Medicine. — *On Porphyrin-modalities.* By A. A. HIJMANS V. D. BERGH, after experiments in collaboration with P. MULLER Sc.D, and A. HIJMANS, chem. engineer.

(Communicated at the meeting of January 26, 1929).

Ever since HOPPE SEYLER we know that from the influence of strong acids on the blood a purple pigment originates, with a very typical spectrum. This colouring-matter has been termed hematoporphyrin. It owes its origin to the deprival of iron from the pigmentous neucleus of hemoglobin. In the same way a porphyrin can be obtained by liberating magnesium from chlorophyl. In course of time it has appeared that besides these compounds, which can be prepared artificially in the laboratory from hemoglobin and chlorophyl, there occur in nature different free, or anyhow much less complexly bound porphyrins. Several prominent chemists have occupied themselves with this problem. Of late years it is especially HANS FISCHER (München) who has contributed largely to our knowledge of the structure of porphyrins.

Basing us on his investigations we may divide porphyrins into two large groups. When we put aside phyllo porphyrin (obtained from chlorophyl), the following porphyrins deserve note.

The first group is formed by the porphyrins that can be obtained from the blood-pigment, either through the influence of chemical substances, or through the action of certain bacteria, which action may also take place in the intestinal canal on taking blood-containing food. The most important among the latter porphyrins is protoporphyrin or KÄMMERER's porphyrin.

To the second group belongs Koproporphyrin, of which in normal stools only traces can be found, but which occurs in normal urine in somewhat larger quantities. In certain morbid conditions, and in cases of intoxication (lead, sulphonal etc.) the quantum of secreted koproporphyrin is increased. It is also found in yeast. In a disease of which I spoke at a previous meeting, the congenital porphyrinuria, we find in the faeces and in the urine, besides small quantities of koproporphyrin, large quantities of a second modality: uroporphyrin. It has been known for a rather long time that all porphyrins can be decomposed into a tetramolecular pyrrolderivation: etioporphyrin. This etioporphyrin consists of four pyrrol-nuclei, each bearing one methyl and one ethyl-group. Kopro-, and uroporphyrin are derivatives of etioporphyrin by replacing 1, resp. 2 hydrogenatoms in the aethyl-groups by carboxyl. So koproporphyrin has 4 of such groups and uroporphyrin 8.

Now, FISCHER's great merit is to have established after years of laborious

TABLE OF THE MOST IMPORTANT PORPHYRINS (After FISCHER).

	Ist Group		IId Group			
	Artificially from blood	From blood by bacteria or some chemical actions	In yeast, in normal urine and stools with intoxication of lead, sulphonal etc.	In urine with congenital and acute porphyrinuria	In urine and faeces patient V. D. N.	In urine patient V. L.
Name:	Haematoporphyrin	Protoporphyrin (KÄMMERER's porphyrin)	Koprophorphyrin I	Uroporphyrin I	Koproporphyrin III	?
Spectrum in 25 % HCl:	505.8 575.5 551.7 527.9 510.5	602.4 582.2 557.2	593.9 574.6 550.9	597.9 577.6 553.6 511.3	(5 % HCl) 595 574 550	(2½ % HCl) 590 570 545
Solubility in aether:	+	+	+	−	+	+
Number of carboxylgroups:	2 (+2 alcoholgroups):	2	4	8	4	?
Melting point of the methylester:	149°	222°	250°	293°	169°	?

