AN INQUIRY INTO THE ORIGIN OF THE ABNORMAL PIGMENTATION OF THE SKIN AND CONJUNCTIVA IN CASES OF KERATOMALACIA IN ADULTS

BY

ARNOLD PILLAT

PROFESSOR OF OPHTHALMOLOGY, PEKING UNION MEDICAL COLLEGE

AND

GORDON KING

ASSOCIATE IN OBSTETRICS AND GYNAECOLOGY,
PEKING UNION MEDICAL COLLEGE

ONE of the most striking clinical symptoms of xerosis epithelialis conjunctivae and of keratomalacia of adults in China is the pigmentation of the conjunctiva. In certain cases there is also a dark staining of the skin, though this is not always so easily recognizable. The pigmentation of the conjunctiva was visible in about 70-80 per cent. of all the cases of keratomalacia seen in Peking in the spring of 1929, but in varying intensity.

As far as the literature is obtainable, only in India and Japan has a similar pigmentation in cases of keratomalacia been reported. But there are considerable differences in the description of the pigmentation, as well as in the real nature of the pigment described, and there are nothing but theories about the origin of the pigmentation.

Wright,² in his paper on "Keratomalacia in Southern India," quotes the description of keratomalacia by Kirkpatrick,¹ who passes the pigmentation with the words (p. 168) "a well-marked icteric tinge is often now (*i.e.*, in advanced cases) added to the pigmentation of the conjunctiva." His description deals more or less with the keratomalacia of children. Wright,² speaking of the pigmentation seen in keratomalacia in adults, makes the following statement: (p. 171) "A very important, but inconstant feature is jaundice. Sometimes it is very marked and gives the scanty conjunctival debris in the fornix a greenish yellow colour. It appears to be more common in adults. It is sometimes associated with a small cirrhotic liver, at other times the liver is large. In one case a fairly well-to-do woman of middle age developed keratomalacia in association with an irregular, enlarged and painful liver, and intense jaundice probably of a malignant nature." And later in his paper he continues: "There are certain clinical observations which suggest that the liver plays a very important part in keratomalacia, but it cannot be assumed that this is more than secondary in its relation to the disease."

Contrary to Kirkpatrick and Wright, who seem to believe that

the pigmentation of the eye in keratomalacia is due to liver disturbances, Sh. Mori³ states that the pigment is melanin pigment, because of its various reactions to different agents, but he does not give any explanation for the origin of the pigment. He says: "The explanation of the whole process of this kind of pigment formation is a very difficult thing to make, but I am at least sure that this melanin pigmentation comes as a result of xerosis and as a result of the epithelium cells losing their conjunctival nature because of abnormal dryness and coming to be like regular skin epithelium."

In the older literature the pigmentation of the conjunctiva is only mentioned by De Gouvea,⁴ but no explanation is given.

Without going into further details, we would like to emphasize this peculiar dark brown colour of the pigmentation in keratomalacia, which has more the appearance of that seen in "argyrosis" or in Bronze-diabetes or in Addison's disease. The pigment itself seems to have the same hue in all cases. Even the slightest beginning of the pigmentation of the conjunctiva is as dark in its individual points as a very advanced case, only the greater number of the pigment dots explains the darker colour. The pigment lies chiefly in the basal cell layer of the epithelium and in the intercellular spaces, according to Mori's³ and Pillat's⁶ examinations. It advances from here into the middle layers and in severe cases extends almost to the surface of the kerato-hyalin layer of the thickened epithelium. The pigment increases in intensity as long as the keratomalacia progresses and disappears in the process of healing, but does so at a much slower rate than the other clinical symptoms.

Whether the discussion which has centred round the origin of the staining of the conjunctiva found in cases of "liver ophthalmia" (Baas, Weiss, Hori, Bamberger, Elschmig and Vollbracht⁵) has any bearing upon the origin of the pigment found in keratomalacia is doubtful. In keratomalacia the pigmentation is dark brown in colour whereas in cases of "liver ophthalmia" the colour is always described as "icteric" or "subicteric."

