CONCLUSIONS.

The conclusions to be arrived at by this analysis are as follows:

1. In the 231 cases of tetanus under review the mortality was 57.7 per cent.
2. Cases with a short incubation were more fatal than those of longer incubation.
3. Most cases occurred on the tenth day after the wound.
4. There are few allusions to the use of antitetanic serum as a prophylactic.
5. In regard to the therapeutic effect of antitetanic serum, the evidence would go to show that this action is not well marked.
6. If antitetanic serum is used—and in such a fatal disease it would seem wrong not to give the patient the benefit, even if doubtful, of the antitoxin—it ought to be injected in the first place intrathecally, as this method would seem to possess advantages over the intravenous and subcutaneous methods.
7. There is no evidence that any benefit accrued to the cases treated by carbolic acid or magnesium sulphate injections.
8. To sum up, the treatment of a case of tetanus might be as follows:

- (a) Place in a quiet, darkened room under care of a sympathetic and capable nurse.
- (b) The best surgical treatment of the wound should be thoroughly carried out to ensure the prompt and complete removal of all septic products.
- (c) The intrathecal injection of at least 3,000 units of antitetanic serum. At the same time 10,000 to 20,000 units may be injected intravenously and subcutaneously. This procedure to be repeated as frequently as the course of the disease seems to demand.
- (d) In addition to this the patient should receive sedative drugs, such as chloral or chlorotone, in full doses.

ON THE HAEMOLYTIC ACTION OF THE URINE IN CERTAIN CONDITIONS.

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This article is a summary of two papers read before the Vancouver Medical Association in April, 1914, and April, 1915, and not yet published. The work is based upon material obtained from the Vancouver General Hospital, while Director of the Laboratory of Clinical Pathology in that institution. Since arrival in England, with the concurrence of Surgeon-General Carleton Jones, D.M.S., Canadian Expeditionary Force, and thanks to the help given me by the National Research Committee, facilities have been granted to me to continue the work at Cambridge, under Professor Gowland Hopkins. I had, however, been able to do little more than demonstrate some of the main phenomena here recorded to Professor Hopkins, and, I may add, in the laboratories at St. Bartholomew's and Guy's Hospitals (to which hospitals I would express my gratitude for the opportunity given to obtain material), when I was called to active service overseas.

I would here express my sincere thanks to Professor A. B. Macallum, of Toronto; Principal Westbrook, of the University of British Columbia; Lieutenant-Colonel Adami, C.A.M.C.; and Professor Hopkins, for the encouragement they have given me in this research.

It seems fitting to place on record the following observations, since a careful search through the literature at my command, and also a search by interested friends through that contained in much larger libraries than were at my disposal in Vancouver, has failed to show that the reaction here described has been noted before, or, if noted, published. The only mention made of the action of urine upon the red blood corpuscles is the loss of shape and colour that these cells undergo after standing for some time in urine which tends to become alkaline, together with certain incidental notes upon changes observed in the red corpuscles in some (but by no means all) cases of haematuria.

It is unnecessary here to detail in full the sequence of observations and deductions which led me to this

particular line of inquiry. It will suffice to say that for the last few years I have interested myself particularly in the various forms of anaemia, and after not wholly successful endeavours to find some reaction whereby to separate sharply the conditions of so-called primary and secondary anaemia, it appeared worth while to test whether change in the blood plasma led to change in the corpuscles, whether these changes, if any, were due to the loss of some protective material, to the presence of toxins, or to the presence of something passed into the plasma for the purpose of neutralizing circulating toxic elements—a something which, while neutralizing these toxic bodies, exerted a coincident deleterious action upon the erythrocytes. Should there be bodies of any of the above types in the circulating blood, it seemed deserving of study whether they undergo excretion and are to be detected in the urine; and the first question to be answered was, Can any difference be made out between the action upon the red corpuscles of normal urine and that of urine from cases of grave (pernicious) anaemia?

METHOD EMPLOYED.

