type. One wonders, however, whether in this case there was present a cyst of the type which Coats described as occurring in myopic retinæ.

Treatment

We have aimed at getting the highest possible concentration of hormone as close as possible to the retina, and have therefore used systemic treatment to achieve this through the blood stream. We have the impression, however, that cortisone injected into Tenon's capsule is a little more effective, and more especially when hyaluronidase is added to encourage its diffusion. Recently a combination of these routes has been used to achieve a maximal concentration.

Conclusions

Clearly no firm conclusion can be drawn from this small series; but we do feel that some of the cases have confirmed the belief that cortisone can affect retinal exudates. It is evident, too, that hard exudates as well as œdema can be encouraged to absorb, and the retinal and field changes seem to suggest that they do so after passing through a stage of liquefaction. This treatment is, of course, no cure, but we believe that it can, if only temporarily, interrupt the course of some of these cases with exudates. The ophthalmoscopic distinction of cases likely to respond favourably remains difficult; but we have tried to throw a little more light upon it from our experience with these patients.

We should like to emphasize our gratitude to the surgeons who have entrusted us with the treatment of their cases and to record our appreciation of the help which we have received from the Department of Medical Illustration of the Institute of Ophthalmology in recording the fundus appearances.

The President said that the case with the dense mass of exudate (Case IX) seemed to him a retinopathy in the group described originally by Coats. It seemed that some benefit was obtained from cortisone. He would not imagine that there was any prospect of removing colloid bodies by cortisone; they were there permanently. On the other hand the lesions affecting the macula or the fovea itself might be different.

He asked whether it was essential that the patient should be hospitalized, or was there any danger in having these patients ambulatory?

Mr. C. A. G. Cook said that his experience of cortisone in the treatment of œdematous conditions of the macula had not been very encouraging although improvement had been obtained in some cases after a time. It was difficult to assess how much of that improvement would have occurred in the natural course of events, probably accelerated by the hospitalization of the patient. His own belief was that this problem would only be solved by extensive and prolonged investigation. His feeling about cortisone treatment of the condition could be summarized by saying that if he had the condition himself, for want of a better remedy he would try cortisone, but he would not be very optimistic and would therefore not be too cast down if no improvement occurred.

Mr. Hobbs, in reply to the President's question, said that, since general complications were not unknown with this hormone treatment he thought it advisable to hospitalize the patient at least for preliminary observation.

He agreed with Mr. Cook that this was not a simple form of treatment to apply.

Precancerous Melanosis

By C. H. Greer, M.B.

The first writer to use the term precancerous melanosis appears to have been Dubreuilh who in 1912 introduced the designation as an improvement on lentigo maligna which he had employed for the same lesion in previous publications (1894). Twenty-one years earlier, however, Jonathan Hutchinson (1891) had drawn attention to the development of epithelial cancer in senile freckles and areas of dermal melanotic staining in adults and his description of these cases constitutes one of the earliest records of precancerous melanosis.

During the last sixty years a small but constant stream of reports has appeared, especially in the French literature, of conjunctival lesions which may now be reasonably identified as malignant melanomata originating in areas of precancerous melanosis. The authors of these reports have employed a wide variety of terms including melanotic sarcoma, melanotic carcinoma, nævocarcinoma, tache mélanique and lentigo maligna. Descriptions of the conjunctival lesion in its precancerous phase are rare but that of Walker (1928) in the *Proceedings* of this Society under the title of "Melanosis of the Lid and Conjunctiva" appears to be a genuine case although no histological examination had been made.

In 1943, Reese somewhat clarified the position in a paper on precancerous and cancerous melanosis of the conjunctiva and skin. He defined cancerous melanosis as a malignant melanoma originating from a pre-existing precancerous lesion and, in a review of the literature, identified 42 definite or probable cases of this condition. On the evidence of the cases in the literature and of his own experience, he believes that cancerous melanosis is by far the commonest type of malignant melanotic growth of the conjunctiva, and that malignant change in a congenital pigmented nævus is rare.

Our experience at the Institute of Ophthalmology is somewhat different. Of 153 pigmented lesions of the conjunctiva, limbus, caruncle and plica semilunaris examined histologically since 1948, 118 (77%) were nævi; 30 (20%) were malignant melanomata; 5 (3%) were precancerous melanoses.