In order to determine what rôle the liver played in the production of this conjunctival pigmentation we undertook special liver function tests in a series of twelve cases of keratomalacia. The tests used were the laevulose tolerance test and the quantitative determination of the bilirubin in the blood serum. In order to facilitate the discovery of possible liver changes only severe and advanced cases of keratomalacia were chosen, no cases of xerosis epithelialis being included, although pigmentation is very often present in this condition.

The functions of the liver are so manifold that it is by no means easy to form a fair estimate of the efficiency of the organ by any

one test. The liver is mainly concerned with the metabolism of carbohydrates, proteins and fats, with the production of bile and with the excretion of various toxic substances from the blood stream into the alimentary canal. Clearly then liver efficiency tests may be based upon the ability of the organ to perform these various functions. The laevulose tolerance test serves as an index of the metabolic capacity of the parenchyma cells of the liver. The estimation of the bilirubin in the blood serum gives an early indication of any accumulation of bile pigment. The eliminative power of the liver may be tested by the intravenous injection of certain substances such as phenol-tetrachlorophthalein: this dye is excreted solely by the liver and the rate at which it is removed from the circulation may serve as an index of liver function. For the purposes of the present investigation, the two first mentioned tests were chosen, as previous experience had demonstrated the clinical value of these methods⁷ in determining the presence of pathological changes in the liver.

1. *The Laevulose Tolerance Test.*—The basis of this test is founded upon the remarkable power which the liver possesses for building up laevulose and storing it as glycogen. It has long been known that the administration of laevulose by the mouth produces practically no effect on the fasting blood sugar level. This is in marked contrast to glucose where a sharp rise in the blood sugar curve follows its ingestion. The reason has been shown to be that in the normal individual the laevulose is quickly absorbed from the intestine and passes through the portal system to the liver where it is rapidly polymerised and stored as glycogen with the result that little if any of the sugar ever reaches the systemic circulation and consequently there is little or no rise in the blood sugar curve. Very different results occur in cases where some pathological lesion of the liver cells exists. The diseased or injured cells are unable to carry out their function adequately and considerable quantities of the sugar escape their action and enter the systemic circulation, giving rise to a marked increase in the blood sugar level.

For practical purposes a patient is starved for eight hours and a dose of 50 gm. of laevulose is then given by mouth (the fasting blood sugar level having been determined immediately previously). Blood sugar estimations are then made half-hourly for two hours. The result of the test is plotted graphically and represents the laevulose tolerance curve. In normal cases the peak of the curve is reached in from half to one hour, the rise does not exceed the fasting level of blood sugar by more than 20 mg. per 100 c.c. of blood and the curve usually returns to the fasting level at the end of two hours. In abnormal cases the peak of the curve is delayed, the rise exceeds the fasting level by considerably more than 20 mg. per 100 c.c. and there is no return to the fasting level after two hours.

In the series of cases under discussion, with one exception, the laevulose tolerance curve yielded normal results. The accompanying Table shows the figures in detail. It will be seen that, excluding Case 4, the rise above the fasting level in mg. per 100 c.c. ranged between 3 mg. and 20 mg. with an average of 11 mg. Moreover, in practically every case the blood sugar curve approximates to the fasting level again at the end of the second hour. Fig. No. 1 shows quite a typical example of what may be regarded as a normal curve, found in Case No. 10.

TABLE SHOWING RESULTS OF LAEVULOSE TOLERANCE TEST
AND SERUM BILIRUBIN ESTIMATIONS.

