TREATMENT OF GONORRHOEA WITH A SPECIFIC ANTITOXIN

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Since the earliest days of medical therapy it is no exaggeration to say that the world has awaited a specific remedy for the treatment of gonorrhoea. All attempts to discover a drug having a specific action, either direct or indirect, upon the gonococcus have failed, and the biological remedies hitherto produced have been equally ineffective.

Urged by Professor E. Mellanby at the beginning of February, 1934, to investigate a new biological approach in conjunction with Dr. Mervyn Gordon, our researches were then directed towards the production of a gonococcal antitoxic serum along the lines which had proved so successful in Gordon's hands for the preparation of anti-meningococcus serum. The two organisms have many points in common. Although their cultural characteristics and pathogenicity to animals are distinctly different, the meningococcus and the gonococcus resemble each other in their microscopical appearance, the negative reaction to Gram's stain, their intracellular habitat within the leucocytes, and the agglutination by identical specific sera, the absorption test being necessary to distinguish them.

Earlier Work

Serum treatment in gonorrhoea is not new. Previous work on these lines, however, has been confined almost entirely to the use of anti-bacterial sera prepared by immunizing animals with cultures of the living organism. The position was well summed up by Minet and Debains (1923) at the Congress of Urology, that "unfortunately, we know little about gonococcal toxin, and we do not know yet how to prepare an exclusively antitoxic serum—we are only aware of an anti-microbic serum, prepared at the Pasteur Institute by M. Nicolle." Clinical reports have shown that such a serum is helpful, but that it falls far short of being a specific remedy. Our investigations had not proceeded very far when our attention was drawn to the successful results obtained by Dr. N. S. Ferry (of the Parke Davis Research Laboratories, U.S.A.) in the production of a soluble toxin from the gonococcus by a method he had used in the preparation of a meningococcal toxin. Ferry, with Clark and Steele, had published a paper on the properties of a bouillon filtrate of the gonococcus. After reviewing previous works on the subject, the most important of which would appear to be the development of sera by de Christmas (1897), Herrold (1925), Herrold and Traut (1927), and Herrold and Hoffman (1930), the authors describe the method evolved in producing the filtrate, and express the view that it exhibited properties which seemed to characterize it as an extracellular toxin. It was found that the toxin was capable of producing skin reactions similar to the Dick reaction in dilutions of 1 in 1,000 and 1 in 1,500. Furthermore, the injection of animals with this toxin stimulated the formation of an antitoxin which neutralized *in vitro* as well as *in vivo*. Repeated subcutaneous injections of increasing doses of filtrate stimulated the formation of antisera with properties unmistakably antitoxic in nature, a characteristic which was evidenced by the fact that antisera prepared from both rabbit and horse neutralized the toxic properties of the filtrate.

Sensible of the possible advances to be achieved by the use of such a soluble gonococcal toxin for the production of an antitoxin to be used in the treatment of gonorrhoea, Parke, Davis and Co. were approached through Dr. Stanley White, their medical representative in this country, in regard to the preparation of a gonococcus antitoxin for clinical trial. Using a method practically identical with that devised by him for the production and standardization of meningococcus antitoxin, Dr. Ferry prepared an unconcentrated gonococcus antitoxin. This was later concentrated by the Banzhaf method, which leaves the antitoxic potency in the pseudo-globulin fraction, a point which Ferry considers supports the evidence in favour of the product being a true antitoxin.

The antitoxin was placed in my hands by the courtesy of Parke, Davis and Co. through the kindness of Dr. White, to whom I am also indebted for assistance, not only on the laboratory side, but also in the subsequent clinical investigation.

Preliminary Trials

Initial trials were made with an unconcentrated antitoxin on complicated cases, both acute and chronic, chosen for their severity as being a more rigorous test. As the dosage and reaction were unknown its use was restricted to in-patients. It was at once noticed that the antitoxin appeared to be exerting a specific effect. The average daily dose of this unconcentrated antitoxin was found to be 5 to 20 c.cm. when injected intramuscularly. Even with these small doses caution was necessary, as in some cases severe reactions occurred. The beneficial results, however, were beyond question, and it was found possible, even after severe reactions, to repeat the injection twenty-four or forty-eight hours later.

