and ephemeral. Re-expansion took place in all instances before the patient was discharged from hospital, and in only one case did prolonged clinical and radiological follow-up reveal residual damage to the respiratory tract, and even here eventual recovery seems to be possible. Kohn *et al.* (1944), in a clinical and radiological study of 222 cases of pertussis, did not mention any sequelae, but Nicholson (1949) reported 22 cases of collapse of more than two months' duration in a series of 48 pertussis patients, and stated that in seven followed for a year the collapse was still present.

Whatever the general incidence of pulmonary collapse in pertussis, its importance is obvious, for its relationship to bronchiectasis seems clear. As in many cases it is impossible to detect atelectasis clinically, an x-ray film before supervision ceases would seem to be the minimum demand on the radiological department. If, however, respiratory symptoms follow pertussis it cannot be too strongly emphasized that a negative x-ray film is of little significance, for atelectasis may have cleared up, leaving bronchiectasis behind. It still does not appear to be widely appreciated that recurrent attacks of cough or "pneumonia" and persistent localized crepitations call for bronchography; even to-day there is a tendency to wait for the appearance of copious sputum and clubbing of the fingers before suspecting bronchiectasis.

If atelectasis is detected during or after the attack of pertussis every effort should be made to promote re-expansion of the affected lung, remembering that this has happened six months after the onset of atelectasis (Raia, 1938), and may perhaps occur even up to a year afterwards. In general, surgical removal of a lobe collapsed for less than a year would appear to be inadvisable. When bronchial dilatation remains after re-expansion of a collapsed lobe it is no longer merely compensatory, and so far as is known will be permanent.

Where bronchial dilatation is pronounced, and evidence of infection obvious, surgical intervention is the treatment of choice, for the prognosis in such cases treated medically, as judged by the work of Findlay and Graham (1927), Roles and Todd (1933), Ford (1948), and others, is poor, though antibiotics and chemotherapy can nowadays generally cope with acute exacerbations. On the other hand, it may safely be said that the prognosis of cases with mild bronchial dilatation and little evidence of infection cannot be stated with any confidence, and a prolonged period of observation before advising lobectomy would appear to be indicated.

Summary

Atelectasis was noted radiologically in 43% of 150 pertussis cases, but in general it was slight in extent and of comparatively short duration. Six instances of virtually complete lobar collapse took longer than two months to resolve; in five of these the bronchi contained in the collapsed lobes were shown to be dilated and were seen to revert to their normal calibre when the lobes re-expanded. In the remaining case bronchography was not performed.

In four partially collapsed lobes slight bronchial dilatation was noted, which disappeared when the collapsed lung re-expanded.

In only one case did the attack of pertussis lead to persistent respiratory symptoms. In this case there was evidence of residual bronchial infection in a lobe which had been atelectatic for eighteen weeks. Although the bronchi in this lobe were markedly dilated when it was collapsed, bronchiectasis was not obvious after re-expansion.

The treatment of atelectatic bronchiectasis in pertussis is discussed, and a trial of artificial pneumothorax mentioned.

