entirely converted into one or two of the latter. Sometimes these appear granular, and at other times they are homogeneous, and usually they seem to be surrounded by a vacuole. On the other hand, retaining its basophil character, the nuclear material may break into basophil granules; while the two forms frequently co-exist, or a red granule may be enclosed in a blue one. At a later stage these nuclear inclusions tend to bulge out the nuclear membrane giving the nucleus a polymorphic shape, and finally they may be extruded altogether into the cytoplasm. Thereafter, if the cell is a superficial one, it appears to be cast off. At any stage before this the process may stop, and the cell return to normal in appearance and staining reaction.

With regard to the regeneration of cells there are two points which are of interest, the very great rapidity with which this occurs, and the comparative rarity with which mitotic figures are observed. Widmark (1901) originally found mitotic figures in the exposed tissues, and he regarded ultra-violet light as a direct stimulant to cell proliferation. Hess (1907) also attributed the repair of the injury largely to mitosis and not to the recovery of the injured cells, although he states that he could adduce no direct evidence of this. Martin (1912) describes numerous karyokinetic figures in the exposed areas; while Verhoeff and Bell (1916) consider that short-waved light does not stimulate but rather tends to depress mitosis. It is to be remembered that in young rabbits, particularly in the capsular epithelium of the lens near the periphery in the region of the equator, mitosis is common in the normal eye; but on the whole, considering the trauma involved after exposure to ultra-violet light and the rapid proliferation of cells after the reaction has died down, mitotic figures are remarkably few in number.

The significance of this reaction is that it is indicative of a chemical change in the proteins of the affected cells. It is only the rays which are absorbed, which can produce an effect, and the typical abiotic lesion is caused by those rays, the frequencies of which correspond with the intra-atomic oscillations within the protein molecule. The energy represented by the ray is thus absorbed into the protein molecule and produces photochemical changes of the nature of denaturation, the presence of which is made evident in the alteration of the staining reaction. When the reaction is pushed to extremes the ultimate result is coagulation of the proteins and eventual death of the cell (Bovie, 1913; Mond, 1922; and others). The latent period which elapses before any reaction is evident is presumably of the nature of a photochemical induction, a practically universal feature in photochemical reactions whereby a change does not at once assume a constant value, but increases at first slowly before a steady level is attained (Bunsen and Roscoe, 1855). The vascular reaction which appears at the limbus seems to be a secondary feature, and is not histologically evident until the abiotic changes are well advanced; it is probably stimulated by the absorption of chemical products of disintegration. The reaction is very marked in degree; there is wide dilatation of existing vessels accompanied by marked diapedesis, and in a few days, at the limbus, for example, large numbers of new vessels encircled by young fibroblasts are evident. Another characteristic feature is the infiltration with blood cells of the affected area: at first these are almost entirely eosinophils, which eventually disintegrate, to be replaced at a later stage by polymorphonuclear cells.

The Cornea and the Therapeutic Effect of Ultra-Violet Light

The marked therapeutic effect of ultra-violet applied upon the cornea in inflammatory, ulcerative, and degenerative conditions has been dealt with in a previous paper (Duke-Elder, 1928). It is probable that this effect depends upon the following five factors :

1. Pathogenic micro-organisms in the superficial layers of the tissues will be directly killed. The lethal action of short-waved light upon such micro-organisms is well known (Downes and Blunt, 1877; and many others); in a transparent tissue like the cornea this action will be much more apparent and will extend more deeply than in an opaque medium like the skin. The actively bactericidal rays are the shorter ones, the maximum effect being obtained with rays under 2,800 A.U. in length (Bang, 1912; and others), that is, with rays of that region of the spectrum which is preferentially absorbed by proteins (Henri, 1913). The cornea in its entire thickness absorbs the great majority of these active rays, and for this reason bacteria in the anterior chamber cannot be directly killed (Duke-Elder, 1926), although their vitality can be much impaired (Hertel, 1903). Where there is much infiltration and inflammatory reaction present in the superficial layers of the cornea, this will absorb most of the abiotically active rays, and any lethal effect will be practically restricted to the surface; but where this tissue is relatively transparent, bactericidal action will be greater and will extend more deeply.

