SIGNIFICANCE OF COLOUR CHANGE IN THE CORNEA*†

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EVERY practising ophthalmologist meets with changes in the colour of the cornea, and it is indeed astonishing that this small gelatinous mantle, hardly more than half-a-millimetre in thickness, can register so many chromatic variations. Abnormal pigmentation may be congenital or acquired, transient or permanent, stationary or progressive, endogenous or exogenous, benign or malignant. It may be confined to the anterior or posterior surface, and may occupy any or all of the intervening layers. It may be disposed in a regular pattern or haphazardly scattered. Sometimes the whole corneal area will be tinged. In other instances we find abnormal coloration limited to the periphery or concentrated at the axis. Bearing in mind all these possibilities, we must admit that classification of corneal colour change is not easy, and our difficulty is enhanced by the fact that such change may be linked with accessory signs not only in the cornea itself, but also in other parts of the eye. Associated abnormality can also arise in the ocular adnexa and in more remote organs.

Some observers have tried to draw a distinction between real and apparent changes in corneal coloration, and from one point of view their attitude seems logical. Nevertheless we do not always find, amidst kaleidoscopic conditions of practice, any sharp line of division between real and apparent colour. In the laboratory we can control the background so as to obtain valid answers from a colorimeter, but the living human cornea is backed by a screen of pigment which widely varies from patient to patient. Thus, for instance, the anterior corneal surface illuminated in a certain way can appear brown by virtue of its uveal background, without any corresponding structural modification in the cornea itself. Similarly, a tint may be imparted to the corneal periphery by changes in the limbal zone of the sclera or in the adjacent network of vessels. The concept of colour has become more and more complicated with the growth of knowledge, so that practising ophthalmologists cannot keep pace with all the modern techniques of investigation. We can nevertheless appreciate that there is a large subjective factor in most of our judgments concerning colour; and there is no call for bewilderment if we find the same structure changing its hue when we gaze at it from another angle, or with a different mode of illumination.

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ASSEMBLAGE OF PATIENTS

Even if we could evolve a simple but comprehensive scheme of classification, we might easily overlook many instances of abnormal coloration in everyday practice. Sometimes the change is so conspicuous as to be noticed by the patient, who accordingly comes to seek an explanation. More often we shall meet the colour change fortuitously during routine examination of a patient who has perhaps come to be refracted, or to seek treatment for some quite different lesion. Then again, we may go out of our way to search for corneal pigmentation as evidence of extra-ocular disease (*e.g.* hepato-lenticular sclerosis, Wilson's disease). Furthermore, the presence of pigment in the cornea may be of medico-legal significance, as, for example, when it points to former injury. Industrial conditions must also be kept in mind, because certain vapourized substances can be directly deposited in the cornea. Other foreign material, or derivatives from such, may be indirectly absorbed by the cornea after having entered the body *via* the skin, lungs, or alimentary tract.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients who display abnormal pigmentation is often aided by re-examination after an interval. Periodical colour photographs can be particularly helpful if malignant neoplasm be suspected, but we should always take a careful history before resorting to these extra diagnostic aids. The history can of course be misleading, as, for instance, when a patient suddenly notices a pigmented patch which has in fact existed for many years, or even since birth. Nevertheless we should try to sift every item of information furnished by the patient, by other members of the household, and by the family doctor.

Although the eye is a small organ, it can present an almost infinite range of abnormal signs, so that ophthalmologists who have already practised for 20 or 30 years often find themselves at a loss for a diagnosis. Pigmentary disturbance of the cornea is no exception to this general rule, and none of us need feel guilty if he fails to offer an immediate explanation for every colour change. Even the inexperienced observer can, however, describe the phenomena; and he should aim at supplying all those details which enable an absent colleague to imagine the lesion. Having recounted the essential points of the history, he should clearly indicate the size, shape, level, and colour of the corneal region, and then proceed to set forth any associated abnormal signs that he may have discovered in the eye or elsewhere. The novice will incidentally find that this exercise of careful description often serves to unveil the aetiology of a colour change which had at first seemed obscure.

