pathology of chronic articular disease, involving the examination of over 200 subjects, I was impressed by the fact that the gross changes in the bone marrow exceeded in severity the lesions in the articulations.

The fuller consideration of these points is beyond the scope of the present paper, the main object of which has been to prove that the *tout ensemble* of the pathological picture of chronic gout is strikingly similar to that seen in chronic infective diseases. From this point of view the presence of uric acid is regarded as the feature which gives "the inflammation its specific character" (Garrod).

Let me, in concluding, draw special attention to the subject title of this paper, which I trust is sufficient to show that the author regards the bacterial element in the disease only as one of the factors in its production.

I have pleasure in acknowledging my indebtedness to Mr. Alexis Thomson, F.R.C.S.E., for the tissues which have formed the basis of this investigation; and also to Mr. Richard Muir for assistance in the examination of the sections, and for the reproductions from the microscopic slides.

ON THE DIACETIC ACID REACTION IN THE URINE,

WITH ESPECIAL REFERENCE TO GASTRIC ULCER.

BY

H. D. ROLLESTON, M.A., and B. N. TEBBS, M.A.,
M.D., F.R.C.P., M.D., B.C.
Physician, House-Physician,
St. George's Hospital.

It has long been known that, while the presence of diacetic acid in the urine may be of the gravest import in such diseases as diabetes and grave acid intoxication, it may also occur under certain other conditions without serious significance. Litten,¹ Lorenz,² Payne,³ von Noorden,⁴ and others have drawn attention to the occurrence of this reaction in conditions of gastro-intestinal disturbance, gastric ulcer, and inanition and starvation. It is also known to occur in certain febrile diseases, and Windle⁵ long ago described it in pneumonia. In this note we wish to deal specially with the occurrence of this reaction in cases of gastro-intestinal disturbance, and more particularly in gastric ulcer.

As a rapid clinical test for the presence of this body, Gerhard's reaction, namely, the production of a port-wine colour on the addition of a solution of perchloride of iron to the urine, is extremely simple; a few drops of liquor ferri perchloridi are added to the urine, and in the majority of cases a whitish-grey phosphatic cloud forms. If diacetic acid be present, the urine assumes a port-wine colour, which is largely masked, however, by the phosphatic cloud. It is best, therefore, to filter this off and add a few more drops of the reagent to the filtered solution. The colour of the solution, if diacetic acid be present in appreciable amount, is a dark cherry-red when viewed by transmitted light. By reflected light it has more of a purplish tint. In some cases where the reaction is very marked the phosphatic cloud does not form. The colour is at once destroyed by the addition of a few drops of a solution of citrate of potash. Previous boiling of the urine, which converts much of the diacetic acid into acetone, diminishes the colour reaction, but boiling for half an hour is not sufficient to convert all the diacetic acid.

A somewhat similar colour reaction is produced when the solution of ferric chloride is added to the urine of patients taking salicylic acid, or any of the numerous compounds of this body, such as salol, aspirin, salicin, or diuretin. Ordinarily the colour thus produced, which is said to be due to salicyluric acid, is of a deep purple colour, rather than the cherry-red produced by diacetic acid. But by altering the degree of dilution or by increasing the amount of ferric chloride solution added to the salicylic urine a colour can be produced which is indistinguishable from that due to the presence of diacetic acid. The colour produced by salicylates is also entirely removed by the addition of a little citrate of potash. The distinction between the diacetic reaction and that due to salicyl compounds is, however, perfectly simple. Previous boiling for five minutes causes a great diminution in the colour, if dependent on diacetic acid, but the colour remains unaltered if due to salicylates. The detection of acetone, either by Legal's, or preferably by the iodoform test, is distinctive. To determine the presence of the

diacetic acid in the urine of patients taking salicylates, etc., the urine must be boiled and then tested for acetone. The colour produced by diacetic acid is not likely to be confused with the brown or black colour following the addition of ferric chloride to urines containing melanin. The urines of patients taking sulphocarbolates, iodides, and phenacetin do not give this reaction. In a recent case of fatal carbolic acid poisoning the urine gave no reaction with ferric chloride. This agrees with a statement of Dr. Garrod's,⁶ though the contrary is often stated. It may be pointed out that, although acetates are said to be excreted as carbonates, the urines of individuals, even when in ordinary health, may give a cherry-red colour after liquor ammonii acetatis has been taken, and that since this drug is often given to patients with a raised temperature, this factor must be borne in mind in estimating the significance of febrile diaceturia.