After these preliminary trials a request was made for a concentrated antitoxin from which much of the extraneous protein had been removed. This was kindly supplied to me with the information that theoretically it should prove five times more potent than the unconcentrated product. In practice this proved to be the case. In no instance was it necessary to administer more than 8 c.cm. of this concentrated preparation at one time, and in most cases 5 c.cm. appears to constitute a maximum dose. The average dose was found to be 1 c.cm. intramuscularly; doses of over 2 c.cm. in many cases caused severe systemic disturbance. Later a routine procedure was adopted of injecting adrenaline simultaneously and mixed with the antitoxin. It appears advantageous to inject the adrenaline with the serum rather than to administer it separately. Three minims of adrenaline chloride solution 1 in 1,000 were given with 1 c.cm. of the concentrated antitoxin; four minims with 2 c.cm.; and five minims with 3 c.cm. In this way the reactions have been controlled to such an extent that it has been possible to treat out-patients with this concentrated antitoxin.

A surprising feature was the comparatively small amount of antitoxin necessary, particularly when one considers the comparatively large doses of meningococcus antitoxin which are essential to combat meningococcal infections, until Gordon suggested that almost certainly both an active and a passive immunity were being obtained.

The question of a reaction attributable to some reason other than a specific effect, such as the protein content of the serum, was investigated. To obtain satisfaction on this point a series of controls with normal horse serum was carried out. In no instance had the serum any influence on the infection or the patient; neither did it cause reactions of any kind, nor was temperature or respiration disturbed.

Clinical Results

The following data refer to 157 male patients treated with the gonococcus antitoxin, and these may be separated into:

Acute uncomplicated cases	...	...	...	42
Acute complicated cases	...	...	...	84
Chronic complicated cases	...	...	...	31

The acute complicated cases included: epididymitis, 37; arthritis, 27; vesiculitis, 8; prostatitis, 6; conjunctivitis, 3; iritis, 2. The chronic complicated cases were: epididymitis, 14; arthritis, 11; prostatitis, 4; vesiculitis, 1; iritis, 1.

It is extremely difficult to summarize the clinical results of such an erratic disease as gonorrhoea. Some cases were obviously more severe than others, and the resistance of the patients varied considerably; but even so the following may be taken as a fair indication of the percentage of successes or otherwise of the antitoxin treatment: excellent, 49.6; good, 26.9; fair, 14.8; bad, 5.9. Clinical relapses occurred in only 6.6 per cent. in this series.

The duration of times mentioned in this paper indicating the periods in which a "cure" or some clinical improvement was attained should not be taken too literally or criticized too severely. Times have been mentioned so that the reader may form an approximate evaluation of the results obtained. The times required to effect a cure in gonorrhoea are subject to so many varying factors, more especially the personal equation of the assessor, that they are seldom published; for who is bold enough to state *precisely when* a gonococcal infection is cured? My tests of cure have been described elsewhere. They are extremely rigid, and a certain period of time, varying according to the type of case, must elapse while they are being applied. In evaluating a cure it is the method in which the disease retrogresses, pathologically as well as clinically, on which the expert mostly relies. Careful notes and the results of the chronological series of pathological findings reveal the evolution of the process of cure, and are more valuable than a single set of tests applied on one day only. Hence a fair estimation of when an infection ceased is most accurately obtained by scrutinizing the case record after the patient has been under observation and tests for a prolonged period. In this investigation, although some "defaulted," each patient was kept under observation as long as possible; no case was discharged at the earliest moment.

Acute Gonorrhoea, Uncomplicated

Dysuria, irritation, and discomfort subside earlier than usual. The patients commonly declare how well they feel, and express their belief in the efficacy of the injections, as they "feel much better for them."

