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"GONOCOCCAL ANTITOXIN" IN THE TREATMENT OF GONORRHOEA

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In a preliminary report Anwyl-Davies (1937) described the results he had observed in a series of 157 cases of gonorrhoea in the male, treated with a serum prepared by Parke, Davis and Co., and described as a "specific antitoxin." The series included forty-two cases of acute uncomplicated gonorrhoea and 115 with complications, eighty-four of them acute, and his conclusions were: (a) that the results were distinctly encouraging; (b) that the "antitoxin" possessed specific therapeutic properties; (c) that clinical evidence suggested that both active and passive immunity were established; and (d) that the "antitoxin" seemed to offer considerable promise in the treatment of gonorrhoea.

The evidence supporting these conclusions was rather indefinite, as was pointed out by W. Lester (1937), but the claims made for the serum were so exceptional that we decided to try it. Our results in 129 male patients treated in these clinics agreed so completely in their lack of any evidence supporting the conclusions arrived at by Anwyl-Davies that we have combined them in one paper. These combined cases are shown in Table I.

TABLE I.—Combined Cases

Type of Case	St. Peter's	Whitechapel Clinic	St. Charles's	Totals
Uncomplicated :				
Acute ..	48	16	3	67
Chronic ..	—	—	—	—
Complicated :				
Acute ..	27	—	13	40
Chronic ..	22	—	—	22
Total ..	97	16	16	129

In this table, and also in the others, the term "uncomplicated" means with urethritis only, and "complicated" means with gonococcal infection of the urethral adnexa or other parts of the body. "Acute" means with infec-

tions of less than three months' duration at the time the patient came under our care, and "chronic" means with infections of more than three months' duration.

The serum used in our investigations was in two forms, described respectively as "unconcentrated antitoxin" and "concentrated antitoxin." According to the makers "unconcentrated antitoxin" is the original preparation made by a method practically identical with the Ferry procedure for the production and standardization of meningococcus antitoxin. "Concentrated antitoxin" is the original preparation after concentration by the Banzhaf method. This is said to remove excess of protein and leave the "antitoxin" in the pseudo-globulin fraction. Theoretically it is five times as potent as the unconcentrated preparation. In his report Anwyl-Davies describes results obtained with the use of both these preparations.

As indicated, the cases were treated in three series and the observations were made independently: those in St. Peter's Hospital, Whitechapel, which are presented first, by J. G.; those in the Whitechapel Clinic by E. T. B. and A. J. K.; and the last series, at St. Charles's Hospital, by A. H. H. At the end of the report we present a summary of our conclusions based on a combined study of all our results. We have not presented comparative findings in a series of controls, for reasons of space and because our results with this preparation have been so bad that the necessity for comparison does not arise.

St. Peter's Hospital Series

The results obtained from the use of the serum in ninety-seven cases at this hospital are shown in Table II. The ages ranged from 16 to 61 years, with an average of approximately 29. Those without complications were treated mostly as out-patients; all the complicated cases received in-patient treatment. All injections of the serum were given intramuscularly on consecutive days.

TABLE II.—Summary of Results from St. Peter's Hospital

Group	No. of Cases	Untoward Effects				Assessment of Results							
		Reactions		Complications		Excellent		Good		Fair		Bad	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Uncomplicated Acute ..	48	9	19	7	14	—	—	—	—	—	—	48	100
Complicated Acute ..	27	10	37	5	18	—	—	—	—	8	30	19	70
Complicated Chronic...	22	4	18	5	23	—	—	—	—	7	32	15	68
Total ..	97	23	24	17	18	—	—	—	—	15	16	82	84

The following is a detailed analysis of the cases summarized in Table II:

ACUTE UNCOMPLICATED GONORRHOEA

There were forty-eight cases in this group. Six were treated as in-patients and eight (19 per cent.) of the remainder had to be admitted to hospital later, either because of reactions which developed or because of the subsequent onset of complications (see below). The majority of cases came under observation within a few days of the appearance of the urethral discharge. Unconcentrated serum was given to forty-one patients and concentrated to the remaining seven. In forty-three cases the serum only was given at first, but in all of these it was necessary to continue with routine methods of urethral irrigations and alkalis by the mouth.

(a) *Unconcentrated Serum* (41 Cases).—This was given to forty out-patients and one in-patient. The dosage was 2, 3, 5, and 10 c.cm. on successive days in fourteen cases; and 10, 15, and 20 c.cm. in twenty-seven. In the group of fourteen patients two (14.2 per cent.) developed severe arthritis within a few days after completion of the course of injections and had to be admitted to hospital. In the group of twenty-seven patients one developed arthritis, one tenosynovitis, and two epididymitis (14.8 per cent.). The complication rate for the combined series was thus 14.6 per cent.

(b) *Concentrated Serum* (7 Cases).—This was used in the treatment of two out-patients and five in-patients. The amount given was 2, 3, and 5 c.cm. in two cases; six doses of 2 c.cm. in three cases; six of 1.5 c.cm. in one case; and 1, 1.5, 1.5, 2, 2, and 2 c.cm. in the remaining case. One patient (14.2 per cent.) developed epididymitis soon after completing the course of treatment.

Results.—The immediate favourable clinical, bacteriological, and serological results were negligible. No patient was cured in under four months. Of the forty-eight patients thirty-three subsequently attended the Whitechapel Clinic. Of these ten (21 per cent. of the total) were cured and twenty-two (46 per cent.) ceased to attend before cure. The criteria of cure were negative clinical examinations with repeated negative microscopical, cultural, and serological findings, and of the ten satisfying these requirements one did so at the fourth month, two at the fifth, three at the sixth, one at the eleventh, one at the fifteenth, one at the eighteenth, and one at the twenty-fourth. Of the twenty-two defaulters five had attended for one month, five for two months, one for three months, three for four months, two for five months, and six for from six to sixteen months. There are records of pathological tests for thirteen of these defaulters. In four cases some negative tests had been obtained at the time of default; in one case gonococci persisted in the urethral smear, and in eight the complement-fixation test was positive in the blood serum. One other patient is still attending at the Whitechapel Clinic after two years. One patient was transferred to another clinic after discharge from St. Peter's Hospital.

