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.

or nearly perfect analgesia, the patient experiencing the sensation of the offending part having been cicatrised over or "enamelled." Suppuration is usually markedly diminished and healing accelerated.

The observations which I have made on the pharmacology and clinical effect of orthoform have been principally confined, on the one hand, to a consideration of such preparations as would be suitable for applying to the upper air passages, and on the other hand, to the effect of the drug on ulcerations of these regions. Orthoform is soluble in water, the basis powder very sparingly and the hydrochloride much more freely. It is also dissolved by ether and spirit. The drug is practically insoluble in normal saline solution, in glycerine, and in paroline, and although suspended in the last-named vehicle, the particles of powder are too large to pass through the ordinary atomiser. The most suitable preparations appear to be:

(1) *The crude powder*, either alone or mixed with equal parts of lycopodium, which should be accurately insufflated on to the required area, since orthoform only takes effect where it comes in contact with the abraded parts, and its influence does not extend to the tissues beyond.

(2) *Pastilles*, with the following formula: R Orthoformi, gr. iij to v; liq. cocci, q.s.; saccharin, gr. $\frac{1}{4}$; glyco-gelatini, q.s. The pastilles are useful in mouth, tonsillar, and posterior pharyngeal affections, but less so than the two succeeding preparations.

(3) *A saturated solution of orthoform in collodion*, forming a species of "varnish." This is useful in those cases in which an ulcer is exposed to much friction, but as it causes acute smarting it is advisable to primarily anaesthetise the ulcer either with cocaine or with orthoform in powder.

(4) *A spray*, with this formula: R Orthoformi, gr. v; sp. vini rect., aquæ, aa, m℥. This is perhaps the best form in which to administer orthoform for nasal and laryngeal ulceration. The spirit evaporates shortly after contact with the parts, leaving the precipitated powder evenly distributed over the affected area.

(5) *An ointment* (10 per cent.) made with any good ointment basis.

(6) *An aqueous solution* (10 per cent.) of the hydrochloride as a paint.

The action of orthoform on the unbroken mucous membrane of the mouth, naso-pharynx, and larynx is, in my experience, the following: Neither the free orthoform (basis powder) nor the hydrochloride anaesthetise sufficiently to allow of surgical action. When applied to the tongue, inner surface of the cheek, or to the pharynx, a numb sensation supervenes in the course of about five minutes, but there is little real anaesthesia. The effect on the larynx is to reduce reflex irritability. A peculiar feeling, described as similar to that produced by cocaine, is experienced in five minutes; in a few more minutes this relative loss of sensation vanishes, but if before its subsidence a probe be introduced and the vocal cords and interior of the larynx touched, although a species of "gagging" ensues, there is no laryngeal spasm or cough. In the same patient a similar procedure without the previous introduction of orthoform causes intense discomfort and a fit of coughing. The intact nasal mucous membrane is also slightly amenable to the influence of the drug. A feeling of numbness is evidenced in about two minutes, and this merges into real anaesthesia, which is, however, feeble and transient.

I have had the opportunity of testing the anaesthetic value of orthoform in eighteen patients who suffered from painful ulcerations of the upper respiratory tract, and a few representative cases are now quoted.

CASE X.—L. F., aged 24. Tuberculous ulceration of the epiglottis; phthisis. The pain on swallowing and on coughing was intense, and the patient had avoided any but liquid food for three months. A 10 per cent. solution of cocaine gave more or less ease for six hours. Five grains of orthoform were insufflated on to the ulcerated surface, and relief began within an hour and lasted for thirty hours. The pain on swallowing and coughing was reduced almost to *nil*, and the patient succeeded in taking food with comfort for the first time for more than three months.

