OCHRONOSIS:

THE PIGMENTATION OF CARTILAGES, SCLEROTICS, AND SKIN IN ALKAPTONURIA.

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HERETOFORE ochronosis has been a pathological curiosity; the two cases here reported in alkaptonuria show that it may have interesting clinical features.

In 1866 Virchow[1] described a remarkable blackening of the cartilages in the body of a man, aged 67 years, who had died from aneurysm. The colour was coal black (as shown in his figures), not ochre-coloured or yellow; but it was not ordinary melanosis, and recognising the unique character of the condition Virchow called it ochronosis. Years passed before a second case was described by Boström,[2] that of a woman, aged 44 years, who had died from strangulated umbilical hernia. The same ebony-black discolouration of the cartilages was present. Then in 1892 Hansemann[3] described a third case, the patient being a male, aged 41 years, with general œdema and aneurysm of the left ventricle. He had had melanuria for 18 years. In a recently issued number of the *Deutsches Archiv für Klinische Medicin* Langstein and Meyer state that the examination of long-kept urine shows that this was not a case of alkaptonuria. There was no reduction of copper and no homogentisic acid could be found. Heile[4] recorded the fourth and fifth cases, one being that of a woman, aged 36 years, who had died from peritonitis after ruptured tubal pregnancy, and the other that of a woman, aged 52 years, with chronic leg ulcer and mitral valve disease. The sixth case was reported by Hecker and Wolf[5] The patient was a man, aged 73 years, with long-standing melanuria and chronic endocarditis. In the eyes on each side some three or four millimetres from the corneal border there were black spots on the sclerotics. The urine was sometimes normal in colour when passed and sometimes brownish. It became black on standing for a day or two. The darkening was present for 11 years but was not constant. Blood, bile-pigment, indican, pyrocatechin, and drug pigments were excluded. It is distinctly stated that the urine did not reduce copper. Hecker and Wolf came to the conclusion that the reactions were those of melanuria. Post mortem there was the ordinary ochronotic blackening of the cartilages, arteries, &c. I am indebted to Dr. A. Garrod for this abstract from the *Festschrift* of the Dresden Hospital and he states that it is pretty certain this was not a case of alkaptonuria. The seventh case is recorded by H. Albrecht,[6] to whom is due the credit of suggesting the association of the condition with alkaptonuria. In a man, aged 47 years, who had died from pulmonary tuberculosis, the urine was dark-coloured and reduced the sulphate of copper, but the presence of alkaptonuria was not proved, for no homogentisic acid was obtained from it. After a week in the hospital he died and the necropsy showed a general ochronosis. A point of special interest was the grey-blue colour of the inner part of the ears, as if due to dilated veins.

I am able to report two cases of ochronosis in alkaptonuria in which the condition could be recognised clinically by the deep pigmentation of the cartilages of the ears and of the sclerotics, and in one by a remarkable ebony-black discolouration of the skin of the nose and cheeks.

CASE 1.—A man, aged 57 years, consulted me on Jan. 16th, 1895, for diabetes and rapid action of the heart. He had been an active business man and a successful politician. I did not question the existence of diabetes, as during a prolonged residence in Europe he had been under the care of several eminent colleagues in Berlin, Paris, and London, one of whom had referred him to me. After repeated examinations Dr. Futcher determined that the copper-reducing substance was not glucose and the case formed the basis of his paper on alkaptonuria in the *New York Medical Journal* in 1898. I need not refer in any detail to the condition of the urine in this case other than to state that it is never black when passed but darkens after a few hours. At my first examination I was impressed by a remarkable appearance of the sclerotics which showed small V shaped areas of deep pigmentation near the cornea. I thought it might be the result of old hæmorrhages, but the patient said that the condition had gradually come on and that it had annoyed him at first but that he now thought nothing of it. There was also a slight pigmentation of the nose and on the cheeks which looked like very thickly set comedones. As he left the room my attention was directed to the deep blue colour of the inner surface of the ears. I have seen the patient at intervals during the past eight years and have taken an increased interest in the deepening pigmentation of his face, eyes, and ears. I searched the literature at intervals for an explanation but without avail and I consulted Dr. de Schweinitz and Dr. Harry Friedenwald with reference to the pigmentation of the sclerotics. It did not seem to conform with any of the reported cases of this rare condition. Lately the patient came under my care in the private ward of the Johns Hopkins Hospital for anæmia and a weak, irregular heart. The pigmentation has extended considerably in the past six years and is now as follows.

Sclerotics.—The exposed V-shaped portions are of a deep black colour, not in the entire extent, as there are areas of normal colour. The staining is in the sclerotic coat, not in the conjunctiva, and it does not extend to the covered parts of the eyeballs. Of late years it has become much darker; there was a brownish tinge in places which has now almost disappeared. There is nothing special to be noticed about the other parts of the eyes. The tarsal cartilages are not affected.

