inite and sudden in onset, becoming localized at McBurney's point. Pain at McBurney's point without temperature or leucocytosis is scarcely acute appendicitis. Again nausea and vomiting are practically always present. In mucous colitis we can get a history of a long standing constipation and digestive disturbances, of pains present heretofore and in other parts of the abdomen. The problem is more difficult in chronic appendicitis. Here a history is often obtained of a previous acute attack with a localization of more or less trouble at the same point ever after, or a careful anamnesis tells us that the trouble has always been in the region of the appendix; observations carried on over a considerable period of time will always bring us back to the same point of localized tenderness, while in mucous colitis the points of tenderness are inclined to shift from one part of the abdomen to another, although they may be present for days in the same locality. A spastic, tender cecum and ascending colon are palpable at times. In chronic appendicitis the appendix can often be felt as an enlarged and tender cord. If adhesions are present pain often occurs on forcible contraction of the psoas.

(2) Renal Colic and Dietl's Crisis: The urine examination and a history in the former, and a physical examination in the latter, will usually settle the diagnosis.

(3) Cholecystitis and Gallstones: There should be no trouble in differentiating it from acute gall bladder disease, but I am convinced the mistake is occasionally made. Attacks of pain in the right hypochondriac region without chills or temperature, without radiation of pain to the shoulder or chest, without a tender point to the right of the eleventh or twelfth dorsal spine, and without nausea and vomiting, are not gallstone colic. Unless one finds at least a majority of the above signs and symptoms one should be chary in diagnosing acute cholelithiasis. (Jaundice is of value in only 14 per cent. of the cases.)

Chronic Cholelithiasis.—Here careful history-taking as to previous acute attacks, character of pain, constipation, Murphy's sign, with repeated examinations of the patient, and with some attention paid to the colon, will usually keep us out of trouble. The disease must also occasionally be differentiated from most of the other conditions causing acute or chronic abdominal pain, but these are legion and too numerous to even mention here. The incrimination of pelvic conditions for the symptoms of mucous colitis is a daily occurrence.

Treatment.—To be successful the treatment must be founded on an accurate diagnosis. If an exciting anatomic cause exists it should receive proper operative attention. In many cases the neurasthenia must be our point of attack. A Weir Mitchell treatment may be necessary. Psychotherapy is often of the greatest importance in individual cases. In other cases the malnutrition must be the point of attack with a roborant and appetizing dietary. A change of climate, a vacation, freedom from household or domestic cares, laying aside the duties of society, or the mere leading of a natural life, will often accomplish remarkable improvement. Visceroptotics usually demand fattening, and an increase of intra-abdominal ballast alone brings about the desired result. In this condition a Rose bandage or a straight front supporting corset may accomplish much. The constipation must always receive attention, and here one must emphasize that *qui bene purgat, male curat*. Various diets have been advanced, and there is still some controversy as to whether the patient should be put on a bland diet (Westphalen) or one rich

in cellulose (von Noorden). In cases where the spasticity is marked the diet should *a priori* be at first of a bland character, switching as rapidly as possible to a diet rich in cellulose. Where the spasticity is slight, and the constipation tends toward the atonic, a diet rich in cellulose is in order. In the spastic cases opium and belladonna will often bring about desired results. One procedure, however, is generally applicable, that is nocturnal injections of one-half pint to one quart of olive or cotton-seed oil after Kussmaul to be retained until morning. Hot fomentations in the painful stages are agreeable and tend to allay spasm. In combating the constipation we may be compelled to resort to our entire therapeutic armamentarium, that is massage, electricity, habit, mineral waters, etc. In severe cases a period in bed should initiate the treatment. Time and trouble is often wasted in a temporizing, ambulatory therapy. The treatment of each case is a problem in itself as varied as is that of neurasthenia, and often solved only after much study. Results can be obtained, however, which, if not as spectacular as in some other fields of medicine, are nevertheless fully as gratifying and permanent.

THE TREATMENT OF GONORRHEAL INFECTIONS BY A SPECIFIC ANTISERUM.*

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In previous communications¹ we described briefly an antigenococcic serum which had been found efficacious in the treatment of some cases of gonorrheal arthritis. The results were so promising that it seemed advisable to give the serum a more thorough test in these cases and also on patients suffering with other forms of gonorrheal infection. The wider experience thus gained has confirmed our earlier conclusions and seems to justify us in the opinion that this serum exercises a specific curative influence on a high percentage of cases of certain forms of infection by the gonococcus. So far as we have been able to determine in a review of the literature, this method of treatment had not been employed previous to our preliminary communication.

PREPARATION OF THE SERUM.