Of the 30 malignant melanomata, 3 showed surviving islands of small, typical, quiescent nævus cells, suggesting a nævus origin and 9 were malignant melanomata, developing in areas of precancerous melanosis of which there was histological evidence in the epithelium at the perimeter of the malignant focus. In the remaining 18 cases there was no *histological* indication of the mode of origin of the malignant growth, which may therefore have developed from a nævus, from a precancerous melanosis or, *de novo*, without a pre-existing lesion. In addition, among the 118 nævi, there were 10 in which increasing size, deepening pigmentation, cellular pleomorphism and histological evidence of commencing submucosal penetration, suggested early malignant change. These figures show that precancerous melanosis of the conjunctiva is a rare condition, and that in the majority of cases excision is not done until the cancerous phase has supervened. In addition, they support the view that malignant change in a conjunctival nævus probably occurs more often than Reese has suggested.

Clinical Features

The lesion commences as a flat pigmented macule and spreads gradually, remaining flat and extending laterally, until eventually the whole bulbar and palpebral conjunctiva, caruncle and adjacent skin of the lids may be involved in a flat finely granular pigmentation. We have observed that, in its early stages, the lesion may reproduce with extraordinary exactitude the appearance of candle wax spread thinly upon the conjunctival surface. Occasionally the precancerous change synchronously develops over the greater part of the conjunctiva, a fact which can be appreciated clinically only by the minutest scrutiny. While the common tendency is for the lesion to spread and enlarge progressively, spontaneous regression has been noted. In one of Reese's cases the lesion became clinically extinct without treatment but later reappeared.

The precancerous phase commonly lasts for 5–10 years but may be shorter or much longer. According to Reese malignancy almost invariably supervenes. One or more malignant foci develop, either simultaneously or successively and although these may become elevated to form obvious tumours they more often remain almost flat and may, indeed, metastasize and kill the patient without becoming appreciably raised above the surrounding epithelial surface. Enlargement, deepening pigmentation and inflammation in the precancerous area have been the common signs of malignant change but these may well escape detection unless the patient is under close surveillance.

Histogenesis

The earliest changes, which closely simulate junctional change in a pigmented nævus, occur in basal cells of the epithelium over a wide area (Fig. 1).

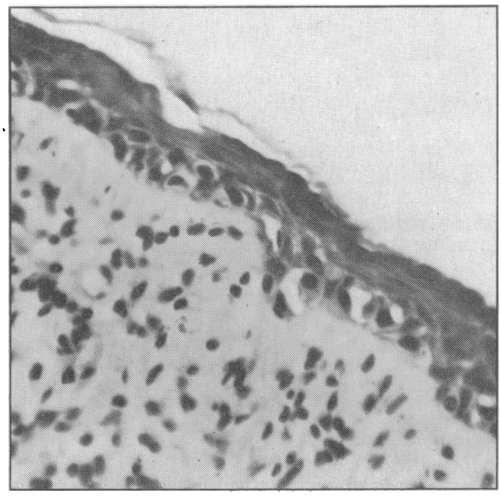

FIG. 1.—Early junctional change showing basal-cell multiplication, hyperpigmentation and vacuolation. × 320.

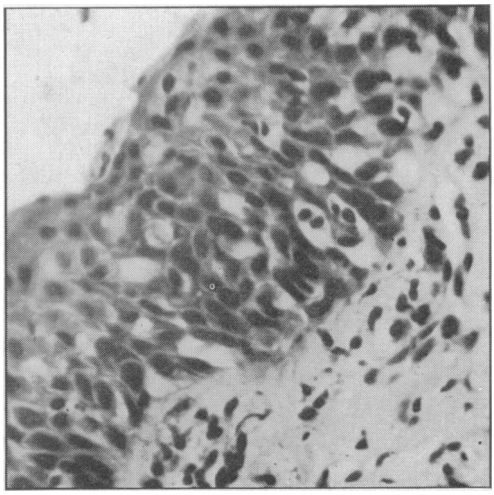

FIG. 2.—A more advanced stage showing the addition of several layers of proliferating cells to the deep surface of the epithelium. × 320.