ACUTE COMPLICATED GONORRHOEA

In this group of twenty-seven cases complications had developed within three months of the onset of the disease. The actual time interval varied from four and a half to six weeks. Nineteen were treated with unconcentrated and eight with concentrated serum. The frequency and distribution of complications at the outset were as follows: epididymitis in twenty, acute prostatitis in three, and arthritic complications (including inflammation of soft tissues) in four.

(a) *Unconcentrated Serum* (19 Cases).—This was given in four doses, of 2, 3, 5, and 10 c.cm. to fifteen patients; in three doses, of 10, 10, and 20 c.cm. to one patient; in four doses, of 5, 10, 15, and 20 c.cm. to two patients; and in six doses of 10 c.cm. to one patient. A patient who had received a total of 50 c.cm. of serum developed epididymitis in addition to his original complication. Another had 2, 3, and 10 c.cm. on consecutive days as an out-patient, and was admitted to hospital when he developed arthritis of one wrist and tenosynovitis of the extensor tendons of the same hand. The added-complication rate was thus 10 per cent.

(b) *Concentrated Serum* (8 Cases).—With each dose a subcutaneous injection of 3 minims of 1 in 1,000 adrenaline hydrochloride was given on the supposition that it might prevent serum reactions. The dosages were: seven injections of 2 c.cm. to five patients; six of 2 c.cm. to one patient; six of 1.5 c.cm. to one patient; and six of 1 c.cm. followed by eight of 0.5 c.cm. to one patient. One patient was admitted for epididymitis occurring on the side opposite to that already treated. Another developed epididymitis and vesiculitis after six injections each of 2 c.cm. of serum. A third developed arthritis of the knees, tenosynovitis of one foot, and acute prostatitis after injections totalling 10 c.cm. of serum. The added-complication rate was thus 37.5 per cent.

Results.—The immediate clinical results indicated that the unconcentrated serum exerted an adverse effect in sixteen cases and did not impede recovery in three. The concentrated preparation appeared to have an adverse effect in four and to exert no effect in the same number. In no instance did any complication clear up more quickly after serum injections than by routine methods. In every case injections of serum had to be supplemented later by other methods of treatment.

The following bacteriological and serological results refer only to the period of stay in hospital, which averaged three weeks for this group. In seven patients treated with unconcentrated serum the smears remained positive in four and became negative in three. In six patients treated with concentrated serum the smears remained positive in three. For the remaining cases bacteriological records are not available. In the nineteen patients treated with unconcentrated serum the complement-fixation test remained positive in fourteen, became negative in three, and was unreadable in two. In all of the eight patients treated with concentrated serum the complement-fixation test remained positive. Of the twenty-seven patients in this series twenty-three have been followed up. Five of these are still attending the Whitechapel Clinic from twenty-one to twenty-four months after completing the course of serum injections. Six patients were cured (22 per cent.): two after six months, one after eight months, two after nine months, and one after eighteen months. There were twelve defaulters (44 per cent.): two within the first month, one at the second, one at the fourth, two at the sixth, two at the ninth, one at the fourteenth, one at the fifteenth, one at the eighteenth, and one at the nineteenth.

CHRONIC COMPLICATED GONORRHOEA

This group of twenty-two cases includes those patients with recent urethritis who had had one or more previous attacks of gonorrhoea and in whom relapse was suspected.

(a) *Unconcentrated Serum* (16 Cases).—Five patients were treated in the first attack and eleven in the second or later attacks. In the former group the time since the onset varied

from four months to two years—average, twenty months. In the latter group the time since the onset varied from three days to six weeks—average, four weeks. The chief complications present on admission were arthritis in ten and epididymitis in six cases. Some of these patients had other complications, such as iritis and keratoderma blennorrhagica. The dosage was 2, 3, 5, and 10 c.cm. in twelve cases; four of 10 c.cm. in one case; 10, 15, and 20 c.cm. in one case; 5, 10, 15, and 20 c.cm. in one case; 1, 2, 5, 10, 20, and 20 c.cm. in one case; 1, 10, 10, 20, 10, 10, and 10 c.cm. in one case; and ten of 10 c.cm. in one case. Two patients received a second series of injections within a few days of the end of the first course. Added complications totalled five (31.2 per cent.), and consisted of iritis in one case, arthritis in one, epididymitis in two, and fibrositis in one.

(b) *Concentrated Serum* (6 Cases).—Four patients had had previous attacks of gonorrhoea. The chief complications present on admission were: arthritis in three cases, epididymitis in two, and iritis in one. The dosage was as follows: seven of 2 c.cm. in one case; six of 2 c.cm. in four cases; and 1, 2, and 3 c.cm. in one case.

The average period of in-patient stay for patients treated with unconcentrated serum was 40.5 days; with concentrated serum it was 40 days for patients with arthritis and 25.7 days for those with other complications. Again treatment with serum had to be supplemented later by ordinary methods.

