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### COMMUNICATIONS

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#### THE NATURE OF THE OCULAR LESIONS PRODUCED EXPERIMENTALLY BY NAPHTHALENE\*

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It may appear a strange digression from clinical ophthalmology to discuss the action upon the eye of such an unphysiological substance as naphthalene. It has long been known, however, that dosage with this substance is a convenient method for the experimental production of cataract, especially in rabbits, and as Burdon Cooper has pointed out (Doyle Memorial Lecture, 1922)—“Naphthalene cataract is one of the most important experimental cataracts, as of all the types it most resembles the subcapsular senile variety, and it gives us some indication where to look for the cause of the human disease.” This view is being justified by the fact that recent investigations of naphthalene cataract, performed from the biochemical standpoint, have yielded results which suggest that naphthalene may produce its effects through a metabolic disturbance rather than by any specific toxic action. The comparison of these biochemical changes with any which may occur in human senile cataract has, however, yet to be made, in order to reveal any similarity between the two conditions.

The lens is by no means the only intra-ocular structure which is

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affected by naphthalene. Retinal exudates, the deposition of crystals in vitreous and retina, and changes in the ciliary body have also been described. In nature and variety they are of sufficient ophthalmological interest to merit description, since they do not seem to have been recorded by any other observers in this country. In addition, although they appear as the result of an artificial process they may add to our knowledge of the way in which pathological changes in one intra-ocular tissue may affect another, and as to how metabolic changes in the body as a whole may affect the eye.\*

In order to bring our knowledge of the subject into a form available for reference, a brief review of the work of previous observers will be made as a preliminary to my own observations. The latter are the result of investigations on about sixty rabbits which were dosed with naphthalene and on which a number of biochemical investigations were made which will be recorded at a later date. Some of the rabbits, which showed typical lesions have been demonstrated previously. (See *Proc. Roy. Soc. Med.*, September, 1929.)

In the second part of this paper an account will be given of certain features of the production and sequence of the ocular lesions, and of the nature of the retinal exudates and crystalline deposits.

### Part I.—A Review of the Literature

The subject may be reviewed under the following headings:—

1. The development of cataract. 2. Retinal lesions. 3. Crystalline deposits. 4. Disturbances in the ciliary body. 5. General and metabolic changes.

1. *The development of cataract.*—A good description has been given of the changes which occur in the lens, and of the manner in which they vary. There was, in fact, a great variation in the times of onset of the lens lesions, and in the dosage requisite for their production. Thus Bouchard and Charrin (1886) obtained bilateral cataract in 20-25 days after a daily dose of 1.5 to 2 gm. of naphthalene, while Panas (1887) gave a larger dose of 3 gm. and still did not get cataract for a month. In striking contrast is the observation of Dor (1887) that lens lesions appeared on the 7th day after a daily dose of 1 gm., while Helbron (1889) records lens striae on the 2nd day after a total dose of 15 gm., and Magnus (1890) got the first opacity within the first 24 hours, after giving a large dose of 10 gm. to an old rabbit or 1 gm. only to a

\* It is interesting to note that few human cases have been recorded, in which naphthalene was administered therapeutically or was acting as an external irritant. Thus Lezenius (1903) and Caspar (1917) observed lens and corneal lesions and van der Hoeve (1907) found choroido retinitis.

young one. Michail and Vancea (1927) for routine experiments began with a daily dose of 1 gm. and increased it by 0.5 gm. each week, so that lens lesions developed in 12-20 days. They found that by keeping animals in the dark, or by sewing up the eyelids, the appearance of cataract was delayed.

Nearly all observers are agreed in their descriptions of the lenticular changes. There is an initial increase in volume of the lens, within a few hours after dosage, which causes irregularities in the anterior surface. Salfner (1904) has proved fairly conclusively that imbibition of fluid actually occurs, while Panico (1928) states that swelling occurs chiefly in the antero-posterior diameter. Both Salfner and Panico have found that lenses placed in the serum of naphthalinized animals show a greater increase in volume and weight than when placed in normal serum.