Melting-point of the methylesters of the isomeric Koproporphyrins prepared synthetically by H. FISCHER.
I 251° III 170°

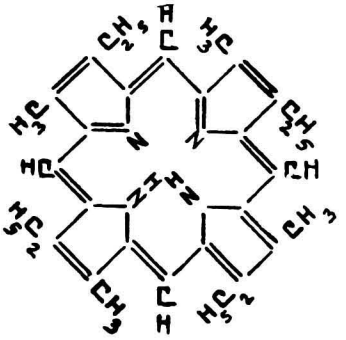
experimentation, especially on the basis of synthesis, the structure of these various porphyrins. He proved the existence of four different isomeric aetioporphyrins which can be expressed by the following formulae and as will be seen, differ inter se in the relative position of the methyl-, and aethylgroups. So it is evident that there must also be four isomeric koproporphyrins and four isomeric uroporphyrins. FISCHER has succeeded in preparing synthetically the four isomeric koproporphyrins, which could be anticipated theoretically. But according to him it is also an ascertained fact that all the kopro-(and uro-)porphyrins occurring in nature must be derived from the aetioporphyrin modality, which he terms aetioporphyrin I. On the other hand it appeared to him that the bloodpigment must be a derivative of aetioporphyrin III. And since it is very improbable, that the two isomers can pass one into the other, he concludes that in the cases known up to now of congenital porphyrinuria the pathologically augmented pigment cannot result from a decomposition of the hemoglobin, but is sure to arise from another source.

I must now remind you of a case treated and described by me before. It

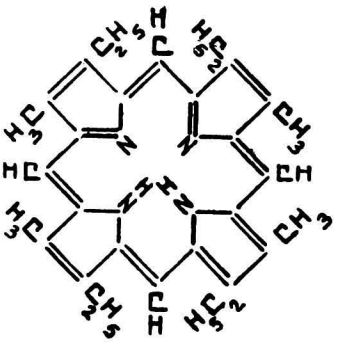
ISOMERIC AETIOPORPHYRINS

(after FISCHER).