Case No.	Age	Diagnosis	LAEVULOSE TOLERANCE TEST Blood Sugar %					Bilirubin in blood serum
			Before Laevulose	1 hour later	1½ hours later	2 hours later	Rise in mg.	
1	24	Keratomalacia	0.110	0.117	0.117	0.114	7	Trace
2	24	..	0.114	0.117	0.110	0.114	3	0.2 Unit
3	22	..	0.096	0.094	0.101	0.094	5	0.8 Unit
4	23	..	0.117	0.156	0.150	0.129	39	Trace
5	24	..	0.091	0.107	0.104	0.104	16	0.8 Unit
6	25	..	0.091	0.104	0.104	0.104	13	1.0 Unit
7	23	..	0.101	0.110	0.107	0.107	9	Trace
8	19	..	0.101	0.107	0.107	0.101	6	Trace
9	33	..	0.114	0.129	0.125	0.117	15	Trace
10	21	..	0.117	0.125	0.125	0.117	8	0.2 Unit
11	16	..	0.114	0.134	0.131	0.121	20	Trace
12	21	..	0.117	0.125	0.110	0.107	8	—

Case No. 4 was the only instance where an abnormally high curve was obtained. The patient had complained of symptoms for twenty days and on presenting himself at the hospital typical signs of keratomalacia were found in both eyes with pigmentation of the fornices. The skin showed numerous acneiform lesions with hyperpigmentation of the papules and scars. Physical examination showed no abnormality in the heart, lungs or abdomen. The

liver was not enlarged or tender. The urine was normal. The laevulose tolerance test, however, showed an abnormal result with a rise of 30 mg. above the fasting blood sugar level. A curve such as this would indicate a moderate degree of liver dysfunction—but it is to be noted that the accompanying bilirubin figure is normal. The significance of this curve, therefore, is not clear.

Fig. No. 1.— Normal Curve (see Case No. 10.)

With this one exception the laevulose tolerance test showed no evidence of impairment of the metabolic function of the liver in any of the other cases.

2. *Quantitative Estimation of Bilirubin in Blood-serum.*—One of the earliest and most constant results of disturbance of hepatic function is the accumulation of biliary constituents in the blood stream. In former years appreciation of this sign depended upon the clinical appearance of jaundice and upon the detection of bile in the urine. The important work of van den Bergh⁸ and McNee^{9, 10} has now rendered possible the estimation of such minute amounts of bilirubin as are present in the normal blood serum. Slight increases of bilirubin in the serum can be readily detected by means of the van den Bergh technique even when

jaundice is clinically inappreciable and the whole subject of "latent" jaundice has thus been given a fresh significance.

In the light of newer views it would appear that the polygonal liver cells are not essentially concerned with the manufacture of bile pigment but chiefly with the transfer of bile pigment from the blood capillaries to the capillaries and ducts of the bile system. The actual manufacture of bile pigment would seem to occur in the cells of the reticulo-endothelial system which are scattered throughout the body in the tissues of the liver, spleen, bone marrow, lymph glands and other organs. The cells of this system are concerned with the breaking down of haemoglobin and the elaboration of bile pigment. The bile pigment in its turn it set free into the blood stream and finally reaches the liver where it is transferred to the biliary ducts. It therefore follows that there is normally present in the blood stream a certain very small proportion of bile pigment. If the liver cells suffer any damage or functional derangement the proportion of bile pigment in the blood serum rises so that the detection of comparatively small increases may have a very important pathological significance.

van den Bergh introduced a technique for the quantitative estimation of these small amounts of bilirubin. He found that in normal blood serum bilirubin was present in quantities varying from 1 part in 1,000,000 to 1 part in 400,000. The estimation of such small quantities necessitated the fixation of an arbitrary standard and he therefore designated a strength of 1 part of bilirubin in 200,000 parts of serum as one unit. Normal serum therefore may contain anything from 0.2 to 0.5 units, rarely more. Further work demonstrated the fact that when the serum-bilirubin content rose to 4.0 units or higher bile appeared in the urine and jaundice became apparent clinically. Cases where the bilirubin content is higher than normal but less than 4.0 units are therefore to be regarded as instances of latent jaundice. The more severe degrees of jaundice would show anything from 20.0 to 50.0 units of bilirubin in the serum, and sometimes readings even higher than these are obtained.

