

THE TREATMENT OF GONOCOCCUS INFECTIONS BY VACCINES.

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SINCE the publication, only a few years ago, of the details of Wright's exhaustive investigation into the principles underlying the phenomena of phagocytosis, and the theory of immunity towards bacterial infections which he deduced therefrom, vaccines have gained a wide field of application. There are now many diseases which have received a prolonged trial by this method of treatment, and judging from the casual references to be met with in current literature and the advertisements of vaccine makers, *gonococcus* infection affords a striking example of the success of vaccine therapy. On the other hand, careful search reveals a remarkable absence of anything approaching an exhaustive record of exact results obtained in extended series of cases, and this fact, we feel, justifies us in detailing here our personal observations and impressions in this connexion.

Literature.—Butler and Long compared 12 cases of vulvovaginitis in children treated with polyvalent stock vaccine in doses of from 1,000,000 to 50,000,000, with 12 similar cases treated with four-hourly douches of permanganate of potassium, followed by applications of 20 per cent. argyrol, and demonstrated the fact that vaccine therapy was more efficient and satisfactory than local treatment alone.

Whitmore recommends for the treatment of gonorrhoeal arthritis the use of stock vaccines prepared from three or four different strains at intervals of from seven to ten days, and records some of the striking and remarkable results which he has obtained; he, however, refrains from expressing an opinion as to the utility of vaccines in the treatment of urethritis.

Loxton advises the use of doses of 40,000,000 to 50,000,000, rapidly increased, either by reducing the interval between the injections or by augmenting the dose, or by combining these measures. He records three cases of simple chronic gonorrhoea treated with stock vaccines injected at intervals of about ten days.

Cole and Meakins treated 15 cases (12 males and three females) who had suffered from gonorrhoeal arthritis for periods varying from 17 days to 18 months, with doses of stock vaccines varying from 300,000,000 to 1,000,000,000. The average number of injections given was four, at intervals of seven to ten days, and the duration of of the treatment was 29 days. The indices of the patients under treatment ranged from 0.2 to 2.0. They noted in one case only a local reaction at the seat of inoculation from 12 to 24 hours after the injection, which diminished in intensity with each succeeding injection, and constitutional disturbance marked by sharp rise of temperature and general malaise also in one case alone. The authors conclude that vaccine treatment is of distinct value.

Irons treated 40 cases of gonococcus infection, of which nine were suffering from arthritis. He used stock vaccines prepared from two or three different strains of gonococci. At first he used doses of 20,000,000 to 50,000,000, but regarded these as of little value, and subsequently employed doses of 100,000,000 and later still 1,000,000,000 at intervals varying from three to seven days. No harm followed his injections, and he considers that although of little value in the treatment of acute clinical manifestations, gonococcal vaccines are very valuable in chronic cases.

Clinical material.—The majority of our cases were derived from the out-patient departments of Guy's Hospital, the Lock Hospital, and St. Paul's Hospital; a small number of patients were in the wards of Guy's Hospital; we take the opportunity of expressing our thanks to Dr. W. Hale White, Dr. G. Newton Pitt, Dr. A. P. Beddard, Dr. John Fawcett, Mr. Alfred Allport, and Mr. E. C. Hughes for kindly affording us facilities for access to cases under their care; the remainder have been taken from our private case books. In point of time the gathering of our material has extended over a period of rather more than three years—

from early in 1906 to the end of March, 1909. According to the clinical signs and symptoms our cases may be grouped as follows:—

	Males.	Females.	Total.
I. Gonorrhoeal septicæmia and sapræmia ...	1	0	1
II. Simple acute gonorrhoea ...	11	3	14
III. Simple chronic ,, ...	4	1	5
IV. Chronic gonorrhoea complicated by orchitis and epididymitis ...	4	0	4
Chronic gonorrhoea complicated by iritis ...	4	0	4
Chronic gonorrhoea complicated by arthritis ...	17	8	25
Total ...	41	12	53

Diagnosis.—The diagnosis of gonococcus infection depends primarily upon the isolation, cultivation, and detection of the gonococcus—a fact which we have always had in mind; but in some of our cases this final proof has been lacking, and we have been compelled to rely upon other data, such as the opsonic index and the effect of vaccine therapy. Take, for example, the case of the female patient attending hospital for severe multiple arthritis (and we have had many of these); the character of the pain, the distribution of the lesions, and the appearances of the affected joints suggest gonorrhoeal arthritis; confirmatory evidence is afforded by a low opsonic index to the gonococcus (0.4 or lower), or, as in some instances, by a high index (3.0), yet careful examination fails to reveal the presence of the gonococcus in the urethra, vagina, or cervix, or in fluid obtained with the aspirating needle from the affected joints. In order to convert what many will regard as merely presumptive evidence into conclusive proof it would be necessary to repeatedly examine the mucous membrane of the genital tract until the engorgement of the organs of reproduction which immediately precedes some future menstrual flow should drive the gonococcus from the deeper layers of the mucous membrane to the surface, where it would be detected by the bacteriologist—a measure obviously impracticable in a large general hospital already suffering from pressure on available beds. It is true the deviation of complement test might be applied to the serum of these patients, but in the time at our disposal it was not found possible to perform this laborious and delicate reaction; moreover, there are sceptics even in the present day who question the reliability of the Bordet and Gengou reaction as a means of diagnosis. But if, pinning our faith to the indications given by the clinical appearances and the movements of the opsonic index, we administer gonococcus vaccine and find that the blood serum gives evidence of the occurrence of a typical opsonic cycle, the joints clear up, and the patient rapidly convalesces, then we consider ourselves justified in including such a case in our series, and as will be seen by the details we have tabulated, we have had the courage of our opinion and have included more cases than one of this nature.