The observations to which we shall refer have been made on the urines of patients under our care during the last three years. Attention has been paid specially to cases of gastric ulcer, most of which have been treated by starvation or rectal alimentation. The occurrence of this reaction in diseases other than those involving the gastro-intestinal tract has been far from frequent, and it is evident that in any febrile case presenting this colour reaction in the urine the influence of practical starvation from non-absorption must always be borne in mind.⁷ Care has, of course, been taken to exclude cases where the administration of salicylate compounds might be a source of error. Although the reaction has been present in several cases of diabetes—in two of them for prolonged periods, up to a year in one case—this subject will not be considered here, as its occurrence and significance are so well recognized.

GASTRIC ULCER.

The total number of cases tested was 44; of these, 3 were cases of perforated ulcer treated by operation and suture, and the remaining 41 were cases treated by purely medical measures. Of the 44 cases, 40 were women, including the 3 cases of perforated ulcer; the remaining 4 were men. As the incidence of the reaction shows well-marked differences in the two sexes we shall consider them separately.

Of the 40 female cases 2 only were allowed food by the mouth from the commencement of treatment, and the reaction was absent in these cases. In the remaining 38 food by the mouth was withheld for periods ranging from two to twelve days, and in all but five of these diaceturia was definitely present. Most of these 5 cases, in which the reaction was not obtained, were among our earlier cases, and the urine was not examined very systematically, so that it cannot be said that diacetic acid was constantly absent. In one case, however, in which careful daily examination was made it was absent throughout. It may be stated here that it appears to make no difference, so far as this reaction is concerned, whether the patient be absolutely starved or nutrient enemata be given, and for the sake of brevity we may refer to the period during which food by the mouth is withheld as the period of starvation.

The reaction usually appears quite early in these cases; in 19 cases in which the urine was tested regularly from the time of admission, it appeared on the day of admission in 2 cases, on the second day in 12, on the third in 1, and on the fourth in 4; it was found to be present when the urine was tested on the third or fourth day in several others. The average date of its appearance after the commencement of starvation would seem to be about the second or third day. The diacetic acid tends to disappear sooner or later after the return to mouth feeding, but the exact date of its disappearance is extremely variable. In our cases it varied from one day to a fortnight, the average being about five days. We have also been unable to establish any relation between the length of time of its persistence after the return to mouth feeding and the duration of starvation. One can only surmise that its disappearance coincides with the restoration of the balance of metabolism.

In the few cases of gastric ulcer in men this reaction either did not occur at all or only appeared after long periods of starvation. In one patient, who was admitted to hospital for chronic gastric ulcer on four separate occasions, it appeared on the first occasion on the ninth, on the second on the tenth day of starvation, and disappeared rapidly; on the third occasion there was a transitory reaction on the fifth day only, and on a fourth it was entirely absent. In a second patient with chronic ulcer we found it present on the eighth day of starvation only. In a third patient in whom food by the mouth was withheld till the ninth day, it was entirely absent.

In the fourth case, too, it was absent, but food was given by the mouth on the third day.

OTHER GASTRIC DISEASES.

We have studied this reaction in certain other gastric diseases, including gastritis, gastralgia, gastro-enteritis, carcinoma, and pyloric obstruction. We find that it is almost invariably absent when food by the mouth is administered. Short periods of starvation in cases of carcinoma ventriculi in men did not produce diaceturia. We obtained the reaction in each of three cases of alcoholic gastritis; it appeared early, on the second or third day of starvation, in all three cases. One of these cases occurred in a man of 33, and diacetic acid appeared on the third day, the earliest date at which we have ever found it in the male sex, but it was much more transient than in the female cases. It is possible that the perversion of metabolism in chronic alcoholism may specially dispose to the occurrence of diaceturia.

CAUSES OF DIACETURIA.