The swelling may be followed within 24 hours by the appearance of vacuoles radiating from the periphery towards the centre of the lens. These disappear quickly (Panico, 1928) and are followed by true opacity of the lens fibres which begins at the periphery and spreads through the cortex first and then through the nucleus. In the final stage the lens becomes milky-white and may develop grey or brown pigmentation (Panas, 1887, Michail and Vancea, 1927). The lens changes are usually complete within about 5 days from their onset, and advance simultaneously in both eyes.

It is the general opinion that cessation of the dose after lens changes have once begun, does not prevent their further development, but Panico (1928) states that complete retrogression may occur if the first two stages are the only ones present, *i.e.*, if there is no true opacity. Takamura (1911) found that a 5 per cent. solution of potassium iodide given to rabbits which had been previously dosed with naphthalene, had no preventive effect.

Histologically naphthalene cataract has been said to resemble senile cataract (Hess, 1887) and even diabetic cataract (Kolinski). Klingmann (1897) describes the separation of fibres by homogeneous material and the later appearance of vacuoles in the fibres. Salfner (1904) found proliferation of the inner layer of epithelium in the posterior capsule of the lens, while Panico (1928) states that the first changes occur in the anterior capsule—and lead to a subcapsular accumulation of fluid. The reader is referred to Busacca (1927) for a minute account of the histology of naphthalene cataract.

2. *Retinal lesions.*—The general description of the retinal exudates is rather vague, since their occurrence has not been emphasised. They seemed to appear first on the 3rd or 5th day as greyish-white globules, scattered over the retina. Each globule had a depressed centre which gave a bright reflex, while later they became confluent. (See Panas, 1887; Dor, 1887; Curatulo, 1889;

Kolinski, 1890; Ovio and Manca, 1896-8; Helbron, 1899; Igersheimer and Ruben, 1910; Takamura, 1911.) According to Dor (1887) the exudates retrogressed after cessation of the dose, and left small haemorrhagic areas in the retina so that the latter resembled the condition found in pernicious anaemia or leukaemia.

Igersheimer and Ruben (1910) describe another type of diffuse retinal exudate, which did not begin as isolated globules and could be identified histologically as an exudate between the pigment cell layer and the retina.

According to Panas (1887) exudates occurred (a) between the retina and vitreous, and (b) between the pigment cell layer and the rods and cones—thus causing localised detachments of the retina. The exudates consisted of albuminous fluid containing a large number of leucocytes. In addition there were a number of degenerative changes, viz., the appearance of cystic spaces among the nerve cells of the retina which were themselves degenerated and showed chromatolysis, while the ganglion-cells were most affected. In the late stage migration of pigment was said to occur from the pigment cell layer into other layers of the retina, while according to Kolinski (1889) and Takamura (1911) the optic disc was oedematous and infiltrated with leucocytes. The choroid was hyperaemic and showed degeneration and pigmentation in the later stages.

According to most observers (see Panas, Dor, Curatulo, Igersheimer and Ruben, Michail and Vancea, etc.) the retinal lesions preceded the lens changes—and Panas (1887) suggested that the latter were due to the lack of nutrition consequent on the atrophic state of the retina. Hess, Magnus, Helbron and Kolinski maintained that the lens changes were entirely independent and might even occur before the retinal changes.

Altogether there seems to have been no clear opinion as to the nature of the histological changes which correspond to those seen in the retina during life.

3. *Crystalline deposits*.—These have been described by Panas, Curatulo, Kolinski, Helbron, etc., as a deposition of bright crystals throughout the vitreous resembling *synchisis scintillans*, followed later by a deposition of crystals in masses on the retina, so that the latter resembles a "clear starry heaven." According to these observers they did not appear until at least three weeks after the initial dose. Snellen (1898) states that their appearance was inconstant, while Hess (1887), Igersheimer and Ruben (1910), Michail and Vancea (1926-7), Panico (1928) make no record of their appearance.

According to Kolinski the crystals have been seen histologically in every layer of the retina except in the rod and cone and inner nuclear layers. In one case, *e.g.*, in a rabbit which had been dosed over a period of 7 months similar deposits were seen in the cornea

and lens capsule. Kolinski found that the crystals in the retina were either needles, plates or prisms, arranged in spheroidal or plate-like groups. Little effort has been made to identify them—since Curatulo, Magnus, Helbron and other early observers were content with the conclusion that they must be naphthalene or failing that, cholesterol. Panas (1887), solely from their microscopic appearance, made the suggestion that they were calcium salts,—sulphates, carbonates, oxalates or phosphates, while Salfner (1904) thought that they might be a naphthalene derivative in combination with calcium.