An analysis of the thirty-six cases that completed the tests of cure and were observed for at least three months shows that a "cure" was effected in two cases in sixteen days; one case, nineteen days; four cases, three weeks; twelve cases, four weeks; five cases, five weeks; seven cases, six weeks; and in five cases, eight weeks.

In a week even the uncomplicated cases of acute gonorrhoeal urethritis have given rise to dissemination of gonococci through the blood stream, although this may not be apparent. If the antitoxin is given early enough, however, complications such as posterior urethritis, vesiculitis, prostatitis, epididymitis, and arthritis seem to be prevented. Among the total of forty-two cases only three relapsed or developed a complication.

In one case the urethritis ceased on the fifteenth day, but recurred slightly on the twenty-first day, although the patient had received fifteen daily doses of 1 c.cm. of the concentrated product. The second case developed a tenosynovitis of the right wrist four weeks after 45 c.cm. of the unconcentrated antitoxin, the dosage being 10, 15, and 20 c.cm. on three successive days.

Epididymitis

In general, complete relief from pain is obtained in twenty-four to forty-eight hours, and occasionally a sudden and astonishing cessation of pain in five to six hours, accompanied by a rapid decrease in swelling. Several patients discharged themselves from hospital within five or six days because "they felt so well." It is also worth recording an experienced and impartial observer's note in one case twenty-four hours after the first injection of 10 c.cm. of unconcentrated antitoxin—namely, that he had "never seen such a rapid and marked improvement before."

An analysis of forty-two cases indicated that one patient was "cured" in sixteen days; four in twenty-one days; one in twenty-three days; one in forty days; one in forty-five days; seven in four weeks; six in five weeks; three in six weeks; one in seven weeks; seven in eight weeks; three in ten weeks; five in twelve weeks; one in fourteen weeks; and one in sixteen weeks. Among fifty cases only one relapsed.

This patient had a bilateral vesiculitis with a left epididymo-orchitis of two months' duration. He then received only 6 c.cm. of the unconcentrated antitoxin, 1, 2, and 3 c.cm. on three successive days, and developed a right epididymo-orchitis four weeks later.

Arthritis

Patients under this category, "arthritis, acute and chronic," include the conditions arthritis with effusion, fasciitis, and tenosynovitis. The time required to obtain "nil abnormal" clinically and pathologically in urine, vesicles, prostate, and urethra (all tests being pathologically clear except for an occasional positive gonococcal fixation test) was as follows: in acute cases, eight in four weeks; six in six weeks; one in seven weeks; two in eight weeks; two in ten weeks; two in twelve weeks; one in twenty-four weeks; and one in forty weeks. In chronic cases, one in three weeks; one in five weeks; three in six weeks; two in eight weeks; and one in nine weeks.

The clinical results are rapid in recent acute cases, pain and swelling ceasing in a few days, sometimes after the first injection. Generally the joint appears normal, has full mobility in a week, and the result is permanent.

For example, a severe case of acute gonococcal arthritis complicated with a bilateral epididymitis, and a very painful arthritis of both knee-joints, tense with fluid, had regained normal movement in both knee-joints on the fifth day; pain was absent and very little fluid remained. In fifteen days this patient was normal clinically and discharged from in-patient treatment.

Similarly with the chronic cases. Generally the patients are able to walk or to use arms or hands without disability, and to leave hospital within eighteen to twenty-one days instead of the usual five to six weeks. In most cases relief from pain occurs within thirty-six to forty-eight hours, with rapid diminution of the effusion and increased mobility of the joint. In one chronic case with four years' history, where a cure was effected after six weeks, the patient made the observation that he had had "no pain, and had not been so comfortable for months." Another case of arthritis, also of four years' duration, was "cured" in nine weeks. All cases recovered

completely, even those which temporarily relapsed. No disability or ankylosis remained in any single case.