The solution of this first problem was not so simple a matter as it might seem. In fact, for a long time I failed to note any difference between them as far as the action on red corpuscles was concerned, red cell emulsions of different strengths and amounts being mixed with varying quantities of urine. The intention was to note if, after the red corpuscles had been exposed to the action of urine, there was any increase or decrease in the resistance of these to the action of a haemolytic serum, or any other change, which could be noted and followed up. Eventually I adopted the following technique by which, while ordinary urines have so far exhibited a complete absence of haemolytic power, those from cases of grave pernicious anaemia show at some period, often daily for a long time, a marked haemolytic activity. I have so far noted it in all cases studied, except in cases of the aplastic type.

The method is as follows:

1. Make an emulsion in the proportion of one drop of blood to 4 c.cm. of 0.85 per cent. salt solution.
2. Collect a dozen or more urines from various cases and take a series of test tubes, 3 in. by $\frac{3}{8}$ in. in size. In each place 15 drops of the urine to be tested.
3. To each tube add 1 c.cm. of the blood emulsion and mix with the urine.
4. Place the tubes in the incubator at 37° C. for two and a half hours, shaking several times during this period, examining at each shaking for evidence of haemolysis.
5. If haemolysis occurs in any of the urines, a series of 1-2-4-6-8-10 drops, added to 1 c.cm. of the emulsion, can then be made up for the purpose of measuring the haemolytic value of the urine giving the reaction.

Notes on Method.

There are certain notes which it is well to make regarding this technique.

I.

To make up the cell emulsion I add the blood—10 or 15 drops—to 15 c.cm. centrifuge tubes filled with 0.85 per cent. salt solution, wash once by centrifuging the cells, and make up the bulk to 40 or 60 c.cm., corresponding to 1 drop of blood to 4 c.cm. of the salt solution, as in the Noguchi-Wassermann system. I have, however, gained the impression that unwashed cells are somewhat more resistant, this being noted best in those cases where very small amounts of urine, say 1 or 2 drops, lacerate the corpuscles, and it is intended to use both washed and unwashed cells in a series of observations on this group.

II.

For the purpose of dropping the urines into the test tubes I use a dropper made from opsonic tubing drawn out in the flame to a capillary of medium bore, and drop with the tube held almost horizontally. After the first 15 drops are measured a mark may be made on the pipette with a grease pencil, and a sufficiently accurate amount of each of any number of specimens may be measured with the one pipette.

III.

I mention 15 drops as the amount chosen, because experience has shown me that whereas with some urines

1 drop added to 1 c.cm. of cell emulsion will induce haemolysis, I have not yet found, where 15 drops of urine do not haemolyze, that 30 drops will. In other words, if 15 drops do not haemolyze, doubling the amount has no effect. While stating this it must be emphasized that a marked difference occurs between urines. With some, 1 or 2 drops added to the cell emulsion will cause almost instant haemolysis. This phenomenon is seen most frequently with urines having an alkaline reaction; although by no means all alkaline urines haemolyze, even in an amount of 15 drops. It has therefore been made a rule, whenever a strongly haemolytic urine is encountered, to test for the smallest amount which will give the reaction. But clearly the laking action is not purely a matter of quantity, for in testing a urine which has been reacting daily, a very curious thing is often noted, in that 1 or 2 drops cause laking before 10 or 15 drops, and indeed 30; and at times the 15-drop doses may require two and a half hours to completely lake the corpuscles, and the 30-drop dose may cause no laking whatever.

And also, if the minimum laking dose of the urine is ascertained, and several doses added to the cell emulsion—where, for example, 1 drop lakes 1 c.cm. of blood cell emulsion—take 3 drops of the urine instead of 1 and add to the 1 c.cm. cell mixture. When complete laking has taken place, add 1 c.cm. more emulsion. This last remains not laked, the excess of haemolytic substance all having been taken up by the first lot of cells. This in alkaline urines.

IV.