At the beginning of these experiments it was considered possible that an antigenococcic serum, to be effective, should exercise some antitoxic influence. Accordingly, as was stated, ascitic broth cultures, from six to fifteen days old, were exclusively used in the inoculation of the animals. A satisfactory serum may be produced in this way, but not as potent a one as by a method which will be described below. The use of ascitic broth cultures was abandoned principally for the following reasons: In the first place protective experiments with guinea-pigs indicated that the immune antigenococcic serum did not exercise the slightest antitoxic activity; and, secondly, the repeated injection of the free gonotoxin in the culture media had a disastrous effect on the rabbits which were used in the production of the serum. Although they suffered little from the first five or six inoculations, soon after they reached a condition of hyper-sensitivity to the toxin and finally succumbed to a dose that would never have proved fatal to a normal animal. This

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1. THE JOURNAL A. M. A., Jan. 27, 1906, 261 and 263.

seems to indicate, as Wassermann and others have pointed out, that the toxin in the culture media is not produced in diffusible form by the living gonococcus cells, but is an endotoxin derived from the dead and disintegrated gonococci.

At this time it was noted that some rabbits, which were being immunized to twenty-four-hour ascitic agar cultures, withstood the inoculations very well and raised a serum, which in high dilutions agglutinated the micro-organisms. Accordingly, a similar method of procedure was followed in producing a serum for therapeutic purposes. The cultures were grown for from eighteen to twenty-four hours on large slants of ascitic agar, the culture tubes averaging one inch in diameter. It is essential to obtain a luxuriant growth. This is best accomplished by planting from an eighteen to twenty-four hour stock culture to medium of the following composition: Meat, peptone, 2 per cent. agar is prepared in the usual way and titrated to 1.5 per cent. acid to phenolphthalein. One part of rich sterile ascitic fluid is then added to two parts of this agar. For the first inoculation the growth from one of these tubes, about three square inches of surface, was emulsified in physiologic salt solution and injected living into the peritoneal cavity of a large rabbit. For the next inoculation the emulsion from two tubes was given. This was continued until the animal had received seven or eight inoculations, about fifteen tubes in all, during a period of two months. All the blood was then drawn from the carotid. The rabbits withstood inoculations of this character far better than when ascitic broth cultures were used.

In producing the first sera various rabbits were given different strains of the gonococcus with the idea of determining if certain cultures were better adapted for the purpose than others. It was soon evident that some cultures raised a far better serum than others, and also that a patient might respond favorably to a serum produced by culture A, but not to that from a rabbit immunized to some other strain, as G. On the other hand, the patient from which culture G was isolated was not benefited by injections of serum produced with culture A. The probability suggested by such data, that the gonococcus family is heterogeneous rather than homogeneous, has been substantiated by agglutination experiments, which have shown that various strains of gonococcus may raise agglutinins which are entirely distinct. The details of these experiments have been published elsewhere.² Because of this evidence of the existence of several groups in the gonococcus family the serum has recently been made as far as possible polyvalent. Cultures representative of the three principal groups, which have been found in the gonococcus family, are employed in immunizing the animals. This procedure seems to have found justification in a higher percentage of favorable therapeutic results.

As far as our experience has gone the agglutination test has proved to be a valuable index of therapeutic potency. A serum which agglutinated in high dilutions the various strains used in its production, always proved to be markedly curative. Such a serum agglutinated some cultures in dilutions as high as one to twenty thousand or fifty thousand. This test, of course, merely indicates that the animal is highly immunized, for the agglutinins themselves have probably nothing to do with the curative properties of the serum. In fact some sera with a low agglutination power may prove moderately effective. Others, however, are valueless and no feasible

laboratory method has yet been found of distinguishing between them.

Rabbits were at first used exclusively in producing the serum. Although a very potent serum may be obtained from these animals, it was found that the serum itself is decidedly toxic for some individuals and may produce a rather alarming reaction. This matter will be discussed presently in greater detail. In order to obviate this serious objection we have experimented with goats and sheep. Similar objectionable properties, although less in degree, were found to be present in goat serum, but from sheep serum they seem to be entirely absent. Accordingly in later work only these animals have been used. They should be full grown, uncastrated males. In immunizing these animals it has been found advantageous to pursue the following plan: The first inoculation may consist of the twenty-four-hour surface growth from eighteen square inches of solid culture medium, emulsified in about 30 c.c. of physiologic saline solution, and heated for one-half hour at 65° C.

We have always employed ascitic agar, made according to the method described. There seems, however, to be no reason, *a priori*, why any solid medium on which the gonococcus grows luxuriantly should not be substituted for ascitic agar, although no experiments have been carried out to determine this point. The inoculations are always given intraperitoneally. After an interval of about a week the second injection should be given consisting of the growth from about thirty square inches, heated as before. On the third inoculation, after the same time interval, about eighteen square inches of unheated culture may be used. On the fourth this is increased to thirty square inches of culture, and on the following inoculations thirty-six to forty-five square inches of unheated culture should be employed. A record should be kept of the weight and general condition of the animal and the amount and the time of the inoculations varied accordingly. It is sometimes necessary to revert to the use of heated cultures. After nine or ten inoculations have been given a little blood should be drawn and the serum tested for agglutinin. If the animal gives evidence of being highly immunized it is bled to death from the carotid and the serum collected. This serum is then filtered and tested for sterility.

The strains of the gonococcus which have been used in producing this serum were selected because, after an extended series of experiments, they gave evidence of being distinct varieties as far as agglutination was concerned. Such a selection of varieties is a long and tedious process, but is essential for the best results. Some strains are much more toxic than others, and obviously the less toxic ones should be used in the first inoculations. If no attempt is to be made to produce a polyvalent serum a strain should be used which raises agglutinins readily and is decidedly toxic. A few experiments will show that there is a great difference in these respects between various cultures of the gonococcus.