Results.—The immediate clinical results indicated that unconcentrated serum had some adverse effect in eleven instances and did not retard recovery in five. The concentrated serum affected four cases adversely and produced no effect in two (both cases of epididymitis). In no instance was a patient discharged from hospital in less than nine days. In six of the ten patients with arthritis the joints had fully recovered on discharge from hospital. In four there was some limitation of movement. The following bacteriological and serological results refer only to the period of in-patient stay. In thirteen out of sixteen patients treated with unconcentrated serum the smears remained positive in nine and became negative in four. Of six patients treated with concentrated serum two showed gonococci in smears on discharge to out-patient treatment. The complement-fixation test in sixteen patients treated with unconcentrated serum remained positive in ten and became negative in five, while in the remaining case the serum was anti-complementary. In the patients treated with concentrated serum the complement-fixation test remained positive in four, became negative in one, and in one no test was carried out. In this series of twenty-two patients sixteen were traced after discharge. Of these, seven (31.8 per cent.) remain uncured after an observation period varying from eighteen months to two years. Nine patients defaulted (41.9 per cent.): three immediately, one at the second month, one at the third, one at the fourth, one at the sixth, one at the sixteenth, and one at the seventeenth. Thus in two years no instance of cure was recorded in this group.

REACTIONS

The majority of the patients treated with injections of serum complained of a variable amount of pain and stiffness at the sites of injection. Twenty-three of the total of ninety-seven had general reactions of one kind or another—namely, fifteen of seventy-six patients treated with unconcentrated and eight of twenty-one treated with concentrated serum. Ten of these suffered from pains in the head and at the injection site, combined with shivering, high fever, pain in the lower limbs, and malaise; the thirteen others developed urticarial rashes combined with a variable degree of headache, malaise, and pyrexia. Such reactions developed within a few minutes or hours of injections in some cases, but in others they were delayed for several days. Of the total of twenty-three patients who had reactions nine were under treatment for uncomplicated urethritis, ten for acute complications of

the disease, and four for chronic complications. The injection of adrenaline solution was not effective in controlling unpleasant symptoms in patients who had previously experienced reactions.

Whitechapel Clinic Series

In order to extend our observations with this preparation supplies of "unconcentrated antitoxin" were purchased through the ordinary commercial channels. Specimens of the serum were submitted to a series of complement-fixation tests with a gonococcal antigen in order to obtain evidence of the presence of gonococcal antibodies. These tests proved to be unsatisfactory owing to the anti-complementary nature of the serum, which was possibly due to the preservatives contained in the commercial product. It is understood that such tests do not form part of the manufacturers' method of standardizing this preparation. At the time these supplies were issued the daily dosage recommended was 3 to 5 c.cm. of the serum, given intramuscularly. It was hoped that, with the aid of this treatment, in favourable cases discharges would subside and gonococci disappear within the space of fourteen days. The serum reactions which resulted from this dosage were so severe that the medical representative of the manufacturers was consulted, and it was recommended that the initial dosage should be 0.5 to 1 c.cm., and that once the first reaction had occurred adrenaline solution should be injected half an hour before serum was given. This advice was followed, and accounts for the considerable variation in the dosage which these patients received (Table III).

The treatment was applied to sixteen male patients with acute uncomplicated gonorrhoea. These were unselected cases except in so far as it was necessary to stipulate the conditions of regular attendance and accessibility for close observation. All were treated as out-patients, and the average age was 25 years, the oldest being 37 and the youngest 18. Treatment was instituted in late June and early July of 1937, and most of these patients have remained under observation or treatment up to the time of writing in early December.

Observation was maintained by daily examination of the patients under treatment. Each day a record was made of the presence or absence of urethral discharge, of microscopical findings in the discharge, of the condition of the urine, of effects of the serum treatment, and of complications of the disease. It was planned to administer serum during the first fifteen days of treatment, withholding urethral irrigations during this time but giving irrigations from the end of the fifteenth day onwards, unless the condition of the patient warranted the cessation of all treatment. In some cases it was necessary to discontinue the injections before the end of the fifteen-day period owing to severe reactions, but in spite of this irrigations were withheld until the fifteen days had elapsed in all but one case. In others injections were continued beyond the fifteen-day limit in the hope of producing a delayed effect, and in these cases irrigations were withheld until the course of injections was completed.

All sixteen patients finally required irrigation treatment and received anterior and posterior urethral irrigation with 1 in 8,000 potassium permanganate solution once or twice daily according to the ability of the individual patient to attend. All the patients received the general treatment and advice which are routine in this clinic for those suffering from gonococcal infections, but no alkalis or other medicaments were given by mouth.

The dosage of serum used in each case is shown in Table III, the figures in parentheses denoting the injections which were followed by reactions and the letter *a* indicating the administration of adrenaline solution. Subcutaneous injections of 1 to 5 minims of adrenaline hydrochloride (1 in 1,000) solution were used according to the size of dose of serum; and in the large majority the doses of adrenaline were given half an hour before the serum was injected.

crippling nature, sufficient to cause interference with or cessation of the patient's work. The pain was accompanied by pronounced tenderness, and in seven cases there was widespread erythema of the skin of the affected buttock. The remaining six complained of varying degrees of stiffness and tenderness at the injection site.

