

CHAPTER III

ALBINISM

WHEREAS the other anomalies here to be discussed manifest themselves by errors of excretion, albinism is clearly an abnormality of a different kind from these, in that the defect lies in the lack of substances which are normal constituents of certain specialized tissues, and which serve purposes of much utility to the organism. Its essential feature is the absence of pigments of the melanin group which play the chief part in the surface coloration of man and the lower animals and shade the underlying tissues from light, and which also serve the important function of rendering the eye a dark chamber, as witness the white hair, unpigmented skin; and pink eyes of the albino. Pigments of other kinds are not wanting, such as the lipochromes which impart their yellow tints to fats and blood serum, and hæmoglobin and its derivatives. In the urine of albinos I have found the same pigments as are ordinarily present. The fact that albinos of certain birds, such as the peacock, which are normally characterized by the brilliancy of the colouring of their plumage, are quite white, does not invalidate the truth of this statement. Their brilliant tints are interference colours, due to physical structure and not to pigmentation, and the absence of such colours is merely due to the lack of a dark background for their display, for such a background the melanins with their sombre hues provide. In the feathers of the albino peacock the iridescent tints are faintly visible in certain lights.

In recent years great advances have been made in the

study of albinism by the work of Karl Pearson, Nettleship and Usher, whose splendid monograph on Albinism in Man, although not yet completed, embodies practically all that is known on the subject. Its heredity has been studied by a number of observers, including Bateson, Castle and Allen, and the Davenports. Erich Ebstein and Hans Günther¹ have dealt with its clinical aspects in an interesting monograph, but very little fresh light had been thrown upon the actual nature of the anomaly until the researches of Bloch, in the Dermatological Clinic at Basle, placed the study of melanin, and of its formation, upon a new footing.

The main features of albinism, the white hair, untinted irides and red pupil-reflex, the constant nystagmic movements of the eyes and the unpigmented skin, are familiar to all, and are seen alike in members of the white and coloured races.

The ordinary physiological causes of pigmentation are not operative in albinos. In them exposure to the sun does not cause the usual tanning of the skin which is seen in normal individuals; a mere hyperæmia results. It has also been observed that in female subjects the pigmentation of the areolæ of the nipples and of other parts, which usually accompanies pregnancy, is not developed.² I know of no observations on the occurrence in albinos of tumours originating in the eye and running the course of melanotic sarcomata. One would expect that such growths, if they occur, would fail to be pigmented. Nor does there appear to be any record of Addison's disease occurring in such subjects, which might throw important light upon the question whether the Addisonian pigment is a true melanin.

Although it would appear that the expectation of life in albinos is less than normal, the many vague statements to be found in the literature, as to the special liability of

¹ *Zeitschrift f. Morphologie und Anthropologie*, 1914, xvii. 357.

² B. W. Richardson, *Dublin Hospital Gazette*, 1856, iii. 73.

albinos to certain diseases, and their intellectual shortcomings, rest upon no very sure foundations, and if they are mentally below the average there are certainly brilliant exceptions to this rule.

In the vast majority of instances the anomaly persists unchanged throughout life, but the evidence is apparently *conclusive that a few individuals born albinotic have acquired pigmentation of the skin, hair, and eyes in childhood or adult life.*

By no means all albinos are pigment-free. In cases of so-called 'incomplete albinism' the hair has various tints from yellow to red, and, as is well known, red-haired members are not infrequently met with in albinotic families. Thus Folker³ described a girl with pink eyes and bright red hair, one of eight children of normal parents, of whom two others were ordinary albinos. If, as there is good reason to believe, the red pigment of hair, which is diffuse and not granular as the dark pigment is, be not a member of the melanin group, such incomplete albinism is not difficult of explanation. It has been stated that the red pigment is a lipochrome, but on what evidence I have not been able to learn. An investigation of this pigment on strictly chemical lines is much to be desired.