2. The superficial cells of the diseased corneal epithelium are killed and cast off with any contained bacteria.

3. The intense vascular reaction round the limbus and the invasion of the cornea by blood cells and inflammatory oedema will flood the diseased area with bactericidal influences.

4. The stimulation to rapid and healthy regeneration of the exfoliated epithelium is a beneficial factor; this is most apparent in chronic and recurrent ulcers.

5. It seems probable that the absorption of the products of the disintegration of the proteins of the corneal cells will influence the immunological reaction for good.

The Lens and Cataract

Many conflicting views have been expressed about the effect of ultra-violet light upon the lens. After radiation Widmark (1889-1901) obtained a well marked opacity, while Bresse (1891), Ogneff (1896), and Strebel (1901) failed to note any change. Herzog (1903) obtained cataractous changes, but these may have been due to heat which readily produces this effect. Hess (1907), Birch-Hirschfeld (1909), in one experiment, and Martin (1912), also in one experiment, found definite histological changes in the lens capsule. Chalupecky (1913) produced coagulation of the lens proteins, and Verhoeff and Bell (1916) confirmed the capsular changes described by Hess, and noted damage to the lens fibres histologically evident in a layer of microscopic thinness immediately under the capsular epithelium. Later investigators, Chotzen and Kutznitzky (1918) Trümpy (1925), and Toulant (1926), reported negative results.

The possibility of an abiotic trauma to the lens depends of course, upon the character of the radiant energy incident upon it and absorbed by it. A considerable amount of experimental work has been done upon this question, and it may be considered to be definitely settled. By spectrographic studies the limit of corneal absorption may be taken to be from 2,930 A.U. to 2,950 A.U., both in man and in the majority of animals (Brucke, 1845; de Chardonnet, 1896; Schuleck, 1899; Soret, 1897; Schanz and Stockhausen, 1908; Birch-Hirschfeld, 1909; Parsons, 1910; Hallauer, 1909; Martin, 1912; Takamina and Takei, 1912; Shoji, 1923; Mitchell, 1922; Graham, 1923). These measurements have been verified lately by Hoffmann (1927) in the living eye of man; throwing spectrally separated ultra-violet light on the cornea, and taking as an index of its transmission the appearance of fluorescence in the anterior chamber after the exhibition of fluorescein salts by the mouth, he found that light of a wave length above 4,930 A.U. was transmitted. Waves of this length and upwards fall upon the lens, and, since these are abiotically active, some abiotic trauma can potentially be caused. It is true, that the effectivity of these longer rays is comparatively small, but such an activity is definitely present up to 3,050 A.U. at least (Henri, 1902-12; Hertel, 1905; Browning and Russ, 1915; Mashimo, 1919; Newcomer, 1918; Hill, 1922). It is evident that the histological changes which have been described above, are direct evidence of a trauma which light can produce.

These changes should be considered from two aspects. In the first place, the sub-capsular epithelial cells are very definitely injured; and the capsule itself becomes swollen in places and loses the histological definition of its outline. The result of this will be an impairment of the semi-permeability which it normally possesses and consequently an abnormal diffusion of electrolytes of the aqueous into the lens will result, a process which will disturb the physical condition of the proteins of this tissue. It is proposed to publish shortly some experimental researches dealing with this subject in more detail from the physico-chemical point of view.