Ears.—From behind and along the free border of the helix the skin looks normal but when looked at from inside there is a remarkable blue-black discolouration, exactly like that produced by dilated veins, as Albrecht remarked. It is deepest in the concha and extends along the antihelix but not to the helix. I did not recognise at first that the pigmentation was in the cartilage. In certain positions and when the light falls into the ears the colour at once attracts attention. It has extended and deepened in the past five years.

Face.—Over the nose and the cheeks, in very much the butterfly distribution of lupus erythematosus, the skin is of a coal-black colour. At his first visit I thought that it was an unusual distribution of very black comedones. The line over the nose is narrow but widens and passes to the cheeks and extends over the malar bones and along the zygomata. There is no thickening of the skin, which can be picked up easily. The colour is remarkable, quite unlike anything seen in the skin in the ordinary pigmentary changes, but at first glance rather suggesting powder marks. Where present it is uniform, not patchy. It is nowhere else on the skin but Dr. Futcher tells me that small black spots have begun to appear on the back of the hands. One of this patient's sons has alkaptonuria.

CASE 2.—The patient is a brother of the patient in Case 1, his age being 49 years. This was one of the first cases of alkaptonuria described in the United States of America. He had applied for life insurance and had been rejected repeatedly. Dr. Marshall, of the University of Pennsylvania, studied the urine carefully and called the new copper-reducing substance glycosuric acid. The man remained quite well after he had got over his fright about diabetes. When the first patient was in the hospital this brother visited him frequently, and what was my surprise to find that he too had pigmented sclerotics and ears. The patches in the eyes were small, two vertically placed bands about five millimetres from the corneo-sclerotic junction. They resembled in size and appearance those in his brother's eyes when I first saw him in 1895. The blue black colour in the ears, not nearly so marked as in Case 1, was confined to the fossæ and could not be seen from behind. The skin was normal, but through it appeared this remarkable leaden colour as though there was a diffuse nævus. The patient had noticed the pigmentation for several years. He was morbidly sensitive about it and it was with the greatest difficulty that I could induce him to come to the clinical laboratory where Dr. Emerson determined the persistence of the alkaptonuria. This patient died in April, 1903, from pneumonia after an

[1] Virchow's Archiv, 1866, Band xxxvii., p. 212.
[2] Virchow's Festschrift, Band ii., 1891, p. 177.
[3] Berliner Klinische Wochenschrift, 1892, Band xxix., p. 660.
[4] Virchow's Archiv, 1900, Band clx., p. 148.
[5] Festschrift, Dresden Hospital, 1899, p. 325.
[6] Zeitschrift für Heilkunde, 1902, Band xxiii., p. 366.

illness of a few days. There was no post-mortem examination.

These brothers presented a singularity in gait, walking with a slight bend or incline at the hips. At first I thought the elder brother had had spinal disease but the spine was straight and the motion of the hip-joints was perfect. He had had rheumatic pains in many joints and there were several Heberden's nodes.

Dr. Ogden of Milwaukee writes with reference to his alkaptonuria patient, whose condition was described in the *Zeitschrift für Physiologische Chemie*, 1895, that "the colour of the inside of each concha is a pearly, light-greyish lead-blue, much the colour of the inside of some of our common mussel shells." This is evidently staining of the cartilages similar to that which exists in the two patients here described and in Albrecht's case.

There is no question that these are cases of ochronosis in long-standing alkaptonuria and they support Albrecht's suggestion that the pigmentation of the cartilaginous tissues is associated with the remarkable disturbance of metabolism which we have heretofore only recognised by the changes in the urine. The condition is thus brought within the range of the clinical physician. Fortunately it is not of much moment, so far as we know, and in the recorded cases there have been no symptoms directly due to the alkaptonuria. Dr. Garrod informs me that there are only two recorded post-mortem examinations in alkaptonuria cases. In Fürbringer's case[7] the patient, a male, aged 29 years, died from phthisis. There is no mention of the duration of the alkaptonuria. The necropsy was made by Thoma and the description is complete. Blackening with alkalies was looked for in the body fluids, but there is no mention of blackening of the cartilages. In von Moraczewski's case (a woman, aged 43 years) the alkaptonuria was supposed to be of late development. There is no mention of the cartilages in the protocol of the post-mortem examination. Some of the cases of ochronosis have not been in alkaptonuria and, as Dr. Garrod writes, it looks as if possibly even the very few cases described may belong to two distinct classes. Of the three cases in which black urine is mentioned two at any rate seem not to have been in alkaptonuria, and in Albrecht's patient Zdarek could not find in the fresh urine either homogentisic or uroleucic acid.