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REFERENCES

- Banyai, A. L., and Cadden, A. V. (1943). *Amer. J. med. Sci.*, **206**, 479.
 Blades, B., and Dugan, D. J. (1944). *J. thorac. Surg.*, **13**, 40.
 Brown, A. L. (1930). *J. Amer. med. Ass.*, **95**, 100.
 Coryllos, P. N. (1930). *Surg. Gynec. Obstet.*, **50**, 795.
 Diamond, S., and Van Loon, E. L. (1942). *J. Amer. med. Ass.*, **118**, 771.
 Doig, A. T. (1946). *Tubercle*, **27**, 173.
 Edwards, A. T. (1939). *British Medical Journal*, **1**, 809.
 Engel, S. (1947). *The Child's Lung*. London.
 Erwin, G. S. (1939). *Brompton Hosp. Rep.*, **8**, 43.
 Findlay, L. (1935). *Arch. Dis. Childh.*, **10**, 61.
 — and Graham, S. (1927). *Ibid.*, **2**, 71.
 — (1931). *Ibid.*, **6**, 1.
 Fleischner, F. G. (1941). *Amer. J. Roentgenol.*, **46**, 166.
 Ford, F. J. (1948). *Glasg. med. J.*, **29**, 1, 19.
 Franklin, A. W. (1938). *Proc. R. Soc. Med.*, **31**, 354.
 Gray, I. R. (1946). *Thorax*, **1**, 263.
 Hennell, H. (1946). *J. thorac. Surg.*, **15**, 239.
 Hinshaw, H. C., and Schmidt, H. W. (1944). *Dis. Chest*, **10**, 115.
 Jennings, G. H. (1937). *British Medical Journal*, **2**, 963.
 Kohn, J. L., Schwarz, I., Greenbaum, J., and Daly, M. M. I. (1944). *Amer. J. Dis. Childh.*, **67**, 463.
 Laennec, R. T. H. (1819). *Diseases of the Chest*, 4th ed. Translated by John Forbes in 1834. London.
 Lander, F. P. L. (1946). *Thorax*, **1**, 198.
 — and Davidson, M. (1938). *Brit. J. Radiol.*, **11**, 65.
 Lisa, J. R., and Rosenblatt, M. B. (1943). *Bronchiectasis*. Oxford Univ. Press, London.
 Nelson, H. P. (1934). *British Medical Journal*, **2**, 251.
 Nicholson, D. P. (1949). *Arch. Dis. Childh.*, **24**, 29.
 Ogilvie, A. G. (1941). *Arch. intern. Med.*, **68**, 395.
 Paulson, D. L., and Shaw, R. R. (1949). *J. thorac. Surg.*, **18**, 747.
 Punch, A. L. (1940). *Lancet*, **1**, 5.
 Raia, A. (1938). *Amer. J. Dis. Childh.*, **56**, 852.
 Roles, F. C., and Todd, G. S. (1933). *British Medical Journal*, **2**, 639.
 Sante, L. R. (1927). *J. Amer. med. Ass.*, **88**, 1539.
 Tannenber, J., and Pinner, M. (1942). *J. thorac. Surg.*, **11**, 571.
 Wearing, J. D. H. (1948). *Lancet*, **1**, 822.
 Wilson, R. (1939). *J. Pediat.*, **14**, 368.

SOME ASPECTS OF COLOUR-BLINDNESS*

BY

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In spite of the existence of numerous tests for colour-blindness, each to some extent based on one of the various theories of colour-vision and largely directed to the selection of personnel for the armed Forces and for certain branches of industry, there is no single test which can be regarded as infallible. This fact perhaps reflects more than anything else the inadequacy of colour-vision theories and the insecure basis upon which most of them rest. The occasion is thus opportune for a review of some of the fundamental aspects of the problem and for an evaluation of certain recent observations on colour-blind subjects.

Ever since the days of Thomas Young the necessity for three variables in the mechanism for normal colour-vision has been recognized, and three separately excited pathways from the eye to the brain have been postulated. More than three such pathways are usually considered unnecessary, though at times more have been suggested in order to account for special aspects of colour-vision. Perhaps because of the common experience of mixing pigments, and among physicists and physiologists of mixing lights, in which three primary colours are required in order to match all the spectral colours, it has generally been assumed that each pathway registers the sensation of one of the primary

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colours—that is, there is a blue pathway, a green pathway, and a red pathway. Each pathway, when stimulated alone, would then give rise to the sensation appropriate to it. When two or more pathways were stimulated, intermediate hues would be obtained—for example, yellow, blue-green, etc. This idea has commonly been elaborated further to suggest that the actual receptor cells in the retina must be of three classes—red receptors, green receptors, and blue or violet receptors.

While the triploid character of normal colour-vision can hardly now be doubted, this somewhat naive conception of the complex mechanism involved must be regarded as inadequate, and the position must be examined afresh.

Activation of the Retinal Receptors

From the information which is available on the behaviour of one class of retinal receptors—namely, the rods and their contained rhodopsin or visual purple—and if it is assumed that the other receptors behave in a similar manner, it seems probable that the retinal receptors in general may be activated by substances with relatively broad absorption spectra, so that they are sensitive to a wide range of wavelengths. This is borne out also when the spectral sensitivities of eyes possessing predominantly cones are considered.