These cells multiply in number, increase in size and become pigmented and separated from one another by clear spaces. The cells now show large pale nuclei and abundant cytoplasm which may be clear, contain fine pigment granules, vacuoles or droplets, or exhibit a fine cytoplasmic network

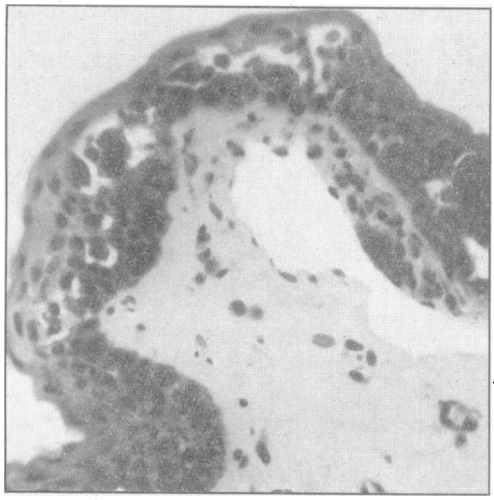

FIG. 3.—The proliferating cells segregated to form intra-epithelial pigmented nests. × 320.

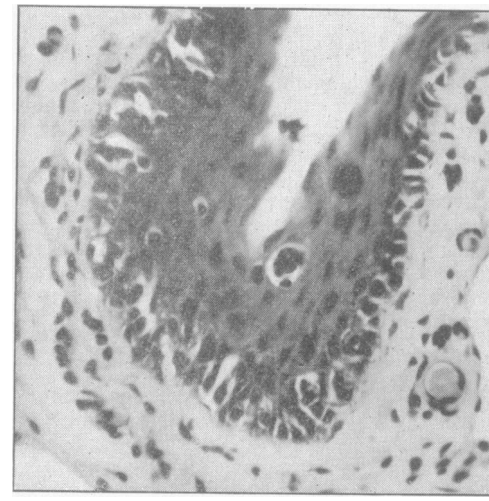

FIG. 4.—Isolated pigmented cells working towards the surface. × 320.

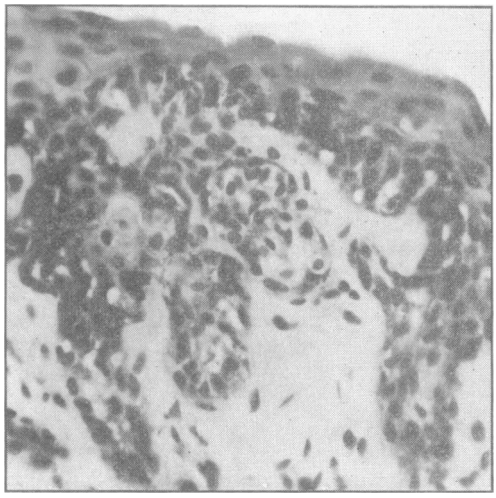

FIG. 5.—Basal cells proliferating downwards in solid buds and branching strands. × 320.

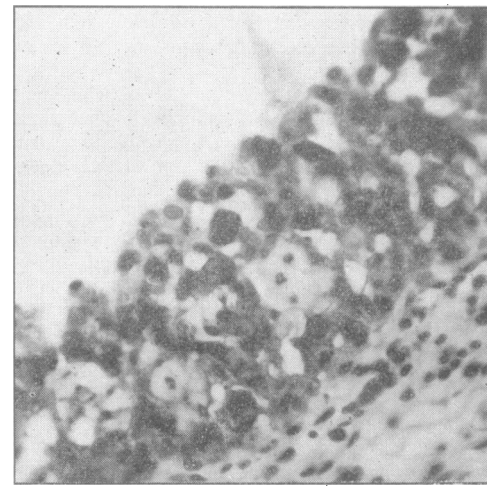

FIG. 6.—Borderline lesion. Neoplastic cells have largely replaced the epithelium without, however, invading the submucosa. × 320.

similar to that seen in foam cells. Contiguous cells fuse to produce spaces containing degenerate nuclear fragments (Fig. 2).

The cells proliferate *intra-epithelially* adding several layers to the deep surface of the epithelium or segregate to form *intra-epithelial* nests which contrast sharply with the normal mucosa in which they lie. It is these pigmented nests which impart the characteristic granularity to the surface of the lesion (Fig. 3).

Isolated clear or pigmented cells may also be seen being worked through the epithelium towards the surface (Fig. 4).

As the lesion develops the proliferating cells push downwards either in strands or solid buds and the submucosa is invaded by chronic inflammatory cells among which macrophages loaded with coarse pigment granules may be seen (Fig. 5).

Histologically the onset of malignancy is indicated by invasion of the submucosa by large, globular, clear or finely pigmented malignant cells from the overlying mucosa where they are present in large numbers throughout all its layers. Nuclear anaplasia and vacuolation and mitotic figures are additional indications, the latter being particularly significant as they are rarely, if ever, seen in the precancerous phase. Submucosal small round-cell infiltration is usually evident (Fig. 6).