TREATMENT.

This serum has been found to be efficacious in the treatment of some of the complications arising from the primary gonorrheal infection. Acute urethritis, vaginitis and conjunctivitis are not markedly benefited by the serum, and for the treatment of these infections it is necessary to resort to other agents. A probable explanation of this peculiarity may lie in the fact that many of the infecting micro-organisms are not reached by the serum circulating in the blood and lymph. However

2. Torrey (J. C.): Jour. Med. Research, 1907, xvi, 2.

this may be, acute urethritis should be allayed by the usual methods in order to obviate the possibility of a subsequent relapse.

The complications which are amenable to serum treatment may be conveniently grouped according to their mode of origin in two classes: 1, Those arising by direct extension of the primary infection into organs like the prostate, epididymis, testicle, bladder and Fallopian tubes, in direct continuity with the primary focus; 2, those due to the entrance of the micro-organism into the circulation, either directly or through the lymphatics. These lesions include arthritis, iritis and the rarer endocarditis, pleuritis and meningitis. Gonorrheal peritonitis may generally be more correctly placed in the first group.

In cases which are pyemic or suppurative in character with abscesses in the joints, tendon sheaths, subcutaneous tissues, periosteum and viscera, there is always the possibility of a mixed infection, and the usual surgical treatment is necessary. After the pus has been freely evacuated the serum may prove useful in freeing the body from any gonococci which have not been eliminated by this treatment.

The pathology and diagnosis of these lesions need not be discussed here as they are matters of text-book knowledge. It is sufficient to call attention to the fact that all of the above complications are more or less amenable to treatment with an antigenococcic serum according to the degree of accessibility of the parts involved to the systemic protective fluids. The major part of our experimental work has been directed to the treatment of gonorrheal inflammations of the joints. The measure of success which has been attained in this field is indicated in the appended report of cases.

METHOD OF ADMINISTRATION.

The serum has always been given in small doses, viz., 2 c.c. or about 40 minims. No experiments have been carried out with larger amounts, as this quantity of potent serum has been found sufficient to act destructively on the gonococci without danger to the patient. This dose has generally been injected into the loose subcutaneous tissue between the deep fasciæ and the skin in the upper arm, using the other arm on the second injection. Any other convenient point, however, may be used. In the treatment of some of the patients the injections have been given in the neighborhood of the affected joints or deep in buttock. It seems doubtful, however, whether any special advantage attaches to this method. The injections have been repeated, as a rule, every other day. In this regard one must be guided by the general condition of the patient and the degree of the reaction to the serum. In some instances it is necessary to allow an interval of four to six days to elapse between the injections.

With ram serum the only reaction that one may anticipate is a varying amount of local swelling, redness, heat and soreness around the point of injection. This does not occur, by any means, in every individual, and is not caused by any antibody in the serum, but is due to the local toxic action of the serum itself. As the same serum has been found to cause reaction in one individual but not in another, it is partly referable to the idiosyncrasy of the patient.

TOXIC EFFECT OF RABBIT SERUM.

As has been stated, rabbit serum was found to be far more toxic to some individuals than that of the sheep. This marked toxicity, however, manifested itself in only

ten of the seventy-five cases treated with rabbit serum. With sixty-five patients there occurred either no local reaction or a very mild erythema. The toxicity may be exhibited by a more intense local reaction, which increases in degree with each injection, or it may take the form of a rather alarming general reaction. The local reaction generally appears in a mild manner after the first injection by moderate pain, redness and swelling. This increases, however, with subsequent treatments and reaches its maximum after three or four have been given. The severe local disturbance occurred in five cases out of seventy-five treated with rabbit serum. As an example of this type the following case may be cited:

CASE 1.—Male, with chronic gonorrheal arthritis and cystitis for five years. Feb. 27, 1906, 2 c.c. rabbit serum injected into the left arm. Moderate pain and swelling for forty-eight hours. March 1, second injection of 2 c.c. rabbit serum into the same arm; pain and swelling as before. March 3, third injection of the same amount of serum. Next day the arm was greatly swollen and very painful. Patient feverish. An abscess feared, but none formed. The fourth and fifth injections, on March 12 and March 17, respectively, were followed by only moderate local reactions.