On the other hand, some recent work on the properties of certain photosensitive substances produced in the laboratory by the breakdown of visual purple may indicate the possibility of active substances with much narrower absorption bands and therefore with greater selectivity; but so far there is no direct evidence that these substances occur under physiological conditions. The sensitivity of the rods lies mostly between 400 $m\mu$ and about 640 $m\mu$, with its maximum at about 500 $m\mu$. Eyes dependent on cones, on the other hand, have a range extending from 440 to 700 $m\mu$, with maximum sensitivity at about 570 $m\mu$. It is well known that when the rods are responding alone, as they may do in very dim light, they give rise to a colourless sensation. The eye under such conditions cannot discriminate between wavelength and intensity. A given frequency of nerve impulses in the optic nerve fibres may be initiated by the appropriate intensity of any wavelength. This observation is also likely to be true for any other single group of receptors so long as they are responding alone, whether they be rods or cones, and whatever the nature of the photochemical activator.

When, however, a second group of receptors, whose spectral sensitivity differs from that of the first group, responds simultaneously, it is at least theoretically possible for differences in wavelength to be appreciated as well as differences in intensity provided that the information obtained from the two sources is not completely "pooled" before reaching the centre in the brain where colour sensations originate. The following observation indeed seems to indicate that this can apply to the rods and the cones as the two groups with different spectral sensitivities.

If one-half of an observation field subtending about 4 degrees at the eye is illuminated with light of any wavelength between yellow and violet, but of such a low intensity that the colour is indistinguishable to a well dark-adapted eye, it is generally believed that the rods alone are being stimulated and that the light is below "cone threshold." Nevertheless it is found that at these very low intensities, if the other half of the field is illuminated by a yellow, orange, or red light of just enough strength to evoke a colour sensation from this half, it also evokes a blue sensation from the other half. The blue disappears if the stimulus to the rods is removed by turning off the

original light. The rods must clearly contribute to this sensation of blueness, and the particular blue which they induce can, by binocular matching, be found to give rise to the same sensation as a spectral band between 460 $m\mu$ and 470 $m\mu$. This experiment is most easily interpreted as indicating that the rods give rise to a colourless sensation when functioning alone, but are concerned in the perception of blue when responding in juxtaposition to active cones—that is, under conditions when a comparison between two separately stimulated pathways is possible. It does not exclude the possibility that there are other conditions of stimulation in the eye which the brain interprets as blue.

An eye which has no hue discrimination, as distinct from brightness discrimination, and which has only one group of receptors or one pathway to the colour centre, is described as monodic and the resulting vision is monochromatic or achromatic.

If there are two types of receptor and two pathways differing in spectral sensitivity the eye is diodic, and though some colour-vision is certainly possible it will be dichromatic in character and thus defective as compared with that of the normal subject. It will be possible to match all the spectral colours by mixtures of only two primaries, if these are suitably chosen. Conversely, if it is possible for an eye to match all spectral colours by mixtures of red and violet then its visual mechanism is diodic (or monodic) and it is unlikely to have more than two independent pathways, or at least the information received by the brain must be treated as arriving through two separate pathways only.

A Third Factor

In order to prevent the confusions characteristic of the diodic system, some third factor must be present in the normal eye. This may take the form of a third receptor and pathway whose spectral sensitivity is different from those of the other two, or it might take the form of a local modification of one of the existing receptors, or even of both, in such a way that the spectral sensitivities are altered in a particular area of the retina and the nerves from this particular area are separately connected to the brain. Such a situation might be brought about by screening some of the receptors, as, for example, behind macular pigment. Alternatively, the products of the breakdown of their own photosensitive pigments may act as colour filters for certain receptors—for example, the rods might be screened in daylight by a filter of the yellow breakdown products of rhodopsin. It is not necessary, therefore, to assume as an absolute essential the existence of three morphologically distinct groups of receptors provided that there is some mechanism by which three pathways, or separate groups of nerve fibres, receive stimuli which are different from each other at least in those parts of the spectrum in which vision is trichromatic in character.