Subjection of the blood cell-urine mixtures to incubator temperature of 37° C. is essential, and I am inclined to believe that neglect to consider this one detail is responsible for this simple phenomenon not having been observed long ago. It is true that at ordinary room temperature, haemolysis, notably with alkaline urines, does at times occur, but a parallel series of tests at room and incubator temperatures shows that warmth is an essential factor in the majority of the reactions, and in all of those in acid urines. Repeatedly no haemolysis occurs in 18, or 24, and often 48 hours in the cool of an ordinary room, when it is decisive in 2½ hours at 37° C.

V.

So far I have never observed haemolytic activity in the urine of healthy persons.

I hope in a later paper to attempt to go more fully into the cause or meaning of this phenomenon.

RESULTS.

As already noted, if carefully studied, the urine from cases of pernicious anaemia will be found to give this reaction. Just as the disease itself has its periods of remission, so is it with the haemolytic activity of the urine; but no relation has been made out between the two, nor do I pretend that I am calling attention to a test which will be of diagnostic or prognostic value in this disease, because this haemolytic action of urine is by no means confined to pernicious anaemia, as was ascertained when urine from other types of disease was studied.

Briefly, this appearance of a body or bodies in urine of a more or less actively haemolytic nature, is a fairly frequent accompaniment of grave disturbances of metabolism. In severe chronic anaemia the reaction is frequent, but not of daily occurrence, and after having tested and cross-tested the red cells of several pernicious anaemia cases, it appears that some patients' cells are much more resistant than others, but also that all are less resistant than normal cells.

The reaction is obtainable in erysipelas, gout, acute rheumatic fever, advanced tuberculosis, and certain cases of syphilis. In acute rheumatic fever, as so far studied, the urine was found to lake blood cells in all cases at some period during the course of the disease, in most cases all through the acute stage. The same has been true of severe erysipelas and streptococcal throat cases. In syphilis the reaction depended on the severity of the symptoms.

In all severe burns the urine has been regularly haemolytic and has remained so until death, or recovery was well assured. In some cases of skin disease, where a large part of the skin surface has been involved laking by the urine has been common and persistent. In two cases of

carbolic acid poisoning the urine, twenty-four hours later, was intensely haemolytic and remained so till death; here possibly other factors may have been at work.

In starvation the reaction appeared to depend upon the severity of the symptoms. In cancer with wasting, the reaction has always, so far, been present. In septic cases also it is common.

To see if possible whether this reaction was the result of some definite acidosis, urine from cases where this condition was well defined was studied—in children and certain post-operative states—and the haemolytic action obtained; so, again, it obtains in diabetes, if coma is approaching, or if after a period of well-being the condition becomes aggravated. Possibly associated with this group of cases I may note that in only four cases of pregnancy did I obtain this reaction (during the last week of pregnancy) and, curiously, all these four cases became eclamptic.

There is also a group of kidney and heart cases which exhibits urinary haemolysis. In so-called chronic Bright's disease laking is uncommon, but if acute nephritis supervenes, then in many cases haemolysis shows itself. In acute nephritis two groups have apparently become manifest, in one of which I have not noted this reaction, and another in which the reaction is present. All the cases of this last group succumbed. In heart cases with broken compensation the reaction is very regularly present, varying apparently directly with the clinical symptoms. One case with ascites was very interesting; the urine was daily haemolytic over a long period, except for a few days following each paracentesis.

Yet another order of cases I am inclined to regard as of importance. In the routine examination of all new cases entering hospital (and altogether I have now tested urine for this reaction from 5,000 cases) I have often observed that the urine obtained the first day following the patient's entry was haemolytic, but never again during his stay of days or weeks in hospital. So also in shock following accidents urinary haemolysis is frequently present in the same way. These observations led me to examine urines from post-operative cases, with the result that this reaction was found the day following operation in many cases; in some only once or twice, in others persisting for days or weeks. I am hoping to continue this study in connexion with the important group of cases of grave shock developing under shell fire.

FACTORS INFLUENCING THE HAEMOLYTIC PHENOMENON.

