

If the epidemic is primarily due either to the Pfeiffer's bacillus or the small streptococcus mentioned, or both, I have no hesitation in saying that one would frequently fail to isolate them by cultures from patients because of the exact conditions necessary for their growth. I would suggest that inability to isolate these organisms in certain cases may be due to errors in the culture medium employed. At any rate, this possibility requires to be excluded before one can definitely claim that the epidemic is due to some organism of an entirely different character.*

(16) *Final Researches on Detoxicated Vaccines.*

A detoxicated vaccine can be used in two forms. It can be made up in the form of a neutral or slightly alkaline solution, or else it can be made up with a weak acid, in which case it is an insoluble precipitate which requires to be shaken well before use. In the majority of cases in Series D described above, the soluble variety was used, and this was injected intramuscularly into the buttock. It was noticed, however, that 10,000 millions caused a transitory drop in the immunity of the patient as estimated by the complement-deviation test. This temporary negative phase with reduction of antisubstances continued, as a rule, for about 20 hours, after which the immunity again commenced to rise.

After ascertaining this fact it occurred to me that it might be better to inject the insoluble precipitate. It is conceivable that an injection of the soluble form might rapidly penetrate into the blood stream and have the immediate effect of combining with existing antisubstances in the circulation, thereby neutralising them. If precipitate, however, were injected it would tend more to remain local, and without neutralising existing antibody in the circulation it would irritate and stimulate the local tissues to produce further quantities of specific immune substances. In consequence I now prefer to inject the precipitate which is made up in a solution of 0.5 per cent. acid sodium phosphate (NaH_2PO_4) containing 0.5 per cent. carbolic acid. The inoculation is made subcutaneously. Cases of gonorrhoea treated by this latter method have done remarkably well, and have shown a rapid rise in the amount of complement-deviating substance in the blood.

Before concluding, I would like to point out that immediate miraculous results must not be expected from any vaccine. It is inconceivable that an injection of dead germs should cause an immediate alleviation of symptoms. Indeed, the first result is a negative phase lasting some 20 hours, during which time the symptoms may be aggravated. After this time antisubstances gradually commence to develop during the next 7 to 14 days. Vaccines should not be injected more often than about once every three to five days. The results obtained are gradual and progressive. One of the great advantages of vaccine treatment is that the immunity is worked up to a high level, and on this account a relapse is a very rare occurrence.

A certain number of disappointments must be expected, since for some reason still obscure certain individuals seem to have very little faculty of developing antisubstances even when large doses are injected. This phenomenon is markedly noticeable also when rabbits are injected with sheep's corpuscles for the purpose of producing hæmolysins towards the latter. Certain rabbits develop an enormous amount of antisheep corpuscle substance, whereas others develop very little. No one, so far, has been able to explain why this difference should occur.

No doubt in the near future, when the conditions which govern the formation of antisubstances are more fully elucidated, we may find it within our power to produce very rapidly even 20 units of immunity. When we have attained this knowledge and power I feel assured that the complete mastery of practically all bacterial diseases will be the result.

References to literature.—1. Wells (1918): *Chemical Pathology*, W. B. Saunders Co. 2. Besredka: *Comptes Rend. de l'Acad. des Sciences*, cxxxiv., 1330, 1902. 3. Nicolle and Blaizot: *Acad. des Sciences, Paris*, Oct. 6th, 1913; also *l'Assoc. d'Urologie*, Oct. 10th, 1913. 4. Torrey (1903): *A Study of Natural and Acquired Immunity of Guinea-pigs to the Gonococcus*, *Jour. Med. Res.*, xviii., 347. 5. Gordon, M. H. (1918): *Observations on the Production of Meningococcus Antidotoxins*, *Brit. Med. Jour.*, Sept. 28th, 1918.

* Since this paper was sent in for publication the evidence recently accumulated by various workers seems to show that Pfeiffer's bacillus was not the primary cause of the great influenza epidemic. It would appear that the causal organism was a filter-passer, but whether this new germ has any relationship to the minute streptococcus mentioned above I am unable to state.

DETOXICATED VACCINES IN THE TREATMENT OF GONORRHOEA:

THE VALUE OF THE COMPLEMENT-DEVIATION TEST IN CONTROLLING THE TREATMENT AND ESTIMATING ITS THERAPEUTIC EFFECT.

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DURING recent years the treatment of gonorrhoea and its complications has aroused much controversy. Very few workers have satisfied themselves that anything like a satisfactory treatment has yet been attained.

Early in 1916, while working in No. 9 Stationary Hospital, B.E.F., I tested on parallel series of cases different modes of treatment, both local and general, and was very much impressed with the results in a large series of cases of a mixed vaccine known as staphgon. The vaccine contained in each c.cm. 150 million staphylococci and 50 million gonococci, and was prepared by Major Dawson, R.A.M.C., and Captain McWhirter, R.A.M.C., pathologists to the hospital. Definitely noticeable were: (1) the mild course of the case treated ab initio with vaccine; (2) the absence of complications; (3) the smaller number of relapses. These impressions were confirmed by Captain Lumb¹ in a large series of cases.