CASE III.—H. H., aged 56, clerk. Epithelioma of soft palate and tonsil. There was an offensive cavity in the position of the left tonsil, a large ulcer to the outer side, and advanced glandular infection. The patient suffered intense pain on swallowing, and also was much afflicted by severe and constant neuralgia from the deep pressure of the growth. Orthoform (5 grains) was blown into the cavity and upon the ulcer, and relief began in the course of half-an-hour. Almost all pain on swallowing was

abolished, and this improved condition lasted a week. The man ate some solid food (about half a mutton chop with bread) within a few hours of the application after a long abstinence from all but liquids. The neuralgia was not diminished at all.

CASE VI.—Mrs. H., aged 35. Tuberculous ulcer on posterior and upper surface of the right arytenoid. Phthisis. There was some dysphagia, and it was a matter of difficulty, owing to the peculiar situation of the breach of surface (exposed as it was to constant friction), to persuade any drug to remain in contact with it. A thick paint of orthoform and collodion was applied, with the result that the patient expressed herself considerably relieved from the dysphagia—this condition lasting about twelve hours.

CASE VII.—E. M., electrician, aged 54. Laryngeal and pulmonary phthisis. Had pain on swallowing for two months before admission to hospital. This was gradually getting worse, and solids, semisolids, and liquids caused great discomfort. He "could not take any breakfast at morning" in consequence. Orthoform (grs. 5 of the basis powder) was insufflated into the larynx, and relief began within half an hour, when saliva could be painlessly swallowed. A solid meal of chop, bread, and potatoes was taken three hours after the application with little or no inconvenience. A feeling of dryness in the laryngeal region began after the meal, but relative relief lasted for twelve hours. The next morning the throat was extremely sore.

CASE II.—H. B., aged 40, striker. Laryngeal and pulmonary phthisis. Interarytenoid thickening and an ulcer on the left cord posteriorly. There was considerable pain on swallowing even liquids or semisolids. The patient—a very intelligent man—was instructed to use a laryngeal spray of a solution of orthoform. After the first application the drug, which "acted like cocaine" (to which he had been accustomed), gave relief in five or ten minutes, and this lasted for four hours. A second application gave comfort for two hours, and a third (of the powder) gave complete ease for three hours and modified comfort for twelve hours. The ulcer rapidly improved, and the pain eventually ceased to trouble the patient.

CASE I.—F. B., aged 19. Scarlatina anginosa with much injection and ulceration of tonsils and fauces. Excessive discomfort on swallowing. Orthoform gave relief for twelve hours, and the youth could take his meals comfortably.

CASE XVI.—L. G. Syphilitic ulcer of left tonsil causing great pain and dysphagia. Pain absolutely relieved by powder in 10 or 12 minutes; the parts were then painted over with a saturated solution of orthoform in collodion. The patient, who had been unable to eat for some days without agony, took, on reaching his home, a good meal of beefsteak with comfort, but was disappointed to find that two hours after the relief commenced the pain was beginning again, and in another hour was as bad as ever. A similar result followed a second insufflation and painting.

CASE IX.—G. S. Intranasal ulcer of catarrhal origin which had become irritated or septic. Situated on floor of nose, about $\frac{1}{2}$ cm. from external nares, and extending on to septum. Infiltration of surrounding parts, and great pain and tenderness of nose generally. After insufflations of orthoform, relief began in 5 or 6 minutes, and lasted several hours. The breach of surface also began to heal rapidly.

I am indebted for the notes of Cases IX, XVI, and VI to my friend, Dr. Haring, whose patients they were.

Toxic effects were not noted in any of the cases, but there was occasionally some slight burning for a few minutes after the application of the hydrochloride. This failure to discover toxicity is compatible with the statements that over 12 drachms have been sprinkled on a broken surface in the course of the week, also that 30 to 60 grains have been administered daily to rabbits, and 45 to 90 grains to dogs, without evil effects during life or the *post-mortem* discovery of visceral changes. Orthoform fails to produce any results on an ulcer unless the dual precaution is taken to apply the drug directly to the loss of surface and to ensure its retention there.

No relief was experienced by patients suffering from either catarrhal pharyngitis or quinsy.