4. *Disturbances in the ciliary body.*—Earlier observers laid great stress on the importance of the ciliary body to the nutrition of the eye, and were of the opinion that naphthalene cataract was entirely due to a disturbance in the ciliary secretion. (See Hess, Kolinski, Klingmann, Sala (1903), Peters (1902), and Lindberg (1922), etc.) Thus hyperaemia, small haemorrhages and vacuoles in the ciliary body have been described, while miosis seems to have been an early clinical feature (Igersheimer and Ruben, 1910). Peters has suggested that the aqueous humour becomes more concentrated, so that its salts and proteins are increased. In opposition to this hypothesis of the deleterious effect of concentrated salt solution on the lens *in vivo*, Salfner (1904) found that injection of a 25 per cent. salt solution into the ear vein of a rabbit did not affect the clarity of the lens. More recently Komura (1928) found a fall in intra-ocular pressure in rabbits after the administration of naphthalene and ascribed it to a defect in the ciliary secretion, since also, the aqueous humour which was regenerated after paracentesis, did not show an increase in protein content comparable with that which occurs in the normal animal. On the other hand, the changes found by Panas, Salfner, Takamura, Igersheimer and Ruben, and Panico were so slight that it is doubtful whether the defect in the ciliary body could be considered as the primary factor.

5. *General and metabolic changes.*—In the majority of cases which developed ocular lesions the animals remained quite healthy, but a few of the younger ones showed toxic signs which occasionally caused death before their eyes were affected. (See Hess, 1885; Magnus, 1890; Kolinski, 1899; Faravelli, 1893; Klingmann, 1897.) According to Igersheimer and Ruben (1910), these cases were exceptionally severe, but it is quite possible that the usual effect of the administration of naphthalene is either the production of a chemical toxin or a disturbance of the normal physiological balance in the body.

It is not proposed to enter fully in this paper into the chemical aspect of the problem, but the history will not be complete without a brief record of previous work of this type. Thus Bouchard and

Charrin (1886), Kolinski (1889), Salfner (1904), van der Hoeve (1907), Igersheimer and Ruben (1910), and Takamura (1911) have studied the effects of the administration of derivatives of naphthalene, while the metabolism of naphthalene in the body has been investigated by Bouchard and Charrin (1886), Penzoldt (1886), Lesnik and Nencki (1888), Filehne (1898), Edlefssen (1904), and Igersheimer and Ruben (1910), without producing any clear proof that the ocular lesions are produced by the toxic action of naphthalene or any of its derivatives.

More recently Kuwabara (1911), Takamura (1911), Goldschmidt (1917), Michail and Vancea (1926-7), Cade and Barral (1928), and Komura (1928) have studied the variation in different constituents of the blood following the administration of naphthalene.

### Part II.—Experimental Work

In the first few experiments there was almost as much variation in the times of appearance and subsequent rate of development of the different ocular lesions as was recorded by previous observers. It was found to be due chiefly to the size of the dose used, especially of the initial dose (*cf.* Salfner, 1904), and to a difference in the animals—young rabbits being very much more susceptible than older and larger ones (*cf.* Magnus, 1890).

In order to standardise the effects as much as possible an initial dose of 3 gm. of naphthalene was given, in liquid paraffin, to an animal of 2-3 kgm. and was repeated daily until the lesions appeared. With this dose, it was usual for retinal exudates and early peripheral lens striae to appear within 24 hours, and this could be ensured if 3 gm. of glucose were given in addition. (The additive effect of the latter substance is probably due to the fact that it aids absorption. Glucose alone or with paraffin is quite innocuous.) Retinal exudates would generally proceed to a fully confluent stage without a further dose of naphthalene but in order to encourage the later development of a complete cataract, the dose was usually repeated for several days.

In contrast to Hess, Magnus and others, it seemed an invariable rule for retinal exudates to appear just before the onset of lens changes. On the other hand the lens often remained in the stage of early striae and never became opaque although the retina had become completely atrophic and detached. In contrast to Panas's suggestion (1887) such a maintenance of transparency would suggest that the lens nutrition is independent of that of the retina.

