A few preliminary observations were also made jointly by myself and Mr. Hammond with a view of determining whether bacteria considered to be in the ordinary sense of the word non-pathogenic, for example, the ordinary water bacteria, could be made to give a serum reaction sufficiently marked to be of service in the differentiation of species, groups, and races. This appeared to be a desirable subject of study owing to the marked influence shown by race peculiarities in the degree of serum reaction obtained in the case of the pathogenic spirilla.

The observations are not sufficient to warrant any general conclusions, and are only mentioned here as suggesting a possible new means of diagnosis with a class of micro-organisms which form a great stumblingblock to progress in the direction of systematic bacteriological classification. We gather that the agglutinative phenomena when slightly manifested serve to indicate racial, rather than specific affinities.

[I would state that while the suggestions in connection with the Picton disease observations came from me, the technical work has, subsequent to the first successful observation, been almost entirely done by Mr. E. W. Hammond. The blood samples used were the same that had been in scale tubes for from 1 to 3 years, and had been left in the laboratory by Dr. Adami, who was absent in England at the time.—W. J.]

ON THE RED ALLY OF UROHÆMATOPORPHYRIN : A RETROSPECT OF TWELVE CASES.

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A CASE of disease is, from one point of view, a great physiological experiment performed by Nature, which often presents us with processes arrested and functions perverted at very instructive stages. The appearance in the urine of the pigment known as hæmatoporphyrin, or one of its allies, in place of the amber-coloured pigment normally there, is an example of an arrested process—that of katabolism of pigmentary matter derived from the blood, and taking place, on the largest scale, in the liver.

The term "urohæmatoporphyrin" dates from 1885, when MacMunn, in a paper¹ on the colouring matters of bile and urine, rechristened what he had five years earlier named "urohæmatin."² In 1880, in a case of rheumatic fever, he found "urohæmatin," and about the same date made it artificially by reduction of the pigment hæmatin. Urohæmatin was then found in a case of pericarditis, and on several occasions in the urine of Addison's disease. Since 1885 this pigment has always been known as urohæmatoporphyrin; it gives to urine an orange colour, and has been detected in a number of diseases, namely, in addition to the three given above—peritonitis, meningitis, cirrhosis of liver, peritoneal blood effusion, croupous pneumonia, typhoid fever, measles, and Hodgkin's disease.³

In all these cases the colour of the urine, if not quite orange, is of a tint of amber deeper than the normal. Examined with the spectroscope, urohæmatoporphyrin shows a four-banded spectrum, the wave-lengths of whose bands are published in many of the above-mentioned monographs, but briefly put the bands are—one in the red to the left of ν , two between ν and ϵ , and one near the F line. This spectrum closely resembles that of a laboratory pigment alkaline hæmatoporphyrin also four-banded, whose bands differ slightly from those of the urinary pigment in situation and intensity. Hæmatoporphyrin as a laboratory pigment has been long known both in acid and alkaline solutions. Thudichum in 1872 called it "cruentine."⁴ The acid solution is two-banded and very characteristic, the pigment is iron-free. MacMunn found it in several of the lower animals, in the integument of certain slugs, star-fishes, the earth-worm, and in some birds' egg-shells.

Previously to 1890 this was all that could be said about hæmatoporphyrin and its urinary ally, but early in that year MacMunn saw for the first time two specimens (sent him by Dr. S. M. Copeman) of a "Burgundy-red urine" which con-

tained no proteid, blood, or bile. Towards the close of the same year Mr. Cant of Lincoln, and Dr. Noël Paton of Edinburgh, each sent MacMunn a specimen of urine similarly pigmented.

Fig. 1.—(1) Acid hæmatoporphyrin. (2) Alkaline hæmatoporphyrin. (3) Acid urohæmatoporphyrin. (4) Alkaline urohæmatoporphyrin. (5) Meio-de oxyhæmatoporphyrin, or α -hæmatoporphyrin, the red ally of urohæmatoporphyrin. (Nos. 1 to 4 are from the charts accompanying MacMunn's paper *Journal of Physiology*, vol. x. No. 5 is from one of my own drawings.)