Value of Vaccine Therapy in Gonorrhoea.

Among the many workers, both in this country and abroad, who have tried vaccine therapy in gonorrhoea, there is an almost unanimous consensus of opinion as to its good therapeutic effect in the complications of gonorrhoea. Broughton-Alcock² in Paris, Semionov,³ Dopter and Pauron,⁴ Culver⁵ in America, and Asch⁶ in Germany have all testified to its good therapeutic effect in this type of case.

The most satisfactory results have been obtained by: (1) increasing the dose to a point at which it was almost toxic (W. G. Brett⁷); or (2) preparing the vaccine so as to reduce its toxicity, either by sensitising it after the manner of Besredka,⁸ or of Howarth,⁹ with the former of which methods Cruveilhier obtained excellent results, or by growing it on a special medium as did Nicolle and Blaizot,¹⁰ whose results and also those of Remlinger,¹¹ were consistently good with a vaccine so prepared and known as Dmégon.

Workers who used ordinary stock vaccines—e.g. Wright, Harrison, Asch, Sachs, and many others—have contented themselves with smaller doses, 5 to 25 millions, initially, and working up to 150 or 250 millions, preferring rather to have small reactions, both general, local, and focal, and never to increase the dose if reaction was great. In America they have preferred higher doses, 50 to 100 millions being average doses in acute cases, while in chronic cases they go as high as 500 millions, and state that in chronic gonorrhoeal arthritis lesser doses have no action at all. The more promising results of American workers are due chiefly, I think, to the larger dosage, and to the fact that in later years they have controlled the dosage and the intervals between doses, not only by clinical observation, but also by serological tests.

From close clinical and pathological observation, I feel convinced that on account of its toxicity our dosage has been too small to produce a large immunity response. The cases which did not give an immunity response to the injection of a vaccine in the early stages were those in which the substance injected, by reason of its toxic nature, more or less destroyed the antibody-producing power of the tissues which nature had just begun. Those in which there was a larger and immediate response to vaccine treatment were the cases in which nature had already taken up the task and the tissues were already well accustomed to producing anti-substances in quantity and only required some additional stimulus to produce more.

This is seen if we compare the serological tests of the two cases of the same duration—say, an epididymitis of six days and an anterior urethritis of six days' standing. The first will almost invariably show 1 to 3 units of anti-substance, while the latter never shows more than $\frac{1}{2}$ to 1 $\frac{1}{2}$. This is borne out by almost all workers who concede that vaccines are of use in the complications of gonorrhoea, but not markedly in early cases of uncomplicated urethritis.

First Series: Aggravated Cases Treated with Detoxicated Vaccine.

During last year, after long, painstaking, and brilliant research, Captain Thomson, R.A.M.C., succeeded in removing the poisonous substance from gonococcus vaccine, and so was able to increase the dose beyond anything previously administered in vaccine therapy. After having had personal experience of the non-toxic results of the injection of Captain Thomson's detoxicated vaccine in doses up to 5000 millions, and after seeing its effect on the blood of normal persons as a specific antigen, I readily consented to test its effect, clinically, on a series of cases, and began the work under the supervision of Colonel L. W. Harrison at Rochester Row Military Hospital.

The most aggravated cases in hospital at that time were chosen. They included:—

(1) Fifteen cases of epididymitis, all acute; 3 of them second attacks in the same epididymis, and 2 in which both epididymes were affected.

(2) Three cases of acute abscess of the prostate gland.

(3) Three cases of chronic enlargement of the prostate with gleet.

(4) Two cases of acute urethritis with acute gonorrhœal rheumatism.

(5) Eight cases of acute, subacute, and chronic urethritis, including 2 treated solely with vaccines and no local treatment, and 4 chronic relapsing cases after various forms of treatment for four months up to four years.

Prior to treatment, gonococci were demonstrated in the urethral discharge or prostatic fluid of each case. The complement-deviation test was performed to confirm diagnosis and to estimate the amount of antibody which nature had already produced.

Summary of Results in First Series.

1. *Epididymitis cases.*—These cases were commenced with doses of 2500 millions detoxicated gonococcal vaccines, given intramuscularly. Doses were given on the 1st, 4th, 8th, 13th, 18th, 25th, and 33rd days, gradually increasing to maximal doses of 10,000 millions—total 50,000 to 80,000 millions. No irrigation until the acute symptoms had subsided, usually in 4 to 5 days. The solution used was 1:8000 pot. permang., followed by mercury oxycyanide or zinc sulpho-carbolate in the subsiding stages of the discharge. The morning smear and urine of each case was examined every four days. Each case had bi-weekly prostatic massage in the declining stage of the disease, and each was urethroscopied before treatment was stopped.