The generalized systematic reaction which appeared in five cases is of a much more serious nature. It is worthy of note that four of these patients were in a very poor physical condition, having suffered from a gonorrheal infection for several years. The details of two of these cases follow:

CASE 2.—C. W., exhibited the prolonged chronic form of gonorrheal rheumatism with involvement of nearly all the joints of the extremities. He received the first injection of 30 minims of rabbit serum Oct. 27, 1905. This was repeated October 29, October 31 and November 3. Then on account of the local inflammation, the injections were suspended until November 11. On this date he received 40 minims of rabbit serum, and in less than a half a minute suffered from a feeling of suffocation, which was accompanied by a general superficial "flush." At the same time there was an effort at coughing. The pulse was very rapid and feeble, and the patient was greatly prostrated. After the administration of a little aromatic spirits of ammonia, the cutaneous blush and the severe dyspnea subsided, but the weakness and rapid heart action continued some hours. The following morning all these alarming symptoms had disappeared, but on the next day, the administration of 20 minims of the rabbit serum caused a repetition of the disturbance, though not quite as severe. Two weeks later, 20 minims of the serum was given without uncomfortable results. When the quantity of serum was again raised to 40 minims, however, a similar train of symptoms, in quite a severe form, resulted. Again, after the lapse of two weeks, 20 minims were given without any toxemia. Thus the quantity of the serum and possibly the time of administration were factors in this peculiar and sudden intoxication.

CASE 3.—S. had suffered from gonorrheal arthritis for several years. Beginning March 26, 1906, the injection of 2 c.c. of rabbit serum was given every other day for three doses without any reaction, but after the fourth injection of the same amount of serum, about eight days after the first treatment, the patient suffered from chills every afternoon. Temperature 102 F. in the afternoon and 100 F. in the morning. The chills were accompanied by general prostration and aggravation of pain in the joints. The same symptoms followed the next three weekly doses, but after that, twelve injections of the same amount of serum were given until September 1, without any general disturbance. About September 23, the patient received an injection of 2 c.c. of goat serum. Within half an hour he became semi-comatose and remained so for about twenty-four hours. Later treatments with sheep serum produced no ill effects.

The histories of these cases have been given in detail for the reason that some of the symptoms are decidedly suggestive of those occurring in guinea-pigs which have

received injections of foreign serum at certain definite intervals. It has been determined by Rosenau and Anderson,³ and also by other investigators, that, although a single injection of normal horse serum may be entirely harmless to the animal, a second injection of a certain amount of the same serum after an interval of over ten days will often prove fatal within an hour. Some of the symptoms of this intoxication are coughing, retching, respiratory distress and coma. This condition of hyper-susceptibility or anaphylaxis (Richet) does not manifest itself, however, if the second injection is given in less than the incubation period indicated. Furthermore, if the injections of serum are repeated every few days the guinea-pigs become immune or, more correctly, refractory (Gay and Southard⁴) to the toxin in the serum instead of anaphylactic. Such being the case, it seems unlikely that the toxemias which arose in these patients after several injections of rabbit serum may be brought in line with the serum anaphylaxis of these animals, for the primary treatments have been given at much shorter intervals than the essential incubation period and should have induced refractory rather than a hyper-sensitive condition. Although some of the symptoms, such as dyspnea and semi-coma, occurring in these intoxications are suggestive of anaphylaxis, they are also characteristic of the poisonous action of endotoxins derived from various proteid substances, such as bacteria and tissue cells. It is possible, then, that we are dealing here with toxemia of this character. As we have stated, sheep serum has never given rise to the slightest generalized toxemia and may be used without fear of untoward results.

REPORT OF CASES.

During the past two years the serum has been distributed widely to applicants from all parts of the country and especially to many of the hospitals in this city. Histories and reports of the cases have been obtained in nearly every instance. About 22 per cent. of them have been treated personally by one of us (Rogers). We have spared no effort to obtain reports from as many cases as possible, whether we had reason to anticipate that the result would be negative or positive. The majority of the patients who have been treated with the serum were suffering with gonorrheal arthritis. We have collected reports of ninety of these cases, in which the diagnosis was reasonably sure and on whom the serum had received a fair test. These were of all degrees of severity and had lasted from a few days to several years. Forty-seven were mono-articular cases and forty-three poly-articular. By the use of the serum seventy-two or 80 per cent. of these patients were entirely cured, or much improved, and eighteen or 20 per cent. showed very slight or no improvement. Fifty-seven of these patients had received other forms of treatment for periods of a week to several years with slight or no improvement and were very much improved or entirely cured by the serum.

For further discussion these cases may be divided into: (a) acute, subacute and early chronic, (b) prolonged chronic.

(a) *Acute, Subacute and Early Chronic Cases of Gonorrheal Arthritis.*—In this list are included those of six months or less duration. Of cases of this character there were seventy-five. Of these sixty-four of the patients, or about 85 per cent., reacted very favorably to the serum, while with eleven, or approximately 15 per cent., the result was negative. These cases were for the most

part of two to eight weeks' duration. The number of injections required averaged five. Thirteen of the patients were cured with three or fewer injections, and of these, four with only two injections. One patient recovered quickly after one treatment. Twenty-three patients were cured in ten days or less, and of these, six in six days or less.

The first injection often causes a transitory increase in the soreness of the joints and sometimes a moderate rise in temperature. Some improvement may be manifest at this point, but it generally appears first after the second or, at most, after the third injection. This is indicated by an approximation of the temperature to normal and a lessening of pain, and sometimes of the swelling. Often, however, the pain disappears from the joint much more rapidly than the swelling. The latter may then be advantageously treated by massage.