The phenomenon known as 'partial albinism' presents more serious difficulties. Albinotic eyes may be associated with pigmented hair and skin, or, on the other hand, melanin may be present in the eyes alone.⁴ Piebald individuals are met with from time to time, in whom large areas of skin are pigmented whereas other areas are free from pigment. White locks of hair may occur in the same situations in members of successive generations of a family, either alone or in association with piebald skin, or again dark skins may be flecked with white. Such piebaldism

³ *Lancet*, 1879, i. 795.

⁴ Thomson, *The Ophthalmoscope*, 1910, viii. 884.

is much more familiar in the lower animals, and presents great interest for students of the Mendelian theory, who rank it as an example of 'mosaic inheritance'. In human subjects it is sometimes difficult to discriminate between such partial albinism and morbid conditions, such as vitiligo. Pearson, Nettleship, and Usher have pointed out that in individuals who appear to the naked eye to be complete albinos, microscopic examination of the tissues may reveal the presence of a few pigmented cells in the eye or elsewhere.

Lastly, mention must be made of the phenomenon of seasonal albinism in arctic mammals and birds.

Three possible explanations of the phenomena of albinism suggest themselves for consideration. We might suppose that the cells which usually contain pigment fail to take up melanin formed elsewhere; or that the albino has an unusual power of destroying melanin; or again that he fails to form it. There is no evidence that the pigmented cells take up pigment from the blood. Some experiments of Kobert, who injected solutions of melanin into albino rabbits, afforded no evidence that the injected pigment was deposited in the tissues in which pigment is normally present, and the fact that the animals excreted melanin, or rather its chromogen, in their urine suggests that they had no exceptional power of destroying this pigment. Everything points to a failure of albinos to produce melanin, and there is very strong evidence that this power is inherent in the pigmented cells, and that in those cells the pigment is formed and also deposited.

If this be so, the failure may again be due to one of three causes, namely a structural peculiarity of the cells which renders them incapable of pigmentation; absence of the material from which the melanin is formed; or lack of a specific enzyme which brings about its formation.

The first of these views is favoured by Karl Pearson,

Nettleship, and Usher,⁵ not on histological grounds, but because they find it easier to grasp the influence of difference of gametic constitution on structure than on chemical process. They suggest that if a ferment be at fault it may be that the structure does not permit of its reaching its destination, or that if the pigment be produced it cannot be stored in the normal manner. Seeing that the gametes must contain those elements which are concerned in the development of the whole of the metabolic activities of the resulting organism, to me at least, their argument, that a defect in one or both gametes can hardly be the absence of a ferment, does not appeal. Such an assumption is at variance with the whole thesis of which this book is an exposition. Moreover, the work of Bloch affords powerful evidence in favour of the view that the defect in albinism is the lack of a specific intra-cellular enzyme, which has the power of producing melanin in certain cells which are normally the seats of pigmentation.

Some earlier experiments having a direct bearing upon this matter were carried out by Florence Durham,⁶ who used expressed extracts of the skins of young or embryo rats, rabbits, and guinea-pigs. To the extracts were added some solid tyrosin and as an activator 1 mg. of ferrous sulphate. The extracts so treated were kept, under toluol, in an incubator and at room temperature, as also were controls with tyrosin alone and with ferrous sulphate alone. The tubes with tyrosin and ferrous sulphate kept at 37° for 24 hours darkened, and a black sediment was thrown down, whereas in the control tubes no such change was observed. With extracts of white or albino skin no pigment was formed, with yellow skin an orange-coloured precipitate was obtained; whence it appeared that coloured skin of such animals contained a tyrosinase which produced a melanin

⁵ *Monograph on Albinism in Man*, 1911-13, part 1 (text), 194.

⁶ *Proceedings of the Royal Society*, 1905, lxxiv. 310.

from tyrosin in the presence of an activator. But Gortner, Onslow, and Ducrey⁷ have been unable to confirm these observations.