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SOME SIMPLE EXPEDIENTS IN PHYSICAL THERAPEUTICS.[1]

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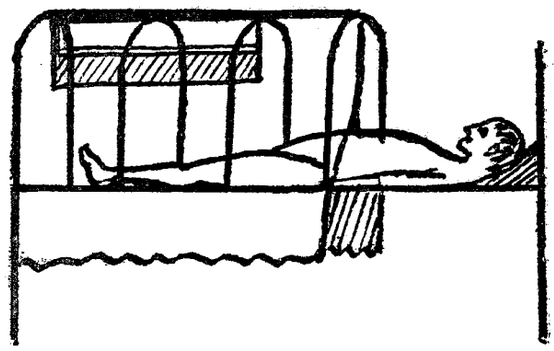
IN the whole range of therapeutics there is no more important subject than the proper and efficient treatment of pyrexia. Without, however, entering upon an exhaustive consideration of so important a theme it will be allowed that while minor and transient degrees of fever can safely be left alone or dealt with by the various antipyretic drugs, and the more serious forms of hyperpyrexia demand rigorous application of cold in the form of bath or ice pack, there remains an intermediate class of continuous fever in which the repeated use of either of these modes of treatment is undesirable. It is only necessary in explanation of this statement to say that all internal antipyretics have a more or less depressant action on the heart and their repeated administration is apt to induce collapse or cardiac failure in the very cases in which steady heart action affords the main road to recovery. On the other hand, while the application of cold to the surface, acting as it does as a tonic to the circulation, effects the reduction of temperature without involving this risk, many of the methods employed for the purpose, such as sponging, packing, and bathing, though undeniably efficacious and wholesome, possess undoubted drawbacks in practice. The use of water in any way involves trouble and difficulty on the part of attendants, not always skilful when available, and such proceedings, adapted as they must be to the severity of the case and the endurance of the patient, and liable if mismanaged to serious mishap, necessarily involve the presence of the medical attendant for a longer period and on more frequent occasions than may be convenient or even possible.

Taking these considerations into account, especially in such a state of continued pyrexia as that of typhoid fever, the system known as *cradling* offers undeniable advantages. It consists merely in arranging a sort of tent over the bed in which the patient lies naked or very lightly covered. The two ends may be left partly open to encourage a current of air or the effect may be intensified by suspending a trough inside containing broken ice. In hospital the tent is usually made of metal hoops covered by a sheet or blanket but in an ordinary bedstead a rod or cord extending horizontally about two feet above the patient and attached to the head- and foot-pieces is all that is necessary. In this way the surface of the body can be exposed indefinitely to an atmospheric temperature of about 60° F. which can be easily regulated, the natural cooling effect of radiation and evaporation being thus enhanced. The great advantages of this method are its simplicity; its remarkable efficiency, the continuity of effect being not only of value in continued febrile states but in reducing high temperatures; its comfort to the patient; the avoidance of the repeated shock and disturbance of applying water; and the freedom and security it gives to the medical attendant who is not called upon to cope with periodical alarming temperatures but can leave the nurse to meet the variations of the thermometer within a reduced range by regulating the draught or by applying ice or a blanket within the tent as indications require (see Fig. 1).

FIG. 1.



Cradle with ice trough.

In dealing with children whose consent and collaboration in times of sickness are less easily obtained than those of adults, as also in delirium and in highly nervous subjects, cradling is of special service and may be continued for ten or 14 days if necessary.

While considering the means of reducing temperature generally it may be useful to mention a simple method for keeping the head cool and controlling the circulation in cases of injuries and diseases of that part. In meningitis, skull fractures, and concussion, and sometimes in the delirium of fever, it has been the practice to apply cold to the head by means of an ice cap or simple bag, or perhaps only by evaporating lotion to the forehead. It is scarcely necessary to remind anyone that, with perhaps the exception of the last named, there is little satisfaction to the patient in any of these, and in unconsciousness or delirium it may exceed the powers of the nurse to maintain any contact at all. Moreover, the regions of the head to which these means are applied—the forehead and vertex—are already the cooler on account of their position, being in the periphery of the circulation and in addition freely exposed to the effect of radiation and evaporation. The part to which cold can be more profitably applied is the occiput and the nape of the neck and this can be done without difficulty or discomfort by using as a pillow an ordinary rubber water-bottle filled with ice-cold water and crushed ice and having a smooth towel pinned round it as a pillow-case. The substitution of this for the troublesome and inefficient appliances hitherto recommended in head cases has justly earned the gratitude both of patients and nurses and is particularly satisfactory to the medical attendant, as when ordering his patient "cold to the head" he can see that he gets it. In the delirium of fever, besides the local effect, this method has the great advantage of notably reducing the temperature and so relieving the condition on which delirium chiefly depends. For the feverish patient a constantly cool, smooth, and elastic water

[7] Berliner Klinische Wochenschrift, 1875, Band xii.

[1] A paper read before the Brixton Medical Society.