Moreover, owing to the connexions and cross-connexions which bring about both summation and inhibition in the retina, the actual responses in the pathways may bear very little resemblance in the frequencies of their nerve impulses to the frequencies which might be expected from the sensitivities of the actual photosensitive receptors. An eye, for example, which depended on only two primary receptors might have at least five sets of nerve fibres each transmitting a different frequency of impulses. Fibre 1 might send impulses corresponding to the spectral sensitivity of receptor A, fibre 2 impulses corresponding to the spectral sensitivity of receptor B; on fibre 3 impulses from A might be inhibited by those from B; on fibre 4 those from A

might antagonize those from B; and on fibre 5 impulses from A and B might summate. Each of these fibres, and an endless series of others relaying other combinations of response, would probably show a different spectral sensitivity of response from all the others, but, since the fibres are not independently stimulated and depend only on re-combinations from the two primary receptors, such an eye would be essentially diodic or dichromatic and would be able to match all spectral colours by means of two primaries only.

It is important to remember at this point that all the nerve impulses which have been recorded from the eyes of vertebrates have been recorded from fibres in which there is every likelihood of such combinations having already occurred in the retinal synapses. It is therefore very dangerous to attempt to correlate directly the spectral sensitivities of such pathways with the spectral sensitivities of the primary receptors, except in the relatively simple case of those dependent only on the known pigment, rhodopsin. More subtle methods have to be used to work back from the impulses recorded to the receptors stimulated.

The Trichromatic System

When the eye is treated as a whole—that is, when relatively large fields are used for the investigation of colour—any spatial differences of activity in the retina tend to be eliminated, and under these conditions the normal eye is definitely a triodic or trichromatic system. It is therefore necessary, in exploring colour-vision, to seek either for three independent receptors or for two main receptors and, in addition, for another factor which will modify the activity of some of these receptors in such a way that they may act as a separate group.

This trichromatic character of normal colour-vision, however, vanishes when vision is restricted to small fields in certain areas of the retina and when the intensity of the light used in the small fields is not so high that the stimulus spreads to neighbouring regions. Under these conditions the extreme periphery of the eye in most subjects is achromatic or monodic. Only light is perceived in this zone, and there is no sensation of colour. A zone rather less far out in the periphery is diodic, and in this zone all spectral colours can be matched with mixtures of two primaries. In the blue-green region of the spectrum there is a colourless or neutral point, and on either side of this point sensations are aroused of blue on one side and of yellow on the other. Thirdly, there is a region in the very centre of the fovea, at the point where form vision reaches its maximum precision, where another form of dichromasy occurs. Spectral colours when flashed momentarily on this area at very low intensity are seen in terms of blue-green, colourless, or orange; with "continuous" vision, yellow is matched with white and all spectral colours can be matched with mixtures of red and violet; at threshold levels, only red and violet remain coloured, all other colours appearing grey at the threshold. Provided that the fields are small enough and are held still enough on the eye, this form of dichromasy may occur elsewhere on the eye also, but it has been less fully investigated under such conditions. The reduced colour-vision which occurs in dim light is also not unlike this type.

Main Types of Colour-blindness

It is pertinent now to ask how these forms of local dichromasy or partial colour-blindness in the normal eye compare with those occurring naturally in colour-blind subjects. Secondly, how are they related to retinal structure? And, thirdly, how do the various types of colour-

blind subjects behave under similar conditions? To these questions only very partial answers can at present be given, the chief reason for this being that there are many types of colour-blindness and there is as yet no histological evidence regarding any peculiarities in their retinal structure. Nevertheless, some progress can be made, and the approach will become clearer if the main types of colour-blindness are first briefly reviewed.

Colour-blind subjects can be divided into three main groups, each of which has several subdivisions.

Achromats or Monochromats.—These have no colour sense whatever and can match any colour with any other colour provided that the intensities are equalized. Some of these are maximally sensitive in the green region of the spectrum at about 500 m μ ; a second group are most sensitive at 540 m μ , and a third group between 560 and 570 m μ . Once again it must be emphasized that monochromasy does not necessarily imply only one type of receptor. It may arise even if three or more receptors are present and the information which they provide is pooled before reaching the brain—that is, if there are not separate pathways each capable of being stimulated somewhat selectively by the various receptors. It is not known, therefore, whether these maxima represent those of three different types of receptor or result from some combination of receptors. The maximum at 500 m μ is thought to indicate the presence of rods only, and it is interesting to note that such subjects, though they may be photophobic, are not blind in daylight.