Technique.—The methods adopted with regard to the collection of material for the isolation and identification of the gonococcus and the preparation of the vaccine necessarily varied somewhat with different cases, but were always planned on the general lines here indicated.

(a) In gonorrhoeal septicæmia an ordinary blood cultivation was made—that is to say, 10 cubic centimetres of blood were withdrawn from the median basilic or median cephalic vein under aseptic conditions into a sterile syringe containing 1 cubic centimetre of 10 per cent. sodium citrate solution. The citrated blood was then distributed amongst several tubes of nutrient (+ 10) broth, or added to tubes of nutrient agar, previously liquefied by heat, and plate cultures poured into Petri dishes, and in all cases incubated at 37° C.

(b) In all other forms of gonorrhoeal infection the isolation of the gonococcus was attempted from the urethra in the male and from the urethra and cervix uteri in the female; the medium used for primary cultures was invariably that known as blood agar. This is prepared by adding a few cubic centimetres of citrated human blood (or on emergency rabbit's blood) to a tube containing 10 cubic centimetres of nutrient agar (+ 10) previously liquefied by heat, mixing thoroughly, and then allowing to cool and set in the slanting position. Upon this medium the gonococcus develops rapidly and remains living certainly for 14 days, and often longer. In making cultivations from the urethra we found the small size (5 millimetre calibre) Kelly's urethroscope of

great assistance. The glans and meatus were first thoroughly cleansed with swabs moistened with perchloride of mercury, then the sterilised urethroscope (smeared with sterile paraffin) was introduced into the urethra to the depth of three or four centimetres. Next the obturator was removed and a sterile platinum spatula was introduced and gently rubbed over the mucous membrane of the urethra beyond the end of the tube. The spatula was drawn back into the lumen of the urethroscope, both instruments were withdrawn from the urethra together, and the material collected on the spatula was then utilised to inoculate two or three blood-agar tubes "in series" and incubated at 37° C. for 24 hours.

For the collection of material from the cervical canal a sterile glass speculum some 18 centimetres long by 1.5 centimetres in diameter, similar in shape to a Fergusson's speculum, was employed; this was passed into the vagina and the end pressed against the os; a sterile cotton-wool swab mounted on a long slender stick was then passed through the speculum into the os, and when infected used to inoculate blood-agar tubes in series. By a repetition of these manoeuvres material was obtained for a cover-slip film preparation, which was subsequently stained and examined. If typical intracellular Gram-negative diplococci were detected microscopically the isolation of the gonococcus was certain, for supposing other organisms were associated with it the colonies on the second or at any rate on the third tube of each series were sufficiently discrete to ensure a pure growth being obtained by means of subculture on to fresh tubes of blood agar. The only associated organism that gave rise to any difficulty in this matter of isolation was *B. xerosis*, a family term embracing several varieties of a diphtheroid bacillus which is frequently met with in the healthy, and rarely absent from the diseased, genital tract. This organism forms moist, translucent, raised colonies on blood agar after 24 hours' incubation at 37° C., which are indistinguishable to the naked eye from those of the gonococcus, and were the cause of many wasted tubes of nutrient media.

The gonococcus, when isolated, was identified by its morphological and tinctorial reactions; the fact that its second generation would grow upon blood agar at 37° C. but not upon ordinary agar or in ordinary broth at the same temperature, nor upon blood agar at the room temperature; that it would ferment only those carbohydrates belonging to the monosaccharide group, and then only when dissolved in serum broth.

For the preparation of vaccines and for all opsonin estimations cultures upon blood agar not more than 24 hours old were employed, as, owing to the rapid appearance of involution forms, older cultures are useless for either purpose. The emulsions were prepared with 0.1 per cent. sodium chloride solution and a homogeneous mixture obtained by shaking the emulsion with sterile glass beads for ten minutes in an electrical shaker. Standardisation was effected by the help of Wright's method of enumerating the organisms present in the emulsion (i.e., by the utilisation of a mixture of equal quantities of emulsion and normal human blood in preparing a film, which, after staining, was examined microscopically and the ratio of red cells to cocci estimated). Sterilisation of the vaccine was performed by exposing the emulsion in a water bath to a temperature of 50° C. for an hour. After the addition of 0.25 per cent. trikresol the vaccine was put up in glass bulbs containing 5,000,000, 10,000,000, 50,000,000, or 100,000,000 gonococci and again heated at 50° C. in the water bath for half an hour.

The opsonic index was in most cases recorded as often as possible. In a few the treatment was carried out by the help of clinical signs only. The emulsion of gonococci employed in these estimations should not be too strong. With a little practice it becomes fairly easy to judge of the strength by the opacity of the emulsion, but it is wiser to stain a drop of the emulsion itself and thus ascertain its strength. A good working emulsion is one which will give from 200 to 300 cocci per 50 leucocytes in the normal preparation. The preparations were always stained by Leishman's modification of Romanowsky's stain.

Treatment.

Vaccines employed.—In every case the treatment was primarily, if not wholly, by vaccine. In some of the cases a polyvalent vaccine, composed of equal numbers of gonococci from three different sources (G^3) was used, and in

others, a polyvalent vaccine composed of ten strains (G^{10}), but in 19 of the cases autogenous (A) vaccines were employed. A comparison of these cases leaves no doubt in our minds that valuable as stock vaccines are, autogenous vaccines are superior.