With reference to the "wall" formation of cells which appears in the pupillary area, several opinions have been expressed, none of which appears to be entirely satisfactory. Hess (1907), who originally described it, attributed its occurrence as secondary to the damage caused to the central cells of the capsule. He observed that these became swollen, and suggested that they thus compressed and heaped up the marginal cells: the appearance of the sections, however, does not suggest that this is a likely explanation, for the phenomenon seems an active proliferation rather than a passive heaping up. Martin (1912) assumed that the proliferation was due to the stimulation caused by submaximal damage to the cells at the pupillary margin, but it is significant that subliminal exposures to the pupillary area itself have never been known to produce any such effect. The proximity of the zone of cells to the margin of the iris might suggest that the effect was due to heat, since the pigment of this structure will absorb all the energy incident upon it and degrade it into heat. It is well known that heat of an intensity just below that necessary to cause tissue destruction produces cell proliferation, but this cell proliferation is always accompanied by considerable karyokinetic activity and never by the acidophil staining which characterises the abiotic response. Verhoeff and Bell (1916), indeed, produced a somewhat similar "wall" by radiating the eye of a rabbit with infra-red rays, but in this case the cells composing the "wall" were in the state of active proliferation characteristic of the response to heat, almost every cell being in some stage of mitosis. In the present case mitotic activity is conspicuous by its absence, and every cell shows profound chemical changes rendered evident by its altered staining reaction. Moreover, a somewhat analogous appearance is seen in the cornea as will be evident from Plate I, Fig. 2, where a somewhat similar "wall" is formed. Here, at the margin of the most traumatized region, the epithelial cells appear heaped up in many layers and to have multiplied considerably without any evidence of mitosis: this effect obviously cannot be due to heat.

In this connection two points are to be noted. First, the changes which are produced by ultra-violet light are purely chemical in nature, and may be simulated by other chemical irritants. It is significant that Verhoeff and Bell (1916), by injecting Lugol's solution into the anterior chamber of a rabbit's eye, produced a similar appearance, the cells showing the presence of eosinophilic and basophilic granules; while a similar "wall" was found four days after the injection of staphylococci into the anterior chamber, although here there was no formation of granules. On the other hand there is evidence that ultra-violet light may stimulate cell proliferation: the rapid regeneration of the exfoliated corneal epithelium after radiation, whether it is done experimentally or therapeutically, even in the case of ulcerated tissue, suggests that this may be so. It is true that this conception is contested by many authorities and that it is requiring further elucidation, but it has been remarked by several investigators. Bovie (1916) concluded that if the decomposition of the protein molecule is not carried too far, there is a stimulation of the cell. Browning and Russ (1918) found that radiated organisms appeared to be stimulated in their growth in the region of the culture-plate lying between two portions which had been exposed. Coblentz and Fulton (1924) also found that a similar increase was always observable, when radiating bacteria on Petri dishes, in the shadowed portion of the dish surrounding the region exposed to the ultra-violet rays. These may be associated phenomena from which it may be legitimate to draw analogies to the peculiar appearances in the lens capsule, or they may not: it cannot be said that any adequate explanation is as yet forthcoming.

With regard to the lens substance the histological evidences of trauma are much less obvious. The microscopic layer of damaged fibres which is seen directly underneath the subcapsular epithelium is probably not of much importance; the chemical changes in the nuclei are perhaps of more significance. Any changes produced in the fibres themselves in the main body of the lens are not of a nature to be demonstrated by histological methods. They are of a physico-chemical nature, affecting the autoxidation system upon which this tissue depends for the continuance of its metabolism (Adams, 1925), and altering the lability of the lens proteins, rendering them more susceptible to subsequent coagulation by other influences. It is proposed to publish further investigations dealing with this subject in the near future, but in the meantime it would appear that (as far as experimental evidence goes) short-waved light cannot be exonerated from participating in the pathogenesis of cataract.