With two patients whose ankles were involved a periosteal tenderness on the plantar surface of the os calcis persisted, although the other symptoms were greatly or entirely relieved. Our statistics seem to show that the serum acted quite as effectively in cases in which there was a marked swelling of the joints with more or less redness, as on those in which the joint symptoms were less acute. There may be room, possibly, for a difference of opinion on this point. The following case reported by Dr. G. W. Webster of Chicago on Feb. 2, 1906, illustrates well the rapidity with which the serum acts on some of these acute cases:

CASE 4.—Patient, male, adult. First attack of gonorrhea two months before. Severe arthritis involving the right knee had been present for three weeks. The joint was much swollen, and the extreme pain rendered it almost immovable. The treatments during this time had included hot air, aspirin, nuxvomica, protargol, urotropin, methylene blue, and oil of sandalwood. The patient was doing badly. At this time several injections of antigonococcic serum were given. After the first injection the pain almost entirely disappeared. It was completely gone at the end of the second day. On the third day he was able to move about freely and put some weight on his foot. At the end of a week the effusion was gone and the patient was walking about the house without the aid of a cane. In ten days from the beginning of the treatment he was completely well.

There seems to be no doubt in such a case that the rapid recovery was entirely due to the specific action of the serum. A second case is similar in character, with the exception that the patient had had several previous attacks of gonorrheal urethritis and the rheumatism was becoming chronic. The serum, it may be said, has acted as favorably in such cases as in those in which the patient was suffering from a primary attack of gonorrhea, but if there have been several previous infections of the joints the case always proves very obstinate. This case was reported from the third medical division of Bellevue Hospital, New York, by Dr. Satchwell, house physician, July 30, 1906:

CASE 5.—Patient, male, single, 30 years old. Has had five previous attacks of gonorrhea; the first ten years previously and the last ten weeks previously. The last attack was treated with injections at a dispensary. A slight discharge continued to time of admission to hospital. Eight weeks ago, after the discharge had diminished, the left wrist and the right knee began to swell. The swelling became marked, but redness was absent. Pains severe, aching in character. Three days later the left hip became painful and stiff. Patient felt feverish, but had no chills. Two weeks previously one of the toes of the left foot began to swell and became very painful. Since then the patient had been unable to move either lower extremity or the left hand on account of pain and stiffness.

July 14, Gram-negative intracellular diplococci were found

3. Jour. of Med. Research, xv, No. 1.
4. Jour. of Med. Research, xvi, No. 2.

in smear from the urethra. On July 16, the left thigh was held in position of flexion and internal rotation. Marked tenderness about the joint; temperature 99 F. July 17, antigenococcic serum injected deep into left buttock. Severe aching pains in the joints, lasting for two hours, followed the injection. A slight rise in temperature. Joint conditions unchanged.

July 18. Tenderness in hip and wrist very much less. Motion in hip greater. July 19. Temperature normal. Serum given into the left buttock. Similar pains as on July 17 for two hours. July 20. Up in a chair. Tenderness in hip and wrist very much less. None in knee. July 21. Serum given into buttock. Pain again for several hours. (NOTE: This transitory pain in the lower extremities is apt to follow the deep injection of the serum into the buttock.) No tenderness. Up and about the ward. Temperature 99 to 100 F.

July 22. Up and about the ward; No pain or tenderness except at the site of the injection of the serum. Walks with a slight limp. July 23. Serum given as before. Pain for several hours. Temperature 100 F. July 30. Discharged from hospital, cured. No pain. No tenderness. Walked well. No limitation in any of the affected joints. Temperature normal. The following leucocytic counts show little change before and after the serum was administered, except an increase in the number of lymphocytes and a drop in the polynuclear neutrophiles.

	Before. July 14.	After. July 24.
Leucocytes	11,200	12,000
Polynuc. neut	63 per cent.	56.5 per cent.
Lymphocytes	28 per cent.	36 per cent.
Large mononuclears	6 per cent.	5.5 per cent.
Eosinophiles	1 per cent.	.5 per cent.

(b) *Prolonged Chronic Cases of Gonorrheal Arthritis.*

—The very chronic or protracted examples of this form of the disease, which may persist for months or years, do not readily recover under any treatment, and when there are pronounced deformities or ankyloses a complete cure is impossible. But with perseverance and the judicious use of a potent antigenococcic serum a great deal of good may be accomplished in a fair percentage of these otherwise hopeless invalids through the cessation of pain and active inflammation. To these patients the serum should be given twice a week for a month and then at intervals regulated by the symptoms. Ordinarily it is not wise to give a second injection before the reaction from the first has entirely subsided, as the discomfort may be considerable.

At the end of a month or more in a favorable case there is a gradual lengthening of the period of well-being after each administration of serum, and it may be necessary to give it only once in two or three weeks. In one of these cases the administration of the serum caused after a time the disappearance of shreds, apparently prostatic, from the urine. The pain in the joints followed a parallel course, decreasing with the disappearance of the shreds. After an interval when no serum was given, signs of recurring inflammation appeared, preceded by the appearance of the shreds. Another injection of serum, however, brought relief again, which continued for a longer period than before. The patient is still under the treatment and is steadily improving.

