more likely to be due to the pathological changes induced inside the eye at the time of injury.

In this series 69.3 per cent. of foreign bodies were extracted, 51.3 per cent. by the scleral route and 18 per cent. by the anterior route. Other authors including 21 Army Group Medical H.Q. state that about 30 per cent. of modern war missiles are extracted by a giant electro-magnet but they do not differentiate the incidence of success by either the anterior or posterior route. Many reported failures by the anterior route might not have been so if the scleral route had been properly tried.

With better X-ray facilities for localisation and a better magnet I feel that the figure of successes in this B.L.A. series might have been higher. For extraction of the feebly magnetic alloys of war missiles it is essential to bring the terminal of a very powerful electro-magnet into the lips of a scleral incision placed as near as possible to the foreign body.

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"BLUE HALOES" IN ATEBRIN WORKERS

BY

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I AM deeply indebted to Dr. H. Wyers for having called my attention to this condition and for the opportunity of examining the cases described.

Since the introduction of atebtrin* for the treatment of malaria and its consequent manufacture on a large scale, certain pathological conditions consequent on handling it in bulk have become known.

* Atebrin is 2-chloro-5-(*ω*-diethylamino-*α*-methylbutylamino)-7-methoxyacridine dihydrochloride and is also known as Mepacrin (B.P.) and Quinacrin (U.S.P.).

The commonest appear to be erythematous and papular skin eruptions on exposed parts, with puffiness of the eyelids, lacrimation and pain over the frontal sinuses. These symptoms occur in certain sensitive individuals who are usually rendered thereby unsuitable for work with the drug and are transferred to other processes. Among those workers, however, who do not show this special sensitivity and therefore continue in the work, a yellow discoloration of the skin and conjunctiva and a curious corneal condition may develop. The present note concerns the eye condition of six workers engaged in the production of the drug and its compression into tablets. This eye condition is not a scheduled industrial disease and so is not compensatable in the ordinary way.

Ocular signs and symptoms.—The patients, healthy men aged 28, 35, 36, 49, 53 and 66 respectively, had been working in an atmosphere which often contained for short periods clouds of very fine atebrin dust. One had worked in the plant for a year, two others for 10 months. All considered that they were not particularly sensitive, and experienced no dermatitis or other discomfort. They wore protective clothing, goggles and masks, but the dust was so fine that in spite of this they soon noticed yellow staining of the conjunctivae and skin, especially of hands, head and neck. The men worked 9 hours a day for five days a week and after some weeks or months they all noticed that when looking at a small source of light at night they saw a blue halo round it. There was no ocular pain, no lacrimation or photophobia. All insisted that the halo was mainly blue, that for a light one metre away it began approximately two inches from the light and was about three inches wide. It was darker blue near the light and pale blue at its outer edge. If the light was placed at six metres, faint yellow, green and reddish brown bands appeared outside the blue ring. These were usually not noticed until asked for, the blue ring being much the brightest. All the men stated that their visual acuity was unimpaired and on examination it was found to be 6/6 in all the eyes. They could see the blue halo at any time by looking at a light and there was never any pain. Two men stated in addition that their nostrils were sore and occasionally bled.

Slit-lamp appearance.—On examination the condition in all six patients was similar. In some it was more severe than in others.

In the fully developed condition there was a yellow discoloration of the conjunctiva in the interpalpebral space (Fig. 1) and in addition a curious corneal condition, just visible macroscopically as a slight dulling and yellowing of the cornea. A slit-lamp, however, resolved these appearances as follows :—

1. The conjunctiva showed a diffuse pale yellow stain in the interpalpebral space only. The vessels were not engorged nor was there any increase in secretion. At the limbus in the exposed portion and also just under the edge of the lower lid; but not at the upper quarter of the limbus, there were aggregations of minute dark brown dots. These are seen in Figs. 2 and 3. They resembled very much the pigment dots seen here in Chinese and other lightly pigmented races and in some Southern Europeans, but they were rather darker, denser and more finely particulate than these. They appeared to be an actual deposit, possibly picked up by cells (macrophages) and lying in their cytoplasm or possibly merely existing as a fine surface dust. They were not movable and could not be washed off.

2. The cornea showed a remarkable change. The whole surface, even that covered by the upper lid, was peppered with very fine dust-like particles. These appeared dark yellowish brown by direct illumination, and quite opaque by transmitted light. The size of the particles varied but at a rough estimate with the slit-lamp they were from $5\text{--}10\mu$ in diameter, *i.e.*, about the size of, or a little larger than, the nucleus of an epithelial cell.* There was no disturbance of the corneal reflex, the surface being perfectly smooth and bright, so that it seems likely that the particles were intracellular or at least situated in the substance of the corneal epithelium. None was seen deeper than this and most appeared to be in the surface layer of cells.