Dosage.—Considerable variation in dosage was tried. Early in 1906 doses of 100,000,000, 250,000,000, and even 500,000,000, were employed, but our experience quickly demonstrated the fact that the gonococcus recently isolated in pure culture was too toxic to the human subject to permit the employment of such enormous doses. During the last 18 months in some cases 5,000,000 were first employed, and then increased to 10,000,000. 25,000,000 were never exceeded, indeed, were only once given, as we found such a dose quite unnecessary and by no means free from risk. In other cases, 1,000,000 to 2,000,000 were tried to commence with and this dose never increased. Taking all things into consideration we are of the opinion that the cases treated with the smaller doses at short intervals did better than those with the larger doses at long intervals.

During the first fortnight or three weeks of infection very small doses only are permissible (from 500,000 to 2,000,000). We have information regarding two acute cases and one chronic case, where the injection of a large dose (from 25,000,000 to 50,000,000) was followed within 48 hours by acute orchitis and epididymitis in one case and joint affections in the others. In one of our recent cases a dose of 5,000,000 was followed by a rise of temperature to 102.4°F., which persisted for some days; clearly even this dose was too strong for the particular patient. One may assume that a dose is always excessive if followed by an appreciable rise of temperature or other constitutional disturbance.

In explanation of the necessity which we found for reducing the size of our doses, we may mention that in the early days of these observations the technique for isolating the gonococcus had not reached its present state of perfection, and the strain eventually utilised for the preparation of the vaccine was sometimes five, six, or more generations removed from the patient's tissues. Such vaccines are less toxic, require larger doses to produce any adequate movement of the opsonic index, and from clinical experience are less potent therapeutically than those prepared from a first or second culture—such as is now employed. A further point, and one of some interest, relates to the preparation of the emulsion. At first the emulsion was shaken with beads, *by hand*, and the vaccine was often far from homogeneous in character, resulting in inaccurate standardisation in the direction of over-estimation. Control estimations of the strength of the vaccine by plating methods sometimes showed an error of 50 per cent. The introduction of an electrical shaker has reduced this error to less than 5 per cent., and the labour of vaccine preparation to a minimum.

Other therapeutic agents.—In addition to the vaccine, very dilute solutions of potassium permanganate were employed in a few cases of urethritis and vaginitis under conditions that will be referred to later. Painful joints were wrapped in cotton-wool, and in many cases a mixture of some sort, generally citrate of potash and sulphate of magnesia or infusion of buchu, was administered by the mouth; for, as all who have studied the hospital out-patient will agree, a bottle of medicine of some sort is an imperative necessity if regular attendance is required. Finally, in a few instances of arthritis, massage and radiant heat baths were employed towards the end of treatment, in order to increase the mobility of the joint.

Gonococcal septicæmia.—Under the heading of gonococcal septicæmia but one case falls into this present series; and as there were special points of interest about that case a few brief notes may be of value.

The patient, a male, was admitted on July 3rd, 1908, for rigors, pyrexia, and arthritis of the wrist of 14 days' duration. The patient had suffered from a gleet for several years, the chronicity of which may have been accentuated by a severe phimosis. Four months before admission there had been a considerable exacerbation of the urethritis, although when first seen the discharge was slight in amount, and no gonococci could be isolated from it. A fortnight later cultures prepared from blood drawn from the median basilic vein showed the presence of the gonococcus. Two doses (with an interval of five days between them) of 5,000,000 and 10,000,000 respectively of a trivalent gonococcus vaccine