The cases all did well and cleared up without any subsequent complications. Those which showed by their weekly complement-deviation test a quick antibody response did best clinically.

E.g., one case with an epididymitis, of the right side, very swollen, tender, and tense, cleared up in 6 days, and left hospital in 18 days.

A second similar case cleared up in 7 days and left hospital in 14 days.

A third similar case cleared up in 15 days and left hospital in 22 days.

Put in tabular form the average clinical and serological results of the 16 cases were as follows:—

(a) Gonococci on admission	All positive.
(b) Complement-deviation on admission... ..	Av. 2.9 M.H.D.
(c) Gonococci not found in morning smear or after prostatic massage	22.5 days.
(d) No urethral discharge	30.4 "
(e) Epididymis and cord normal... ..	32.8 "
(f) Average complement-deviation at maximum	7.6 M.H.D.

All cases were kept under observation in hospital on an average of 12.6 days without treatment after the clinical signs had cleared up. All of them reported every one to two weeks for two months or more after returning to full duty with their units. No case up to that time had shown any signs of relapse.

The points noted during the treatment were as follows:—

1. Reactions: Local, very slight in all cases. Focal, not appreciable after first two doses. General, temperature rose from 1° to 1.5° and never lasted more than 24 hours. 2. Remarkably rapid disappearance of gonococci in most cases. After the first two or three doses they were almost always extracellular and showed a tendency to clumping. 3. The markedly purulent discharge so often seen as the epididymis goes down was never so profuse and disappeared fairly quickly. 4. The tense swelling and acute

pain subsided after one or at most two injections of vaccine. 5. There was no appreciable thickening of the cord or epididymis left, except in one case with two previous attacks.

2. *Acute prostatitis.*—Dosage as in epididymitis cases. Three cases of urethritis with abscess formation in the prostate gland and retention of urine were treated. They were rather more resistant during the earlier stages and showed a tendency to have more general and focal reaction than the epididymitis cases, and did not produce such a quick immunity response. After the retention symptoms and the tenderness in the prostate had disappeared the cases were irrigated with pot. permang. 1:8000, followed in the declining stages by hyd. oxyc. 1:5000, and prostatic massage bi-weekly. The average results, clinical and serological, were:—

(a) Gonococci on admission	Positive.
(b) Complement-deviation before beginning treatment	Av. 2.3 M.H.D.
(c) Gonococci not found in morning or prostatic smear	45.5 days.
(d) No urethral discharge	59 "
(e) Prostate normal... ..	62.5 "
(f) Complement-deviation at maximum... ..	8.3 M.H.D.

All were kept under observation in hospital for 10 days subsequently without any treatment. They have since reported weekly and have shown no apparent clinical or pathological signs of disease.

3. *Chronic prostatitis with gleet.*—Three cases. Dosage as above. In these cases the vaccine was well borne; local, general, and focal reactions were very slight and never for more than 24 hours. Additional treatment consisted in prostatic massage bi-weekly, irrigation once daily at first, and later twice weekly with zinc sulphocarbolate lotion. The average results were as follows:—

(a) Gonococci in urine threads or prostatic smear	Positive.
(b) Complement-deviation before treatment	Av. 2.6 M.H.D.
(c) Gonococci negative in smear or urine	6 days.
(d) No urethral discharge	21 "
(e) Prostate healthy... ..	24 "
(f) Complement-deviation at maximum	5.2 M.H.D.

4. *Acute urethritis and gonococcal rheumatism.*—Two cases. In the first case the right knee-joint was red, swollen, and tender, also right ankle and left ankle; left knee-joint was slightly swollen and tender; left shoulder-joint not swollen, but tender on palpation. This patient was bedridden. The joint condition developed 8 days subsequent to urethritis; he came under treatment 6 days later on. Both lobes of the prostate were slightly enlarged and tender. Irrigation with pot. permang. for 21 days and prostatic massage, bi-weekly, from the 16th day. The patient was able to get about by the 20th day. 5000 million detoxicated gonococcal vaccine were given and subsequently 5000, 7500, 10,000, 10,000, and 10,000 millions on 1st, 4th, 8th, 12th, 19th, and 26th days. The results were as follows:—

(a) Gonococci on admission in urethral smear	Positive.
(b) Complement-deviation on admission	3 M.H.D.
(c) Gonococci negative in urethral smear and urine	5 days.
(d) No urethral discharge	16 "
(e) Joints normal and able for full duty	51 "
(f) Complement-deviation at maximum	10 M.H.D.