ASSOCIATED SIGNS

Mistakes and omissions in clinical work are needlessly multiplied if we concentrate too soon and too exclusively on the part to which our attention is first directed. Looking at the whole patient from a distance often supplies the key to diagnosis, and we should not rush into slit-lamp microscopy before making a preliminary survey. For example, impregnation of the cornea by exogenous pigment will often be accompanied by discoloration of the exposed skin. Associated signs of abnormality in the affected eye will sometimes clinch the diagnosis,

as happens in chalcosis, when we find sunflower cataract and brilliant lenticular polychrome linked with blue coloration of Descemet's membrane near the limbus. Refractive changes are occasionally relevant, as in keratoconus victims, when astigmatism against the rule may be noted in association with a broken pigmented ring surrounding the salient portion of the cornea. Krukenberg's spindles are often accompanied by myopia.

CLINICAL CLASSIFICATION

The clinical varieties of corneal coloration may conveniently be divided under the following headings:

(1) Normal or physiological colour	(5) Pigmented scars
(2) Congenital coloration	(6) Neoplasms
(3) The Hudson-Stähli line	(7) Coloration linked with systemic disease
(4) Coloration in corneal dystrophy	(8) Pigment derived from the inner eye
(9) Exogenous coloration	

(1) *Physiological Colour*.—Even in the normal cornea, free from epithelial oedema, we often see faint bedewing of the anterior surface beside the limbus under indirect illumination; and a brown iris may communicate its tint to the bedewed zone of epithelium. Whatever the colour of the iris may be, the normal endothelium, which is only visible in the zone of specular reflection, shows up as a golden tessellation. Blood-vessels normally ramify in the superficial layers of the cornea for a distance of about one millimetre from its junction with the sclera; and these twigs, though colourless under the direct beam, look red when indirectly illuminated.

(2) *Congenital Coloration*.—This is rare, and it seems probable that many alleged instances are spurious. The shape and distribution may be quite irregular, but the limbus is more likely to be implicated than the axis. Most of these congenital blemishes are situated in the superficial layers and are usually associated with opacity.

(3) *The Hudson-Stähli Line*.—This is a brown or yellow line, continuous or interrupted, limited to the surface epithelium approximately on a level with the lower margin of the pupil. It sometimes runs straight across, but more often describes a slight curve with its convexity downwards. Occasionally it *divaricates* at one or both ends, and its origin remains a mystery. Reference will presently be made to pigment arising in old corneal scars, but this Hudson-Stähli line is not associated with any evidence of former inflammation or trauma, and does not impair vision. Some authorities have looked upon it as a disintegration product of haemoglobin, but the evidence is unconvincing. To say that it is derived from uveal pigment, as some have done, is even less convincing, because, if that explanation were true, how could the coloured matter reach the anterior surface without leaving a trace in the corneal substance? The only established aetiological factor is age. We hardly ever find a Hudson-Stähli line in a patient less than 30 years old.

It will be remembered that Stähli (1918) gave a detailed account of this pigment line as observed with the slit-lamp, but many ophthalmologists are unaware that Hudson (1911) had already found it before Gullstrand's original demonstration of his slit-lamp at the International Congress of Ophthalmology held in Heidelberg

in the same year as Hudson's paper appeared. Hudson was an exceptionally acute user of the uniocular loupe, and indeed the ability to see this tenuous line without recourse to the slit-lamp is a sure sign of having been well-apprenticed into loupe-technique.

(4) *Coloration in Corneal Dystrophy*.—Opacity and impairment of lustre sooner or later become conspicuous in most cases of corneal dystrophy, but the only human dystrophic condition in which pigment regularly figures is keratoconus. Except in the early stages of this disease, there is usually a ring of brown superficial pigmentation, not always continuous, surrounding the axial region of the cornea. The nature of this pigment has not been identified, but may well be similar to that of the Hudson-Stähli line. It may be of interest to recall that some breeds of dog, especially those with prominent eyes (e.g. boxers and pekinese), are liable to a progressive form of corneal dystrophy characterized by surface irregularity, vascularization, and pigment deposits. Roberts (1954) looks upon this disease as second in importance only to cataract as a cause of blindness in dogs. Tudor Thomas (1955) reported one instance of dense epithelial pigmentation as a congenital lesion involving both eyes of a foal.