In a few cases a contraction of the pupil, which was unaffected by atropine, occurred within the first few hours. Usually the retinal exudates were the first noticeable change and they may therefore be described first.





FIG. 1.

Retinal changes on 3rd day after the administration of 3 gm. naphthalene daily. Small exudates are seen near the optic disc, while large confluent exudates occupy the periphery. (Rabbit IV, weight, 2.8 kgm.)

*Retinal Lesions.*—They appear typically as small white spots at the extreme periphery of the fundus, and are often seen within 6-7 hours after the initial dose. They increase rapidly in size and number and spread in towards the optic disc. On ophthalmoscopic examination in this stage the globules reflect bright points of light, while within 24 hours they coalesce to form fluid exudates which are often so transparent that the choroidal vessels can be seen through them. (See Fig. 1.) In a few animals, especially young ones, the globular stage did not occur, but the whole retina was very hazy and oedematous. This was frequently associated with such a marked oedema of the orbital conjunctiva that the latter was raised up in folds, while the distortion of the lens probably from gross imbibition of fluid was such that it was impossible to see details of the fundus. This condition of oedema, which often seemed to affect the lungs as well, usually subsided on the third day, while the ocular lesions followed their ordinary course of development.

An examination was made of the eyes from a number of animals with the retinal condition illustrated in Fig. 1. It was usual to find a clear cornea, and a perfectly normal iris and anterior chamber. The lens was transparent but slightly swollen, and surrounded by a small subcapsular collection of fluid. Small peripheral radiating striae or vacuoles between the lens fibres were visible even through the intact capsule. In some cases on cutting into the substance of the lens and leaving it exposed to the air, it gradually acquired a golden tinge comparable to that seen in human senile cataract (*cf.* Gatti, 1905). Also the vitreous in these cases, on being removed from the eye was seen to have a yellowish colour and while at this stage it was still a gel, its consistency was not so firm as usual.

Small brown gelatinous areas in the retina were visible to the naked eye and appeared to correspond to the "exudates" seen in life. Sections were prepared by fixing the eye in Zenker solution and cutting either in paraffin or celloidin. As will be seen in Figs. 2 and 3 the retinal changes of Fig. 1 can be identified histologically. Fig. 2 shows two small areas corresponding to globular exudates occurring near the disc. The same section showed extensive changes also at the periphery corresponding to a large confluent exudate which was observed in life.

So far the retinal changes have been described as "exudates," first globular, and then confluent,—as these terms are best suited to their ophthalmoscopic appearance. Figs. 2 and 3 show that the affected areas in the retina are really localised patches of oedema. No albuminous or cellular exudates were seen between the choroid and retina (*cf.* Panas, 1887) nor was any other abnormality observed at this stage in the other tissues of the eye save a slight hyperaemia



of the ciliary body and choroid, and a few leucocytes deposited on the back of the cornea.

In sections stained with haematoxylin and eosin the oedematous areas stained poorly with haematoxylin, while the rods and cones showed a marked affinity for eosin.

It will be seen that the supporting cells immediately below the horizontal band of nerve fibres are swollen and broken down so as to form an irregular cystic space below the fibres. This space is filled by granular cell debris probably the remains of broken down ganglion cells. Similar debris is found on the anterior surface of the retina. The ganglion cells are much shrunken, are reduced in number and have small granular nuclei of about half the normal size. Numerous spaces are visible in both nuclear layers the nerve cells being fewer and apparently pushed apart by fluid. A number of cells in the inner nuclear layer show well-marked chromatolysis. The rod and cone layer is decreased in thickness and rather granular.

Atrophy of the retina rapidly follows the oedema. In 4-5 days the oedematous areas appear white. Usually the whole retina is affected, and is white and parchment-like. In a week or 10 days it may become detached, possibly through shrinking or because the vitreous becomes fluid and no longer supports it. The retina often splits horizontally above and below the bands of opaque nerve fibres, and the peripheral retina then floats forward into the vitreous in the manner shown diagrammatically in Fig. 4. In the course of 4-6 weeks the retinal vessels show a marked diminution in size until finally they may extend only a few millimetres beyond the disc. The choroid also becomes degenerated and heavily pigmented—while small fragments of atrophic retina may remain attached to it. The histological picture is one of marked degeneration. The layers of the retina can still be recognised but are vacuolated and ill-defined, while the choroid shows marked pigmentation especially in the vascular sheaths. There are deposits of fibrin and leucocytes on the inner surface of the retina, and on the choroid where the latter is exposed by detachment of the retina.