Across the lower part of each cornea was a series of wavy yellow lines, like a very marked Hudson's line, but wider and brighter than this and branching. This is seen in Fig. 3. The lines were composed of very closely aggregated dots similar to the others over the rest of the cornea, but closer together and much brighter yellow. There was also a more diffuse yellow colour across the cornea in this region, resembling the pale yellow staining of the conjunctiva and suggesting a substance in solution.

The substantia propria was entirely normal, as were the internal parts of the eye. Fig. 4 shows the slit-lamp appearances. The corneal band is on the left and shows the yellow colour of the massed deposits, the general surface speckling and the normal substantia propria. The band of light reflected from the iris shows the yellow dots to be opaque or dark brown on retro-illumination, and to the right of this they are visible as greyish dots seen by scattered light (total internal reflection).

Course and prognosis.—The history of one patient throws some light on the time sequence and on the prognosis. This man,

* The nucleus of a corneal epithelial cell measures roughly $5\times 7\mu$ and the whole cell $10\times 18\mu$.

FIG. 1.

Macroscopic appearance of eye of atebirin worker, aged 66 years.

FIG. 2.

Slit-lamp appearance of the limbus of a patient, aged 35 years. (Inset diagram shows areas of distribution of the pigment dots).

FIG. 3.

Composite slit-lamp drawing of cornea of atebirin worker aged 49 years, showing innumerable yellowish dots and aggregations of these in the lower part. (The dots are not drawn small enough).

FIG. 4.

Slit-lamp appearance of a portion of the cornea shown in Fig. 1.

J.D., aged 35 years, was first employed on the work two years ago. After a little less than a year he noticed the blue haloes and that the whites of his eyes were yellow. He was then put on light work where he was not exposed to the chemical. After two months of this the "blue rings" disappeared and he considered his eyes quite normal. After a further month, during which he remained well, he went back to work with atebrin. He remained well for six months and then began to notice faint haloes. These became intensified by nine months, at which time I examined him, but he stated that the rings had not yet reached their previous intensity. He showed the limbal deposits of brown dots and his corneae were very faintly and finely peppered, but there were no yellow lines and the whole appearance was much less marked than in most of the other patients. Without a slit-lamp he would have been passed as normal.

This case seems to show that the condition may be very slow in developing and that if the patient comes off the work it clears away completely, only very slowly coming back on re-exposure. No permanent damage appears to result and the visual acuity is unimpaired throughout. The time for disappearance of the rings after stopping the work is about two months and the time taken to reappear (and to appear originally) is six to nine months.

Differential diagnosis.—The complaint of haloes round lights always arouses a suspicion of glaucoma, but in all these cases the tension was normal, the discs not cupped and the visual acuity 6/6 with full fields. The absence of any signs of glaucoma and the presence of the appearances described above should make the diagnosis simple. In addition, the patients have always been exposed to atebrin dust for some time before the symptom is noticed.

Discussion of pathology.—It would seem that the punctate deposit on the cornea is the cause of the haloes and that they are produced by a diffraction effect. Three points of interest present themselves for investigation, namely, the route by which the deposit reached the cornea, its nature and its position.

Since the men were exposed to atebrin dust two routes to the eye were open, either the direct surface involvement, *i.e.* the dust settling on the eye, or the systemic route, the dust having been inhaled, swallowed or absorbed through the skin and passed to the eyes *via* the blood stream or the lymphatic system.

In order to decide this, two observations were made, one on man, the other experimentally on rabbits. In the first, two other men, aged 27 and 36 respectively, were examined. They were volunteers in an experiment on the effects of atebrin administration in normal people. They had both taken 100 mg. a day by mouth and occasionally more, for seven months and were still taking it when seen. Their

hands and faces and skin generally showed a pale yellow staining, but their conjunctivae were perfectly normal as were also their corneae. They both stated that they had no symptoms, that they had never seen blue haloes, that their sight was unaffected (it was 6/6 right and left in both) and that at no time had the whites of their eyes been yellow. This would seem to indicate that the corneal condition in the atebtrin workers is due to direct surface contamination with very fine dust, which gets embedded in the corneal epithelium and is only slowly cast off.

A second observation to confirm this was made on three rabbits. It was found that atebtrin dust blown directly on to their eyes with an insufflator twice a day produced a similar slit-lamp appearance in six days, with no systemic effects.

It would therefore seem certain that the corneal condition is caused by direct surface contamination with atebtrin.

The particles seen with the slit-lamp cannot, however, be atebtrin itself, since this is completely soluble in the tears. Their exact nature is speculative, but it seems possible that they are precipitates of an insoluble breakdown product of atebtrin formed in the cells of the corneal epithelium which have absorbed the atebtrin itself in solution in the tears. We have some evidence that selective absorption of substances from the tears does take place, but so far as I am aware, no previous instance of intra-cellular precipitation of such an absorbed substance is known.