Malignant melanoma supervening upon precancerous melanosis has been termed by Reese cancerous melanosis. This seems an unnecessary elaboration of an already confused nomenclature, for cancerous melanosis is clinically and histologically a superficial malignant melanoma and is identical with the superficial melanocarcinoma of Allen and Spitz (1953).

Discussion

Reese defined precancerous melanosis as an acquired neoplastic change occurring in the conjunctiva of middle-aged and elderly persons, and noted that it also occurred in the skin. He distinguished sharply between precancerous melanosis and the pigmented junctional nævus on the grounds that the nævus is a congenital, circumscribed, and elevated lesion, which rarely becomes malignant and is radio-resistant; while precancerous melanosis, on the other hand, is acquired in adult life, is flat and diffuse, inevitably becomes malignant and is radio-sensitive in its early stages.

These contentions appear to be based on a very small series of cases—17 in all, of which 5 were in the precancerous and 12 in the cancerous phase. Our experience with pigmented lesions of the conjunctiva leads us to suspect that malignant melanomata not infrequently originate in pre-existing nævi. In addition, the view that precancerous melanosis eventually becomes malignant in every case does not seem to have been satisfactorily proved. Further clinico-pathological observations seem desirable to illuminate this point in particular.

Becker (1954), who is one of the few writers who makes any direct reference to conjunctival precancerous melanosis, believes it to be a form of lentigo maligna, occurring in a mucous surface, but otherwise strictly comparable in morphology and evolution with epidermal lentigo which he regards as melanoma in situ or a premelanomatous condition.

Allen and Spitz (1953) describe an uncommon superficial malignant melanoma (melanocarcinoma), principally in the female external genitalia, which remains flat while spreading centrifugally over wide areas. This is histologically identical with Reese's cancerous melanosis and it seems not unreasonable to suppose that it is sometimes preceded by a precancerous phase. Indeed, it is possible that precancerous lesions occur in other sites such as the oral and nasal cavities, upper respiratory tract and ano-rectal junction, but often remain unrecognized because they are not readily seen and because they produce few symptoms until malignancy supervenes. These authors (1954) also stress the poor prognosis of malignant melanoma in mucous membranes and suggest that the paucity of early symptoms, the misinterpretation of the histological picture of border-line lesions and the difficulties of adequate surgical excision, are among the contributory causes.

For reasons previously mentioned, the introduction of the term cancerous melanosis seems unnecessary, and the question must inevitably arise whether conjunctival precancerous melanosis can be profitably distinguished from the pigmented nævus. We believe that it can and that the two lesions exhibit sufficient differences to merit separate consideration. The reasons for this view may be briefly stated as follows:

(1) Clinically, precancerous melanosis has a characteristic flat diffuse and progressive habit of growth.

(2) Histologically, the junctional proliferation is diffuse and intra-epithelial and the "dropping down" of innocent nævus cells into the submucosa, which is characteristic of nævi, is absent. Indeed, any infiltration into the submucosa of proliferative epithelial cells from a precancerous area must be interpreted as a sign of early malignant change.

(3) Therapeutically, the two conditions differ in that precancerous melanosis is reported to be sensitive to irradiation in its early stages while most nævi are insensitive.

In conclusion it may be said that precancerous melanosis is a proliferation originating in the basal cells of the conjunctival epithelium, analogous to Bowen's intra-epithelial carcinoma or extra-mammary Paget's disease, where that condition can be divorced from any primary malignancy in the underlying apocrine glands. This view receives support from Stout's (1938) observations upon a rare intra-epidermal amelanotic melanoma in the skin characterized by long duration, superficial spread and a histological picture closely simulating Paget's disease.

It would seem that further clinical and pathological observations are necessary before the nature, habits and relationships of precancerous melanosis can be regarded as finally settled.

I wish to express my indebtedness to Dr. N. Ashton and Dr. H. Haber for their advice and to Dr. P. Hansell for the photomicrographs.

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The President said that he had records of 4 cases which bore upon this subject, dating from 1923, 1929, 1935 and 1937. The first, Annie W., was reported at the Ophthalmological Society's Congress in 1951, having been mentioned briefly in the *Proceedings* (Neame, 1929, 1951).