In the second case the joint condition developed 11 days subsequent to the urethritis. Both lobes of prostate enlarged, soft, and boggy. Joints involved were: All metacarpophalangeals of left hand and interphalangeals, especially of first and fifth fingers, left tarso-metatarsal and intertarsal joints of left foot, right ankle, and right tarsal joints. All were red, swollen, and acutely tender. Irrigation for 20 days with pot. permang.; prostatic massage bi-weekly from 17th day. Patients was able to be up from 16th day. The results were:—

(a) Gonococci on admission in urethral smear... ..	Positive.
(b) Complement-deviation on admission	3 M.H.D.
(c) Gonococci negative in smear and urine	3 days.
(d) No urethral discharge... ..	17 "
(e) Joints normal. All in 33 days, except 1st metacarpophalangeal joint, which remained resistant for 61 days.	
(f) Complement-deviation at maximum	8 M.H.D.

Both cases were kept under observation for seven days and subsequently have reported fit and are on full duty. Reactions: General, temperature 1° to 1.5° for 24 hours only. Focal, pain temporarily increased with each of the first three injections, but always much easier in 12 to 24 hours. Local, nil.

5. *Urethritis*.—Eight cases of acute and subacute urethritis, in all of which the posterior urethra was involved.

The first two cases were treated by vaccines alone and no local or general treatment administered. They were begun with doses of 250 million detoxicated vaccine, and were worked up gradually to 5000 millions in 50 days; total, 30,000 millions. Reactions: Local, very slight or negligible. Focal, very slight at first and later on not apparent. General, temperature rose 1° to 1.5° and never lasting more than 12 to 24 hours. The results were:—

- (a) Gonococci on admission Positive.
- (b) Complement-deviation on admission 2 M.H.D.
- (c) Gonococci negative in morning or prostatic smear Av. 30 days.
- (d) No urethral discharge " 34 "
- (e) Complement-deviation at maximum " 7 M.H.D.

Both cases had also syphilis and were under observation for 60 days in hospital. They have since reported to hospital and shown no signs of urethritis subsequent to cessation of treatment.

Two cases of acute posterior urethritis with involvement of prostate but not suppurating. Irrigation with pot. permang. 1 : 8000, gradually increased to 1 : 4000 twice daily, was carried out. Detoxicated vaccines were given, starting with 2500 millions, and increasing up to 10,000 millions in 24 days—total, 40,000 millions. The average results were:—

- (a) Gonococci on admission Positive.
- (b) Complement-deviation on admission 1.25 M.H.D.
- (c) Gonococci negative in morning or prostatic smear Av. 17.5 days.
- (d) No urethral discharge " 22.5 "
- (e) Prostate normal " 31.5 "

Both cases were subsequently seen weekly for one month, and showed no symptoms of disease.

The remaining 4 cases were extremely interesting. One had a chronic urethritis which had persisted for eight or nine months, due to a soft infiltration of the urethra. A second had a recurring urethritis due to involvement of prostate and to periurethral abscess. The third had a hard infiltration of posterior urethra and involvement of vesicles of four years' standing, while the last case had a marked litritis.

The reactions, except in the first case, were only slight, the focal reaction being marked at first, but after two injections negligible.

In the first case the subject was phthisical and he had a very marked general reaction after the first two doses, the temperature rising to 104.2° and 103.6° and remaining so for 24 hours after the first and second injections respectively, and accompanied by slight rigors and pain in the præcordium. His immunity response, however, was very marked (*vide* Chart 2 in preceding article by Captain Thomson), and the clinical signs cleared up very rapidly as the antibody increased. The result was:—

- (a) Gonococci at beginning of treatment Positive.
- (b) Complement-deviation at beginning of treatment... .. 2½ M.H.D.
- (c) Gonococci not found from any source... .. 42 days.
- (d) Discharge disappeared 61 "
- (e) Complement-deviation at maximum 11 M.H.D.

This patient has reported to hospital regularly for over two months and no clinical or pathological signs of urethritis are present. He had 12 doses of detoxicated gonococcal vaccine in 56 days, containing altogether 56,500 million gonococci (*vide* Chart 1, Captain Thomson's paper).

The other three cases, one of which had previously been on autogenous and ordinary vaccine treatment, also did well. Their antibody increased rapidly and concurrently their clinical symptoms disappeared. All were discharged and have reported well at intervals since and had no return of symptoms.

Comparative Series of Cases.

The gratifying results in this series of 31 cases made me anxious to test the effect of detoxicated vaccine in the ordinary run of cases as admitted to a military hospital, and I was able to do so under the supervision of Lieutenant-Colonel Bolam at Brighton Grove Military Hospital, Newcastle-on-Tyne. I suggested to Captain Thomson that it would be advisable to test parallel series of cases and to take them alternately as admitted, and put them on the various forms of treatment as mapped out. Eighty consecutive new admissions were taken and 20 cases put on each of the following courses of treatment.