A glance at the table given above will make it clear that no significantly high readings were obtained. In six of the cases only a trace of bilirubin was present which means that the concentration was below 0.2 unit. In two cases the low normal level of 0.2 unit was found.

In the remaining three cases in which the test was performed slightly higher readings were found (0.8 unit, 0.8 unit and 1.0 unit). A separate consideration of these cases may be justified.

Case No. 3.—The palpebral and bulbar conjunctivae of the right eye showed marked discoloration of a dirty brownish nature. Only slight discoloration was present in the left eye. The skin showed

many scabietic lesions with marked brownish hyperpigmentation. The heart and lungs were normal, but in the abdomen a tender area at the level of the umbilicus and to the right of the middle line was discovered. The liver and other organs were not palpable. The possibilities of cholecystitis or a liver abscess were borne in mind, but all abdominal symptoms disappeared in a couple of days and did not reappear. In this case the laevulose tolerance test was normal and there was 0.8 unit of bilirubin in blood serum.

Case No. 5.—Marked pigmentation of the conjunctivae was present, especially in the fornices. The colour resembled that found in argyrosis. The heart, lungs and abdomen were normal. The liver was not enlarged or tender. The laevulose tolerance test was normal and there was 0.8 unit of bilirubin in the serum.

Case No. 6.—There was slight greyish pigmentation of the conjunctivae. The heart, lungs and abdomen were normal, and the liver was neither enlarged nor tender. In this case, again, the laevulose tolerance was normal and there was 1.0 unit of bilirubin in the serum.

It will be seen that in each of these cases the bilirubin level was only slightly above the limits of normal, not approaching the 4.0 unit level at which jaundice ceases to be latent and becomes manifest clinically. It is doubtful whether so slight a rise would warrant the conclusion either that definite liver damage was present or that the conjunctival and cutaneous pigmentation owed their origin to an excess of bile pigment.

The present investigation, therefore, would seem to show that it is improbable that any marked degree of impairment of liver function is present in cases of keratomalacia and that the pigmentation found in such cases is probably not of biliary origin.

REFERENCES

1. **Kirkpatrick.**—See Wright.
2. **Wright, R. E.**—Keratomalacia in Southern India. *Brit. Jl. of Ophthal.*, Vol. VI, p. 164.
3. **Mori, Sh.**—The pathology of the pigmentation of bulbar conjunctiva in xerosis epithelialis conjunctivae. *Jl. of Oriental Med.*, Vol. II, No. 1924.
4. **De Gouvea.**—Beiträge zur Kenntnis der Hemeralopie und Xerophthalmie aus Ernährungsstörungen. *Arch. f. Ophthal.*, Vol. XXIX, p. 166, 1883.
5. **Vollbracht, F.**—Beitrag zur Frage der Leberophthalmie. *Zeitschr. f. Augenheilk.*, Vol. XXIV, No. 4, 1903.
6. **Pillat, A.** Does keratomalacia exist in adults? *Arch. of Ophthal.* (In Press.)
7. **King, G.**—A study of the laevulose tolerance test for hepatic efficiency. *Lancet*, Vol. CCXII, No. 1, p. 385. London, 1927.
8. **van den Berg, A. A. H.**—La recherche de la Bilirubine dans le plasma sanguin. *La Presse Médicale*, Vol. XLV, p. 441, Paris, 1921.
9. **McNee, J. W.**—The use of the van den Berg test in the differentiation of obstructive from other types of jaundice. *Brit. Med. Jl.*, Vol. 1, p. 716, London, 1922.
10. **McNee, J. W.**—Jaundice: a Review of recent work. *Quarterly Jl. of Med.*, Vol. XVI, p. 390, Oxford, 1923.