Nor is clinical evidence on this point entirely lacking. Carlo (1914) described the case of an engineer, aged 36 years, who had worked for three years with mercury vapour lamps, and ultimately developed a posterior cataract. Scheerer (1926) described two similar cases where after therapeutic treatment of lupus with ultra-violet light, a posterior opacity, morphologically of the same type as a typical glassblowers' cataract, was produced. It would seem, indeed, that opacities of much the same clinical form are produced by the absorption by the lens of any part of the energy-spectrum. Thus the long infra-red (heat) rays have frequently been shown to produce opacities experimentally (Vogt, 1912; Richen, 1913; Grinella, 1924; Müller, 1924; Kranz, 1925; Bückler, 1926; Duke-Elder, 1926), while its clinical occurrence is well known in the cataract of glassblowers (Royal Society Report, 1928), iron workers (Cridland, 1913), tin workers (Healy, 1921), chain workers (Roberts, 1921), and gold smelters (Brinton, 1913). Similarly, the very short X-rays and the emanations from radium have been found to produce experimental cataract (Birch-Hirschfeld, 1904-8; Tribondeau and Belley, 1907), and therapeutic exposures to these rays have frequently been observed clinically to produce lenticular opacities, the majority of which are in the posterior cortex and are of the same nature (Birch-Hirschfeld, 1908; Paton, 1909; Axenfeld, 1915; Wilkinson, 1920; Salzer, 1921; Horay, 1922; Dor, 1923; Pfahler, 1924; Ziegler, 1924; Ascher, 1925; Scheerer, 1925; Erggelet, 1928; Stock, 1928; Rohrschneider, 1928; Meesmann, 1928).

The Retina

The interpretation of the changes produced in the ganglion cells and in the inner nuclear layer of the retina presents several difficulties. Attention has already been drawn to the fact that similar changes were noted by Birch-Hirschfeld (1904) alone among former observers, as occurring to a slight degree in the normal rabbit, and to a more marked degree in the aphakic rabbit. Other writers have consistently failed to find them, among whom Verhoeff and Bell (1916) made detailed experiments with a view to their investigation, using both normal and aphakic rabbits, monkeys, and in one case the eye of a woman prior to its excision for carcinoma of the lid. It is to be noted that the retinal changes produced by ultra-violet light are completely different from those caused by direct sunlight, for example in eclipse blindness. Here the lesion is a thermal one; the light traverses the superficial layers of the retina until it reaches the pigment epithelium where it is absorbed and degraded into heat. A burn is produced, which spreads from this point as a centre, giving rise to a lesion on either side, in the choroid and in the retina. In the latter tissue the layer of rods and cones is primarily affected, and the lesion spreads with progressively decreasing intensity outwards. In the case of ultra-violet, however, the greatest effect is produced in the layer of ganglion cells, and the changes diminish progressively inwards; moreover the latter reaction has all the appearances of the abiotic response and is quite different from that which results from heat. If any changes of this nature occur after an injury due to concentrated sunlight, they are completely masked by the preponderating effect of the thermal lesion.

If short-waved light can produce an injurious effect, there are two ways in which this can be brought about: either by a direct abiotic action upon the tissues of the retina, or by an over-stimulation of the physiological mechanism of vision. The first of these possibilities depends on the nature of the light which is transmitted by the lens, since this tissue has a greater absorbing power than the other dioptric media. As with the cornea, the transmission and absorption of light by the lens has attracted a great deal of research. The amount absorbed varies very largely with the age of the individual and the degree of sclerosis of the lens, but on the whole it appears that comparable results are obtained both in the laboratory animals and in man.