Dichromats.—These are able to match all the colours of the spectrum with mixtures of red and violet, and they may be divided into at least three clear groups. There are the protanopes (sometimes called red-blind), who have low sensitivity to the red end of the spectrum and are most sensitive at 540 m μ . They match a point in the blue-green region (about 490 m μ) with white. Secondly, there are the deuteranopes, and these form a more heterogeneous group. On the one hand the spectral sensitivity curve may not differ from that of the normal subject, and on the other it may have its maximum displaced towards the red end of the spectrum to about 575 m μ . The neutral point—that is, the point in the spectrum which can be matched with white—varies between 500 m μ and 520 m μ . Both these types of colour-blindness are congenital.

Tritanopes.—These are much rarer, and very often, if not always, tritanopia results from pathological changes in the eye. It is characterized by a neutral point at 570 m μ and generally a low sensitivity to blue and violet, though the maximum sensitivity is within the normal range.

In each of these groups the subjects habitually make certain well-defined colour confusions, and indeed it is upon these confusions that many established tests for colour-blindness depend. Protanopes and deuteranopes can match red with green on a 2-degree field. In general they seem to separate colours into blues, corresponding to wavelengths between violet and the neutral point, and yellows from the neutral point to the red end of the spectrum, and it is interesting to note that the maxima of their sensitivity curves correspond rather closely to the maxima of those found in the monochromats.

There is another group of subjects who cannot match all the spectral colours by means of only two primaries—that is, they are trichromats, but in making matches of yellow, for example, with mixtures of red and green, they require different proportions of these colours from those required by normal people. Probably the majority of these "anomalous trichromats" have some degree of true colour-blindness—that is, they are tending towards protanopia, deuteranopia, or tritanopia, but are not sufficiently abnormal to be able to dispense with the third primary altogether.

Finally, when the Ishihara plates are used as a test for colour-blindness, some individuals are found who would be diagnosed as red-green blind—that is, as either protanopes

or deuteranopes—but on further testing they are able to distinguish all the spectral colours correctly and cannot match red with green or even with yellow on a 2-degree field. These subjects apparently associate colour in a different way, and there is some instability in their colour sensations. For example, an orange field may be correctly named if standing by itself, but will be called green if placed next to a red, or red if next to a green field. On the Ishihara plates the various spots are recognized as different and are often correctly named, but they may be grouped quite differently from the way in which they are grouped by normal subjects. Consequently the plates are read incorrectly or not at all, but for a quite different reason.

Normal Vision and Colour-blindness Compared

The behaviour of normal subjects when different parts of their retina are investigated by means of small fields may now be compared with that of colour-blind subjects both when using the whole eye and also when their vision is similarly restricted. The dichromatic zone in the periphery at about 60–70 degrees from the optic axis exhibits a type of deuteranopia. Its neutral point lies in the blue-green or green region of the spectrum, and there is no evidence of any markedly decreased sensitivity to red as compared with green when the eye is maintained in a steady light-adapted condition.

Structurally the retina is much simpler in this region than it is towards the centre, and attention may be called to the limited number of ganglion cells and thus to the limited number of separate pathways to the brain from this area. A detailed analysis of these ganglion cells and their connexions would probably prove of great interest. There are certainly two main histologically distinguishable classes. Some very large cells with well-defined Nissl's granules are interspersed among numerous much smaller cells with less-granulated Nissl's substance. In the extreme periphery the ganglion cells are still less abundant while the receptors themselves are not much reduced, so the achromasy of this zone probably results from the paucity of optic-nerve fibres. These peripheral regions of the eye in all probability represent parts which have not evolved so far as the more central regions, and may therefore offer clues concerning the evolution of the colour-vision mechanism.

In contrast to the deuteranopia of the peripheral zone, the foveal centre of the normal subject behaves as a tritanopic system and makes the confusions characteristic of this type of dichromasy. Its neutral point is in the region of 570 $m\mu$. It thus behaves as if it possessed only two pathways and as if the pathway sensitive mainly in the violet region of the spectrum was absent or physiologically inactivated.

Foveal Centre of Those who are Red-green Blind

If the foveal centre is investigated in the same way in those dichromats who are red-green blind—the protanopes and the deuteranopes—it is found then to be completely colour-blind or monochromatic. That is to say, when the field of vision of the protanopes and deuteranopes is confined to the foveal centre all sense of colour goes and any spectral colour can be matched with any other when there is equality of brightness. The area behaves as if one pathway alone was functional. In the protanopes this pathway has its maximum sensitivity at 540 $m\mu$. In the deuteranopes the most sensitive region ranges between 555 $m\mu$ and 580 $m\mu$, of which the former does not differ from that of the normal observer.