In his investigations Bloch⁸ adopted the following procedure. Sections of skin of men and animals, cut with a freezing microtome, were treated, in a shallow dish, with 1:3 per mille solutions of various aromatic compounds, amongst which were tyrosin, hydroquinone, homogentisic acid, adrenalin, pyrogallol, tryptophane, paroxy-phenyl-ethylamine, with none of which was any selective staining produced. When, on the other hand, a solution of 3:4-dioxy-phenylalanin was employed deep pigmentation of a highly selective character resulted. There was some pigmentation of the granules of the leucocytes and in the cells of the sweat glands, such as is produced by non-specific ferments, such as the polyphenol-oxydase of Battelli and Stern. This has no connexion with the special reaction peculiar to the aromatic substance in question, which is confined to the epithelial elements of the skin, to the protoplasm, as distinguished from the nuclei, of the cells of the basal layer, the prickle cells of the epidermis, the tubes of the hair follicles, and the cells of the outer root sheaths of the hairs. When the reaction is intense the pigment is seen not only in the ordinary epithelial cells, but also in peculiar dendritic cells, with long processes, the so-called melanoblasts.

Absolutely no reaction was obtained with the skin and hairs of albinos, nor with the white areas of the skin of piebald animals. The amount of pigmentation produced varied in different cells of the same epidermis. As a rule only some of the basal cells were affected, and only when the reaction was intense was uniform staining of all the

⁷ Gortner, *Trans. Chem. Soc.*, 1910, xcvi. 110. Onslow, *Proc. Roy. Soc.*, 1915, lxxxix, B, 36. Ducrey, *Inaugural Dissertation*, Basel, 1917.

⁸ *Zeitschrift f. physiol. Chemie*, 1916-17, xcvi. 226.

basal cells obtained. The reaction was increased by external stimuli, such as thorium X radiation or chemically active light rays. In pigmented nævi the reaction was intense, and it was absent in the white patches of vitiligo.

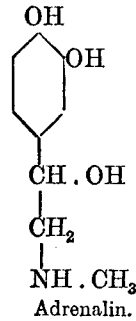
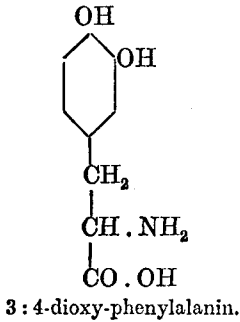
Investigation of the enzyme *in situ*, for Bloch has not yet extracted it from the tissues, indicates that it is a very labile ferment, destroyed by a temperature of 100° and weakened by heating to 57°. It is easily destroyed by ferment-poisons; saturated and half-saturated solutions of ammonium sulphate destroy it, but fat-solvents have little effect.

Bloch's researches led him to the conclusion that an aromatic compound which yields this reaction must fulfil the following requirements:—It must be a derivative of pyrocatechin, i. e. must have two hydroxyl groups in the 3:4 positions on the benzene ring; it must have a side chain with at least three segments, and there must be an amino-group in the side chain. Even methylation of one of the hydroxyl groups inhibits the reaction. Seeing that 3:4-dioxy-phenylalanin was the only one of the compounds tried by him which yielded the reaction, and did so both in its dextro- and lævo-rotatory forms, he inferred that this, or a closely allied compound, was the natural precursor of the cutaneous melanin. For brevity and convenience he shortens the name of dioxy-phenylalanin to 'd.o.p.a.', and speaks of the reaction as the dopa-reaction and of the enzyme which brings it about as dopa-oxydase.

3:4-dioxy-phenylalanin is not known to occur as a product of animal metabolism, but it has been isolated by Guggenheim⁹ from the pods and seedlings of *Vicia faba*, the broad bean. It may well be a previously unrecognized protein-fraction, for, as Guggenheim showed, it would be converted into a black pigment by acid-hydrolysis, and so would fail to be isolated by such means. Of known meta-

⁹ *Ibid.*, 1913, lxxxviii. 276.

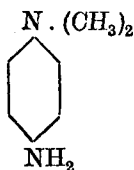
bolic products adrenalin resembles it most closely, as the respective formulæ show :



Adrenalin, like dopa, is a derivative of pyrocatechin, whereas tyrosin, which only differs from dopa in having one less hydroxyl-group upon the benzene ring, is not. Adrenalin itself does not yield the dopa-reaction, although it is very susceptible to the action of tyrosinases, but the fact that it is a normal animal product shows that derivatives of pyrocatechin have a place in animal metabolism, and it is not improbable that the parent substance of melanin, whatever that substance may be, is an intermediate product on the path to the formation of adrenalin. However, Kreibich¹⁰ has since found another aromatic compound which yields the dopa-reaction as well as dopa itself. With it Kreibich obtained deep staining of the cells of the basal layer of the epidermis, and also of the melanoblasts, the finest processes of which became filled with black pigment granules.