TABLE OF CLINICAL DETAILS.¹*Acute Gonorrhœa.*

No.	Age.	Sex.	No. of attack.	Duration of illness before treatment.	Clinical features.	Diagnosis.	Brand of Vaccine.	No. of doses.	Size of dose in millions	Range of index.	Average interval.	Under observation.	Result.
10	20	M.	2	2 weeks.	Simple acute.	Gonococcus isolated.	G ³ + G ¹⁰	5	5-10	0.4-2.5	8 days.	6 weeks.	Cured.
11	29	M.	1	3 "	—	"	G ¹⁰ + A	4	½-25	1.0	15 "	9 "	"
6	27	M.	1	10 days.	—	"	G ¹⁰	8	3-10	0.8-1.4	9 "	—	"
14	55	M.	7	1 month.	—	"	G ¹⁰ + A	9	2-25	0.8-2.0	10 "	3 months.	Great improvement.
12	34	M.	2	3 weeks.	—	"	G ¹⁰	4	5-10	0.52-1.0	7 "	1 month.	"
13	30	M.	1	3 "	—	"	G ¹⁰	2	10	—	7 "	2 weeks.	"
8	23	M.	1	2 "	—	"	G ¹⁰	8	1-3	0.6-1.7	5 "	6 "	"
2	31	M.	1	1 week.	—	"	A	3	5-10	0.7-2.0	4 "	3 "	Cured.
3	25	M.	1	1 "	—	"	G ¹⁰	3	2.5-5	1.54	7 "	1 month.	Improved.
4	19	F.	1	1 "	—	"	A	6	1-10	0.33-2.06	6 "	3 months.	Cured.
9	18	M.	1	2 weeks.	—	"	A	5	5-10	0.4-3	6 "	2 "	"
5	8	F.	1	1 week.	—	"	A	4	1-5	0.4-1.7	5 "	1 month.	"
1	28	M.	1	5 days.	Ophthalmia.	"	A	3	20-100	—	4 "	10 weeks.	Urethritis improved. Ophthalmia not affected if not aggravated.
7	29	F.	Married.	17 days.	—	"	G ¹⁰	4	2-10	—	5 "	1 month.	Cured.
<i>Simple Chronic Gonorrhœa.</i>													
4	30	M.	10	8 months.	Simple chronic.	Gonococcus isolated.	G ¹⁰	8	5-25	0.5-2.6	8 days.	9 weeks.	Improved.
3	37	M.	2	4 "	—	"	G ¹⁰	4	2-10	1.0-1.8	7 "	4 "	Great improvement.
1	29	M.	1	5 weeks.	—	"	G ¹⁰ + A	6	5-25	—	7 "	2 months.	Cured.
5	25	M.	2	11 months.	—	"	A	3	5-10	—	7 "	1 month.	Great improvement.
2	24	F.	1	3 "	—	"	A	6	5-25	0.9-1.8	7 "	3 months.	Cured.
<i>Orchitis.</i>													
4	27	M.	3	12 months.	Orchitis.	Gonococcus isolated.	G ¹⁰	8	1-5	0.5-1.9	9 days.	11 weeks.	Improved; relapse; cure.
3	26	M.	1	9 "	"	"	G ¹⁰	3	1-2	0.8-1.5	7 "	3 "	Rapid cure.
1	28	M.	1	5 weeks.	"	"	A	—	—	—	—	—	—
2	26	M.	2	6 "	"	"	A	4	10-25	—	7 days.	2 months.	Cure.
<i>Iritis.</i>													
4	30	M.	3	10 months.	Iritis, 3 months.	Gonococcus isolated.	G ¹⁰	6	2-10	0.75-1.35	7 days.	6 weeks.	Cured.
3	25	M.	1	5 "	" 1 month.	"	G ¹⁰	3	2.5-5	—	10 "	4 "	"
2	23	M.	2	1 month.	" 1 "	"	G ¹⁰	4	1-2.5	0.9-1.6	5 "	3 "	"
1 ^a	22	M.	1	1 "	" 3 weeks.	"	G ¹⁰	3	1-2.5	—	6 "	3 "	Improved.
<i>Arthritis.</i>													
1	37	M.	1	3 weeks.	Multiple arthritis.	Gonococcus isolated.	G ³	3	250	0.76-1.9	7 days.	6 weeks.	Cured.
2	26	M.	1	3 "	" "	"	G ³	3	250	0.6-1.44	7 "	7 "	"
8	31	F.	Married.	5 "	" "	"	A	2	250	—	10 "	6 "	"
3	22	M.	1	3 "	" "	"	A	3	500	—	9 "	2 months.	Relieved.
4	26	M.	1	3 "	" "	"	A	3	100-200	0.7-3.66	12 "	5 "	Cured.
25	30	F.	—	—	—	"	G ¹⁰	3	250	—	7 "	2 "	"
19	28	F.	Married.	6 months.	Right knee.	"	A	4	5-50	—	9 "	6 "	Relieved.
13	35	M.	2	3 "	Multiple.	"	G ³	4	10-50	—	10 "	6 weeks.	Cured.
18	?	M.	3	4 "	Right ankle, right hip.	"	G ³	7	10-50	—	10 "	10 "	"
12	32	M.	1	2 "	Multiple.	"	A	4	5-25	—	6 "	6½ "	"
5	30	F.	Married.	3 weeks.	"	"	G ³	4	5-10	1.22-3.0	3 "	2 "	"
6	28	M.	1	3 "	"	"	G ³	3	5-7.5	6	6 "	3 "	"
14	24	F.	?	3 months.	"	"	G ¹⁰	6	5-10	0.4-1.6	10 "	7 "	"
7	27	M.	1	3 weeks.	"	"	G ¹⁰	8	1-10	0.8-2.6	10 "	11 "	"
12 ^a	38	M.	6	9 "	"	"	G ³	3	5	0.7-1.8	10 "	4 "	Improved.
11	21	M.	1	2 months.	Left elbow.	"	G ¹⁰	5	5-10	0.5-1.1	10 "	8 "	Cured.
22	22	M.	1	8 "	"	"	A	8	5-25	0.6-2.5	10 "	4 months.	Improved.
15	30	M.	3	3 "	Multiple.	"	G ³	5	5-25	—	9 "	5 weeks.	"
16	"	"	Relapse three months later.	—	—	"	G ¹⁰	12	5-15	—	9 "	3 months.	"
9	28	M.	1	1 month.	Right wrist.	"	G ³	11	25-50	—	10 "	4 "	Cured.
10	28	M.	1	1 "	Ankles.	"	A	3	500	0.76-1.9	7 "	1 month.	"
23	49	F.	Married.	9 months.	Multiple.	Index 4.0	G ³	3	5-10	1.22-4.0	7 "	1 "	"
17	32	F.	"	4 "	Metatarsals of right hand.	Gonococcus isolated.	G ³	2	25	—	10 "	1 "	"
24	29	M.	1	12 "	Multiple.	"	G ³	4	25	—	10 "	2 months.	"
20	28	F.	Married.	6 "	Left shoulder.	Index 3.0	G ¹⁰	3	5	0.3-1.53	5 "	1 month.	Improved.
21	45	M.	2	6 "	Knees.	Gonococcus isolated.	G ³	7	10-25	0.4-1.5	20 "	5 months.	Relieved.