In 1917 the late Mr. Creswell of Cardiff had removed a small growth from the surface of the right eye. In 1919 a recurrence was removed at Moorfields Hospital and a radium plaque was applied to the site. On November 24, 1923, an area of conjunctiva stippled with small discrete pigment spots was removed from the lower ocular conjunctiva, as well as two small projecting growths, by Mr. P. G. Doyne. Dr. Norman Ashton had kindly examined these sections later and reported "a tumour of undoubted malignancy. The cells appear to be rapidly dividing and mitotic figures are numerous. One can see the remnants from the pre-existing nævus from which this arose." On December 15, 1927, Mr. Doyne had excised the eye on account of multiple nodules of recurrent growth at several parts all around the cornea, lying on the sclera. In addition there was a strip of ocular conjunctiva separated by a narrow band of normal-looking conjunctiva below the cornea, once more presenting brown pigment patches. The pathological report on sections was ". . . epibulbar growth part like spindle-celled sarcoma, part alveolar. Slight superficial scleral invasion." This seemed to have settled the matter, for in reply by post to his inquiries in 1929, 1946, 1950 and 1953, Mrs. W. stated that she had had no further trouble, and in 1950 her doctor examined the socket and said it was "splendid".

The second case was reported by the late Mr. J. F. Cunningham (1929). The first examination had been made at the Central London Ophthalmic Hospital on February 21, 1929, and the condition at that time was "a fleshy elevation which moves with the conjunctiva". In addition "pigment is seen to be passing along the conjunctival vessels from the outer side and is encroaching on the cornea". The man's age was 49. It was proposed to remove the fleshy mass and examine it histologically. He had been unable to trace the in-patient notes on this case.

The third case came within the same category by reason of the presence of a very dark brown pigmented spot, about 2 mm. in length, just within the limbus and adjacent to the lower nasal angle of a conjunctival growth. It was a brown pigmented vascular mass with abundant blood vessels converging upon it to the temporal side of the left eye, in a man aged 56. The superficial layers of the cornea were shaved off with a Bier's knife to include the pigmented spot, and incisions carried into the conjunctiva so as to remove the growth in one piece with a margin of apparently healthy conjunctiva. The histological report was "superficial structure suggestive of a mole. No evidence of deep extension". A large, deeply pigmented mass had been noted on the temporal side fixed to the sclera four years later. Exenteration was advised but postal information revealed that the patient died six months after the last visit, at the Miller Hospital, Greenwich, from pneumonia. Post-mortem examination disclosed no evidence of metastatic growth.

The fourth case did not display melanosis except in the presence of fine pepper-like pigmentation on the corneal side of the small growth. The photograph showed the marked vascularization suggestive of early malignancy. This was in a woman aged 60.

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Dr. Norman Ashton said that as yet no one had had sufficient experience of cases in which the clinical and pathological pictures were correlated to come to any final conclusions about the true nature and prognosis of the disease. A useful analogy could be made between precancerous melanosis and Bowen's intra-epithelial carcinoma. The characteristic feature in both cases was the limitation of the tumour cells within the epithelium for long periods, but once frank malignancy developed with dermal invasion, there appeared to be little histological difference between the ordinary type of melanocarcinoma on the one hand and epidermoid carcinoma on the other. Thus precancerous melanosis would appear to be merely a variety of melanoma and one should be cautious of accepting the view that it had a distinct histogenesis: it had been suggested, for instance, that precancerous melanosis arose from basal cells whereas nævi were neuro-ectodermal in origin. He would not have thought that there was likely to be any difference in radio-sensitivity between the two types of melanomata in their malignant phases. Careful follow-up of cases was urgently required and it would be some years before much of value could be added to Dr. Greer's account.

Mr. E. F. King enquired whether this change in the conjunctival epithelium was also seen in the corneal epithelium. He had treated a patient for some time for superficial punctate keratitis which was extremely resistant. Later this patient developed a small fleshy nodule at the limbus which was excised and which examination showed was a malignant melanoma which had not been suspected. The eye was removed and pathological examination showed extensive changes of precancerous melanosis in the epithelium of the cornea and conjunctiva on both sides of the limbus.

Dr. Greer, in reply to Mr. King, said that, in his limited experience of this rare condition, corneal involvement was not uncommon if the lesion was near the limbus. In one case which he had seen, the histological picture suggested that the corneal epithelium was actually undergoing precancerous proliferation. This was impossible to prove conclusively but it certainly appeared to be the case.