General Effects.—The frequency of these is shown in Table III. Reactions which could be classed as severe occurred in thirteen patients, and in two they were moderately severe. The remaining patient had no symptoms attributable to the

TABLE III.—*Dosage given in the Whitechapel Clinic Series (c.cm. of Serum).*

Case	Days of Treatment																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	22	23	26	27	28	29	31				
1	3	3	3	3		(3)		(3)	1a	1a	(1)a	1a	1a																	
2	3	3	3		3	(3)		(1)a	1a	1a	1a	1a	2a	3a	3a	3a	3	3	3											
3	3	(3)	1a	1a	(2)a																									
4	3	3	3	4	(5)	1	1	1	1	(1)																				
5	3	3	3	4	4	(5)	(5)	(5)	(5)	(5)		1a	1a	1a	1a															
6	3	3	3	4	4	(3)	3	1	(1)	1a	1a		1a	1a	1a															
7	3	3	3	3	3	(3)		(1)a			($\frac{1}{2}$)a	$\frac{1}{2}$ a		$\frac{1}{2}$ a	1a	1a	1a		1a											
8	3	3	4	4	(5)	(3)	(1)	1	$\frac{1}{2}$	(1)																				
9	3	3	3	3		(3)	3	(3)	(1)a	1a	1a	1a	1a	1a	1a															
10	3	3	3	4	3	(3)	1a	1a	(1)a																					
11	$\frac{1}{2}$	$\frac{1}{2}$	1	1	1	1	1	1			1	1										1a	1a	1a	1a	1a				
12	1	1	1	1	(1)	$\frac{1}{2}$ a	$\frac{1}{2}$ a	$\frac{1}{2}$ a	$\frac{1}{2}$ a	($\frac{1}{2}$)a	$\frac{1}{2}$ a																			
13	1	1	1	1	1	(1)			($\frac{1}{2}$)a		($\frac{1}{2}$)a																			
14	1	1	1	1	1		(1)	($\frac{1}{2}$)a			($\frac{1}{2}$)a																			
15	1	1	1	1	1	(1)		$\frac{1}{2}$ a	$\frac{1}{2}$ a	($\frac{1}{2}$)a	$\frac{1}{2}$ a	($\frac{1}{2}$)a	$\frac{1}{2}$ a	$\frac{1}{2}$ a																
16	1	1	1	1	1	(1)	$\frac{1}{2}$ a	($\frac{1}{2}$)a		$\frac{1}{2}$ a	$\frac{1}{2}$ a		$\frac{1}{2}$ a	$\frac{1}{2}$ a	$\frac{1}{2}$ a				$\frac{1}{2}$ a	$\frac{1}{2}$ a	$\frac{1}{2}$ a									

a = Administration of adrenaline.

Figures in parentheses = Dose followed by reaction.

TABLE IV.—*Whitechapel Clinic Series: Clinical and Microscopical Findings*

Case	Persistence of			Subsequent History	Complications
	Urethral Discharge	Gonococci	Haziness or Pus Threads (Urine)		
1	12 weeks	11 weeks	14 weeks	Defaulted after 15 weeks, during tests for latency. Then successfully treated with sulphanilamide. Treatment for urethritis continues. Five relapses with gonococci. Treatment for urethritis continues.	Gonococcal arthritis of right knee-joint. Infection of right Tyson's gland. Multiple gonococcal arthritis and rheumatism.
2	18 $\frac{1}{2}$ "	18 $\frac{1}{2}$ "	18 $\frac{1}{2}$ "		
3	5 months, and continues	5 months, and continues	5 months, and continues		
4	9 weeks	9 weeks	20 weeks, and continues		
5	18 "	18 "	18 weeks	Treatment for arthritis and chronic prostatitis continues.	Gonococcal arthritis of right knee-joint. Infection of right Tyson's gland. Multiple gonococcal arthritis and rheumatism.
6	5 months, and continues	8 "	16 "	Under treatment for chronic gonococcal prostatitis and rheumatism.	
7	8 weeks	7 "	8 "	Treatment for chronic prostatitis continues.	
8	7 "	11 days, then defaulted temporarily	7 "	Self-treatment without observation 11th to 29th day. Treatment for chronic prostatitis continues.	
9	11 "	11 weeks	11 "	Defaulted after 11 weeks. Unimproved.	Left epididymitis.
10	10 "	10 "	10 weeks and continues	Treatment for urethritis continues.	
11	4 $\frac{1}{2}$ "	4 $\frac{1}{2}$ weeks, then defaulted	4 $\frac{1}{2}$ weeks	Defaulted after 4 $\frac{1}{2}$ weeks. Unimproved.	
12	11 "	11 weeks, then defaulted	11 "	Defaulted at 11 weeks. Unimproved.	
13	9 "	4 weeks	14 "	Defaulted at stage of clinical cure. Had evidence of chronic prostatitis.	Multiple gonococcal arthritis and rheumatism.
14	4 weeks, then defaulted temporarily	3 weeks, then defaulted temporarily	4 weeks, then defaulted for 6 weeks	Treatment for chronic prostatitis continues.	
15	7 weeks	7 weeks, then to hospital	7 weeks	Admitted to hospital at 7 weeks. Later returned with chronic prostatitis.	
16	8 "	8 weeks	8 "	Defaulted after 8 weeks. Unimproved.	

REACTIONS

Only one patient remained free from symptoms or signs attributable to the injections of serum; the other fifteen suffered from both local and general reactions. In most cases these occurred after the fifth to the seventh injection, and thereafter it was difficult or impossible to control them.

Local Effects.—Nine complained of pain at the site of injection in the buttock, and this pain was often of a severe and

injections. The severe effects included fever varying from 100.2° F. to 103.8° F., and this occurred in all thirteen patients. Almost all complained of severe headaches, malaise, "feverishness," and sweating. Skin eruptions appeared in eight patients, of whom three had generalized urticaria, three had a purpuric rash on the skin of the lower limbs, and two had papular erythematous rashes on the skin round the ankles and lower legs. Two had herpes of the lips. Generalized arthralgia occurred in nine cases, and in three there were joint effusions. Many of the patients complained of generalized muscle pains.

It will be clear from this description that at any rate thirteen of these sixteen patients were really ill as the result of the treatment, and it must be regarded as a considerable credit to the resolution of this group of men that only three of them refused further injections in consequence of these symptoms. The two patients who suffered reactions of moderate severity had pyrexia, malaise, and muscle pains in less marked degree.

•Injections of adrenaline did not appear to counteract or prevent reactions, but on the whole the effects were less persistent and less severe with smaller dosage of serum.