Mr. Cant's case was that of a woman, aged 40, with exophthalmic goitre, who had excreted red urine for three years (corpuscles 2,250,000 per c.mm. and HBO_2 40 per cent. of normal). She had taken a good deal of sulphonal. There was some patchy pigmentation of skin, and bullæ filled with a red alkaline fluid. To three of these urines Dr. Halliburton⁷ alludes on p. 751 of his *Textbook* (1891), in a footnote, where he states that MacMunn regards this red pigment as "intermediate between urohæmatoporphyrin and hæmatoporphyrin." He refers the reader to two other similar cases (described by Drs. Ranking and Pardington⁸), which occurred in neurotic women and terminated fatally. The spectroscopic report on these two urines was made by Dr. MacMunn—the pigment was the same as in the first four cases, of deep garnet-red colour, yielding a four-banded spectrum resembling urohæmatoporphyrin, but differing, on careful comparison, in the position of the wave lengths of the absorption-bands: these were, however, not published, nor was the pigment named.

Two other cases of Burgundy-red urines were met with in 1890, both by Dr. Vaughan Harley⁹—one in Edinburgh (in the Royal Infirmary under Dr. John Wyllie), the other in Christiania. Both were of women who had been taking sulphonal, and who exhibited "nerve disturbances" and sleeplessness. The urine had no proteid, blood, or bile; in the foreign case the wave lengths of the centres of the absorption-bands were published: first band at $\lambda 562$, second at $\lambda 526$, third at $\lambda 482$, besides a feeble absorption in the violet.

On March 21st, 1891, Dr. Halliburton showed to the Physiological Society a specimen of red urine from a case of a lady, aged 30, who had excreted the pigment for seven weeks. She had been taking sulphonal since the previous November, and for more than a year had suffered from melancholic monomania. The urine was similar on examination to that of the former eight cases. The specimen was sent him by Drs. Blandford and Alliot, of Sevenoaks.

In 1894 Dr. Oswald,¹⁰ then assistant-physician to the Glasgow Royal Asylum, watched a case of mania in a woman to whom large doses of sulphonal were given. Between April and August she took 2,200 grs. of sulphonal, and at intervals during that time excreted a "claret"-coloured urine, which had no bile and did not give the guaiac test. Though the case was described as an example of hæmatoporphyrinuria, there is now no doubt that the pigment was not urohæmatoporphyrin, but the red ally of it.

In December, 1896, I saw for the first time a Burgundy-red urine, sent me from the wards in the Western Infirmary, Glasgow, from a patient under the care of Dr. McCall Anderson.¹¹

The urine contained no proteid, sugar, blood, or bile, gave

a four-banded spectrum convertible, after treatment with cold concentrated H_2SO_4 , into the characteristic two-banded one of acid hæmatoporphyrin. This reaction the majority of the observers above alluded to had used with the same result. The case was that of a young fisherman, aged 25, from Stornoway, who had suffered annually from April to October from an eruption of a vesicular kind to which at first the name dermatitis herpetiformis bullosa was given, but which was subsequently named hydroa æstivale. His corpuscles were normal in number, but his HbO_2 only 60 per cent. of normal.

In August, 1897, I was sent from the same wards a second specimen of dark red urine with a note saying it was being passed by the brother of the man who had been a patient in December, 1896.¹² His urine was precisely similar to that of his brother, and in it, without any dilution, I measured the wave lengths of the four bands of absorption which are in millionths of a millimetre.

First band (in red) from $\lambda 638$ to $\lambda 620$, centre at $\lambda 630$.

Second band (orange region) from $\lambda 586$ to $\lambda 551$, centre at $\lambda 563$.

Third band (green region) from $\lambda 538$ to $\lambda 522$, centre at $\lambda 530$.

Fourth band (near green-blue junction) from $\lambda 517$ to $\lambda 490$ or $\lambda 488$, the right hand edge is hazy, and varies with the dilution, centre about $\lambda 498$, besides considerable absorption in the violet.

Comparing these bands with those above detailed as published by Harley, we find that in the pigment he described no band to the left of D, that is in the red, was found. I regard this as very peculiar, since every kind of hæmatoporphyrin has a band in the red region, its exact position varying with the different pigments. In acid hæmatoporphyrin and acid urohæmatoporphyrin it is very close to D; in the two alkaline solutions of these, respectively, it is farther from D, while in the case of the red ally it is most distant of all from D. On diluting the solution it quickly disappears. All that I can suggest is, either that there was less pigment per cent. present in the foreign case or that it was diluted for the examination. There can be no doubt that it was this red α -hæmatoporphyrin. I would say a band in the red was one of the characteristic features of the absorption-spectra of all the hæmatoporphyrins.