When the deuteranopes are investigated further the possible meaning of this divergence becomes clear. If, for simplicity, it is assumed that the normal eye has three receptors, R, G, and B, so lettered as to indicate the region of the spectrum (red, green, or blue) in which they are most sensitive, then the foveal centre behaves as though B were absent or suppressed, thus leaving only R and G functional. Now red-green dichromats might be expected to have reduction of the R receptor (protanopes) or of G, or they might well possess both R and G receptors but have no differentiation of the pathways arising from them. The foveal centre of the red-green blind might therefore have a sensitivity corresponding to R, to G, or to R + G. By adapting or fatiguing the eye to selected wavelengths it should be possible, by studying the effects of such adaptation on the ensuing sensitivity, to decide whether the foveal centre of dichromats contains one or two types of receptor.

A study of some twenty deuteranopes in this way has given a very clear indication that they tend to be divisible into two classes. In the first class, the spectral sensitivity is normal and the effects of selective adaptation are identical with those found in the normal subject. Since, however, these dichromatic subjects are monochromatic in the central fovea, they presumably have receptors R and G, but their effects must be combined on to one pathway—that is, they behave as R + G. At the other extreme, five subjects have been investigated in whom there is no selective adaptation. In them it is immaterial what wavelength is used for the adapting light; the thresholds for violet, or blue, and red are always raised equally by adapting lights of equal subjective brightness. These subjects have their maximum sensitivity at about 575 $m\mu$ and probably possess receptors of the R type only, so their spectral sensitivity curve probably represents the spectral sensitivity of the R receptor of the normal eye. The shape of this sensitivity curve is very similar to that of the visual purple absorption spectrum, but the curve is shifted towards the red. Moreover, it is of special interest to find that the sensation which these subjects record from the foveal centre is "colourless," just like the sensation aroused by rods only, but it becomes coloured when comparisons are possible. Between these two extremes there are other deuteranopes who show intermediate stages with regard both to the adaptation effects and to the position of the luminosity curves.

Insufficient protanopes have so far been examined by the method of selective adaptation to say whether the maximum sensitivity of their fovea at 540 $m\mu$ corresponds to the action of the G receptor only or whether more than one receptor enters into the formation of this pathway. The first experiments indicated that perhaps two receptors were involved, but later experiments throw some doubt on this interpretation, and the point is not yet settled.

Once again, detailed examination of the structure of the foveal centre, not only with regard to the receptors but also with reference to the bipolar cells, ganglion cells, and their central connexions through the lateral geniculate body, is required in order to establish the nature of these pathways. There are, for example, some indications that the very large ganglion cells of the periphery are not present among those connecting with the central foveal elements. The "mop" bipolar cell, which relays mostly from rods, is also scarce in or absent from this area. Moreover, there are indications of at least two types of cone in the foveal centre of monkeys, and the participation of rods, among which histology reveals two separable groups in monkeys and frogs, cannot now be so confidently excluded from daylight vision as was done by earlier investigators. In fact, one of the

main problems in vision to-day is the question of what the rods are doing under photopic conditions.

Conclusion

Enough has been said to indicate that the rigid trichromatic theory and the dogmatic assertion of the presence of three types of cone in the fovea of the normal eye are not entirely satisfactory. The study of specific retinal areas, functionally by the use of small fields, structurally by the use of reliable histological methods, and electrophysiologically in other animals, is now the obvious method of approach. Further work on the same lines with colour-blind subjects can almost be guaranteed to yield further dividends. In particular, a more enlightened approach to the evolution of visual mechanisms may well give clues on the nature of the mechanism for colour-vision: thus, there are many indications that the colour-sense may have arisen when a central apparatus was evolved for comparing and evaluating the information already reaching the brain through separate channels previously developed for other purposes—for example, for night and day vision, for increased visual acuity, etc. The time has now come, therefore, for a more biological and comparative approach to the subject. The working of the human eye cannot be treated in isolation as a purely physical or psychological problem; it must be studied in relation to the evolutionary history of vision as a whole.