RESULTS

An attempt was made to assess the results of this treatment on the basis of the persistence of gonococci and urethral discharge, the spread of infection as judged by clinical findings, the duration of evidence of infection in specimens of urine, the effect on antibody content of the blood as measured by the complement-fixation test for gonorrhoea, the development of complications of the infection, and the application of tests for latency at the stage of clinical cure. At the beginning of treatment four patients had shown evidence that the infection had already extended to the posterior urethra. In the remaining twelve the signs suggested infection limited to the anterior urethra. All these developed signs of posterior urethritis while under treatment. Table IV summarizes the clinical and microscopical findings.

In none of these patients did the smears become negative or the discharge cease as the result of serum treatment alone. All required urethral irrigations. Six patients suffered a relapse of urethral discharge when the irrigations were discontinued after apparent clinical cure. Microscopical examination of these discharges showed gonococci in five cases. In four the symptoms and signs finally disappeared with urethral irrigations. In one patient (Case 2) it was necessary to use large doses of sulphanilamide after the gonococci had persisted for eighteen and a half weeks, a measure which resulted in disappearance of gonococci and urethral discharge within three days. The other patient (Case 3) has relapsed five times and still has gonococci after five months' treatment. In this case also it is proposed to use sulphanilamide.

As regards the effects on serum tests the most striking feature was the frequency with which specimens of sera were reported as "anti-complementary"—an unusual occurrence in the routine of clinic practice. Twenty-six such reports were received on specimens of blood from eight patients in this series, but the significance of this finding is not clear. The sera of three patients gave strongly positive (+ + or + ±) reactions to the complement-fixation test after periods ranging from three to five weeks. Four others showed a positive (+) test in periods of from one week to four weeks. In five a weakly positive (±) reaction was recorded in the first few weeks. In four the tests remained negative throughout.

Complications of the Infection (5 Cases).—Four patients developed gonorrhoeal arthritis and rheumatism whilst under irrigation treatment subsequent to serum injections. One developed epididymitis on the left side, and one of the patients with arthritis had at the same time an acute inflammatory condition of Tyson's gland on the right side. Thus 31 per cent. of these patients developed acute complications of gonorrhoea.

END-RESULTS

The end-results are shown in Table IV, and may be summarized as follows. Three patients who have been under treatment from eighteen to twenty weeks have signs of persistent urethritis and so remain under treatment. One other patient proved entirely refractory to treatment

for eighteen and a half weeks until large doses of sulphanilamide were used, and has by this means reached the stage of clinical cure. Five defaulted after periods varying from four and a half to fourteen weeks; of these, four had persistent urethritis and one had reached the stage of clinical cure after fourteen weeks' treatment. One patient was admitted to hospital with gonorrhoeal arthritis and persistent urethritis after seven weeks of treatment and returned later with chronic prostatitis. The remaining five patients have reached the stage of clinical cure after treatment over a period of eight to eighteen weeks and are being submitted to tests of latency, which consist of complete clinical examination, including urethroscopy, prostatic smears, cultures of vesiculo-prostatic fluid, and complement-fixation tests of the blood serum. Up to the present undoubted evidence of latent gonococcal infection has been found in four of these. The results may be conveniently set out as in Table V:

TABLE V.—*Summary of Results in the Uncomplicated Acute Group of the Whitechapel Clinic Series*

No. of Cases	Untoward Effects				Assessment of Results							
	Re-actions		Complications		Excellent		Good		Fair		Bad	
	No.	%	No.	%								
16	15	94	5	31	—	—	—	—	—	—	16	100

St. Charles's Hospital Series

In this series injections of "unconcentrated gonococcus antitoxin" were administered to sixteen male patients, the average age of whom was 24 years, the maximum being 30 and the minimum 19. Fifteen were in-patients at St. Charles's Hospital, and were treated during the period July 6 to October 19, 1937. One, who received his injections at the Dreadnought Hospital, was subsequently transferred to St. Peter's Hospital, Covent Garden. We are indebted to Mr. P. P. Cole for details of this patient's previous treatment. None of the patients had previously had injections of serum. There were three cases of acute uncomplicated gonorrhoea, eight cases of acute gonococcal epididymitis (in one of which the symptoms of acute prostatitis were also present), and five cases of acute gonococcal arthritis. Smears of the urethral discharge were examined daily for leucocytes and organisms, and a record was kept of the condition of the first morning specimen of urine. The blood sera were tested at weekly intervals by the Wassermann and Kahn tests for syphilis and by the complement-fixation test for gonorrhoea.

The dosage of the serum is shown in Table VI. In some of the cases injections of a solution of adrenaline hydrochloride (1 in 1,000) were given with the serum; in others they were given fifteen minutes before or fifteen minutes after. The dosage of adrenaline hydrochloride corresponded in minims with the number of cubic centimetres of the serum. The time at which the adrenaline was given did not appear to influence the local or general reactions. No irrigation treatment was given during the course of injections, but the patients with acute arthritis had 5 per cent. iodine solution applied to the joints affected, and radiant heat was administered twice each day. Irrigations were withheld until at least four days had elapsed after cessation of serum treatment.