To gain, if possible, some understanding of the nature and significance of this reaction I have instituted a detailed study into the haemolytic activity of the various urinary constituents. This study is not yet complete, but is being continued by Mr. S. W. Cole at the Bio-chemical Laboratory at Cambridge. We hope to publish the results later. At most I would lay down:

1. Haemolytic action does not depend upon the acidity or alkalinity of the urine alone, although it is true that the majority of the most powerfully haemolytic urines are alkaline.

2. A urine with alkaline reaction does not increase in haemolytic power when kept at room temperature for twenty-four or forty-eight hours. Many lose markedly in strength. Paradoxically, a urine which is alkaline on passing I have never yet found to haemolyze at once, but only after standing for three or four hours after having been passed.

3. Acid urines tend to lose their haemolytic power on standing twenty-four or forty-eight hours, although the reaction remains acid. In this connexion the study has revealed a fact which I have not seen noted elsewhere: that urines seem to be of two orders—(1) one which is alkaline on passage or becomes so in a short time; (2) an acid group which remains acid despite bacterial contamination and fermentation. I have, indeed, incubated this type of urine for twenty-four hours without causing an alkaline change. As these observations have proved of interest and application outside this particular research, it is thought best to bring forward this study in a separate note later.

4. Bringing the urine to the boil appears to have different effects. It has no action on some urines, and in others weakens or inhibits the laking power. I have still to study the effects of boiling for longer periods.

5. The results of a study of the haemolytic powers of

the various urinary constituents may be summed up by saying that although alkalis like ammonia, acids such as acetic acid, and acid salts such as acid calcium phosphate, possess haemolytic powers, it is evident that these are not responsible for the phenomenon seen in actively haemolytic urines. The amounts of all these necessary to induce a similar haemolytic effect when added to (a) NaCl 0.85 per cent. solution, or (b) normal urine, being far greater than exist in urines that are found to haemolyze.

My observations during this work yield, as might be expected, different results as regards alkaline and acid haemolytic urines respectively, and must be left for full discussion later. Here I would only call attention to the protective action of sodium bicarbonate.

It was found, in the first place, that normal sodium bicarbonate solution, when added to a haemolytic urine in varying amounts, from 10 to 40 drops per 10 c.cm. of urine, prevented the haemolytic action, and this whether the urine was previously acid or alkaline, more being required in the case of a very powerfully haemolytic acid urine than in a correspondingly powerful alkaline urine. Following this observation, it was discovered that in patients affording a haemolytic acid urine the administration of sodium bicarbonate by the mouth in sufficient dosage caused the haemolytic action of the urine to disappear. This was tried only in a few cases with very powerful haemolytic acid urines, and never in a case with alkaline urine, and although in my few cases the administration seemed to be of clinical value, they are far too few to use as a basis for treatment.

6. The attempts at removing or neutralizing by the various absorbents, precipitants, filtration, etc., and the influence, if any, of the H ion concentration, as well as other studies, will be left for future discussion.

SUMMARY.

1. A phenomenon of fairly constant occurrence in certain morbid states, which apparently has hitherto escaped notice, is here described, namely, the rapid laking of blood corpuscles by the urine.

2. It has never been noted in the urines of normal individuals.

3. The agent causing this haemolysis is left an open question, but there seems no doubt that it is not a normal constituent of the urine.

4. Save in the case of certain strongly haemolytic alkaline urines, of which one drop sometimes causes instant laking of the blood emulsion at room temperature, the haemolytic process requires incubator temperature of 37° C.

5. Sodium bicarbonate definitely influences the reaction *in vitro*, and possibly when administered to patients by mouth.

6. A curious and apparently definite grouping of stable and unstable urines, so far as change of reaction from acid to alkaline is concerned, has been remarked. This group of unstable urines may perhaps be found of prognostic value.

URETERAL CALCULUS: ITS SYMPTOMS AND TREATMENT.

WITH A FEW ILLUSTRATIVE CASES.

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(Continued from p. 561.)

TREATMENT.

Expectant Treatment.

THE treatment must depend upon an exact appreciation of the state of the patient and of the morbid condition present. If there is reason to believe that one ureter only is blocked, and that the kidney on the opposite side is healthy, it is advisable to wait the course of events, as in many instances the obstruction is relieved spontaneously within a short time and no permanent harm results. This is especially to be recommended when there is evidence that the obstruction is incomplete or transitory, or when the patient is suffering little pain and the stone is known to be a small one.