The compound in question is dimethyl-phenelene-diamine, which, as will be seen, fulfils none of Bloch's requirements, in that it is not a derivative of pyrocatechin, and has no side chain.

¹⁰ *Dermatologische Wochenschrift*, 1918, lxvi. 193.



Dimethyl-phenylene-diamine.

This observation shows that the search for the precursor of melanin need not be confined within very narrow limits, but dimethyl-phenylene-diamine is far more unlike any known product of metabolism than is dopa itself, which latter, as Fromherz and Hermanns¹¹ showed, is to a great extent burnt in passage through the animal organism.

It is obvious that Bloch's results constitute by far the most important contribution yet made to the study of surface pigmentation, and incidentally they throw valuable side-lights upon the nature of albinism. They indicate clearly that the absence of pigment from the skin and hair of albinos is attributable to the lack of a *specific enzyme* in the cells which are normal seats of pigmentation, but they also suggest that the same cause is responsible for the white areas of the skin of piebald animals, and even for the white patches of vitiligo. They indicate, moreover, that the formation of melanin is a function of the individual cells in which it is found.

But any theory which claims to offer an explanation of the phenomena of albinism must needs account for the absence of ocular pigment, as well as of that of the skin and hairs. So intimate is the association of ocular with cutaneous albinism that it is difficult to believe they are not due to one and the same cause, rather than that two independent modes of pigment formation are both in abeyance in the albino. But it must be confessed that up to now

¹¹ See chap. v, p. 86.

there is no evidence forthcoming that the lack of pigment in the eye is due to lack of the dopa-oxydase.

In a paper published in 1918 Bloch¹² emphasized the fact that his results were obtained with hair and skin, and did not necessarily apply to pigment formation in the eye and in malignant growths, and adds that it is possible, but by no means certain, that in them the pigment formation follows the same lines as in the skin. He states that he has already carried out experiments with dopa upon the pigmented tissues of the eye, on the same lines as those with skin, but hitherto with negative results. This, he thinks, may be due either to far greater difficulty of technique, or to a difference in the method of pigment formation in the two structures.

Schreiber and Schneider,¹³ when engaged in staining tissues for spirochaetes, lit upon the fact that the intracellular pigment, and also what they regard as the chromogen or colourless precursor of melanin, took the silver stain. They do not mention any observations upon albinotic skin, but they failed to obtain any evidence of the presence of the chromogen in the stroma cells of the uvea, or in the cells of the so-called pigment-epithelium layer of the retina of an albino rabbit. This would suggest that not only the dopa-oxydase, but also the material upon which it works, are wanting in the albinotic eye.

Bloch's results have been criticized by a number of other observers on various grounds.¹⁴ Some of them are not convinced by the evidence of the existence of the dopa-enzyme, and lean to the view that the reaction is a chemical one, and, in a critical review recently published, Gustav Herold suggests that the dopa merely acts as a reagent

¹² *Archiv f. Dermatologie und Syphilis*, 1918, cxxiv. 156.

¹³ *Münchener med. Wochenschrift*, 1908, lv. 1918.

¹⁴ Bittorf, *Deutsches Archiv f. klin. Med.*, 1921, cxxxvi. 314. Heu-
dorfer, *Archiv f. Dermatol. u. Syphilis*, 1921, cxxxiv. 339.

causing pigment formation in cells which contain the chromogen of melanin.

The controversy, into which it is unnecessary to enter here, as to whether pigment formation is confined to ectodermal structures, or occurs in mesodermal structures also, has once more become acute.¹⁵ Recently Bloch¹⁶ has somewhat modified his original opinions in view of the work carried out in his laboratory by Sato¹⁷ and Bahrawy upon blue nævi and on the blue patches of Mongolian infants.