The question may be approached from three aspects. By the method of spectrographic registration it has been demonstrated that, on the average, the limit of transmission varies from the region of 3,210 A.U. to 4,000 A.U., although the amount transmitted below 3,500 A.U. is relatively small (for bibliography see cornea). In a child, Hallauer (1909) found some transparency down to 3,100 A.U.; Mitchell (1922) to 3,040 A.U.; Shoji (1922) demonstrated that, at four years of age, wave lengths of 3,050 A.U. were transmitted, of 3,083 A.U. at seventeen years, and of 3,125 A.U. at twenty-three years, while in the average rabbit the limit was 3,211 A.U. Graham (1923) obtained a limit in young human subjects of 3,134 A.U., and Sheard (1923) of 3,150 A.U. In old people, on the other hand, the limit is much higher, being above 4,000 A.U. (Hallauer, 1909; Graham, 1923). The absorption of light by the lens may also be studied by the observation of the phenomenon of fluorescence; this is particularly evident from 3,500 A.U. to 4,000 A.U., with a maximum from 3,700 A.U. to 3,800 A.U. (Hallauer, 1909; Hoffmann, 1927). Provided we admit the sensation of vision is excited by all wave lengths in this region of the spectrum, the lower limit of transmissibility may also be determined by observing the lower limit of spectral visibility. In the estimation of this, some confusion has arisen from a lack of adequate experimental technique, and from a failure to eliminate the effect of fluorescence in the lens; for this reason some of the work of the earlier observers can only be accepted with caution. The lower limits given in the literature are these; Stokes (1852) 3,350 A.U.; Helmholtz (1855) 3,180 A.U.; Listing (1865) 3,720 A.U.; Sekulic (1872) 3,580 A.U.; Mascart (1883) 3,130 A.U.; Soret (1893) 2,940 A.U.

(probably wrong); Eisenlohr (1856) 3,950 A.U.; Sauer (1875) 3,950 A.U.; Chardonnet (1883) 3,420 A.U.; Widmark (1898) 3,860, and in aphakic eyes 3,130 A.U.; while Birch-Hirschfeld (1908) obtained comparable results. Glancy (1923), using an adequate technique, found that the spectral lines began to fall off in intensity below 4,000 A.U., but that they were still visible at 3,170 A.U.

It would appear, therefore, that while practically all rays above 4,000 A.U. are transmitted to the retina, the lens begins to absorb an increasing amount up to 3,500 A.U., and then the greater portion of the incident light up to a limit of 3,150 A.U., below which absorption is complete. It would appear therefore that in the average eye the retina is reached by no rays shorter than 3,150 A.U., and only by very small intensities for a considerable spectral range above this. It is generally accepted that light of these wave lengths exerts no observable abiotic action, the upper limit of which, as we have seen, is usually put at 3,050 A.U.; even here the action is extremely slight, requiring long exposures at high intensities. Two workers, it should be noted, have recorded observations which suggest that some abiotic action, as is rendered evident by a bactericidal effect, is possible for rays longer than this: Bayne-Jones and Lingon (1923) putting the limit at 3,500 A.U., and Coblenz and Fulton (1924) putting it at 3,650 A.U. Even if these latter results be accepted, any action is extremely slow and requires very high intensities of energy, much higher than was possible under the conditions of our own experiments. In our own investigations we have been completely unable to obtain any abiotic effect either on the cornea, which can be radiated with very great intensity, or on the lens capsule, by rays longer than 3,050 A.U. (Duke-Elder, 1926), a finding which corroborates the work of Verhoeff and Bell (1916), and Trümpy (1924). The conclusion seems therefore forced upon us that if the retinal lesions are due to the direct abiotic action of light, then this tissue must be in some way sensitized to rays longer than those to which other tissues normally respond, just in the same way as a photographic plate is sensitized to visible rays. There is nothing, of course, intrinsically impossible in this.

The distribution of the lesions which were observed, however, would suggest that direct abiotic action is not responsible for these retinal changes. If it were so one would expect that the lesion would be confined to a small area in the posterior pole of the eye, corresponding to the image of the source of light. Its distribution would thus be comparable to the thermal effect produced in the macular region in sun-blindness. In the present case, although an area in the posterior pole of the eye was the most markedly affected, yet changes were observed over a very widespread region. A similar widespread distribution was observed by Birch-Hirschfeld

(1909), and this strongly supports his suggestion that the cause is an over-stimulation of the retinal mechanism of vision.