While a stone in the ureter is certainly a source of danger, being liable to cause obstruction and its consequences—sepsis, haematuria, and hydronephrosis—it does not necessarily demand operation. Whenever a stone is suspected, x-ray detection is used, and, as a consequence, we find that a goodly proportion of ureteral stones are evacuated spontaneously. By having an x-ray plate taken from time to time its progress can be watched, care being taken to keep the patient under supervision. At regular intervals a thorough examination must be made, including a cystoscopic inspection, to ascertain that there is no blocking of the ureter. The following case is a good illustration:

CASE V.—Repeated Attacks of Renal Colic during Nine Months: Descent of Calculus Watched: Ultimately passed per Urethram.

The history was that of repeated attacks of renal colic, with the passage of gravel on several occasions. With x-ray a stone was discovered in the first instance (January, 1904) at the level of the transverse process of the fourth lumbar vertebra. The patient was examined at intervals of two months, and on September 9th, 1905, an x-ray photograph was taken, when the shadow of stone was found corresponding in position to the union of the lower and middle third of the left ureter—that is to say, well below the brim of the true pelvis. On some earlier examinations the stone was seen much lower down; therefore, was freely movable. On September 10th a cystoscopic examination was made, when the mucous membrane of the bladder was found to be practically normal, but, on account of the enlargement of the middle lobe of the prostate, the examination was difficult. The orifice of the right ureter was normal; that of the left was considerably dilated and the shape of a melon seed. The margins were very slightly thickened, and on the left lip the line of the mouth was obscured by a trickle of blood escaping from it, so that the whole contour was not clearly seen. The line of the ureter was very distinctly marked, and the mucous membrane covering it was pigmented and congested. On September 11th I received a letter from the patient saying that he had passed the stone on the evening of September 10th, and that he "felt alright now," but should I wish him to do so he was willing to undergo another cystoscopic examination.

A second x-ray photograph was taken on September 11th, and failed to show the shadow seen in the first plate, proving that the shadow seen was due to the stone which had been passed. A second cystoscopic examination showed the same appearances as formerly presented, with the addition that close to the middle of the upper lip there was a small submucous haemorrhage, and a similar spot was seen on the margin of the lower lip, but no blood was found escaping from the orifice. The stone passed was the size of a horse bean, but very irregular in shape and distinctly nodulated. It is worthy of remark that the passage of this concretion caused no laceration of the lips of the ureter or other injury recognizable with the cystoscope further than the minute submucous haemorrhages just described.

I have occasionally found that the ureter stones escape soon after a cystoscopic examination, which, I suppose, may be explained by the manipulation inducing a certain amount of muscular contraction or spasm of the muscular fibres of the ureter, which are often greatly hypertrophied in the presence of calculus.

While the patient is under observation attacks of colic may be prevented or relieved. In such cases the use of massage, shampooing, and the application of fomentations sometimes relieves the spasm. Pain may be alleviated during an attack by the administration of anodynes such as morphine, belladonna, and opium, but the latter drug must be employed with great care, as even a small dose may produce alarming effects when there is any interference with the proper action of the kidneys. It is much safer to employ hot fomentations, emollient enemata, and hot baths; should the pain be extreme, it may be necessary to place the patient under the influence of an anaesthetic, which not only has the advantage of relieving the suffering of the patient for the time being, but may also, by abolishing spasm, facilitate the passage of a calculus from the ureter. Under similar circumstances, warm diluents and diuretics have been given with the view of forcing the calculus down by an increased secretion of urine, but probably the beneficial action of these remedies is due more to the power they possess in reducing the irritating qualities of the urine than to any mechanical effect the increased flow of urine may exert. Changes in the position of the patient sometimes give relief from suffering by altering the situation of the stone, by dislodging it from the position where it causes most complete obstruction; in the same way external manipulation in the renal region or along the course of the ureters has been