If there is no sign of a change for the better in a chronic case after four injections, we have found it useless to continue the treatment. It is impossible, of course, to explain every negative result, but if there is no improvement after treatment with a potent serum there is a possibility of an error in diagnosis or of infection by a strain of gonococcus for which the serum contains no specific antibodies.

As an example of the treatment of these prolonged cases, the following history may be cited:

CASE 6.—J. H., aged 31, single, male, had a first attack of gonorrhea in October, 1897. There was a constant urethral

discharge for about one year, during which an epididymitis occurred and persisted for some weeks. In March, 1899, there still existed a moderate gleet. At this time the right hip became painful and stiff. Some months afterward, the left hip became involved and then the joints of the feet and spine. The patient tried every available "cure," including a severe course of mercury and iodid of potash at Hot Springs, Ark., but the rheumatism persisted, sometimes a little better and again worse. In March, 1907, he was able to dress himself only with assistance and was just able to get about. Both shoulders were stiff and painful; the "knuckles" of the hands were painful and swollen; the knees and ankles were in the same condition and showed over each joint one or two sharply limited areas of maximum tenderness. The urine contained an abundance of shreds, but in them no gonococci could be definitely identified. There was an increased frequency of urination and the prostate was slightly sensitive, but not appreciably enlarged.

During March, April and May, 1907, sheep antigenococcic serum has been administered about every eighth day. After each injection there occurred a noticeable improvement in the joint symptoms and the patient was able to put on his shirt and coat without assistance for the first time in years. As the pain decreased, the sleeplessness was greatly improved. The symptoms, however, would recur several days after receiving the serum, but was relieved by another injection. At first there was no change in the second glass of urine and it was not until the end of April that the shreds became noticeably less. This patient is still under treatment, but at present attends to all his affairs and moves about like a normal man. There is only a moderate amount of thickening around the basal joints of the right index and middle fingers, and some tenderness around the arches of both feet. The latter seems to be incipient flat-foot condition, as it is made worse by long standing or walking, and the muscular condition is poor.

In the following case, reported by Dr. W. A. Germain, of Sioux Falls, S. D., the recovery was rapid and complete:

CASE 7.—Patient, male, suffering with chronic gonorrheal arthritis and cystitis, had been under treatment for five years. During this period he had received almost every form of treatment, including deep injections, prostatic massage and thermotherapy. The patient received six tubes of antigenococcic serum during the period from Feb. 27, 1906, to March 30, 1906. After the first injection a quantity of shredded mucus was voided with the urine and the pain in the neck of the bladder entirely disappeared. The rheumatism was not improved. After the second injection, there were pus and shreddy mucus in the urine, but no improvement in the rheumatism. The urine became clear after the third injection, but the joint symptoms remained the same. The fourth injection brought about a decrease in the rheumatic pains, and after the fifth they disappeared. The patient since then has not had any return of the symptoms. The rabbit serum, which was used, caused a marked local swelling, which soon subsided.

Tendosynovitis.—Reports have been received from six cases of tendosynovitis which were treated with the serum. In four instances a cure was effected, while in two a primary improvement was followed later by a relapse. As a rule, these cases have responded very quickly to the serum and have required only three or four injections.

Infections of the Genito-Urinary Organs.—Dr. George K. Swinburne,⁵ of New York, has already published a report of the treatment of several cases of epididymitis with antigenococcic serum. Further experience has borne out the promise of the earlier results. We have received reports from eight cases of this character. Six were entirely cured within a few days, one was very much improved, and in one there was no improvement. One to three injections have generally proved sufficient to effect a cure. The pain has markedly lessened or

5. THE JOURNAL A. M. A., Jan. 26, 1907.

ceased in nearly every instance after the first injection. The following case, reported by Dr. Swinburne, is of interest:

CASE 8.—The patient appeared at 10 p. m. with a first attack of epididymitis, which had started at 2 p. m. of that day and had steadily increased. The epididymis (left) was exquisitely tender, and distinctly enlarged. An injection of serum was given. At noon on the next day there was no pain and the testicle was not nearly as tender. On the following day there was no trace of any trouble. Another injection of serum was given. Two days later the urine was clear for the first time in a month.

This case illustrates the value of the serum in aborting incipient cases. The following report on a case of chronic gonorrheal cystitis is also furnished by Dr. Swinburne:

CASE 9.—W. K., aged 28, single, contracted gonorrhea first in 1902. This was followed by some prostatitis and cystitis. In May, 1906, massage of the prostate was begun and followed by some improvement, but there was a constant slight urethral discharge and the urine was always cloudy with pus. In November, 1906, the prostate was practically normal, but both the first and second glasses of urine were cloudy with pus and contained Gram-negative intracellular diplococci. Massage of the prostate and bladder irrigations with 10 per cent. argyrol solution were continued for four weeks, without improvement. Between January 5 and Feb. 2, 1907, the patient received nine injections of antigonococcic serum (sheep), and on February 9 all traces of the disease had disappeared. One month later, after a "beer test," the urine was found to be clear.