Series I.—Irrigation with pot. permang. from 1 : 8000 to 1 : 4000, followed by Hg. ox. 1 : 5000 or zinc sulph. 1 : 2000 as symptoms indicated.

Series II.—Irrigation as above, and in addition doses of ordinary polyvalent gonococcal vaccine beginning with 5 millions and going up to 150 millions in 18 days: Total, 225 millions.

Series III.—Irrigation as above, and in addition polyvalent gonococcal vaccine, starting with 25 millions and increasing to 250 millions: Total, 725 millions.

Series IV.—Irrigation as above, and in addition polyvalent gonococcal vaccine detoxicated, beginning with 2500 millions and going up to 10,000 millions in 18 days; Total, 40,000 millions.

The vaccines used in II., III., and IV. series were from the same strains, only in Series IV. detoxicated, and the intervals in each case between doses was three days. All vaccines were given intramuscularly into the buttock.

The blood of each patient was taken at weekly intervals and tested by Captain Thomson at Rochester Row Military Hospital as regards the amount of complement deviated, so as to ascertain what the output of antibody was during the course of the disease, and how this output was affected by the different forms of treatment; and the different dosages and the different type of vaccine.

The various series were made up as follows:—

	I.	II.	III.	IV.
Anterior urethritis	cases. 2	cases. 2	cases. 1	cases. 1
Posterior urethritis	14	15	15	14
Urethritis and chronic rheumatism ...	—	—	—	1
Epididymitis	1	2	1	—
Epididymitis and prostatitis	—	—	—	2
Relapsed case or 2nd attack	1	—	2	2
Acute prostatitis	—	1	—	—
Subacute prostatitis	2	—	1	—

All cases were rested for the first four or five days and put on light diet. About the 7th day physical training was taken part in by all, except the prostatic, epididymitis, and joint cases. Diet was gradually increased from the 8th day. I append their clinical, pathological, and serological progress in tabular form in averages:—

Series.	C.D. on admission	Gc. on admission	Dry in days.	Neg. to pus and Gc.	C.D. av. at max.	In hospital under observation.
I.	2.1	Positive.	46 days.	36 days.	3	58 days.
II.	2.1	"	33 "	22 "	4.9	45 "
III.	2.8	"	30 "	20.2 "	5.25	42 "
IV.	2.1	"	17 "	14 "	8.05	35 "

The test of cure was made more stringent than is customary in military hospitals, all cases being kept under observation without treatment in hospital for 12 days in the case of Series I., II., and III., and for 18 days in Series IV. During those 12 days morning smears and urine after prostatic massage were examined, and were negative to pus and gonococci microscopically. Four irrigations with 1 : 500 magnesium chloride solution were given during 48 hours in the middle of that period to cause an outflow of serum and bring to the surface any gonococci which might be latent. Subsequent to this provocative irrigation prostatic massage was carried out and the smear after it examined microscopically. Morning smears and urine the following morning were taken and examined, the former microscopically for pus and gonococci and the latter macroscopically for threads, &c. In the case of the detoxicated series every case stood the tests and was negative to pus and all organisms in an average of 23.7 days, and no case relapsed after provocative irrigation. They were negative to gonococci in an average of 14 days. Of the other series No. III. was distinctly ahead of No. II., and No. II. of I. Complications such as periurethral abscess, prostatitis, and epididymitis occurred in both II. and I. series.

Very few of the non-vaccine-treated cases stood the test primarily, and in several of them mag. chlor. 1 : 500 alone as an irrigation was sufficient to cause a return of purulent or muco-purulent discharge.

Features in Detoxicated Series of Cases.

The noticeable features of the detoxicated series were:—

- (a) The rapid disappearance of purulent discharge and of gonococci. In five cases there was no apparent clinical sign of the disease after the 3rd, 5th, 7th, 8th, and 9th days respectively.
- (b) Complications after commencing treatment were entirely absent.

7th day in hospital. This proved remarkably resistant to treatment, and one was able to keep him under observation and test his blood successively for 11 weeks and watch the gradual fall in amount of the antibody produced after it was no longer stimulated either naturally by a gonococcal focus or by active immunisation with vaccine.

Captain Thomson had found, through experimental inoculation of normal non-infected persons, that antibody remained after active immunisation for roughly four months, and this

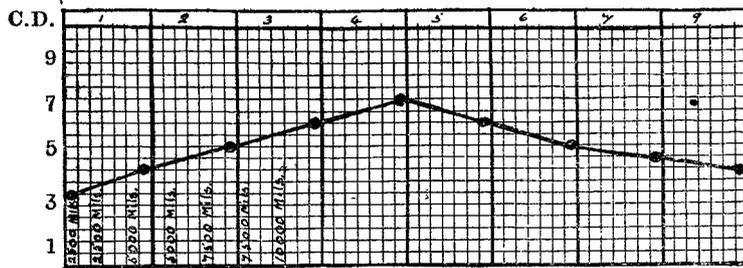


CHART I.—Case I, Series IV., gonococcal urethritis. Shows gradual increase in antibody during administration of detoxicated vaccine (40,000 millions). C.D., amount of complement deviated in successive weeks.