The drug in doses of 8 to 16 grains is said to be of value as an anodyne in ulcer or cancer of the stomach. In cases of ulcer, complete relief for three or four hours has been obtained, and one patient with cancer benefited in this way for twelve hours. Orthoform is also declared useful in burns, ulceration of the vulva, chronic cystitis, traumatic lesions of the urethra, gonorrhoea, and other cases.

The antiseptic action of orthoform appears to be demonstrated by the rapid diminution of purulent exudation in several of the cases encountered, and the speedy healing of the ulcer. In a case of acute gonorrhoea injections of orthoform solutions were followed by the disappearance of gonococci in four days, and the complete cessation of the blenorragia.

Finally, if further observations confirm the results already published, it would appear that orthoform is entitled to take a position in the gamut of local anaesthetics applicable to the upper air passages. It seems probable that it will replace—by virtue of its insolubility and innocuousness—its relative, cocaine, when long anaesthesia on ulcerated surfaces is wished for; be replaced by the more reputed drug when short insensibility of intact mucous membrane is desirable, and on occasion supplement it.

My best thanks are due to Professor Dr. Einhorn, of Munich, who has on several occasions assisted me in the most courteous manner; also to Drs. Hodgkinson, Hutton, Moritz, Haring, and Fenn, on the staff of the Manchester Consumption Hospital; to Dr. Wild, Physician to the Manchester Skin Hospital; to Dr. Mercer and Dr. Hodge, all of whom have very kindly given me clinical material or other generous help.

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A NEW VOLUMETRIC METHOD OF ESTIMATING URIC ACID IN URINE.

By F. W. TUNNICLIFFE, and OTTO ROSENHEIM,
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In a preliminary communication in the *BRITISH MEDICAL JOURNAL*,¹ one of us (Tunncliffe) drew attention to the solubility in water of urate of piperidine, the salt formed by the action of piperidine on uric acid. This property of piperidine to combine in molecular proportion with uric acid and the solubility of the resulting salt form the fundamental principles of our method.²

If the uric acid is separated from the urine by any of the known methods, and the resulting acid be suspended in water to which a few drops of an alcoholic solution of phenolphthalein have been added, there will be no colour reaction upon the addition of piperidine solution until all the acid is dissolved. If after this point has been reached any further piperidine be added it will remain as such, and by virtue of its alkaline reaction will cause the development of a red colour. Until all the uric acid is dissolved, any piperidine falling into the liquid will be at once converted into piperidine urate, which latter produces no colour reaction with phenolphthalein. By using a solution of piperidine of known strength, the amount which must be added to produce the clearing of the liquid and the development of the purple colour, gives by a simple calculation the amount of uric acid present.³

The method resolves itself into three distinct procedures:

1. The preparation of the standard piperidine solution.
2. The obtaining of the uric acid in a pure state from the urine.

3. The titration of the same with the standard solution.

1. We found a $\frac{1}{10}$ normal piperidine solution most suitable. This may be standardised by estimating the amount of it which is required to neutralise a certain amount of a $\frac{1}{10}$ normal acid solution. We do not purpose here giving any fuller directions with regard to the preparation of the $\frac{1}{10}$ normal piperidine solution. To those possessed of a chemical training this would be superfluous, those unpractised in the preparation of standard solutions are advised to purchase the solution from a firm of manufacturing chemists.⁴

2. The uric acid may be obtained from the urine in several ways. The one which we have used, and consider the best, is the method described by Hopkins,⁵ which consists in precipitating the uric acid from the urine with ammonium chloride, that is as ammonium salt, and subsequently decomposing with hydrochloric acid. The uric acid obtained from 100 c.cm. of urine by this method is carefully filtered and freed from hydrochloric acid by washing with water until the washing shows no reaction with Congo paper. For this purpose we have found 15 to 20 c.cm. of water suffice, if an unreasonable excess of hydrochloric acid has not been taken.