Coloured or colourless crystals are sometimes visible in arcus senilis, arcus juvenilis, and in diffuse lipid dystrophy of the cornea. They may also be found in nutritional or trachomatous keratomalacia. There have been a few recorded instances of bilateral corneal dystrophy in which crystal-formation was the main clinical feature, but probably some of these patients were suffering from an obscure derangement of metabolism.

(5) *Pigmented Scars*.—Sometimes we find entangled in corneal scars a few fragments of foreign matter as a residue of old injury, but that situation is dealt with below under the heading of "exogenous pigment". The present heading includes only endogenous pigment developing long after the active trouble has subsided. A line of superficial yellow pigment, sharing certain features with the keratoconus ring and the Hudson-Stähli line, can be detected in a considerable proportion of old corneal scars. One might have expected that this adventitious coloration could supply a clue to the aetiology of the original lesion, but in fact it supplies no firm guidance. The scars of old injuries, phlyctenular ulcers, interstitial keratitis, and many other conditions all have the capacity to evolve one or more of these imperfectly understood yellowish-brown lines. Crystalline deposits, either coloured or colourless, are manifest in some of these longstanding scars, but they also seem to lack any differential significance.

(6) *Neoplasms*.—Small nests of benign pigmented cells are commonly found upon the surface of the globe during routine examination; and the limbal region is a favourite site for these co-called innocent melanomata. Sometimes we find them encroaching upon the corneal margin, and no special action is needed except to reassure those patients who have themselves noticed the blemish. If the pigmented area arouses any suspicion of malignancy, or if we feel the need for extra precaution, we can obtain colour photographs at intervals. Slight changes in the intensity of coloration do not necessarily mean danger, and such variations are especially apt to occur side-by-side with gradual cystic transformation.

Diffuse malignant melanomatosis can develop with astonishing speed, and in

such cases we usually see multiple foci of the disease on the eyelids as well as on the surface of the globe. Every practising ophthalmologist has a wholesome dread of missing a malignant growth at the stage when it can be easily removed. He also recognizes the possibility that a hitherto innocent collection of cells can fall into malignant metaplasia under the stimulus of surgery. Indeed these pigmented lesions in the neighbourhood of the limbus can occasion great anxiety, but, unless the evidence for malignancy is strong enough to convince several other colleagues, most of us will surely lean towards conservatism. Even if malignancy is proved, radical surgery is by no means always feasible. One rare but well-established vehicle of corneal pigmentation is an epithelioma arising at or near the corneo-scleral junction.

(7) *Coloration Linked with Systemic Disease.*—It is interesting to recall that Osler (1904), who described scleral pigmentation (ochronosis) in alkaptonuria, did not encounter any corresponding change in the cornea. Corneal pigment in this condition was, however, recorded by Sallmann (1926) and later by Smith (1942). Paget's disease (osteitis deformans) has long been known to be associated with angioid streaks in the retina, but it is sometimes forgotten that deposits of pigment in or near Bowman's membrane may also occur in Paget's disease. One rare but important variety of corneal pigmentation is pathognomonic of Wilson's disease (hepatolenticular sclerosis). Here we find a golden-brown coloration of Descemet's membrane, most intense beside the limbus, implicating only part of the thickness of the membrane, and fading towards the corneal axis.

From time to time the literature contains reports of crystalline deposits in the cornea associated with various metabolic and endocrine disturbances, and a few authors have traced instances of the inheritance of this condition, but it is evidently rare.