The history of our only case of gonorrheal salpingitis, which recovered quickly after operation and one injection, indicates that the serum may prove of value in this condition. It is, of course, impossible to determine exactly to what extent the serum hastened recovery after the evacuation of the pus:

CASE 10.—E. J., aged 21, domestic, entered St. Francis Hospital April 29, 1907, with a history of leucorrhea and cystitis for the past week. Five days previous to admission pain began in the pelvic region and later forced her to go to bed. Examination showed a moderate purulent leucorrhea, extreme tenderness and marked rigidity in the hypogastrium, uterus fixed and immovable, lateral fornices very tender, and a large, painful and tender mass behind and at the sides of the uterus. Temperature 103 F, pulse 120. April 30, under ether, a small puncture was made in the vault of the vagina behind the cervix and about six ounces of creamy, thick puss evacuated. Irrigation and drainage tube. This pus contained a very few organisms resembling gonococci, but no growth could be obtained.

May 1: Temperature 102 F. in the morning and the patient still complained of pain and tenderness. Considerable purulent discharge. In the afternoon 40 minims of antigonococcic serum (sheep) was injected.

May 2: Temperature 100 F., discharge much less.

May 3: Temperature normal, no discharge, no complaints, drainage tube removed. After this there was rapid improvement and on May 8 vaginal examination revealed nothing abnormal except the small granulating wound in the vault.

With three cases of orchitis, this serum therapy has effected a cure after two to four injections. Chronic urethritis, however, has not yielded readily to serum treatment. In two out of the three cases of this character, there was no improvement after a few injections of serum had been given, but in one the symptoms disappeared. In this case of fourteen months' standing, the first injection caused a profuse discharge from the urethra, but this gradually subsided until after the third injection it entirely ceased and did not reappear. As has been explained in treating cases of acute urethritis, it is useless to employ the serum.

Infections of the Eye.—A number of cases of conjunc-

tivitis have been treated with the serum, both by local application and by injection, with little or no benefit. The negative results with such patients is doubtless due to conditions similar to those present in acute urethritis. With iritis, on the other hand, the results have been very promising in the two cases treated by the method. One of these, reported by Dr. Arnold Knapp, of New York, has the following history:

CASE 11.—Male, aged 22, gonorrhea two years previously, chronic discharge for eight months. One year previously, iritis in left eye, lasting two months. Recovered. Feb. 24, 1907, left eye became inflamed. Entered hospital. March 1, 1907, ciliary congestion, retina hazy, urine normal. Three injections of serum were given on consecutive days. This resulted in more congestion and the appearance of fibrinous exudate in the anterior chamber. Two more injections were given on the following days, resulting in the disappearance of the exudate. Patient felt better. During the week, March 8 to March 15, four injections were given. As a result the congestion of the conjunctiva became less, the iris normal, the pupil fully dilated, but some opacity existed in the retina. A week later the patient was discharged with the left eye practically normal. Since then there has been no relapse.

MODE OF ACTION OF THE SERUM.

The question remains: What particular properties of this serum exercise the curative influence? In attempting to discuss this point the following clinical phenomena, sometimes accompanying the administration, are of importance. With four patients who had had a more or less chronic discharge from the urethra, the first injection greatly increased this discharge, but after the second or third the flow of pus stopped entirely. Again, in a case of iritis, the first three injections of serum caused a greater congestion and the production of a fibrinous exudate in the anterior chamber of the eye, but after two more injections this all disappeared and the eye was much improved. Finally, in many cases of gonorrheal arthritis, especially in cases of long standing, the first two or three injections cause a transitory increase of pain and inflammation in the affected joints and may, in fact, "awaken" other articulations which have lain dormant for some time, but after a few more injections the pain and swelling generally disappear and the joints regain their normal condition.

At least two possible explanations may be offered of this frequent transitory increase of inflammation, occurring in some instances within a few hours after the administration of the serum. Wassermann and Bruck⁶ have advanced the theory that the increase of inflammation and rise of temperature after the injection of tuberculin into a tuberculous patient is due to the interaction of the tuberculin with an antituberculin present in the tissues. If a similar explanation is advanced for the phenomena under consideration, it would be necessary to prove that the antigonococcic serum contains a derivative from the gonococcus analogous to tuberculin. Although our experiments in this direction are incomplete, we have thus far found no evidence that this serum contains any appreciable amount of gonotoxin.

A second explanatory hypothesis, which may be advanced, is that the serum injected into the patient has brought about a local disintegration of the gonococci and a liberation of endotoxins. The presence of this toxin in the tissues would cause an inflow of exudate and pus, as has been determined by Schaffer⁷ and others in man, and by Malvoski⁸ through experiments on ani-

6. Deutsche med. Wochschr., March 22, 1906.

7. Fortschr. d. Med., 1897.

8. Ann. de Gynecol. et Obstet., 1899, III.

mals. From the evidence at hand this second view seems to us the more probable.