*The development of cataract.*—The changes observed in the lens need only a brief reference since they agree with those described by previous observers. An initial swelling of the lens is followed by the formation of radiating striae or fluid vacuoles at the periphery. The latter resemble the early striae in human senile cataract when they are examined in light reflected from the fundus. In the second stage which occurs in 2-3 days, the lens fibres themselves become opaque, first in the posterior cortex and then in the anterior cortex (see Fig. 5). The nucleus is the last part of the lens to become opaque, but in the final stage the whole lens is coagulated and yellowish-white in colour. The cataract usually

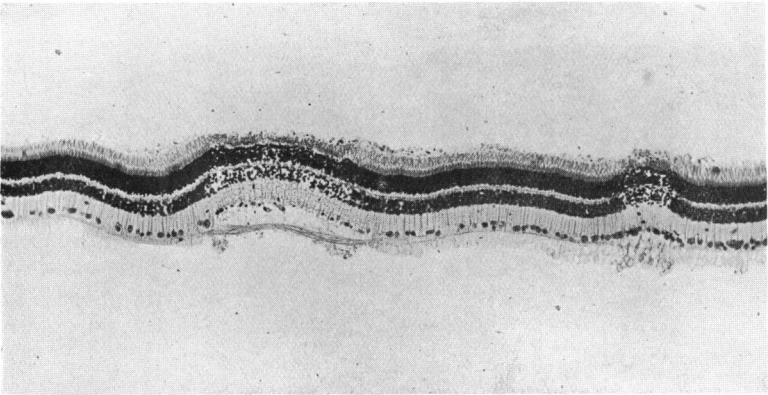


FIG. 2.

Section of retina showing two of the early exudates near the disc. (Rabbit XXX, weight 1.9 kgm. 24 hours after single dose of 3 gm. naphthalene.)

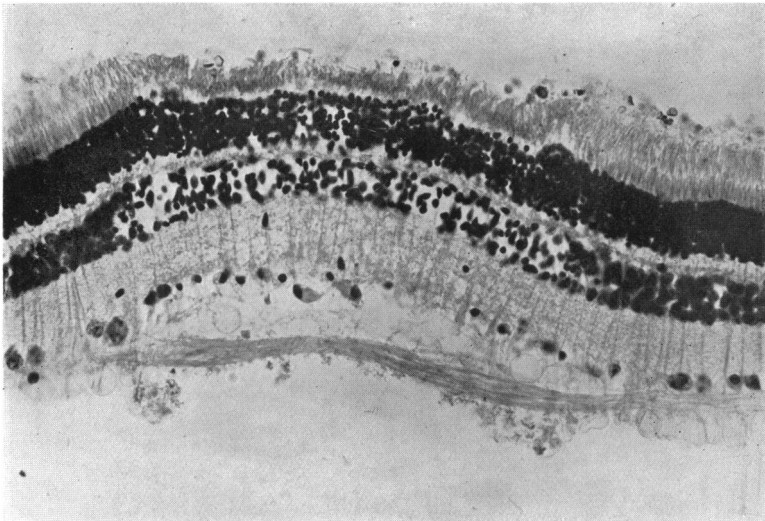


FIG. 3.

A magnification of the retina shown in Fig. 2. For description see text.