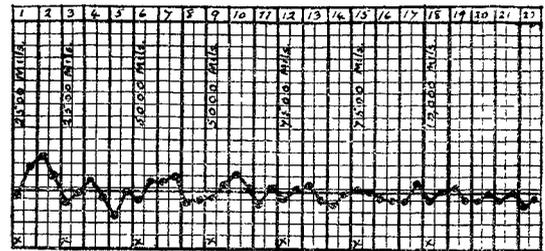


CHART II.—Case I, Series IV., showing general reaction after administration of detoxicated vaccine, denoted by x.

(c) Mixed infection with secondary organisms was much rarer in this series, four only showing any signs of it, due largely, I think, to the very slight damage which the gonococcus was able to cause to the urethral mucosa on account of its rapid disappearance in these cases.

(d) Patients had a sense of wellbeing, and their general health improved, the all-too-frequent attitude of despondency seen in gonorrhoeal patients was absent. This was noticeable in all the vaccine-treated cases.

(e) In all cases the clinical and serological results were in unison, and the more rapid the increase of antibody the more quickly did the objective symptoms subside and disappear.

Charts I., III., IV., V., and VI. show the weekly antibody response during the course of the infection of a typical case in each series.

would seem from this case to be borne out also in the case of an acquired infection, as seen in Chart I.

Case 2 showed very resistant gonorrhoeal rheumatism of the knee-joint. After four months in hospital without much apparent improvement he was transferred to my ward. His joint was swollen and full of fluid, but not tender. Gonococci were present in the urethral discharge, and his thigh muscles were wasted through long rest in bed. By the 8th day all signs of urethritis were gone and the swelling

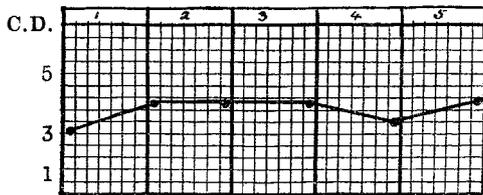


CHART III.—Case in Series I., gonococcal urethritis. No vaccine. The small rise in antibody is typical of the no vaccine cases.

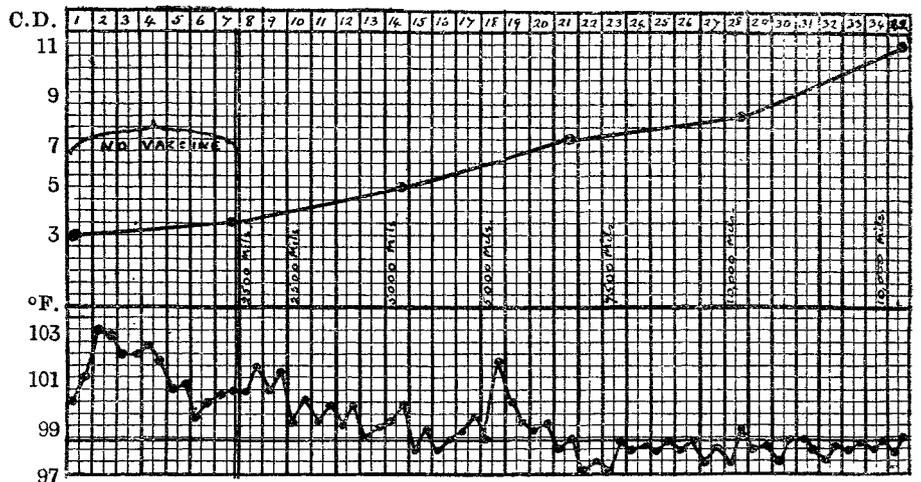


CHART IV.—Series IV., case of acute gonococcal arthritis; detoxicated polyvalent gonococcal vaccine (precipitate).

TABLE I.

Case.	On admis- sion.	7th day.	14th day.	21st day.	28th day.	35th day.	42nd day.	Case.	On admis- sion.	7th day.	14th day.	21st day.	28th day.	35th day.	42nd day.
1	3	4	5	6	7	6	5	11	1½	5	6	8	8	10	8½
2	3	5	7	7	—	—	—	12	1½	5	5	5½	—	—	—
3	1	5	6	8	—	—	—	13	3	4½	6	7	6	6	—
4	2	5	7	9	9½	—	—	14	2½	5	7	8	7	9	—
5	2	4½	7	9	—	—	—	15	1½	5	7	9	9	10	9
6	2½	4½	7	8	7½	—	—	16	2½	4	5	7	6	5	—
7	2	4	6	8	10	—	—	17	2	4	5½	7	6	5½	—
8	1	4	6	7½	8½	8½	9	18	2½	5	7	8	8	7	—
9	1½	4	5	7	7	6	—	19	2½	4½	6	7	6	5½	5½
10	2	3	4	4	4	3½	—	20	2	5	7	8	9	10	—

The first case in the series, 1 in the table (see Chart I.) illustrates remarkably well the rapid increase from 3 + to 7 + of antibody in 28 days. This case showed no symptoms whatever after the 8th day, and could have been discharged by the 12th or 13th day, but for the fact that he developed a soft sore on the glans penis about the

had much decreased. By the 14th day he was able to do physical drill, and left hospital on the 21st day fit for full duty. He has since reported well.