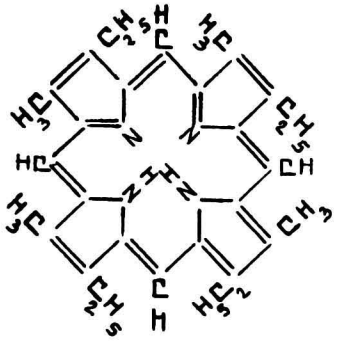
I



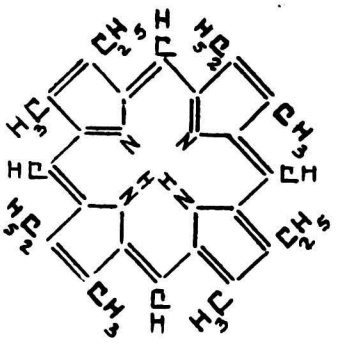
II



III

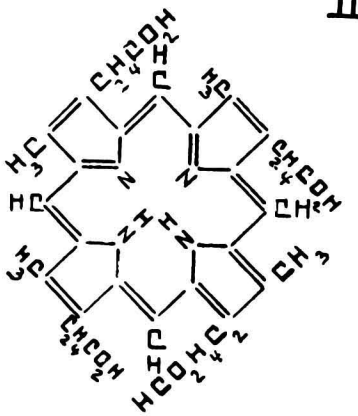


IV



KOPROPORPHYRIN

III



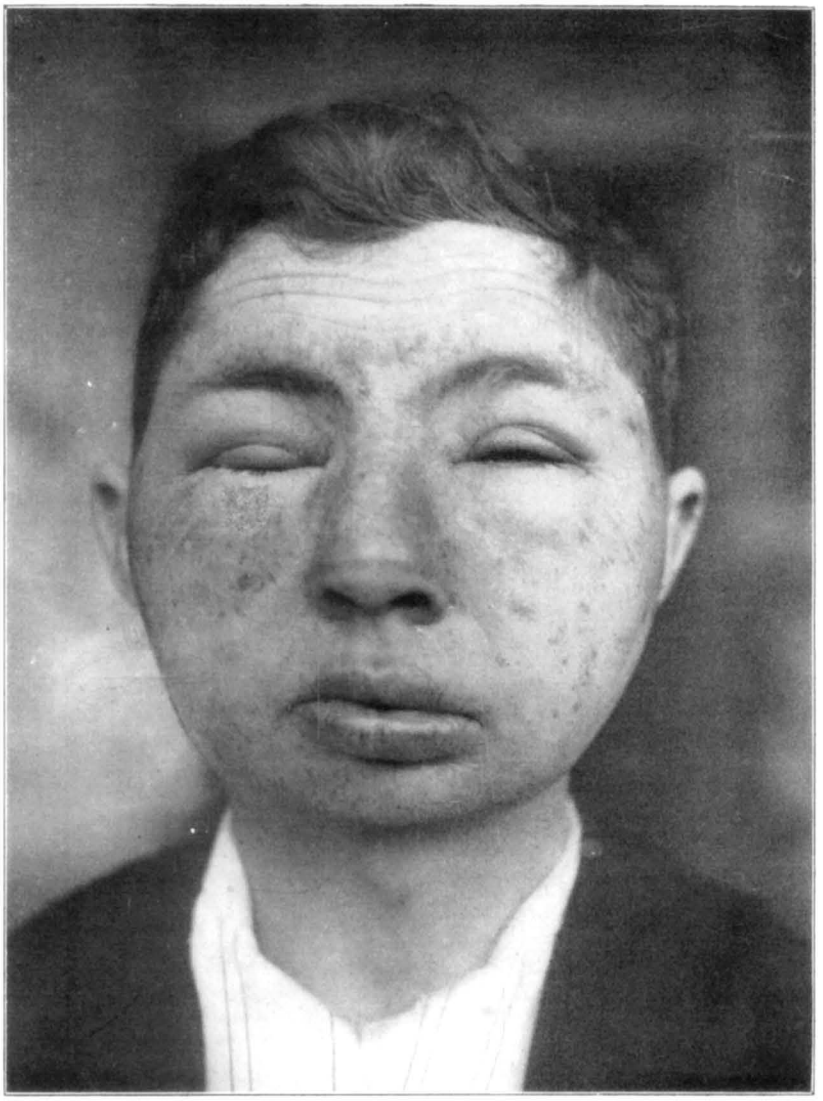
was the case of a man, now dead, who showed all the symptoms typical of a congenital porphyrinuria. In the dark-coloured urine and in the stools he excreted comparatively large quantities of the pigment, which could also easily be recognized in large amount in the red blood-corpuscles as well as in the serum. It is beyond doubt that these also imbued his tissues, for numerous ulcers and scars on the denuded parts of his body proved that his skin was hypersensitive to the action of the sunlight. Just as in the cases of congenital porphyrinuria recorded in the literature, the changes of the skin increased extensively and intensively, according as the sunlight, to which it was exposed was stronger, especially so in summertime.

However, the patient's case differed in one respect from those treated previously. Whereas in the latter uroporphyrin, which is insoluble in ether, was found in the urine, the urine of our patient contained the ether soluble koproporphyrin with a spectrum typical of this substance, which spectrum differs slightly from that of uroporphyrin. So, contrary to all other cases of congenital porphyrinuria, described up to the present, this urine contained koproporphyrin. Now it chanced that about the same time another patient came to consult us, who presented the same symptoms of porphyrinuria. On this plate I show you the face of the man as he looked after having been exposed to the sunlight during a short railway journey. The urine of this man also contained a substance which had to be considered as koproporphyrin, as it was soluble in ether, and it exhibited the typical spectrum. Unfortunately the patient was a serious psychopath, who had asked for admission to the clinic 3 or 4 times in succession, but on getting nervous left hospital every time after some hours. This prevented us from collecting larger quantities of urine for a careful chemical examination.