In order to investigate the exact position of the particles, one of the rabbits mentioned above was killed at the time when the slit-lamp appearance of the cornea resembled that in man. Microscopic examinations of scrapings and flat preparations were made of the corneal epithelium. Yellow granules in the cytoplasm could be seen in unfixed specimens, but fixation with saturated mercuric chloride solution in absolute alcohol and staining with Leishman's stain gave the best results. Granules were then visible, stained faintly blue, and lying well within the cytoplasm of the epithelial cells. Each individual granule was very small and amorphous. Aggregated they formed a granular blue mass either encircling the nucleus or lying beside it, if it happened to be eccentric in the cell. The granules were optically inactive. It is obvious that the opaque yellow dots seen with the slit-lamp are not the individual granules but the whole aggregation within the cell containing them. The nature of the granules is not known. It has been suggested by Dr. H. J. Barber of the Research Laboratories, May & Baker, Ltd., in a personal communication to Dr. Wyers that they may be composed of 2-chloro-7-methoxyacridone, an exceedingly insoluble substance which is slowly formed by hydrolysis of atebtrin. He considers that this substance might well become fixed within cells

and stain them, since both atebrin itself and methylene blue to which it is related have marked staining properties. It is interesting to note that 2-chloro-7-methoxyacridone does not occur in the formula for acriflavine and that no complaints of haloes or of corneal staining have come from acriflavine workers. It does occur, however, in the newer 5-aminoacridine and workers in this material should be watched for development of any signs or symptoms.

That the substance composing the granules is in some way derived from the solution of atebrin in the tears and is not deposited in the cells direct from the dust is indicated by the fact that the granules occur all over the cornea, even under the upper lid. This distinguishes the appearance from that due to a chemical injury with some substance (*e.g.*, mustard gas vapour) which acts directly on each epithelial cell it touches, without going into solution in the tears first.

Once the granules have appeared in the cells they do not re-dissolve but remain until the cells are cast off and repaired in the ordinary course of events. The affected cells tend to become pushed by the movements of the lids into a more or less horizontal band just below the centre of the pupil (position of Hudson's line) and during the process of recovery (in rabbits) can be detected longest here.

That more severe contamination than that received by the six patients described might produce more severe and permanent results than they displayed was suspected. Two of the rabbits were therefore exposed to large insufflations of atebrin powder twice daily. One of them developed oedema of the substantia propria of the cornea, shedding of the epithelium, marginal vascularisation and iritis. The other showed slight iritis and no corneal oedema. In both the diffuse yellow colour of the atebrin in solution appeared to extend through the whole thickness of the cornea and even to stain the endothelium. Complete recovery took place in both cases on stopping the insufflations.

The nature of the haloes seen by the patients.—The halo is obviously a diffraction effect due to the opaque granules in the epithelial cells. Such haloes are always blue on the inside and red on the outside of the ring. The blue, being brighter, is more readily noticed. Duke-Elder (Text Book of Ophthalmology, Vol. I, p. 801) states "The nature and site of the structures causing the halo can be deduced from the angular diameter of the rings . . . The radius of the halo, divided by the distance of the nodal point of the eye from the light gives the tangent of the angle." An attempt was made to measure the angular diameter of the haloes in this way in three of the men, using a monochromatic filter (transmitting 5500 Å). The results lay between 3° 17 min. and 3° 52 min.

Extreme accuracy of measurement was not possible, but the result indicates that the particle size is roughly a little smaller than a normal epithelial cell. The usual angular diameter of the haloes in glaucoma is 7° — 12° and here we know that the size of the droplets causing them is that of a swollen oedematous epithelial cell. Haloes due to mucus on the corneal surface are larger still (up to 14°).

An attempt was also made to calculate the actual particle size by measuring the haloes seen with monochromatic filters (5500 Å and 5400 Å) and using the formula

$$d = 1.22 \times \frac{\lambda l}{r}$$

where d = diameter of particle

r = radius of first dark ring in cm.

l = distance of eye from screen

λ = wave-length in μ

the actual measurements were difficult to do accurately and the results of a number of trials gave values for d varying between 7μ and 11μ . This, though not conclusive, points to an intra-cellular cause for the diffraction effect and would seem to correspond with the massed amorphous particles.

The investigation of this new industrial disease is chiefly of interest from the physico-chemical point of view and from the importance of the differential diagnosis of glaucoma which its history suggests.

Summary

A new industrial disease of the cornea is described in atebtrin workers. It appears to be caused by an intra-cellular deposit of an insoluble derivative of atebtrin.

Its only symptom is the seeing of coloured haloes (mostly blue) round lights. Its prognosis is excellent on removal from contact with atebtrin dust.

SUBJECTIVE "LIGHTNING STREAKS"*

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IN the October, 1935 number of this Journal I published a series of cases of a symptom complex under the above title (p. 545), and later, an additional series in *The American Journal of Ophthalmology*

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