A considerable amount of work has been done which shows that definite histological changes occur in the retina on stimulation by light, apart from the gross thermal lesions produced by concentrated sunlight. Benissenko (1887) noted widening of the pericellular spaces around the ganglion cells, and similar changes in the nuclear layers. Angelucci (1887-94) noted somewhat similar changes, and Mann (1895) observed a lessening of chromatin in these two regions in the retina of the dog. Bach (1895) could detect no difference between the dark-adapted and the light-adapted eye of a rabbit; Abelsdorff (1901) and Schüpbach (1905) obtained similar negative results. Pergens (1896), however, demonstrated a lack of chromatin in the ganglion cells, a result confirmed by Birch-Hirschfeld (1900-4-6-9). Shiarni (1904) found the chromophil bodies in the ganglion cells less distinct, Carlson (1904) noted a lack of Nissl granules in these cells, and Sgrosso (1905) found that the cells of the nuclear layers tended to take on a staining with fuchsin in the light, while they stained preferentially with methylene green in the dark. These changes have a resemblance in kind, though not in degree, to those noted by Birch-Hirschfeld (1904) as following ultra-violet light radiation, and to those described in the present paper; it is interesting that with the still shorter waves, X-rays and radium, Birch-Hirschfeld (1904) obtained gross changes in the outer layers of the retina which progressed to complete disintegration of the cells.

Furthermore, there is evidence that ultra-violet light produces functional impairment of the retina. Birch-Hirschfeld (1908) noted the development of colour scotomata and a constriction of the peripheral field in workmen after the photophthalmia following habitual exposures to a mercury vapour lamp, and his findings, up to a certain extent, were confirmed by Simon (1921). In snow-blindness, also, functional disturbances have been noted—amblyopia (Widmark, 1893), and a central scotoma (Best and Haenel, 1907); while there is evidence that these functional disturbances are more evident in aphakic eyes (Hayashi, 1925). Further, according to the observations of Behr (1912) and Heine (1926) there is a marked reduction in the adaptation power after prolonged exposure to sources rich in short-waved light. It must be admitted, however, that measurements such as these are readily susceptible to functional fallacies (see Birch-Hirschfeld, 1927), and the work of Siegfried (1928) would seem to indicate that this impairment of the power of adaptation cannot be detected under experimental conditions.

Little is known of the intimate mechanism of the physiological processes which the stimulation of light excites in the retina, but certainly these processes are fundamentally photo-chemical reactions. The action of short-waved light on any tissue is also photo-chemical in nature, and presumably bears some relation, though not necessarily a completely parallel one, to the changes occurring normally in the retina. The shorter waves of light have a greater chemical activity than the longer waves, and it would seem possible that a chemical process which remains within physiological limits when initiated by the latter, could readily overstep these limits and attain pathological dimensions when excited by the former.

These observations may perhaps be interpreted as lending some colour to the suggestion of van der Hoeve (1919) that senile macular degeneration (Haab) may depend in some degree upon the influence of an excess of short-waved light upon the retina. Van der Hoeve supported his theory by statistics which tend to show that this disease rarely occurs in combination with senile cataract, and he argues that, while an opaque lens will protect the retina by absorbing and dispersing the light, a transparent lens will allow some actinic rays to pass through, which may eventually exert a deleterious action. His statistical evidence is supported by Gjessing (1925); but the statistics of Fischer (1926) and of Birch-Hirschfeld (1927) are not so unequivocal. They certainly show that the one disease is not by any means exclusive of the other, but van der Hoeve (1927) interprets their figures as showing that a relative antagonism does exist. While the cumulative action of small amounts of damage accruing over many years is a factor which must be taken into account, the conception must be viewed with reserve and the theory regarded as unproven.