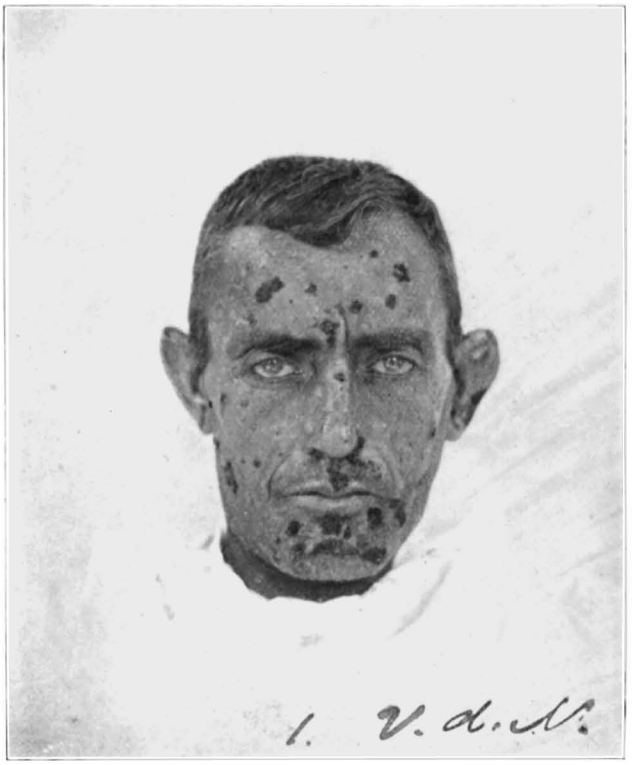
Now let us revert to the urine of our first patient. The pigment isolated from it, though it was soluble in ether, and showed the typical spectrum, and — as said — contained 4 carboxyl-groups, was not quite identic with the koproporphyrins that have so far been found in nature. As to the spectrum, however, there was complete identity, while just as the koproporphyrin, it also contained 4 carboxyl-groups. The melting point of the methyl esters however was quite different from that of the esters of the koproporphyrins, occurring in nature, which just as that of the corresponding koproporphyrin I, prepared synthetically by FISCHER, is about 251°.

Our substance yielded an ester melting at about 169—170°.

This case induced Prof. FISCHER to enter into communication with us. He had found namely that the melting point of the koproporphyrin prepared by him from aetioporphyrin III lies at 171°. As I stated before, up to this day this porphyrin-modality had not been met with in nature. It is quite conceivable, therefore, that FISCHER says in his latest publication: "Von grossem Interesse ist natürlich die Frage, ob Kopro- und Uro-porphyrin, die sich von Aetioporphyrin III ableiten, in der Natur vorkommen oder nicht. Auf grund der bisherigen Experimentaluntersuchungen lässt sich ein Urteil



2. *v. L.*



nicht fällen, da zumeist der Nachweis der Porphyrine im Harn und Kot leider nur spektroskopisch erfolgt, und die isomeren Koproporphyrine nach den bisherigen Untersuchungen mit einander spektroskopisch identisch sind. Im Schmelzpunkt der Ester ist jedoch zwischen den einzelnen Porphyrinen ein grosser Unterschied."

So we have exchanged our preparations : he sent us his koproporphyrin prepared synthetically, derived from aetioporphyrin III, and we sent him the porphyrin (in esterform) isolated by us from the urine and the faeces of our patient.

To sum up we can say that Prof. FISCHER (and his co-worker TREIBS) obtained with our preparations the same results as we ourselves did, while in our turn we were in a position to fully corroborate FISCHER's experience with his synthetic preparation.

The melting-point determinations (also the determinations of the mixing melting points) yielded complete agreement between the methyl ester of the koproporphyrin obtained by us from the urine and the faeces of our patient and that of the koproporphyrin prepared synthetically by H. FISCHER from aetioporphyrin III.

It follows from this that we were in a position to establish for the first time in the pigment excreted by our patient the presence of the koproporphyrin to be derived from etioporphyrin III, whose existence had been anticipated theoretically by FISCHER and which had then been prepared synthetically. This experience lends support to FISCHER's conception regarding the structure of porphyrins. Furthermore our inquiry has also shown that chemically it is possible that in our patient the porphyrin has originated from the blood-pigment, which after FISCHER's investigations was considered highly improbable in all the other cases of congenital porphyrinuria so far described.