¹ The numbers in the first column give the order of duration of illness in each section. (About half the cases referred to in these tables formed the subject of a thesis by one of us (B.H.S.) which was accepted for the degree of M.D. Cantab.)

were administered. Ten days later treatment with autogenous vaccine was commenced, and two doses of 2,500,000 and 5,000,000 were given at intervals of three days. On Aug. 28th, and again on Sept. 9th, the blood drawn from veins in the arm appeared quite sterile, the arthritis had subsided completely, the urethritis had disappeared, and the patient was convalescing rapidly. On Sept. 25th the patient experienced several rigors, with marked pyrexia, headache, and drowsiness. Cultures from the median basilic vein gave a pure cultivation of pneumococcus, no gonococci could be detected, and it is of interest to note that a few days previously the beds on either side of the patient had become occupied by a case of acute pneumonia and a case of empyema which had been drained. A pneumococcus vaccine was prepared and a 5,000,000 dose was injected on Oct. 1st. On Oct. 6th the patient died from general pneumococcal septicæmia. The interest in this case lies in the fact that either the simple factor of rest in bed or the treatment with the vaccine had led to the disappearance of the gonococcus from the patient's blood stream, but that the lowered resistance entailed by the illness had left him unable to cope with the pneumococcus, and a second attack of septicæmia, due to a different organism, resulted in a fatal termination.

Acute gonorrhœa.—It is exceedingly difficult to estimate the value of vaccine treatment in acute gonorrhœa, for in the first place we have experienced a lamentable dearth of early cases. In the present series we have only two which came under observation during the first week of infection; in one the urethral discharge preceded the conjunctivitis for which the patient was admitted by about 36 hours only (probably both the urethra and conjunctiva had been infected on the same occasion four days previously), and in the other vulvitis and urethritis made their appearance some five days after admission for vague abdominal pains, at which date all the evidence of recent defloration was present. But whilst there is undoubtedly in man an inherent predisposition to successful auto-immunisation against the gonococcus, which in a certain small percentage of cases leads to rapid and complete cure without the intervention of either physician or surgeon, there is another type of case which is predestined to become chronic, and it is not until the defects in the mechanism which regulates the process of immunisation have become apparent and the chronicity is an established feature that these cases come under observation. Speaking generally, we are of the opinion that the immediate value of vaccine therapy in the first type of case is of negligible value, but in so far as its general adoption in all acute cases would probably reduce the numbers comprised in the second type, we are strongly in favour of the use of gonococcus vaccine in all cases of acute gonorrhœa.

The injection of a moderately small dose of vaccine (say 5,000,000) was in most cases followed by a definite train of clinical symptoms. 1. For the first 36 to 48 hours there was marked increase in the discharge, which sometimes was altered in character; increased pain on micturition and erection; slight general malaise; in other words, the patient appeared worse in all ways as a result of the injection. This phase is followed by (2) marked improvement, and frequently by complete disappearance of the discharge, decrease of pain, and general constitutional improvement. This stage lasted usually from three to four days, according to the dose injected; at the end of this time the discharge would gradually return. The injection of a further dose of vaccine at this stage would result in a repetition of the symptoms. Usually the discharge quickly became slight, thin, and watery; in some cases it disappeared for a short time after each injection, only to reappear in a few days. The temporary improvement would be so marked that patients repeatedly thought themselves cured before this happy result had been attained. In one instance, where considerable benefit seemed to be derived, whenever the discharge ceased for a few days the patient indulged in a drinking bout with the inevitable consequences; this happened on no less than three occasions.

The explanation of the symptoms that follow an injection of vaccine is readily appreciated from an inspection of the opsonic chart. An immediate negative phase is produced, lasting from 36 to 48 hours, followed by a rapid rise to a positive, which may reach 3 or 4 or even higher. The increased discharge, pain, and discomfort are noted during the negative phase, and the improvement follows the rising

index; a recurrence of symptoms is noted in a few days, as the index again falls below normal. The larger the dose the more pronounced the negative phase, which may fall as low as 0·2 or 0·3, and the longer its duration; hence the danger of the larger injections.

The opsonic index of the average acute case, that is not doing especially well, shows many and rapid variations. The index will rise high above normal, commence to fall immediately, and a day or so later will be considerably below the normal line. This feature is no doubt due in the majority of cases to the lack of rest during the active pursuit of the patient's ordinary avocations—exercise resulting in repeated auto-inoculations, involving enormously toxic doses which are irregular in quantity, quality, and time, and giving rise to prolonged and extreme negative phases, accompanied by increased susceptibility to the inroads of the gonococcus. It is probable that great and rapid fluctuation of the index is the chief contributory factor to the tendency to chronicity, and we therefore regard such frequent and extreme variations as undesirable. Again, the opsonic chart of a patient receiving large doses at intervals of a few days shows similar rapid changes of index, and thus *the condition found in untreated cases that are not progressing favourably is artificially reproduced and affords a powerful argument against the use of large doses.* The small doses (from 500,000 to 3,000,000) are sufficient to confer all the benefits of the large doses and are unaccompanied by their corresponding disadvantages. The small dose is followed by practically no negative phase, and the positive phase, though not marked, is not delayed but comes on rapidly. A case thus treated, with the additional advantage whenever possible of rest in bed, rarely shows a high index (i.e., above 2), but, on the other hand, the negative phase is practically abolished. *Small doses, repeated at short intervals, steady the index, and possibly hereon lies their chief value,* as the steadying of the index prevents a state of affairs which would prove detrimental to rapid recovery. Moreover, small doses can with safety be repeated at intervals of a few days, whereas a longer interval is necessary where larger doses are employed.