Inclusion Bodies

It is impossible to study the corneal changes that occur in the abiotic reaction to light, without being struck by the strong resemblance to some of the changes which have lately been described in the corneal lesions of herpes. It will be remembered that Grüter (1912-1914) first made successful experiments with the vesicular fluid of herpes corneae, showing that it was transmitted from cornea to cornea in rabbits. His work was not published until 1920, when he obtained successful inoculations of a rabbit's fluid in a blind human eye. The first published work on experimental herpes was that of Löwenstein (1919-20) who described in the corneal epithelium "elementary corpuscles" resembling those depicted by Lipschütz as occurring in molluscum contagiosum. In the next year Lipschütz (1921) described in great detail acidophilic "nuclear inclusions" in the corneal lesions of herpes. They occurred mainly in the corneal epithelium, were sometimes homogeneous, sometimes granular, and usually surrounded by a clear zone; they had a strong affinity for acid dyes, were most numerous twenty-four hours after inoculation, and had disappeared within seven days. He considered them as an expression of an oxyphil reaction of the nuclear chromatin to the herpetic virus, and stated that these bodies indicated the local presence of the virus of herpes itself. He identified them with a class of intra-nuclear inclusion bodies or "chlamydozoa" which occur in other diseases as variola, vaccinia (Tyzzer, 1906), molluscum contagiosum (Lipschütz), and trachoma (Halberstädter and Prowazek, 1907; Greef, 1907; and Noguchi, 1915).

During the years that followed a vast amount of work was done upon the question. The researches of Doerr (1921), Blanc (1921), Caminopetros (1921), Gaviati (1922), Friedenwald (1923), and Levaditi and his associates (1922-7), and many others fully confirmed the experimental appearance of the inclusion bodies both in the corneae of animals and of man (Fuchs and Lauda, 1921); moreover, Levaditi (1921), Zdamski (1923), da Fano (1923), and others demonstrated their occurrence in the central nervous system; while Goodpasteur and Teague (1921) found them in a large number of tissues in herpetic lesions (cornea, retina, conjunctiva, buccal mucosa, skin, liver, adrenal, ovary, testis, spinal cord, etc.). Similar appearances were also described in vaccinia, chicken pox, small pox, and several other infections, in many of which their presence was not confined to the epithelial cells alone. A considerable time previously, Head and Campbell (1900) had demonstrated an increased affinity for acid dyes in sections of the posterior root ganglia in lesions of herpes zoster.

The interpretations put upon these inclusion bodies were, however, by no means in agreement. On the one hand Kooy (1921) believed that they were the actual infective agent itself in herpes. Lipschütz (1921), it has been noted, considered that their presence indicated the presence of a combination of the cell substance with the virus. Levaditi, Harvier, and Nicolau (1921-27), and Doerr and Schnabel (1921) regarded them as peculiar nucleolar changes caused by the virus. Luger and Lauda (1921), on the other hand, regarded them as cell degenerations of dubious specificity, and cast doubt on their necessary association with herpes. Goodpasteur and Teague (1923), on the contrary, maintained that they were specific, and regarded their occurrence as the only reliable histological criterion of the presence of the herpetic lesion. They considered that their growth and increase in size were due to the proliferation of the virus, and they concluded that "their presence is *prima facie* evidence of the local presence of herpes or a similar virus," while that in their absence a lesion could not, from the histological standpoint alone, be definitely attributed to herpes.

Summarising the position in 1923, da Fano pointed out the universal presence of these intra-nuclear inclusions, but he considered that a definite opinion could not be expressed as to their nature, although he surmised that they were not specific. Cowdry and Nicholson (1923), commenting on the various types of inclusion bodies (found in the brain) divided them into oxyphil bodies and basophil bodies, which they interpreted as coagulations of the nucleoplasm, minute bodies, which they considered mainly as nuclear débris, and large extra- and intra-cellular inclusions, regarding the nature of which they accepted da Fano's explanation as representing in large measure a progressive fragmentation of the nuclei. They concluded that they represented no concrete class, but were of variable composition and were derived from various sources, an opinion which Zdamsky (1923) confirmed. In contradistinction to this, Löwenthal (1927), considering these bodies the most regular microscopical finding in the herpetic cornea, suggested that they were specific and diagnostic, and represented a stage in the cycle of development of a protozoon.