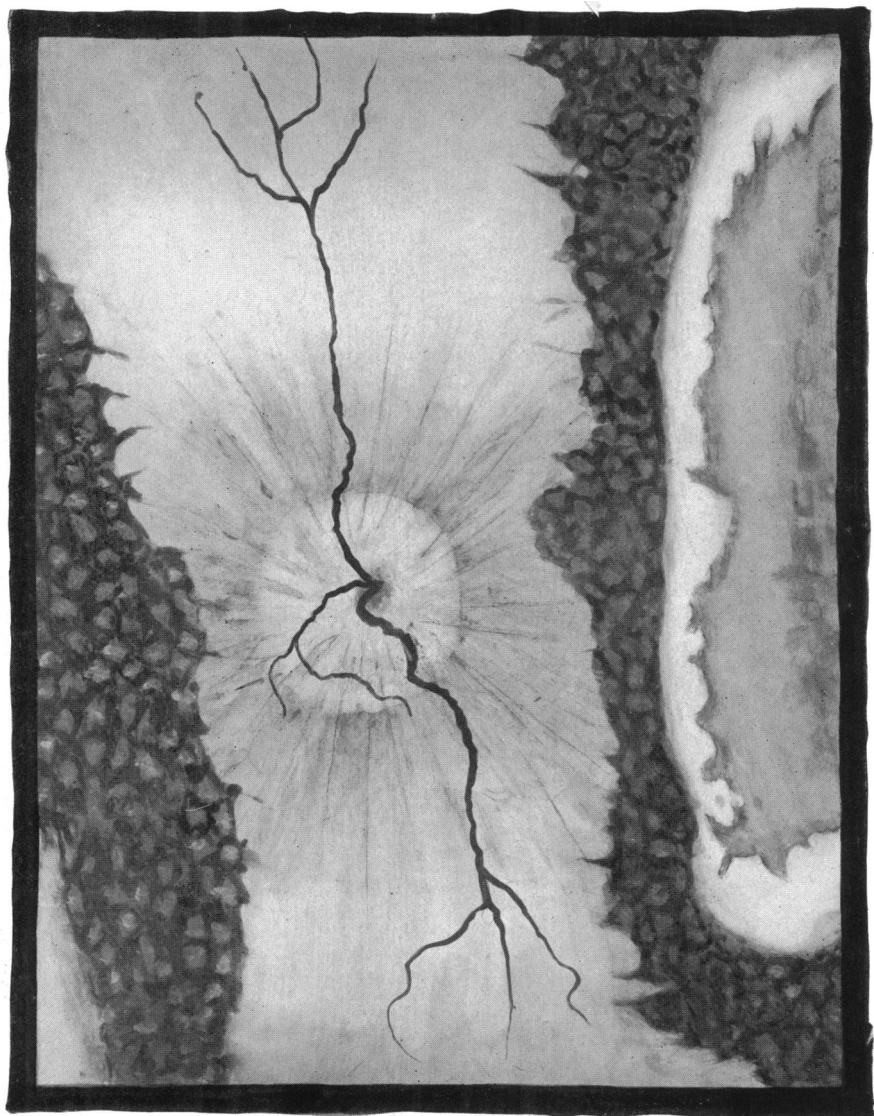


FIG. 4.

Final stage of retinal atrophy and detachment. Note horizontal splits in retina above and below the disc. (Rabbit IV, 14th day, *cf.* Fig. 1.)

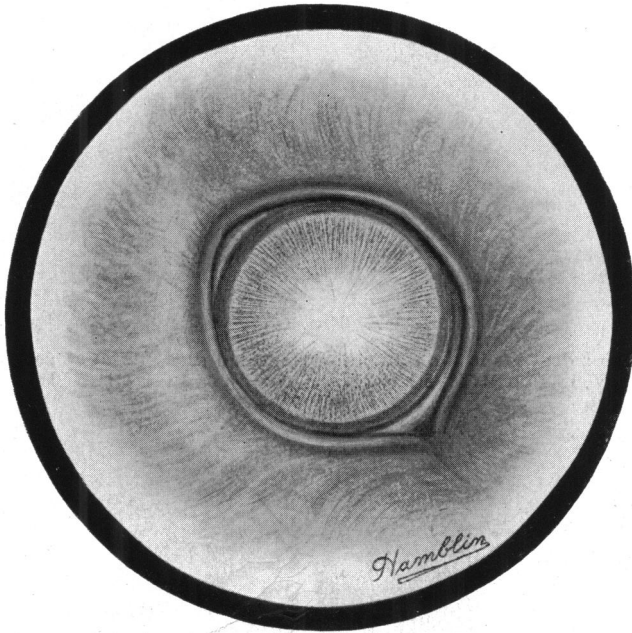


FIG. 5.