It is clear that, although we are undoubtedly nearer to a solution, the problem of albinism, and especially of the absence of ocular pigment in albinos, is not yet solved.

G. R. Mudge,¹⁸ starting from the assumption that, if albinism be due to lack of an enzyme, a chromogen is presumably present in the tissues which are normally seats of pigmentation, obtained some curious results by the action of oxydizing and reducing agents upon the hair and skin of albino rats. When a dead albino rat was immersed in a mixture of equal volumes of 10 per cent. formalin and 70 per cent. alcohol, its hairs assumed a vivid yellow colour, and subsequent immersion in 20 volume hydrogen peroxide solution changed the yellow colour to a brownish tint. If the process was reversed, no yellow colour was obtained. Similar treatment of a piebald rat caused some yellow tint of the white areas, not comparable with the brilliant yellow of albinos. With albino mice these phenomena were not observed, but with a modified procedure a pink colour developed. It is not obvious what inferences may be drawn from these experiments.

In conclusion, reference must be made to certain remarkable observations which suggest that the differences

¹⁵ Meirowski, *Dermatol. Zeitschrift*, 1917, xxiv. 705. Bloch u. Rijnher, *Zeitschr. f. d. ges. exper. Medizin*, 1917, 179.

¹⁶ Bloch, *Archiv f. Dermatologie und Syphilis*, 1921, cxxxvi. 231.

¹⁷ Sato, *Dermatol. Wochenschrift*, 1921, lxxiii. 1073.

¹⁸ *Journal of Physiology*, 1909, xxxviii; *Proc. Physiol. Soc.*, lxvii.

between albinos and normal individuals are not confined to the absence or presence of melanins in their tissues. In animals differences have been observed in the matter of liability to certain infections, which lend some support to the statements sometimes made regarding lowered resistance of human albinos. Halliburton, Brodie, and Pickering¹⁹ found that intra-vascular injections of nucleo-proteins failed to produce in albino animals such clotting as they cause in pigmented ones. Mudge,²⁰ who has carried out a number of such experiments, found that all albinos do not behave alike in this respect. Differences were also observed between the results of the injection of nucleo-proteins derived from albino and pigmented animals respectively. He arrived at the conclusion that an albino animal requires a larger dose of nucleo-protein per kilogramme of body weight to cause death by intra-vascular clotting.

Pickering's²¹ remarkable observation that the Norway hare, when in its winter coat, behaves like an albino when injected with nucleo-protein, but in its summer coat as a pigmented animal, suggests that such differences may be due not to any special peculiarity of albinos, but to the fact that the surface pigment shades the underlying tissues from light, the powerful influence of which agent upon physiological processes is becoming more and more clearly recognized.

Some aspects of this subject will be discussed in the chapter on hæmatoporphyria, but the following passage from Darwin's *Origin of Species* may here be quoted as an example in point.

'From facts collected by Heusinger, it appears that white sheep and pigs are injured by certain plants, whilst dark-

¹⁹ *Journal of Physiology*, 1894, xvii. 148.

²⁰ *Proceedings of the Royal Society*, 1907, series B, lxxix. 103.

²¹ *Journal of Physiology*, 1896, xx. 310.

coloured individuals escape. Professor Wyman has recently communicated to me a good illustration of this fact; on asking some farmers in Virginia how it was that all their pigs were black, they informed me that the pigs ate the paint-root (*Lachnanthes*) which coloured their bones pink, and which caused the hoofs of all but the black varieties to drop off; and one of the "crackers" (i. e. Virginia squatters) added, "we select the black members of a litter for raising, as they alone have a good chance of living."

The same explanation applies to the observations of Bickel and Tasawa²² upon the effect of bright light upon the red corpuscles of coloured and albino animals. When exposed for several weeks in succession, for two hours daily, to the light of a mercury-vapour lamp, coloured rabbits showed a progressive increase of erythrocytes and of the hæmoglobin content of their blood, whereas, when albino rabbits were similarly treated only a very slight increase resulted. Bickel and Tasawa themselves attribute the observed differences to presence or absence of cutaneous pigment.

²² *Charité-Annalen*, 1913, xxxvii. 248.