Granting the probability that the serum brings about the destruction of the gonococci in the tissues, two views may be taken of its mode of action: First, that the primary bactericidal action has taken place directly through the presence of specific immune bodies in the serum injected; second, that it has been brought about indirectly by phagocytes, which have been aided by an opsonic action of the serum. The weight of evidence seems to be rather in favor of the first hypothesis, because the increase in inflammation occurs often so soon after the injection of the serum, indicating that the endotoxins have been liberated directly into the fluids and not into the protoplasm of the leucocytes. Experiments, which will be published in detail later, also indicate that immune bodies are present in abundance in this serum. And, finally, because it is evident that the primary destruction of gonococci in immunized guinea-pigs takes place directly through the agency of the fluids and not by phagocytosis. An objection might be raised to this view on the ground that 2 c.c. (the usual dose) of serum would be diluted several thousand times by the blood and serous fluid of an adult man. Other potent bactericidal sera, however, have been found to act as at high dilutions *in vitro*, and antigonococcic serum to be effective must come from very highly immunized animals.

It is quite possible, furthermore, that the gonotoxin liberated in the tissues may play indirectly an important part in the curative process, in that it causes an inflow of exudate containing leucocytes. These phagocytic cells are then able to take up and digest more readily the remaining gonococci through their having been acted on by the serum. This idea is not an hypothesis unsupported by evidence, but it is substantiated by the increase of specific phagocytic action in guinea-pigs immunized to gonococcus. The details of these experiments will be given elsewhere. As has already been emphasized, there is no evidence that this serum is in any sense an antitoxin.

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THE LARYNX IN LOCOMOTOR ATAXIA.*

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About five years ago, at the suggestion of Dr. Charles W. Burr, I examined the larynges of patients with *tabes dorsalis* at the Philadelphia Home for Incurables. Later I examined all the cases of that disease under Dr. Burr's care at the Philadelphia General Hospital, and also the cases then under the care of Drs. Spiller and Weisenburg at that hospital, these gentlemen having kindly placed their patients at my disposal for the purpose. This report of the examination in these cases may be considered a negative one, for practically nothing of great interest was discovered, but it seems worth while to bring up the subject for discussion because, in the text-books and elsewhere, one is led to believe that laryngeal trouble is rather frequently found in locomotor ataxia.

Of the cases at the Home for Incurables examination was possible in four, and the results are given in detail.

CASE 1.—E., male, *tabes* for eleven years; no history of throat involvement. Arytenoids swollen and edematous. If there was any paralysis of vocal cords it was on the right side; left cord came past middle line and approximation of cords was good.

CASE 2.—W., female, married; *tabes* for twelve years. Ptosis of eyelids; no throat involvement; cords normal.

CASE 3.—L., male; *tabes* for eight years; no throat involvement; cords somewhat thickened.

CASE 4.—G., male; *tabes* for nine years; arytenoids thickened and swollen; cords normal. No history of throat trouble.

A summary of the cases at the Philadelphia General Hospital can be tabulated as follows:

Total cases examined	27
View of larynx imperfect in	7
Cases in which examination was satisfactory	20
Larynx normal in	6

In twelve cases the left cord was found hyperabducted during respiration, its movements restricted during phonation; the ventricular bands had lost their tonicity and were flabby. In two cases the right cord was thus affected but not the left.

Of the twenty cases two were women, one having the left cord in the hyperabducted position. In none of the twenty cases was there any evidence of loss of sensibility. All patients suffered from chronic nasopharyngitis of various kinds and degrees, and the condition of the larynx was what one might expect to find in the average individual of their age and class of life. No constant lesion was observed except the one noted above, namely, hyperabduction of the vocal cord, and that was present on the left side in 60 per cent. and on the right side in 10 per cent., making a total of 70 per cent.

I have been unable to find a tabetic case with laryngeal crisis, and neurologists of my acquaintance say that they have rarely seen cases of that kind. To show the trend of opinion on this subject I shall quote from some of the recent books and periodicals:

Touche¹ states that twelve out of forty cases studied by him had laryngeal crises. Of these twelve one only did not have visceral crises also. Ten had gastric crises, three had crises of diarrhea and three had rectal crises. No record is given of laryngeal examination in Touche's cases.

A case is cited² in which the onset of *tabes* in an actor was heralded by laryngeal crises induced by overuse of the voice, and this suggests that the crises of locomotor ataxia may arise in a point weakened by previous strain or disease.

Dorendorf³ reported the case of a man aged thirty-three, who suffered from bilateral posticus paralysis caused by *tabes dorsalis*. There was marked narrowing of the glottis with every inspiration. The condition persisted after tracheotomy, and was due to active contraction of the adductor muscles.

A case of bilateral abductor paralysis of the larynx in a tabetic was reported by Wishart.⁴ The paralysis came on slowly in the first years of the disease and persisted after tracheotomy.

Greene reported⁵ the results of examinations made in sixty cases of *tabes*. Out of the sixty cases examined nine (15 per cent.) presented laryngeal complications; six (10 per cent.) showed undoubted paralysis of one or both vocal cords; seven (12 per cent.) were affected with the laryngeal crises, three of these without evident paralysis of either cord, and one presented a jerky move-

1. Presse Med., August, 1899, lxi, 121.

2. Deutsche med. Wochschr., April 16, 1905, xxxi.

3. Berliner klin. Wochschr., Sept. 15, 1902.

4. Laryngoscope, October, 1902, 756.

5. Boston Med. and Surg. Jour., Jan. 25, 1906, 97.

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