Case 3 was remarkably rapid. There was no sign or symptom of gonorrhoea after the 4th day. He stood every test during the succeeding 12 days and has reported since perfectly well.

Detoxicated Vaccine given Subcutaneously.

Subsequent to this series Captain Thomson suggested to me the advisability of giving detoxicated vaccine subcutaneously in the form of a precipitate, instead of a solution intramuscularly, with the idea of (1) gauging more accurately the local reaction, and (2) of getting more prolonged effect due to the precipitate remaining local and being ingested slowly by the cells which form antibody. In this way little of it is neutralised, because the antigen is not as a precipitate circulating in the blood to the same extent as when a solution is used, and so cannot unite with the already circulating antibody and be rendered inert.

I have now tried the effect of the precipitate subcutaneously in 7 cases and the results are, if anything, better than with the solution of detoxicated vaccine, although the local reaction is quite marked and remains for 2-3 days and often longer. The general reaction is not any more marked than with the solution, and never lasts for over 24 hours.

It was first tried in a man aged 40 who had contracted gonorrhoea in 1917, was treated in France for 10 weeks and discharged with gleet. Subsequent to this in 1918 he was treated in England for gleet and stricture for eight weeks. He had a history of exposure to infection 10 days before admission, and on admission had a profuse purulent discharge. Both knee-joints were red and swollen, tense, and painful to touch, and his left ankle was similarly affected. The temperature was swinging from 99.8° to 103°. Gonococci were numerous in smear. Both lobes of the prostate were tender and enlarged. He was given 2500, 2500, 5000, 5000, 7500, 10,000, and 10,000 millions on 8th, 10th, 14th, 18th, 23rd, 28th, and 35th days. By that time his urethral symptoms

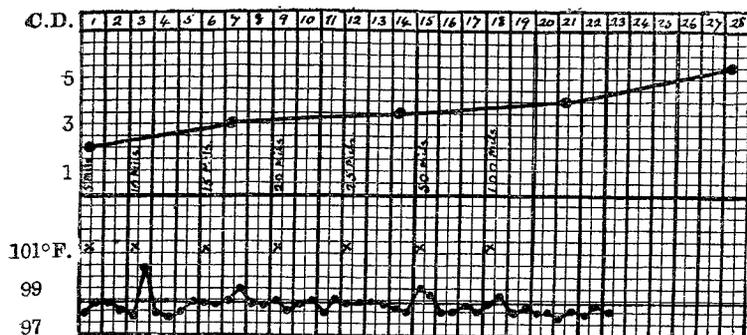


CHART V.—Case in Series II., gonococcal urethritis. x denotes injection of ordinary gonococcal vaccine.

had entirely cleared up, and his joint condition was so much improved that he was able to take active physical exercise. He left hospital for full duty in 60 days after commencing vaccine treatment. He had three injections after his course, making a total of 60,000 millions in all, and after none of them were the reactions severe except the fourth. (Chart IV.) His serum showed 3 units of antibody on admission, and seven days later before treatment was started, and in successive weeks, 5, 7, 8, 9, and 11 units of antibody substance after a course of detoxicated vaccine.

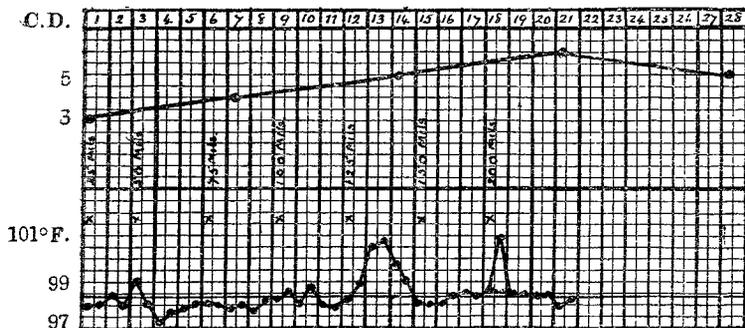


CHART VI.—Case in Series III., gonococcal urethritis, ordinary polyvalent gonococcal vaccine, 725 millions.