The second stage of lens changes in the development of naphthalene cataract.

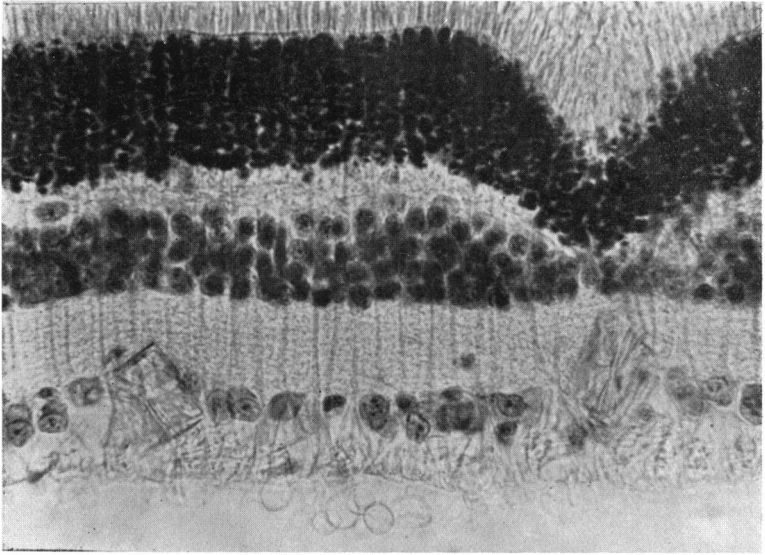


FIG. 6.

Crystalline deposits in the retina after repeated small doses of naphthalene. (Rabbit V, section  $\times 650$ , stained haematoxylin and van Gieson.)

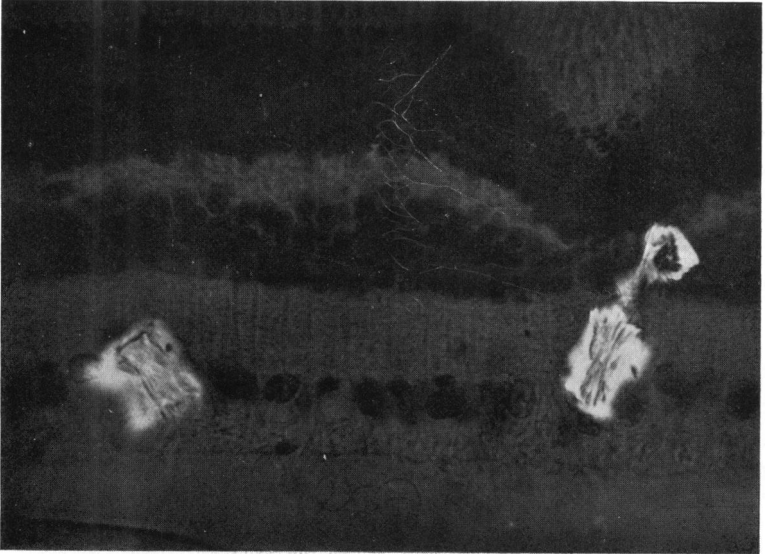


FIG. 7.

The same section as Fig. 6 viewed under crossed Nicol prisms.

becomes complete in about 14 days, and resembles a human senile cataract in the fact that all the glutathione, of which a normal lens has a considerable store, has been lost. It is difficult to discover the factors which lead to the completion of the lens changes, since the latter appear to be proportional neither to the severity of the retinal changes, nor to the extent nor length of time of the dosage with naphthalene. When once the second stage of true opacity has begun I have not seen any retrogression (*cf.* Panico, 1928)—but on the other hand further development does not always follow. It is hoped that a study of the biochemical changes will reveal the factors which influence the lens.

*The deposition of crystals.*—This is yet another phase of this interesting problem. Beyond the fact that the crystals did not seem to appear in less than three weeks, previous observers made no reference to the accompanying conditions. In my series of rabbits crystals were observed under the following conditions:—

1. In 2-3 weeks as the result of repeated small doses of naphthalene, *e.g.*, 0.5-1.0 gm. per day.

2. In 5-10 days in certain large healthy animals of 3.0 kgm. or over, to which the usual dose of 3 gm. naphthalene had been given daily.