(8) *Pigment Derived from the Inner Eye.*—Uveal tissue readily becomes entangled in the cornea when this structure has sustained a perforating wound, and pigmented fragments can usually be detected after healing, even if the prolapsed tissue has been promptly excised. Fresh inflammatory precipitates adhering to the posterior surface of the cornea are usually colourless, but as time goes on, an increasingly large proportion of these deposits will become shrunken and pigmented. In recurrent uveitis we often see fresh round colourless precipitates side-by-side with old pigmented deposits on the back of the same cornea. Small scattered granules of uveal pigment are found adhering to the posterior corneal surface in the eyes of many middle-aged people, and in a still larger proportion of elderly eyes, even if they have remained free from disease. Sooner or later we all shed our iris pigment layer into the aqueous, and this universal tendency is accelerated and intensified by trauma, inflammation, diabetes, and glaucoma.

Myopia is another powerful disrupting influence, and it is interesting to note the close association of this refractive state with Krukenberg's spindles. Some authorities used to contend that Krukenberg's spindle was a congenital abnormality, but that opinion can no longer be taken seriously, because no one has ever produced a genuine instance of this condition in a child. Slit-lamp examination of an eye harbouring a Krukenberg's spindle will always show, in addition to the main fusiform aggregation, a number of less densely disposed granules on other parts of the posterior corneal surface, and similar particles floating in the

aqueous fluid. In certain other myopes we may find numerous dots of pigment upon the back of the cornea without any special arrangement into a spindle-pattern. We know that the aqueous currents vary from person to person, and the mere presence of granules is evidently not enough to create a spindle. We are forced to conclude that there is no sharp line of division between a Krukenberg spindle and an amorphous array of pigment granules; and the important thing to remember is that myopia predisposes to both situations.

Persistent hyphaema together with raised intra-ocular pressure can produce an astonishing succession of colour-effects in the corneal substance. We may find the laminae tinged green, blue, heliotrope, and brown, as happens in bruises elsewhere. Detailed chemical and histological studies has shown that this play of colours arises from the disintegration products of haemoglobin released from those red corpuscles which are, so to speak, thrust into the interlamellar spaces from compressed aqueous of high viscosity.

(9) *Exogenous Coloration*

(a) The simplest form of exogenous coloration occurs when *pigmented foreign matter is directly implanted* upon the cornea. Thus we may find vegetable fragments, metallic or other inorganic particles, and various dye-substances. Stains from aniline pencils, unless the accompanying corneal abrasion is large, seldom give rise to much trouble, because the colour fades spontaneously within a few days. Fluorescein stains disappear even more quickly. Rust-rings readily form around iron-containing fragments unless these are promptly removed, but a moderate amount of rust does not greatly interfere with vision, and slow spontaneous fading is its usual fate. Therefore it is seldom advisable to attempt radical clearance of the stain when we remove a piece of iron or steel that has already been embedded long enough to create a rust-ring. Certain corneal injuries may introduce scores of pigmented gritty particles into all layers of the substance. In such cases it is clearly impossible to remove all the foreign material without producing extensive scars, but fortunately these particles often prove chemically inert. Therefore the affected eye may settle down remarkably well, and with far less impairment of vision than we might have anticipated in the early stages. A transitional period of irritability and photophobia is usual, because the cornea needs time to adapt itself to the multiple foreign bodies, even when these are innocuous.

(b) *Pigment is deliberately introduced* into the cornea in the operation of tattooing, which was devised in order to modify the disfigurement of a corneal leucoma. Numerous different techniques have been recommended, and several disadvantages have arisen. Sometimes the implanted material has become dislodged. In other instances it has provoked keratitis. Then again, the cosmetic improvement often shows less than was anticipated. In properly selected cases corneal tattooing can still offer benefit, but is far less often indicated nowadays than it was in the past, for two reasons: first, the incidence of dense corneal leucoma has been greatly diminished by chemotherapy, antibiotics, and avoidance of so-called heroic measures of therapy; secondly, corneal grafting is now performed upon many of the patients who would have been regarded as eligible for tattooing in bygone days.