In the remaining cases, owing to the more prolonged action, when given subcutaneously, of the precipitate, and to the increased local reaction, I lengthened the interval between injections by one day, and the results have been even more favourable in acute cases, both complicated and uncomplicated.

Conclusions in the Comparative Series.

The objects of the comparative treatment in the above series were: 1. To compare the degree of toxicity of the vaccines, ordinary and detoxicated, as shown by (a) reaction, local and general; (b) loss of weight of patient or otherwise. 2. To compare the rapidity and amount of increased production of antibody (a) by nature, (b) by varying doses of ordinary polyvalent vaccine, (c) by detoxicated vaccines, as determined by the amount of complement deviated in the complement-deviation test of the patient's blood serum.

The conclusions in the comparative Series I., II., III., and IV., were as follows:—

1. (a) The local reactions are so negligible when vaccine is given intramuscularly that there is no appreciable difference as to toxicity in Series II., III., and IV., in spite of the great difference in dosage. (Vide Charts II., V., and VI.)

The general reaction was less apparent in Series II. than in Series III., and less in Series III. than in Series IV. In only one case in the latter series, however (No. 15), was the maximum temperature more than 100° F., and in no case did it last more than 24 hours. In this case the patient had had

15,000 millions in 9 days, and temperature reached 104° for about 10 hours subsequent to the third injection. He showed no general reaction after any subsequent dose and his complement deviation, which gradually rose from 1½ to 7 from the 1st to 14th day of his disease, and to 10 on 35th, showed that there was no marked negative phase produced by the violent reaction.

(b) No patient in the series lost weight, and the vaccine-treated series, especially Series IV., improved in their general health more than any of the other series.

2. (a) Antibody is only very slowly produced by nature, the average being from 2.1 to 3 units in 28 days as estimated by blood test.

(b) Antibody production is increased by vaccine treatment according to the amount of antigen injected, the average where dosage of 225 millions in 18 days is used, being from 2.1 to 4 units in 28 days, and where dosage of 725 millions is used, being from 2.8 to 5.25 units in 28 days.

(c) Antibody is increased rapidly and in greater quantity by detoxicated vaccine than by any other antigen used, the average increase in 28 days being from 2.1 to 8 units. The rich antisubstance formed passes into the blood serum and gets directly to the focus of infection and helps to prevent the propagation of the cocci in the tissues, both by agglutination and also by favouring their ready phagocytosis by the leucocytes and endothelial cells.

General Conclusions.

1. It is essential in gonorrhoea as in syphilis that the bacteriologist and the clinician work together, and the causal organism should be identified in all cases.

2. Vaccine therapy in gonorrhoea in the form of a solution or precipitate of gonococcus stroma, minus its toxin, can provoke a specific reaction, with the rapid production of specific antibody when given in sufficient doses. It is the most logical, scientific, and effective way of treating gonorrhoea and its complications.

3. Even in doses of 2500 millions up to 10,000 millions no such thing as a negative phase was produced.

4. No other form of vaccine, sensitised or otherwise prepared, and no phylacogen produces such rapid and great specific reactions unless used in toxic doses.

5. Detoxicated vaccine as prepared by Captain Thomson's method is practically non-toxic and in large doses very rarely causes a severe general reaction. It acts directly on the tissues and not by protein shock.

6. Every case treated by vaccines should be treated locally as a surgical condition, the vaccine being used as a valuable adjunct to the treatment, and the dosage of the vaccine regulated according to the serological results, and by close observation of the bacteriological process of the disease, and the reactions obtained. Only thus can we do justice to this most valuable and scientific method of therapeutics in gonorrhoea, as in other infections.

7. All vaccine-treated cases run a much milder course, and there is an absence of complications and less tendency to relapse, due to the fact that the patient has circulating in his blood for several months after the symptoms have disappeared sufficient antisubstance to protect him for some considerable time.

8. Removal of the toxic substance from vaccines opens up an immense field for the prophylactic and curative use of them in all diseases due to micro-organisms. During the recent influenza epidemic I have used detoxicated influenzal vaccine and a compound detoxicated catarrhal vaccine, &c., with so far promising results, both as a prophylactic and as a cure.

9. When secondary organisms are found in the urethral discharge it is advisable to use, in addition to gonococcal vaccine, one made up from the micro-organisms found present.

10. Detoxicated gonococcal vaccine should be of incalculable value in the complications of gonorrhoea in the female where local treatment is so limited.

I must express my thanks to Brevet Colonel Harrison for his valuable advice and guidance in the work, to Lieutenant-Colonel Bolam for his continual help and encouragement, to Dr. Allport for examining by urethroscope many of the earlier cases, and, finally, to Captain Thomson for his untiring zeal and enthusiasm in performing serological tests for me in such a large series of cases over a period of several weeks, during which his interest was not stimulated either by clinical knowledge of the case or of its treatment.

(Continued at foot of next page.)