3. The pure acid is rinsed with 20 to 30 c.cm. of hot water off the filter paper into a small vessel. Although the urate of piperidine, as we have shown elsewhere, is soluble at 15° C. to the extent of 5.3 per cent., we regard it as advisable in order to obtain a sharp end reaction to bring the fluid which is to be titrated up to the boiling point. A few drops of an alco-

holic phenolphthalein solution are then added, and the piperidine solution allowed to run in from a burette, the liquid being the while kept hot. The complete saturation of the uric acid present is shown by the appearance of a red colour which remains on shaking, and also by the fact that no uric acid remains undissolved.

Since 1 c.cm. of a $\frac{1}{10}$ normal piperidine solution corresponds to 0.00425 g. piperidine, and this is equal to 0.0084 g. of uric acid, the number of c.cm. required to produce the end reaction described above multiplied by 0.0084 will give the amount of uric acid present. In those cases in which 100 c.cm. of urine was the amount originally taken, it is obvious that the number thus obtained will give the percentage of uric acid in the urine.

It may be of interest here to subjoin the following comparative table, which gives the amounts of uric acid present in several urines, as estimated by weighing and by titration with piperidine. The method was to take two portions, of 100 c.cm. each, of each urine, and to estimate the uric acid by titration in one case, and by weighing in the other.

	Uric Acid by Weighing (Hopkins).	Uric Acid by Titration.	Difference.
			Mg.
Urine with an abnormally large percentage of uric acid	0.1056	0.1042	- 1.4
Normal urine	0.0809	0.0809	± 0
"	0.0818	0.0827	+ 0.9
"	0.0849	0.0846	- 0.3
"	0.0640	0.0647	+ 0.7
"	0.0799	0.0786	- 1.3
"	0.0550	0.0559	+ 0.9
"	0.0424	0.0422	- 0.2
"	0.0716	0.0728	+ 1.2
"	0.0809	0.0809	± 0
"	0.0923	0.0909	- 1.4
"	0.0799	0.0777	- 2.2
"	0.0674	0.0674	± 0
"	0.0426	0.0423	- 0.3

From these experiments it will be seen that the average difference between these two methods amounts to $-\frac{1}{10}$ mg. The difference is so small as to be practically negligible. The probable explanation of it is that the urinary pigments thrown down with the uric acid are, in the case of the weighing estimations, weighed with it; in the case, however, of the titration, they remain unattacked by the piperidine solution, and thus do not vitiate the result.

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¹ February 27th, 1897. ² For the proof that piperidine and uric acid combine in molecular proportions readers are referred to the authors' article in *Centralblatt für Physiol.*, xi, No. 14. ³ *BRITISH MEDICAL JOURNAL*, February 27th, 1897. ⁴ At the request of the authors Messrs. Baird and Tatlock, of Cross Street, Hatton Garden, have undertaken to supply the piperidine solution ready for use. ⁵ *Jour. of Path. and Bact.*, 1893, p. 458. See also G. v. Ritter, *Zeitsch. für phys. Chemie*, xxi, 288.

MITRAL STENOSIS: A STATISTICAL INQUIRY.

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In [the *BRITISH MEDICAL JOURNAL* of November 28th, 1896, I communicated a paper on the above subject, and endeavoured to show, from the *post-mortem* statistics of cases of mitral stenosis during four years at Guy's Hospital, that "the characteristic alteration in the left auricle in mitral stenosis is not dilatation but hypertrophy," and that the necropsy excessively exaggerates the importance of dilatation, which probably is introduced only with the auricular breakdown, and is thus an "old age phenomenon in the history of mitral stenosis."

I have lately analysed the *post-mortem* reports of all the cases of death at Guy's Hospital in the ten years 1886 to 1895 inclusive, in which stenosis of the mitral orifice was found present. The results appear to me sufficiently interesting to be worth recording.

In 4,791 necropsies during this period, there was a total of 196 cases (about 4 per cent. therefore of all examined) in which