REACTIONS

Fourteen of the patients had severe local and general reactions and two developed only slight local reactions; seven had generalized urticarial eruptions. Most of these

occurred after the sixth injection, regardless of the dosage. One appeared after the third and another was delayed until fourteen days after the last injection. In thirteen patients there was severe pain, swelling, and tenderness in the buttocks; in three of them a local erythematous blush was observed, and in these areas there were numerous purpuric spots which took several days to disappear. One other patient showed purpuric lesions in both antecubital fossae. It seemed as if the serum

TABLE VI.—*Dosage of Serum given in the St. Charles's Hospital Series*

Case	Days when Injections were given and Dosage* of "Gonococcal Antitoxin" in c.cm.														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	3	3	3	3	3	3	—	3	3	—	3	3	3	3	3
2	3	3	3	3	—	3	—	3	3	—	3	3	3	3	3
3	3	3	3	3	3	3	—	3	3	—	3	3	3	3	3
4	1	1	1	1	1	1	1	1	1	—	—	—	—	—	—
5	5	5	—	5	5	5	5	5	5	5	—	—	—	—	—
6	1	1	1	1	1	—	—	—	—	—	—	—	—	—	—
7	1	1	1	1	1	1	1	—	—	—	—	—	—	—	—
8	2	2	2	2	2	2	2	2	2	—	—	—	—	—	—
9	2	2	2	2	2	2	2	2	2	—	—	—	—	—	—
10	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—
11	2	2	2	2	2	2	2	2	2	2	—	—	—	—	—
12	2	2	2	2	2	2	—	2	—	—	—	—	—	—	—
13	2	2	2	2	2	2	2	2	2	2	—	—	—	—	—
14	2	2	2	2	2	2	2	2	2	2	—	—	—	—	—
15	2	2	2	2	2	2	2	2	2	2	—	—	—	—	—
16	3	3	3	3	3	3	3	3	3	3	—	—	—	—	—

* At the outset of the investigation an initial dose of 3 to 5 c.cm. was recommended by the manufacturers. Severe reactions resulted, and it was then advised that the dosage should be reduced.

contained a substance which damaged the vessel walls and increased their permeability. From one patient (Case 3) a fading purpuric lesion was excised. On microscopical examination no appreciable change in the epidermis was found. The superficial blood vessels in the corium were slightly dilated and had a lymphatic cell infiltration around them, and here and there were a few eosinophils and some extravasated corpuscles. In fact, this was a typical section of skin purpura. An itchy papular eruption on the forearms was seen in two patients; and one of them, who also had a generalized giant urticaria, subsequently developed a nummular eczema.

In many of the patients the constitutional disturbance was pronounced. The temperature rose as high as 103° F. It was surprising that the fever produced by the injections did not have the usual beneficial effect on the course of the disease, as the results obtained will show. One patient had a severe asthmatic attack on two occasions following injections of serum, and each time there was almost instantaneous relief after a subcutaneous injection of 3 minims of adrenaline hydrochloride. There was no history of previous asthmatic attacks.

Two patients (Cases 7 and 9) complained of nausea during the treatment, and one (Case 9) vomited at night after the sixth injection and each night subsequently. This continued for three nights after his last, or ninth, injection.

RESULTS

The microscopical findings in the urethral discharges gave no evidence that benefit had been derived from the injections; and at the end of the period of treatment with serum gonococci were found in smears of the urethral discharges from all the patients treated. One patient (Case 7), who was admitted with arthritis of a week's

duration, had received a course of urethral irrigations elsewhere. No gonococci were found in the urethral smears or in the urine at the first examination, but after four injections of serum large numbers of gonococci appeared in the daily urethral smears until irrigation treatment was recommenced.

The clinical results were all unsatisfactory. Urethral discharges in the majority of cases became more profuse during treatment. There was no indication that the condition of the joints of those suffering from acute arthritis was improved, and in three patients the joint pains were increased for several hours after each dose of serum. The injections seemed to have no influence in preventing other joints from becoming infected, and in four out of the five patients with this complication further joints became involved. One patient (Case 5) who was suffering from acute arthritis of the right knee with a metastatic gonococcal conjunctivitis developed, after three injections each of 5 c.cm. of serum, acute infection of the left temporo-mandibular joint, right elbow, left wrist, and the proximal interphalangeal joints of the fourth and fifth fingers of the right hand. Another patient (Case 7) was suffering from acute arthritis of the metatarsophalangeal joint and the first interphalangeal joint of the left big toe; after three injections of 1 c.cm. of serum he also developed acute arthritis of the right knee and the right ankle. Another (Case 9), with acute arthritis of the interphalangeal and metatarsophalangeal joints of the left foot and the right midtarsal joint, developed acute arthritis of the right knee and a bursitis over the right ischial tuberosity after three injections of the serum, each of 3 c.cm. A fourth (Case 13), who was suffering from acute arthritis of the right hip and right midtarsal joints, also developed acute arthritis of the left knee after he had had three injections, each of 2 c.cm. of serum. One patient (Case 3), admitted with acute prostatitis and left epididymitis, developed arthritis of both knees after the ninth injection of 3 c.cm. of serum.

It will be noted that extension of the infection to other joints during serum treatment occurred in 80 per cent. of the patients suffering from arthritis. On reference to the case records of eighty other patients with gonococcal arthritis treated by orthodox methods at St. Charles's Hospital and elsewhere, it was found that in only 11.25 per cent. had the metastatic involvement extended to other joints.

LABORATORY TESTS

Study of the literature has revealed no references to the possible effects of injections of serum on Wassermann and Kahn reactions in the blood serum. As already stated, these tests were carried out at weekly intervals in fifteen cases, and in nine of the patients one or other test became positive during the period of administration of serum or shortly afterwards. In eight of these nine patients there was no correlation between the positive findings in Wassermann and Kahn tests. In all but one case both tests had become negative without antisyphilitic treatment before the end of the observation period. In the other case the Kahn reaction was positive at the end of this period, but the Wassermann reaction remained completely negative.

When the patients first came under observation the gonococcal complement-fixation test was positive or weakly positive in seven and completely negative in eight cases. Of the latter group, six subsequently developed positive reactions. The serum appeared to exercise no influence on the strength of the complement-fixation test in the seven who originally had positive reactions. The results of these tests were often reported as "anti-complementary."