Not only do the inclusion bodies which are found in the abiotic reaction resemble very closely in structure and development those described in the lesions of herpes, but other changes—the presence of oxyphil and basophil granules, the swelling and oedema of the cells, the desquamation of the epithelium and the course of the general reaction—show many points of analogy. It seems, moreover, to be definitely established that these bodies occur in diseases other than herpes. In the case of the abiotic injury caused by light, the presence or action of a specific virus does not enter into the question: the reaction is merely the expression of chemical changes of degeneration occurring preferentially in the nucleus. It seems impossible to avoid drawing the analogy that similar appearances described in herpes (and also, for that matter, those in trachoma, although the resemblance is not so close) are of a similar non-specific nature, being essentially an oxyphil degeneration representing chemical changes in the nuclear proteins consequent on a traumatism by the virus.

Conclusions

The clinical and histological appearances of the abiotic reaction to light as seen in experimentally radiated animals are described in the cornea, the conjunctiva, the iris, the lens, and the retina. The changes observed in all these tissues are the same in kind although varying in degree. The most interesting and characteristic of these changes is an oxyphil degeneration affecting particularly the nuclear chromatin, which may progress to the formation of acidophil granules or of granular or homogeneous nuclear inclusions. Originally intra-nuclear, these may be extruded into the cytoplasm with disintegration of the nuclei, a process which may culminate in death and disintegration of the cell. The reaction is characterised by an intense vascular engorgement, in places where that is possible, and is followed by rapid regeneration and resolution in which the absence of karyokinetic activity is notable.

The nature of the general abiotic reaction of living tissue is discussed, and it is pointed out that its basis is a photochemical denaturation affecting the proteins of the cells.

With regard to the cornea, the therapeutic effect of ultra-violet light in inflammatory, degenerative, and ulcerative conditions is discussed.

With regard to the lens, two separate effects are demonstrated, the first, markedly evident histologically, affecting the capsule and the subcapsular epithelium, the second, less histologically evident, affecting the lens substance. The significance of both of these in the pathogenesis of cataract is dealt with. It is concluded that, in common with other regions of the energy-spectrum, ultra-violet radiations cannot be exonerated from a share in the aetiology of this condition. The subcapsular epithelial "wall" is described, but although several relevant influences are dealt with, no satisfactory explanation of its occurrence seems forthcoming; a similar appearance is seen in the corneal epithelium.

Definite abiotic changes are described in the retina affecting mainly the ganglion cells and the inner nuclear layer. These consist essentially of a chromatolysis and an acidophil tendency. The significance of these changes is discussed, and the conclusion is suggested that they are rather of the nature of a pathological intensification of physiological processes of vision than a direct abiotic response, although the occurrence of the latter in a specially sensitized tissue is not altogether impossible.

An analogy is suggested between the nuclear appearances of abiotically traumatized tissue and the inclusion bodies described as occurring in the lesions caused by the herpetic and other viruses, and possibly also in trachoma. The analogy tends to support the opinion that these appearances are degenerative in nature and non-specific in origin.

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ANNOTATION

Ophthalmic Treatment in the early XIXth Century

In the *Farington Diary*, Vol: IV, 1807, occurs the following account of an ophthalmic condition and its treatment. On September 19th, "at ½ past 1, called upon Mr. Watkin Phipps, oculist, in Cork Street, Burlington Gardens, who examined my eyes and told me that my complaint was seated in the *eye lids*, which from having been overexerted had lost their tone, and did not properly supply moisture for their functions. He recommended me to apply a large sponge, steeped in water *as hot as I could bear it* to my eyelids for the space of 6 or 7 minutes 4 or 5 times a day, and to call on him again on Monday next, when he shd. better be able to determine what to do. I dined alone. His hours for receiving patients from ½ past 1 till 4 every day except Sundays. I gave him one guinea. Sept. 21st. Watkin Phipps I went to who applied a sharp stimulus to my eyes. Directed an ointment to be touched to the edges and corners of my eyes for a