To these points we attach great importance; for example, we know no other therapeutic agent that will completely check an acute urethral discharge in this abrupt manner. *This and other considerations afford proof that the vaccine exerts a marked influence over the disease; that it acts rapidly and with a tolerable degree of certainty; and that it exerts a definite powerful influence on the local and general condition of the patient.*

We consider the ideal treatment to be as follows: The patient should from the first have absolute rest in bed, bland diet, plenty of fluid (e.g., from five to six pints a day of barley water or milk and soda), and a mixture that is both aperient and diuretic, containing also some urinary antiseptic, such as urotropin. No urethral injections should at first be used, for the drainage is excellent, and the constant flushing of the urethra by frequent micturition is sufficient. An autogenous vaccine should be prepared and the opsonic index taken daily; if large variations in the index are observed, these should be steadied by very small injections of vaccine, such as 500,000 to 1,000,000; if, however, the variations are small 2,500,000 may be injected. Under these conditions many cases rapidly convalesce. If, however, about the third or fourth week, the discharge has not ceased but appears likely to become subacute, other methods must be adopted. Thus, after the injection of a dose which previous observations on the case have shown will produce on the third or fourth day a well-marked positive phase that will last about three or four days, the index should be carefully watched, and as soon as it has reached its maximum point irrigation of the urethra with a very weak astringent and aseptic solution should be instituted. Usually the result of this procedure is little short of marvellous—the cure is complete before the index has fallen to normal. It is advisable, however, to give one or two more injections before terminating the treatment.

Chronic gonorrhœa.—Thirty-eight subacute and chronic cases have been under treatment. Of this number five were simple and the remainder were complicated with troubles other than urethral. Twelve cases were treated with vaccine prepared from the patient's organism, and the rest with stock preparations.

Simple chronic gonorrhœa.—A chronic urethral inflammation is not as a rule a simple infection. The ravages of the gonococcus over a long period leave the superficial and deeper layers of the urethral mucous membrane in a condition little calculated to resist the invasion of other organisms or to encompass the destruction of the gonococci themselves. It is not surprising to find that the presence of the gonococcus alone, in cases of chronic urethritis or cervicitis of nine months' duration or longer, is the exception rather than the rule. The organisms found, in addition to the saprophytic *B. xerosis* and its variants, in the order of the frequency with which they occurred in cases we have investigated, are as follows: (1) *Staphylococcus albus*, including a large variety of this organism: (?) *S. gigas urethræ*; (2) *staphylococcus albus* associated with gonococcus; (3) gonococcus alone; (4) *staphylococcus albus* associated with *bacillus coli communis*; (5) *bacillus coli* alone; (6) gonococcus associated with *bacillus coli*; and (7) *bacillus influenzae*.

In the present communication we have limited ourselves to a presentation of those cases of chronic gonorrhœa in which the sole or the predominating organism in the urethral discharge was the gonococcus, leaving the consideration of secondary infections to some future occasion. Several of our cases were extremely chronic, and were the subjects of repeated infections. One man came with his tenth attack, and had not been free from gleet, with frequent exacerbations, for years. Another case of eight months' duration was the ninth attack. Yet another was of two years' standing; others of 18 months to two years. Now the time that the infection has persisted tells greatly against the patient. In the earlier stages the body has made strenuous efforts to throw off the disease; later, the local and general powers of resistance are lowered. The attempt to limit the area of infection has resulted in the shutting off of the inflamed tissues by exudative products, which in turn diminish the intensity of the stimuli transmitted to the immunising machinery, and so limit the output of antibodies and at the same time prevent the ready access of such antibodies as are formed to the area of infection. Under such conditions vaccine treatment should obviously be of value, for the introduction of dead bacteria, with their endo- and exo-toxins, into the tissues at a distance from the infected and infiltrated area, forcibly stimulates the formation of those anti-substances whose manufacture, owing to the reasons we have already set out, has been reduced to a minimum.

Chronic gonorrhœa with complications.—In some of our chronic cases complications arose during treatment; in others they were present when the patients were first seen. They comprise: (1) Iritis (four cases); (2) arthritis (25 cases); and (3) epididymitis and orchitis (four cases). Cystitis occurred in one case, but was transitory and quickly subsided. Although every case was of several months' duration the gonococcus proved to be the only pathogenic organism infecting the urethra. It is noteworthy that in the chronic cases in which complications arose the gonococcus alone was found in the discharge. It may be inferred from this that when a gleet has ceased to contain this organism complications, such as orchitis, epididymitis, &c., are not likely to arise.

Orchitis and epididymitis.—One of these cases is typical of all four. The patient was suffering from acute epididymitis when first seen. He was in great pain, could hardly walk, and looked extremely ill. The left epididymis was swollen and exquisitely tender. In view of the acuteness of the condition a small dose of stock vaccine (1,000,000 only) was injected, and the patient was told to return in three days. Examination then showed slight improvement and a further injection of 1,500,000 was given. Nine days later the man returned. He walked briskly and the drawn and haggard look was gone from his face. The testicle was practically normal and could be pressed with considerable force without causing pain. A remarkable feature is that during this time he took no rest but struggled about during the daytime as well as he was able. He stated that there was perhaps very slight increase of pain on the day following the first injection which was scarcely noticeable, but that within 24 hours he felt considerably better and rapidly improved without once looking back. Evidently with these small doses the negative phase was elided, or at all events was extremely slight and transient. A final dose of 1,000,000 was given a fortnight from the date of the first injection, and when last seen the

improvement was maintained and the patient was perfectly well. It is most improbable that in the ordinary course of events the condition would have cleared up with such rapidity when no rest whatever was being taken.