3. Occasionally in healthy animals of average size, in which early retinal exudates appeared in 2-4 days and remained in this stage without any further progress, while a day or two later the deposition of crystals began.

When first seen, the crystals are very like *synchisis scintillans*. They are in the posterior layers of the vitreous and on the surface of the retina, and as dosage is continued they become deposited quite heavily in irregular plaques on the retina. The animals are always healthy and undisturbed by the naphthalene, while in types 1 and 2 the fundus, vitreous, and lens remain quite normal. In fact the deposition of crystals seems to be the ocular sign of an established resistance, or, of compensation to the effects of the naphthalene.

Crystals are found on the adjoining surfaces of retina and vitreous and are also visible in the sections of any retina which contained them during life. They occur chiefly in the ganglion cell layer and less often in the inner nuclear layer, and produce very little disturbance in the surrounding tissues. Occasionally the ganglion cells in the immediate neighbourhood are more palely stained and show slight chromatolysis. As will be seen in Figs. 6 and 7 the retina may be kinked at the point of deposition, with a scattering of the cells of the outer nuclear layer. It is probable that the latter is a mechanical disturbance produced in the cutting of the section.

*The nature of the crystals.*—They are doubly refractile (see Fig. 7), colourless, 4-sided plates of irregular shape which occur in rosettes or overlapping one another in groups. As might be expected from the fact that they are resistant to all the reagents employed in the preparation of the sections, the crystals were found to be inorganic, thus suggesting that naphthalene can indirectly cause a disturbance of the normal physiological constituents of the body fluids, so as to lead to the deposition of some inorganic salt. From this point of view it was considered worth while to investigate the nature of the crystals. After having excluded the possibility that they were derived from any external reagent, their reactions were found to be as follows :—

1. On being heated on the warm stage of a microscope to 195°C., the crystals were quite unchanged. At higher temperatures they fused to an amorphous residue.

2. *Solubility.*—Insoluble in all organic reagents. Readily soluble without effervescence in weak sulphuric (1.3 per cent.) and nitric acids, and less rapidly in hydrochloric acid. Soluble in cold saturated cupric acetate. Insoluble in hot or cold water, acetic acid, oxalic acid, ammonium hydroxide and caustic alkalies.

3. Tests for sulphates, sulphides, carbonates, phosphates, amino acids, uric acid and such tests as were possible microscopically for ordinary metallic radicles (except calcium)—were all negative.

4. A test for calcium by irrigation with  $H_2SO_4$  and 40 per cent. alcohol yielded fine needles characteristic of calcium sulphate.

A number of minor tests were also performed.

It is admittedly difficult to obtain a convincing proof from chemical tests which have to be performed under the microscope—but the appearance and behaviour of the crystals is such as to lead to the conclusion that they are undoubtedly calcium oxalate. In confirmation of this it may be mentioned that they exactly resemble the illustrations given by Krause (1926) of deposits *in vivo* of calcium oxalate in human renal epithelium in a case of oxalic acid poisoning; and in the duodenum of rabbits to which oxalic acid had been given. I have myself seen exactly similar deposits in a rabbit's kidney after repeated small doses of oxalic acid.

*Conclusion.*—It would be fallacious to attempt to find an adequate explanation of the action of naphthalene merely from the character of the ocular lesions to which it gives rise. Although at first they appear to be so diverse that it would be impossible to attribute them to any one causative factor, yet they present certain features which suggest that they may all be due to a disturbance in the normal balance of the inorganic constituents in the body, rather than to any direct toxic effect of naphthalene or its derivatives. For instance, the early change in both lens and retina is an imbibition



of fluid, and this process may be associated with oedematous changes in other parts of the body. As an alternative, there is the deposition of an inorganic substance in crystalline form, a type of pathological change which occurs comparatively rarely, *e.g.*, in atheromatous deposits, calculi, *synchisis scintillans*, and which is dependent on certain specific conditions such as acidity, alkalinity or hypercalcaemia, etc. A knowledge of the particular factors which determine the extent to which any or all of the ocular changes shall occur after the administration of naphthalene, can only be gained by a more thorough investigation of the accompanying biochemical changes than has been attempted up to the present.

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