(c) Next we should consider pigment derived from *medicaments applied to the eye*, but this form of coloration is increasingly rare. Prolonged topical use of

silver nitrate used to be far commoner than it is today. The most obvious effect was a diffuse dull-grey staining of the conjunctiva, but detailed inspection revealed corneal changes, especially in Descemet's membrane, which developed a grey or greyish-green tint in the neighbourhood of the limbus. In some cases the substantia propria is curiously reticulated and coloured a faint grey. Copper sulphate stick, which used often to be applied to the conjunctiva of trachoma victims at regular intervals for years, was apt to produce a faint blue stain upon an irregularly scarred and vascularized cornea. Greyish-blue coloration of the corneal surface has also been recorded after prolonged treatment with yellow oxide of mercury ointment.

(d) *Medicaments introduced elsewhere* than into the eye can sometimes find their way into the cornea. Thus corneal argyrosis was recorded by Ascher (1924) in a woman who had undergone a course of silver salvarsan injections for syphilis. Bonnet and Bonamour (1936, 1937) published a fascinating account of small gleaming granules on the anterior surface of Descemet's membrane. The patient whom they recorded was receiving gold salts as a remedy for tuberculosis. Who would have thought of Descemet's membrane as a bank for surplus gold? Beddard (1909) reported ocular ochronosis in a patient whose varicose ulcers had been treated for a long time with carbolic acid. We have already seen that ocular ochronosis may be linked with alkaptonuria, and we shall presently meet it in another context.

(e) *Contamination by industrial substances* is another cause of pigmentation. In former times certain silver foundry workers became deeply pigmented all over the body, and incidentally manifested the same ocular changes as those which followed prolonged local medication with silver nitrate. In Switzerland, peripheral coloration of Descemet's membrane has been noted in several craftsmen working with silver. Blue, green, and golden tints have all been mentioned, so that presumably this metal can be assimilated in various chemical combinations. Controlled observation has shown that the conjunctiva remained unstained in all craftsmen who scrupulously refrained from touching their eyes with contaminated fingers. Therefore the changes in Descemet's membrane are probably due to *indirect* absorption of silver.

Reference has already been made to ocular ochronosis in alkaptonuria and in poisoning with carbolic acid. A similar condition has been reported by Miller (1954) among patients exposed to hydroquinone, which is a derivative of benzene. This substance is widely used for combating discoloration of motor fuels, and in the manufacture of perfume and paint. As a powerful reducing agent, it avidly attacks the cornea, showing a predilection for the most exposed position, *i.e.* the interpalpebral zone. First the epithelium takes up a faint sepia-brown tint, and then, if the patient remains exposed, successive layers of the substantia propria become infiltrated. Later the affected cornea displays ulceration, calcification, superficial vascularization, and folds in Descemet's membrane. An arcus senilis, with its high fat content, is particularly quick to take up the stain. Similar conjunctival discoloration fades when the victim is removed from further contact with hydroquinone vapour, but the corneal stain is irreversible.

Now that the danger from hydroquinone has been authoritatively described, all necessary precautions are in force at the factories concerned, and it seems reasonable

to hope that hydroquinone ochronosis of the eye is now an obsolete industrial disease. Factory owners are progressively anxious to avoid invalidism among their employees, not only for humanitarian reasons but also for the sake of industrial peace and co-operation. As soon as any volatile by-product of industry has been adjudged dangerous, special apparatus is immediately contrived to eliminate it from the atmosphere.

(f) Of possible *metallic intra-ocular foreign bodies*, iron and copper are the most important, and each produces associated changes in the lens, which need not here be catalogued. Signs of an entry wound are evident in a large proportion of the affected eyes. Intra-ocular iron imparts a diffuse yellow stain to all layers of the substantia propria, especially in the corneal periphery. With copper-containing fragments the inflammatory effect may be so fierce that the characteristic phenomena fail to develop, but in a classical case of chalcosis we find the peripheral zone of Descemet's membrane decorated with a vivid blue.

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