Arthritis.—Practically all these cases were first treated—on the diagnosis of chronic rheumatism—with salicylates and other anti-rheumatic remedies and local applications of belladonna, &c., and only on the failure of these measures did the cases come under our observation. Frequently some slight pyrexia was present at first, but rest in bed or of the affected joint caused its early disappearance, but without any relief of the pain. The effect of vaccines was practically identical in all cases. In from 12 to 24 hours after the administration of doses of 5,000,000 or 10,000,000 the affected joints were subjectively more painful, and in many cases distinctly more swollen, red and tender, and movements more limited. These symptoms corresponded with the negative phase. In from 36 to 48 hours these symptoms cleared up, pain and tenderness passed off, and movements became much more free. Any urethral discharge that was present underwent the changes already detailed in connexion with simple acute gonorrhœa.

Iritis.—All these cases were transferred from the ophthalmic department of Guy's Hospital, where the diagnosis was originally made, to the vaccine department. On account of the importance of this uncommon complication we are tempted to give further details of these cases.

CASE 1.—The patient had suffered from gleet for ten months in this, his third, attack of gonorrhœa. The right pupil was dilated (atropine) and irregular; some chemosis; conjunctiva very injected, lacrymation; no purulent discharge, and the eye extremely painful. By the second injection the pain had almost disappeared from the eye, which in all ways appeared better. Ten days after the second injection the patient said that the eye had been free from pain for a week, for the first time for nearly six months. The earlier injections had the usual effect on the urethral discharge, which eventually disappeared. Treatment was carried out for two and a half months, and at the expiration of this time the iritis was cured and the sight was perfect.

CASE 2.—Present attack of gonorrhœa contracted five months ago. Three recurrent attacks of conjunctivitis (both eyes), but no pain or loss of sight. Present attack, left eye only, starting one month previously; great pain, congestion, and loss of sight. Conjunctiva very injected—ciliary injection; iris muddy; no reaction to light; pupil irregular—cornea hazy, with deposits in anterior chamber. Pain on admission very bad, and getting worse. Pain relieved within 48 hours of first injection—gone in four days; sight returning—eye steadily improving; patient feels better in general health two or three days after each injection. No relief of pain prior to vaccine, whilst under treatment by fomentations and atropine.

CASE 3.—Present attack of gonorrhœa contracted one month before commencement of iritis. Lids injected and swollen, muco-purulent discharge, but gonococci absent; conjunctiva injected; chemosis; cornea healthy. 11 days after admission arthritis of knee and elbow. Iritis well and patient discharged cured in a month from first vaccine inoculation.

CASE 4.—Patient admitted with "cold" in the right eye; marked conjunctival injection; discharge; very severe pain—especially at night; cornea cloudy, pupils dilated, iris dirty coloured; condition getting worse. One month from date of admission eye greatly improved; no discharge, iris clear; no conjunctivitis; cornea clear. Pain relieved after first injection; cured after the second.

SUMMARY.

I. *Acute gonorrhœa.*—1. Gonococcus vaccine is markedly toxic and exerts a profound influence over the disease.

2. For routine work (hospital out-patients, &c.) vaccine treatment is not devoid of danger and requires the exercise of considerable caution.

3. A stock vaccine, comprising a dozen different strains, gives results only slightly inferior to those observed when using a vaccine prepared from the patient's own organism. This is not the rule in most other diseases.

4. Small doses, repeated at short intervals, are more effective than large doses at lengthened intervals.

5. Small doses of vaccine (from 1,000,000 to 10,000,000) are safer and more satisfactory than the large doses (from 50,000,000 to 100,000,000) which are often prescribed.

6. After an injection of from 500,000 to 2,000,000 the negative phase is either absent or extremely transient.

7. An inoculation of from 5,000,000 to 10,000,000 causes a negative phase of usually not longer than 48 hours' duration, followed by a positive phase of from three to five days.

8. Vaccines in small doses serve the double purpose of raising and steadying the opsonic index. A steady index just above normal is found to be the most favourable condition for rapid recovery.

II. *Simple chronic gonorrhœa.*—1. Where the gonococcus has ceased to be the infecting organism these cases are on a par with other chronic inflammatory states, but are frequently

more difficult to cure owing to environment and local conditions.

2. Chronic cases where the gonococcus is the sole infecting organism have a better prognosis from the point of view of treatment by vaccine than a mixed infection or one of staphylococcus only.

III. *Chronic gonorrhœa with complications.*—1. The estimation of the opsonic index is helpful to diagnosis and is a useful means of determining *approximately* the opsonic state of the blood. Chronic gonococcus infections, however, present clinical features which themselves afford valuable indications during the course of vaccine treatment.

2. Where the gonococcus alone is the infecting organism, if the opsonic index cannot be obtained as frequently as is desirable, routine injections of from 1,000,000 to 2,000,000 doses every three to five days are safe and satisfactory; a lapse of five to seven days after doses of 5,000,000; an interval of eight to ten days after inoculation of 10,000,000. Larger doses than these are seldom desirable.

3. Treatment by small and gradually increasing doses at frequent intervals should at all times be observed; the use of large doses is even more dangerous than in acute cases, and may be followed by disastrous consequences.