INFLUENCE OF ASCORBIC ACID ON THE HEALING OF CORNEAL ULCERS IN MAN

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It is accepted that the repair of collagenous tissue is dependent on an adequate supply of ascorbic acid (Höjer, 1924; Menkin, Wolbach, and Menkin, 1934; Wolbach and Howe, 1926). Furthermore, ascorbic acid has been shown by Schmid and Bürki (1943), Henkes (1946), and Pirie (1946) to exist in a relatively high concentration in the cornea. The cornea is largely composed of collagen. It is, moreover, avascular. Thus vitamin C may play an unusually important part in the metabolism of this special tissue and possibly also in the resolution of corneal lesions.

Galloway, Garry, and Hitchin (1948), working with guinea-pigs, found that the healing of superficial injuries made with a dental burr and involving only the epithelium was not delayed even when the guinea-pigs were in a subscorbutic state. In their experiments, however, healing may have been effected predominantly by a sliding of epithelial cells from the corneal margin (Arey and Covode, 1943; Buschke, Friedenwald, and Fleischmann, 1943; Mann, 1944). In such injuries there was no occasion for new formation of collagen.

Campbell, Ferguson, and Garry (1950), using heat injuries to the epithelium alone in scorbutic guinea-pigs, confirmed the findings of Galloway, Garry, and Hitchin (1948); but they showed that deeper burns, involving the anterior two-thirds of the corneal stroma, took approximately 30%

longer to heal in scorbutic guinea-pigs than in those fully saturated with ascorbic acid. Furthermore, even after epithelial healing was complete, structural weakness of the wound persisted for as long as three weeks after the injury in the scorbutic animals, while in the saturated guinea-pigs the strength of the cornea was restored in 11 days.

These results suggest that ascorbic acid may be of value in the treatment of human corneal lesions. In order to test this possibility we undertook the present investigation. Our study was restricted to the healing of small corneal ulcers in man so as to simulate the animal experiments conducted by Campbell, Ferguson, and Garry (1950). Suitable cases can readily be collected in sufficient numbers to justify statistical analysis.

Such an investigation on human beings can never hope to be so clear-cut as that on the guinea-pigs, in which the experimental group was reduced to a subscorbutic state and the control group had an ample intake of vitamin C. All our patients were eating a more or less normal diet, the intake of vitamin C probably reaching 50 mg. daily in some cases. Therefore, in order to produce blood levels in sufficient contrast with the group on a normal diet, we gave half our patients very massive doses of vitamin C.

Method

The patients studied in this investigation were in attendance at the out-patient department of the Glasgow Eye Infirmary between November, 1949, and March, 1950.

Approximately half the patients received 0.5 g. of ascorbic acid three times daily; the remaining patients received control tablets containing no ascorbic acid, but of identical appearance and taste. Thus the patients in the principal group probably received 30 to 50 times as much ascorbic acid as the patients in the control group, who received ascorbic acid only in their diet. Administration was continued until healing was complete.

The clinical examination of the patients was carried out by one of us (T. A. S. B.), who throughout the experiment was unaware of the type of tablet administered to each patient.

A detailed clinical history was obtained from each patient. This was followed by a careful examination of the lesion, and such details as its size and position on the cornea were noted.

To assess the extent of the ulcer one drop of a 2% aqueous solution of sodium fluorescein was instilled into the conjunctival sac. After one minute exactly, excess fluorescein was washed off with a stream of isotonic sodium chloride solution delivered from a pipette. The intensity of fluorescence of the ulcer was then measured in a dark room by placing alongside the patient's eye a series of standard strips of filter paper impregnated with varying concentrations of sodium fluorescein. Fluorescence was induced by exposure to a mercury vapour lamp fitted with a Wood's glass screen, and situated about 2 feet (60 cm.) from the patient.

Our standard consisted of five strips, 1 by $\frac{1}{2}$ in. (2.5 by 1.25 cm.), of No. 1 Whatman filter paper impregnated with fluorescein so that the intensity of fluorescence increased in approximately linear steps (Campbell and Boyd, 1950). Table I gives details of these standard strips.

As healing of a corneal ulcer progresses, the intensity of the fluorescence decreases and finally ceases when epithelialization is complete. The time of healing was recorded as the interval between the first examination of the ulcer and the cessation of fluorescence. Observations were carried out daily.