These results, then, show a special disposition on the part of the female sex to the development of diaceturia. In Litten's 81 cases of diaceturia there were 46 females and 35 males. The essential factor for its production is certainly starvation, for while patients are being fed by the mouth they do not tend to develop diaceturia. The question suggested itself as to whether the reaction might be associated with the acute ulcer, as this is commoner in the female than in the male, and this seemed to be supported by one of our cases, in which an extremely chronic ulcer in a woman of 42 (as verified at operation) was associated with absence of diaceturia, although the patient was starved for a period of five days. But on examining the ages of our female cases, we find that of the 46 cases, 13 were 30 years of age or over, 3 of them being over 40, and therefore presumably cases of chronic ulcer, and of these 13 cases, 11 gave the reaction. The reaction, moreover, appeared as early and was as marked in women over 40 as in women under 20. The only conclusion that can be drawn is that the determining factor is a matter of sex, and that neither the age of the patient nor the chronicity of the ulcer has any noticeable effect on the development of diaceturia.

Nor does the reaction appear to be determined by any actual lesion of the stomach itself; the direct cause is starvation. Thus in a woman under our care presenting the symptoms of epigastric pain, vomiting, and haematemesis, who was diagnosed and treated as a case of gastric ulcer, diaceturia was extremely marked and persistent, although the condition present was subsequently ascertained to be one of cholelithiasis and not gastric ulcer.

In other diseases where the brunt of the morbid process falls on the intestinal tract, females and children seem to develop diaceturia more readily than males. Thus in 7 cases of appendicitis the reaction was present in three children under 12, and in two females of 16 and 23, absent in two males of 23 and 30; and in 4 cases of enteric it was present in one female and absent in three males; in 4 cases of influenza it was present in two out of three females, absent in one male.

In pneumonia, on the other hand, we found there was no special tendency to its occurrence in female cases. The reaction was found to occur in a case of general tuberculosis, in a woman aged 22 years, associated with wasting, but it was transitory. We have also found it in cases of colitis, in mitral disease in children and young females, and in malignant disease, and generally in conditions associated with inanition. The reaction may be present after abdominal operations, involving a certain amount of temporary starvation, especially if the operation is followed by vomiting. But in all these cases there is a tendency for it to develop more readily in children and females. We have tested the urine in 9 cases of hepatic cirrhosis—of which 8 were in men—to ascertain whether the effect of grave hepatic disease on carbohydrate metabolism would influence this reaction, but diacetic acid was present in one case only.

Apart from diseases of the gastro-intestinal tract, we have examined the urine of patients suffering from various disorders in about 80 cases. The occurrence of the reaction in these cases was uncommon, being present in 9 only. The only cases in which it was present in men were in chronic nephritis (2 cases), herpes zoster, and pneumonia. We have never found it present in cases of morbus cordis in the adult male, although we have found it to occur, as already mentioned, in the case of mitral disease in children and young females.

THE INFLUENCE OF VARIOUS FACTORS ON THE APPEARANCE OF THE REACTION.

Feeding.—The exciting cause which determines the appearance of the reaction is starvation or defective absorption. As already mentioned, it apparently makes no difference whether the patient be absolutely starved or nutrient enemata be given. The question of the efficacy of rectal alimentation, on which much doubt has been cast, will not be raised here. Like von Noorden,¹ we have found that the addition of sugar to the water injections or nutrient enemata does not diminish the diaceturia. As a curiosity, it may be mentioned that, in the case of a man with gastric ulcer, the addition of sugar to the injections was followed by the appearance of the reaction, which had previously been absent. The administration of sugar by the mouth was, however, followed in most cases by a rapid disappearance of the diaceturia.

Drugs.—The administration of bicarbonate of soda should have a marked influence on the diaceturia. In a recent case of acute acid intoxication under the care of Sir Isambard Owen, transfusion with 4 pints of saline solution containing 1½ drachm of bicarbonate of soda to the pint was followed within an hour by almost complete disappearance of the acetone bodies from the urine. In some of our cases of gastric ulcer bicarbonate of soda in small doses of 20 gr. was given with the rectal injections, but did not produce any change in the reaction. In one case with persistent vomiting the same drug was administered in doses of 15 gr. by the mouth with the two-hourly feeds of milk, but it did not exert any appreciable effect on the diaceturia. The absorption of bicarbonate of soda is slow, and probably no noticeable effect would be produced unless it were administered in such doses as would tend to upset digestion. Morphine, which exerts a decided influence on metabolism, did not appear to influence the reaction, whether administered by the mouth, hypodermically, or in the form of suppositories.

Association with Vomiting.—In patients with severe or persistent vomiting there is usually an especially well-marked reaction.