4. In orchitis small doses of vaccine quickly relieve pain and cause a more rapid abatement of symptoms than obtains by the usual routine treatment alone.

5. In iritis the severe pain, which is a marked and obstinate feature, is relieved in 48 hours after an injection, and disappears in from three to four days; cure is much hastened.

6. In arthritis the treatment is of considerable value.

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THREE CASES OF DELAYED CHLOROFORM POISONING.

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By the kindness and courtesy of Mr. P. MacGregor and Mr. J. G. Rowell I have been permitted to publish the notes on these cases, which, taking into consideration the cases which have been published recently, are not, I think, without interest.

CASE 1.—A girl, aged four years, was admitted to the Huddersfield Infirmary for operation for genu valgum, which was performed on the afternoon after her admission, and which consisted in a single osteotomy of the femur. The child appeared to be healthy and in good condition at the time. The anæsthetic used was the A.C.E. mixture, of which about six drachms were administered. The patient was returned to bed about 3 o'clock in the afternoon, and her progress was very satisfactory until about 4 o'clock on the following morning, when she vomited a large quantity of fluid. Nothing special was noticed, and the patient again fell asleep. At 8 o'clock, four hours later, she vomited again; this time the vomit was typical "coffee ground," and the constitutional disturbance was very considerable; the pulse became fast and weak, and the child was comatose. From this time onward the condition was that of "dulness alternating with apathy." The pulse became very rapid, in fact, quite uncountable, the respirations were hurried, and the temperature gradually rose, until before death 20 hours later it had reached 106° F. There were slight distension of the abdomen and some tenderness, and very slight yellow tinging of the skin. The pupils were very variable, sometimes dilated and sometimes contracted, and the corneal reflex was nearly always present. The persistent vomiting was a marked feature; in fact, everything that was taken by the mouth was returned immediately. The urine, of

which only about one ounce could be obtained, showed a marked reaction to the acetone test—i.e., sodium nitroprusside and ammonia.

The treatment consisted in a large draught of sodium bicarbonate in water at the commencement, after which stimulants were tried, champagne and brandy, but nothing was retained. Dextrose as suggested by Dr. A. P. Beddard was also given and saline solution was administered by the rectum together with sodium bicarbonate; saline infusion subcutaneously seemed to have not the slightest effect on the downward progress. I would like to call attention to the small amount of chloroform used, and also the effect of the different forms of treatment suggested. A post-mortem examination was not permitted.

CASE 2.—The patient, aged 26 years, was admitted with symptoms of ovarian cyst with twisted pedicle. The operation was performed a few hours after admission and consisted in removal of the cyst which was slightly adherent to the intestines. On the following day her progress was satisfactory. The patient had slept well and she felt well, except for some slight vomiting after the operation. On the following evening—24 hours after the operation—my attention was called to the small quantity of urine passed, only about 16 ounces since the operation; a catheter was passed but no urine was found in the bladder. On the following morning, the patient was distinctly jaundiced and the general condition was not good. About 10 A.M. she vomited a large quantity of "coffee-ground" fluid. The stomach was then washed out and some saline and sodium bicarbonate solution was left in. The patient's condition seemed to improve. Plenty of fluid was given and was retained; five grains of calomel were also given. The patient again vomited at about 10 P.M. and from that time onward her condition was gradually getting worse. There was not much vomiting, but gradually becoming weaker she died at 2 o'clock on the following morning—60 hours after the operation and 14 hours after the first appearance of the "coffee-ground" vomit, so distinctive a feature of these cases. The temperature had never risen above 99° F., the pulse had gone up to 160 per minute, and the respirations had been normal. The urine, of which about four ounces had been obtained after the symptoms had set in, had given no reaction to the acetone test.

A limited post-mortem examination was made. No peritonitis was found. The specimens, which were kindly examined for me by Dr. Gough, showed the following points of interest. (a) The liver showed very characteristic changes. The centres of the lobules were quite disorganised, the cells were nearly all necrotic, and much brown pigment was present, and the peripheral parts of the lobules were in a state of advanced fatty degeneration. (b) The spleen showed little change except that many of the cells contained brown pigment granules. (c) In the pancreas the gland cells showed degenerative changes. No trypsinogen granules were present, but numerous fat globules were found in the protoplasm. (d) In the kidneys the glomeruli were normal and the cells of the convoluted tubes were in some places in a state of advanced fatty degeneration and in others broken down into the lumen. (e) In the heart the fibres had almost lost their striation and were filled with fine fat droplets. The condition was not patchy, as in fatty degeneration usually found in anæmic states, but every cell was affected.

CASE 3.—A male patient, aged 18 years, was admitted for operation for appendicitis. The operation was performed on the same evening. The appendix was removed and a small abscess cavity was drained. The progress of the patient was all that could be expected for more than three days, when—80 hours after the operation—I was called to see him, severe collapse having set in, and he had just vomited a large quantity of "coffee-ground" fluid. On the next morning the skin was distinctly yellow in colour. The general condition was very similar to that of the last case. A fair quantity of fluid was retained, the vomiting not being very frequent. The pulse rose from 80 per minute at the onset of the vomiting to 130 immediately before death, which occurred nine hours after the onset. The temperature rose to 102° F. from the 99° at which it stood when I was first called to see the patient.

A limited post-mortem examination was made. No general peritonitis was present, but owing to an accident all the specimens except that of the liver were lost. The urine gave a negative result to the acetone test. Dr. Gough's report on