One patient (Case 10) refused further treatment after two injections and demanded his discharge from hospital.

TABLE VII.—*St. Charles's Hospital Series: Findings during the Periods of Treatment and Observation*

Case	Period of Observation	Type of Case	Urine : Persistence of Haziness or Pus Threads	Subsequent History and Progress	Complications arising during Treatment
1	9 weeks	Acute right epididymitis	6½ weeks	Chronic urethritis. Defaulted in 9 weeks	
2	4 "	Acute epididymitis	4 "	Refused further treatment	
3	8 "	Acute left epididymitis and prostatitis	8 "	Transferred unimproved. Readmitted in 3 months with epididymitis	Gonococcal arthritis both knees
4	3½ "	Acute left epididymitis	3½ "	Transferred : unimproved	
5	14 "	Acute mono-articular arthritis with metastatic conjunctivitis	12 "	Finally improved with sulphanilamide and irrigations	Mono-articular arthritis became polyarticular
6	5 days	Acute uncomplicated urethritis	5 days	Refused further treatment	
7	7 weeks	Multiple acute arthritis	4½ weeks	Improved with sulphanilamide and irrigations	Further joints became involved
8	5 "	Acute right epididymitis	5 "	Improved, but relapsed, with gonococci	
9	6½ "	Multiple acute arthritis	6 "	Improved with irrigations and sulphanilamide, then defaulted	Further joints became involved
10	3 days	Acute right epididymitis	3 days	Refused further treatment	
11	18 "	Acute left epididymitis	18 "	Transferred : some improvement	
12	22 "	" " "	22 "	Transferred : unimproved	
13	6 weeks	Acute polyarticular gonococcal arthritis	3 weeks	Improved with sulphanilamide and irrigations	Further joints became involved
14	9 "	Acute polyarticular gonococcal arthritis	8 "	Finally improved with sulphanilamide and irrigations	
15	7½ "	Acute uncomplicated urethritis	7½ "	Transferred : unimproved	Acute prostatitis
16	15 "	" " "	15 "	Finally cured with sulphanilamide	

Two others refused to continue with this form of treatment after five and seven injections respectively. Table VII indicates the findings in this series of patients during the periods of treatment and observation.

The assessment of results has been made with due regard to the effects observed during and immediately after the administration of the serum and also to the subsequent clinical course of the disease, on which the natural powers of immunity and the irrigation treatment used in all these cases must be held to have exerted considerable effect. Seven of the patients received sulphanilamide by mouth in addition to urethral irrigations before the infective process finally subsided. The results of the sixteen cases are summarized in Table VIII.

TABLE VIII.—*Summary of Results in the St. Charles's Hospital Series*

Group	No. of Cases	Untoward Effects				Assessment of Results*							
		Reactions		Complications		Excellent		Good		Fair		Bad	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Uncomplicated													
Acute ..	3	3	100	1	33	—	—	—	—	—	—	2	66
Complicated													
Acute ..	13	13	100	5	38	—	—	—	—	1	8	11	85
Total ..	16	16	100	6	37	—	—	—	—	1	8	13	92

* The percentages given in respect of assessment of results are calculated upon the fourteen patients out of the sixteen in whom an assessment was made.

Summary of the Combined Series

The results obtained in the combined series of 129 cases treated with "gonococcal antitoxin" at the three clinics are set out in Table IX.

TABLE IX.—*Results in the Combined Series*

Series	No. of Cases	Untoward Effects		Assessment of Results			
		Reactions	Complications	Excellent	Good	Fair	Bad
St. Peter's ..	97	23	17	—	—	15	82
Whitechapel ..	16	15	5	—	—	—	16
St. Charles's ..	16	16	6	—	—	1	13
Total ..	129	54(41%)	28(21%)	—	—	16(13%)	111(87%)

The contrast between these combined results and those reported by Anwyl-Davies will be clear from comparison between Table IX and Table X, in which his results are summarized.

TABLE X.—*Percentages of Results Given in Preliminary Report (Anwyl-Davies, 1937)*

Excellent	Good	Fair	Bad
49.6	26.9	14.8	5.9

In a personal communication Dr. V. E. Lloyd, director of the venereal disease clinic at Guy's Hospital, states that serum was given to three male patients, but the reactions were in every case so severe that it was not considered justifiable to adopt this method of therapy with any further patients.

The main facts which emerge from our combined experience are these:

(a) With this "antitoxin" a disquietingly high proportion of patients developed reactions so severe as to cause interference with or absence from work.

(b) An abnormally high percentage of out-patients had to be admitted to hospital during and subsequent to serum treatment on account of reactions and complications.

(c) The serum not only does not prevent complications of the infection but it appears to render patients more prone to them.

(d) The administration of this serum to patients suffering from metastatic lesions appeared to encourage rather than to prevent extension to other sites.

(e) Favourable results were not obtained by serum alone, but only after the subsequent adoption of routine methods. Even then good results were delayed beyond the usual period in which they are obtained in patients treated without serum. We take this to indicate that the serum reduces or temporarily destroys the patient's immunity. This is the probable explanation of the high complication rate.

(f) The cases which, after the cessation of serum therapy, responded most favourably were those treated with sulphanilamide. But here, again, that agent did not act any more rapidly than it does in patients treated without serum.

(g) Certain anomalous results in respect of the Wassermann and Kahn tests occurred in non-syphilitic patients during the serum therapy. This finding is of manifest importance to those who use this serum in the treatment of gonorrhoea.

(h) The results obtained in these series were most unsatisfactory and were at complete variance with those reported in the preliminary account of the use of this preparation.

Conclusions

1. The serum described as "gonococcal antitoxin" appears to have no specific anti-gonococcal effect.

2. It appears to delay the development of the active immunity essential to recovery from gonorrhoea without substituting any compensatory passive immunity.