Being led to reflect upon the genetic relationship of these pigments to those of bile and urine,¹³ I found it awkward not to have a name for the red ally of urohæmatoporphyrin, and so devised one which endeavoured to express what MacMunn believed to be its position relative to hæmatoporphyrin and urohæmatoporphyrin, namely, its being intermediate as a reduction product, between the two. I therefore named it meio-de-oxyhæmatoporphyrin. It might, however, be well to call it by a term that connoted no particular view as to its origin, so that the red pigment might be merely known as α -hæmatoporphyrin and the orange one as β -hæmatoporphyrin. In a sense they are both urohæmatoporphyrins probably in different stages of reduction.

Of the twelve cases mentioned, seven have been in women, and in four of these, sulphonal had been administered. In all there was grave nervous disturbance. Of these seven cases, five were fatal. Having already discussed, to some extent, elsewhere, the seat of origin of these pigments, I refrain from again entering upon that topic, but would only say that the liver is probably the chief seat of the abnormal katabolism of blood pigment through hæmatoporphyrin (iron-free) to the iron-free pigments of bile and urine. Had I not seen Professor McCall Anderson's first case, in which the excretion of red pigment has recurred for years and the man is still living, I should say this red urohæmatoporphyrinuria was a most grave symptom, a precursor of a fatal issue—such at any rate it seems to be in the case of women.

I ought to add that α -hæmatoporphyrin is very stable. In the first specimen of it, which I received a year ago, the pigment has preserved its chemical and spectroscopic integrity. In this respect it is exactly like laboratory acid hæmatoporphyrin which never seems to decompose. Its presence has also some power in greatly retarding the putrefaction of the urine itself.

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THE LOCAL TREATMENT OF PAINFUL ULCERATIONS BY ORTHOFORM,

WITH SPECIAL REFERENCE TO THE UPPER AIR PASSAGES.*

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UNDER the name of orthoform, a new synthetic product related in constitution to cocaine has been introduced by Professor Einhorn and Dr. Heinz, of Munich, for the production of local anæsthesia.¹ From a chemical² point of view the history of the building up of orthoform is of some interest, and may be epitomised as follows. The authors of the investigation set themselves the task of finding the hypothetical molecule hidden in cocaine or its derivatives which would produce local anæsthesia without accompanying toxic effects.

It is assumed that cocaine is constituted of a double ring in which a benzoyl-oxy-piperidine-carboxylic methyl-ester (having a methyl group attached to the nitrogen) is associated with a hydro-aromatic ring of the hydr-benzoyl-oxybenzoic methyl-ester. The analytical observations of Stockman,³ Filehne,⁴ Ehrlich,⁵ and Poulsson,⁷ who split up the molecule and showed that none of the products obtained by this process were capable of producing local anæsthesia; and the more or less synthetical experiments of Liebreich, Poulsson, and Ehrlich elucidated matters so far that it became a question as to whether the peculiar anæsthetic quality of cocaine was dependent on its double-ring nature, on some property of the first ring, or on an influence existing in the hydro-aromatic ring. The last was a reasonable hypothesis, more especially since it was known that certain other aromatic substances, such as methylene blue,⁸ possessed the property of relieving pain. Impelled by the foregoing considerations, a prolonged and elaborate investigation was undertaken by Einhorn and Heinz into a large number of these substances, with the result that they were led to conclude that all aromatic amidoxyesters cause local anæsthesia, though in differing degrees of intensity and with varying powers of irritation. A substance (p-methyl amido-m-oxybenzoic acid) of this class, to which the trade name of "orthoform" has been given, appeared to act most strongly as an anæsthetic and not at all as an irritant. It has the following constitutional formula⁹:

Orthoform is a white voluminous crystalline powder without taste or smell; it is not hygroscopic, and melts at 120°C . Free orthoform combines with hydrochloric acid, forming a hydrochloride which is more soluble than the basis powder, but causes irritation to some mucous membranes on account of its acid reaction. The hydrochloride (price 6s. 6d. per ounce) is the preparation on the market, and the dose is 8 to 16 grains. The anæsthetic presents a triple claim to recognition, in that it is sparingly soluble, is non-toxic, and is powerfully antiseptic. On the other hand, it is a disadvantage that the substance will not act on unbroken skin nor, with certain reservations, on intact mucous membranes, for its strong anæsthetic properties are only manifested where nerve endings are exposed. The slow solubility leads the anodyne to exert its action economically on the tissues, and, unlike its rapidly soluble congener cocaine, only sufficient is dissolved to produce and keep up local insensibility, which therefore becomes prolonged. In from 5 to 10 minutes after application anæsthesia of the denuded surface to both touch and pain commences, and it reaches its consummation within a short period of time. The effect lasts from a few hours to five or six days, and there is, in the majority of cases, perfect

* Read before the Manchester Therapeutical Society.