It appears, then, that the development of diaceturia in cases of gastric ulcer is determined chiefly by starvation, and that it appears much earlier, persists longer, and is generally more marked in women than in men. Further, apart from this particular disease, diaceturia develops more readily in the female and in children than in the adult male. Grave acid intoxication appears, moreover, to be more frequent in the female. Drs. Dreschfeld and Moore² have recently published 3 cases, all in females; Kraus (quoted by Edsall¹⁰) 2 cases, both females. The case to which we have already alluded was in a female; while Edsall¹⁰ records 1 case in a male.

The interesting question arises as to whether in women with gastric ulcer there is not some underlying condition of subacidosis to account for the marked tendency to diaceturia. It has appeared to us that in gastric ulcer vomiting as a symptom is more marked in the female, and persistent vomiting we have found to be always associated with marked diaceturia. May not an underlying condition of subacidosis be the primary cause of this vomiting? This is suggested by Edsall's¹¹ observation that the cyclic vomiting of children is associated with the appearance of diacetic acid in the urine, and that the attacks can be prevented by the administration of alkalis.

Thus, as this condition of subacidosis occurs more readily in females than in males, and as diaceturia has been found to be associated with cyclical vomiting, the speculation arises whether some cases which are usually regarded as gastric ulcer, but which Dr. Hale White¹² suggests may be "really suffering from a different disease," may not be reasonably explained on the hypothesis that subacidosis is the primary condition which sets up vomiting and disposes to haemorrhage. The acidosis associated with these cases of gastric ulcer must be slight in degree, and does not attain the proportions of the more advanced stage of acid intoxication, for none of our cases, although showing well-marked diaceturia, has ever exhibited symptoms of drowsiness or respiratory disturbance. Moreover, Dr. F. Golla,¹³ who examined some of our cases, found that there was no appreciable diminution in the CO₂ contents of the blood, as there theoretically should be in grave acid intoxication.¹⁴

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THE INCUBATION PERIOD OF PNEUMONIA.

By EUSTACE M. CALLENDER, M.D. BRUX., L.R.C.P. LOND.,
M.R.C.S. ENG.

ALTHOUGH the pneumococcus (Fraenkel) does not conform to Koch's postulates, there is, I take it, little or no doubt in the minds of most physicians that it is the specific micro-organism of acute pneumonia. The same micro-organism is almost constantly found in the mouth, but seldom, if ever, in the nasal passages and cavities in health. In acute inflammatory affections of these passages and cavities it is, I believe, very generally present; in fact, it is probably the cause of many of these inflammations as well as of at least some cases of acute otitis media.

Several endeavours have been made to fix a more or less definite period of incubation in pneumococcus infections, and most writers appear to agree in believing such periods to be short. Mr. T. B. Franklin Eminson says: "It is the general opinion that the incubation period is very short—a few hours to a few days." Dr. Parsons says: "The length of the period of incubation is doubtful, but it appears to be short, from a few hours to two days."

The difficulty in fixing a definite incubation period in any disease must always be due in great measure to the difficulty in ascertaining the actual source of infection and the time of exposure. In the *Lyon Medical*, April 28th, 1889, is published an exceedingly instructive series of three cases in which the source of infection could be accurately ascertained and a definite time of exposure to infection ascertained. In these cases the incubation period was almost accurately forty-eight hours.

I venture to think that the series of cases now published is even more striking and instructive.

CASE I.

P. M., female, aged 13 years, living at home with her parents, showed definite symptoms of a severe nasopharyngitis on the evening of May 8th, 1904. When first seen on May 11th her left antrum was full of muco-purulent secretion, and there was a profuse nasal discharge. Temperature was 102° F., and there was a very marked prostration.

CASE II.

C. M., male, aged 49, father of Case I. was in good health on the evening of May 10th, but had a severe headache on rising the next morning (May 11th). He went as usual to his office in the morning, but returned home at 1 p.m., too ill to work. I saw him some two hours later. He had a typical left basal pneumonia. His illness was of the most severe type, and he died of toxæmia on the eighth day of the disease.

CASE III.

Mr. B. had two conversations with the last patient (Case II) on the morning of May 11th, one in his private office, and one in another part of the same building. He was well on rising on May 14th, but had a sharp rigor during breakfast, and vomited two or three times during that morning. His illness was of a somewhat indefinite character, and ended favourably with a very definite crisis on May 21st, the eighth day of illness.

CASE IV.