3. Its use in gonorrhoea is inadvisable on account of its lack of therapeutic value, its serious side-effects, its frequent interference with recovery, and possibly also the risk of its rendering patients liable to suffer from serious allergic reactions in the event of their requiring at some future date treatment with antitoxic sera for other bacterial infections.

[In a communication published after this paper was written Anwyl-Davies (*St. Thomas's Hospital Reports*, 1937, 2, 67) states that since his first report appeared many additional patients have been treated with an improved unconcentrated antitoxin. The precise number of patients is not stated, but the results claimed are: "excellent" and "good" together, 78 per cent.; "fair," 18 per cent.; "bad," 4 per cent.; with no clinical relapses to date.]

The London County Council accepts no responsibility for the opinions or conclusions expressed in this article.

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A HUMAN INFECTION WITH ACTINOMYCES CAPRAE

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The subject from whom this organism was isolated was one of two cases (Case I) of acholuric jaundice in a brother and sister. The following are the clinical histories.

Case I

A girl aged 14 was admitted to hospital on May 22, 1936, with a diagnosis of acholuric jaundice and splenomegaly. Her father was alive and well, with no history of jaundice and no evidence of jaundice or splenomegaly when he was examined on June 6, 1936. Her mother was healthy and active and without jaundice. One brother (Case II) had jaundice and splenomegaly. Four other children were alive and well.

Clinical History.—The patient was healthy at birth, but developed jaundice, which persisted. She had measles when a small child, and while in hospital in 1930 she contracted diphtheria. She was sent to the fever hospital and recovered without complication. The patient suffered from attacks of abdominal pain, mainly on the left side, associated with vomiting and a cold in the head. These attacks occurred every two or three months. The yellow colour increased with the attacks of vomiting. The motions had been normal in colour and the urine had not been dark.

Examination.—The patient was seen to have an adenoid facies and a marked icteric tinge of the skin and conjunctivae. There were petechial haemorrhages on the arms and trunk. Her weight was 74 lb. (the average for 11½ years). The right tonsil was larger than the left, and her teeth were normal. No abnormality was found in the heart and lungs. The spleen was greatly enlarged, and extended to one inch below and two inches to the right of the umbilicus. It was firm and not tender. The liver was slightly enlarged. There were no enlarged lymph glands. The urine was dark; bile was not present, but the test for urobilin was positive, and albumin was found. The deposit showed numerous cellular casts but no organisms. A blood count showed: red cells, 2,280,000 per c.mm.; haemoglobin, 46 per cent.; colour index, 1.0; white cells, 7,200 per c.mm. Differential count: polymorphs, 64 per cent.; lymphocytes, 22 per cent.; mononuclears, 6 per cent.; eosinophils, 8 per cent. All the red corpuscles were small, and two nucleated red cells were seen. There was some anisocytosis, poikilocytosis, and punctate basophilia, and platelets were present. The van den Bergh reaction (indirect) was positive. The icteric index was 55, the bleeding time two and a half minutes, and the coagulation time eight minutes. In the test for fragility haemolysis began at 0.66 and was complete at 0.54 per cent. (a normal control began at 0.32 and was complete at 0.28 per cent.). The sigma reaction was negative. Blood group, IV. An x-ray report on the hands showed no signs of rickets, but there was slight osteoporosis of the metacarpals. The patient was kept under observation in hospital for a month and was given large doses of potassium iodide, but no change occurred in the size of the spleen.

Operation.—This was performed by one of us (R. H. R.-I.) under gas-and-oxygen anaesthesia (Dr. Duigan). The spleen was exposed by a V-shaped incision. The head of the pancreas was found to be closely adherent to the pedicle of the spleen. There were some adhesions, which were ligatured, between the spleen and the stomach and kidney. The pedicle was carefully divided and the spleen removed without any excess of bleeding. The wound was closed with silk-worm-gut sutures to the skin surface.

Progress.—The jaundice disappeared within a week and recovery was uneventful. The patient was discharged to a convalescent home on July 27, 1936. In October, 1937, she had grown and put on weight, and was more normal in appearance, without jaundice, though the tonsils were very large. A blood count showed: red cells, 4,990,000 per c.mm.; haemoglobin, 90 per cent.; colour index, 0.9; white cells, 17,000; reticulocytes, 0.07 per cent. The differential percentages were: eosinophils, 4.5; metamyelocytes, 1.5; neutrophils, 55.5; large lymphocytes, 2; small lymphocytes, 35.5; monocytes, 2.5. In the film there was slight anisocytosis, and most of the red corpuscles appeared smaller than normal. Poikilocytosis was slight, and no polychromasia, punctate basophilia, or nucleated forms were present. The fragility began at 0.4 per cent. and was complete at 0.32 per cent.—less than before operation and only slightly above a normal control.

Case II

A boy aged 7, brother of Case I, was admitted to hospital on May 22, 1936, with a diagnosis of acholuric jaundice and splenomegaly. He had been a full-time normal baby, weighing 8 lb., and was breast-fed. Jaundice persisted from birth, and he also had measles when 4 years old. He was always tired. The jaundice varied somewhat, and he had frequent attacks of sickness with pain in the abdomen, sometimes being constipated. The stools were normal in colour.

Examination.—He had an adenoid facies, with an appearance of having a large head; measurement, however, gave a circumference of 20½ inches (normal for age). His weight was 49½ lb. His intelligence was rather below the average. There was general slight jaundice, which included the conjunctivae. Petechial haemorrhages appeared on arms, legs, abdomen, and chest. The left tonsil was larger than the right. The upper and lower central incisors were notched along the cutting edge, but there was no suggestion of