M. S., aged 28, female, domestic servant. This patient was for a short time on the mornings of May 12th and 13th in the sick-room of Case II. On the morning of the 14th she was too ill to work, and I was asked to see her. She was flushed and obviously ill. She complained of "sore throat" and very considerable dysphagia. Temperature was 102° F. There was marked prostration and very obstinate constipation. The fauces and pharynx were to the naked eye normal, but the patient complained of constant discomfort in the throat, which amounted to pain on deglutition. Pain was most severe on swallowing saliva, rather less on drinking, and least of all when swallowing solids. The reasons for detailing these symptoms will appear later. This patient's illness was not severe. She was ill for a week, becoming rapidly better during the seventh day. Her temperature was easily kept in check with quinine and diaphoretics.

CASE V.

Mrs. W., aged 63, a relative of Mr. C. M. (Case II), was in the house during the whole of this latter patient's illness, but never entered the sick-room until the early morning of May 17th (2 a.m.). Having helped the nurses in their duties for a few minutes, she lay down on a couch at the foot of the sick bed, and fell asleep. She remained thus for about one hour, and then left the room. On May 19th she left London by a morning train, was taken ill in the train, and reached home in Worcestershire with a temperature of 103° F. She died of acute pneumonia on the morning of May 22nd.

Now granting that all these were cases of pneumococcus infection, they form, I think, a very instructive and remarkable series, and show a very fairly regular length of incubation period.

Of the nature of the disease in Cases II and V there can be no doubt. Case II was seen in consultation on two occasions by Dr. James Galloway. It was a typical case of virulent pneumonia. Case V I did not personally see, but there can be no doubt of the nature of her fatal illness. No one is likely to question her having become infected, in all probability, between 1 and 2 a.m. on May 17th by Case No. II.

Of the three remaining cases—I, III, and IV—can they be claimed as cases of pneumococcus infection? I believe that they can. With regard to Case I, I had a precisely similar illness myself in December, 1903. It commenced with marked prostration, obstinate constipation, and considerable dysphagia. The dysphagia exactly corresponded with that present in Case IV, and I was struck at the time with the fact that the fauces and pharynx appeared to be absolutely normal. After a few days there was a profuse muco-purulent nasal discharge, accompanied by very severe supraorbital and infraorbital neuralgia. I consulted my friend, Mr. Ernest B. Waggett, who found the left antrum full of muco pus.

Examined bacteriologically by Mr. G. Leslie Eastes, this muco-pus was found loaded with pneumococci. I now much regret that a similar examination was not made in Case I, but naturally I had no idea of the developments which were to follow. Still I do not hesitate, looking at all the facts, to attribute to this case the production of the others of the series. Was Case III a case of pneumococcus infection? I did not see this patient myself, but I have been favoured by his medical adviser, Dr. James Brown, of Tring, with the following account of the case:

Mr. B. got up feeling quite well on May 14th, but had a sharp rigor during breakfast, and was sick two or three times. He was seen in the course of the morning, his temperature being 102°, and his respirations rather hurried. He made no complaint of pain, but said he felt a little stiff over the right side of the back below the scapula. The bread sounds in that situation were rather feeble, but there was no dullness on percussion, and no abnormal sounds either there or over the rest of the chest. He did not look very ill, was not flushed, had a slight cough, bronchial in character, but no expectoration either then or at any time during his illness. I have not been able to give you a record of his respirations, as Mrs. B. unfortunately destroyed the chart . . . but it varied from 20 to 48, and never gave him any distress except when he was moved. On May 18th I thought I could detect a few very fine crepitations on the left side of the back at the angle of the scapula, and on May 20th there were a few on the same side in front about 2½ in. below the nipple, but they were not very marked in either situation. He had a marked crisis on May 21st, and has gone on well since, but there have been no sounds in his chest, and practically no cough. He has a slight rheumatic tendency, with a permanent systolic murmur. At the beginning of the attack this became much more marked and rougher in character, but it quieted down again about the fourth day.

The onset, the indefinite pulmonary signs, the very marked increase of frequency of respiration, the definite crisis at the end of the seventh day or the beginning of the eighth, I think more than suggest a pneumococcus infection, especially when we remember his two interviews with Case II on May 11th, who was then suffering from pneumococcus infection of a most virulent type. There only remains Case IV, a very indefinite case undoubtedly. Her symptoms, however, so exactly resembled those I suffered from myself, and