Three acute cases relapsed. The first, an acute arthritis of the left knee, improved, but relapsed four weeks after 6 c.cm. (1, 2, and 3 c.cm.) of the concentrated serum. The second, a severe polyarticular case in which both ankles, wrists, and the right knee were involved, improved temporarily with 6 c.cm. (1, 2, and 3 c.cm.) of concentrated serum, but four weeks later a slight effusion returned in the knee-joint, although the other joints had recovered. The third, an acute urethritis of three weeks' duration, had an effusion in both wrists and knee-joints. Initial improvement followed 20 c.cm. (2, 3, 5, and 10 c.cm.) of the unconcentrated serum, but the fluid returned in the left wrist ten days after the last injection. The focus was in the right vesicle.

One chronic case of seventeen years' duration relapsed. It was particularly severe, being complicated by an acute epididymo-orchitis, iritis, bilateral vesiculitis, and prostatitis. Two months after 78 c.cm. of the unconcentrated antitoxin had been given an effusion developed in the knee-joint. After a second series of injections (20 c.cm.) no relapse occurred over a period of nine months' observation.

Reactions

No fatality has occurred among the cases treated. All the reactions, of whatever type and degree of severity, have been transient and left no permanent disability. Provided the dosage does not exceed 15 to 20 c.cm. in the case of unconcentrated antitoxin, and 3 to 4 c.cm. in the case of the concentrated antitoxin, the reactions are not alarming or more marked than those caused by the sera commonly used in other infections.

Urticarial serum rashes develop earlier with the concentrated than with the unconcentrated antitoxin, generally within three days after the last injection, instead of within four to ten days with the unconcentrated preparation. With the concentrated product the rash is more transient, and generally localized to the buttocks. With the unconcentrated serum the rash has been more generalized about the trunk and limbs, and takes longer to disappear.

The duration of the rash with the unconcentrated product was as follows: in two patients, one day; in one patient, two days; in one patient, three days; in three patients, four days; in three patients, five days; and in one patient, six days. In four patients the rash developed one day after the last injection; in three cases, two days; in nine cases, three days; in two cases, four days; in three cases, five days; in one case, seven days; and in one case, ten days. In ten cases the rash appeared on the buttocks.

Serum sickness occurred in five cases; two of these had no other signs of a serum reaction. Stiffness in the shoulders, headache, rigors, pain in the back and joints or in the limbs were also reported. "Thermal reactions" due to the serum were also experienced in fourteen patients in a series of 112 cases. Two developed a sore throat with an accompanying pyrexia of 103.6° in one case and 103° in the other. In both cases the pyrexia and sore throat had subsided within twenty-four to forty-eight hours, and were not septic in character.

Apart from the customary reactions already enumerated, certain additional phenomena, including some types of pyrexia to be mentioned later, provide additional evidence of specific action. A period of approximately five hours after an injection seems of peculiar significance in all types of case, both acute and chronic. About this time the following phenomena have been experienced by different patients: sudden cessation of pain, "collapsed feeling," rapid pulse and pyrexia, rigors, profuse perspiration, transient nausea, and faintness.

At this time one case of salpingitis with a temperature of 102.2° felt "as if she had been doped," and then lapsed into a deep sleep. When she woke ten hours later both pain and pyrexia were absent, and remained so. Another patient with a gonococcal septicaemia and a bilateral salpingitis had a sudden rise of temperature from 101° to 104° during this five-hour period. Then she complained of pains in the body and limbs, and became delirious for three hours.

One out-patient with acute uncomplicated urethritis who had received 1 c.cm. of the concentrated antitoxin daily for seven days, on the eighth day experienced a mild rigor, which was followed directly after by a profuse macular rash covering both legs up to the knee-joint. Independent observers agreed that this was not a typical serum rash; it had no urticarial characteristics, and did not irritate. The only possible conclusion was that the patient was experiencing a gonococcal skin reaction which, although rare, has been noted by me on occasion. This again is supportive evidence that the antitoxin has a specific effect. Incidentally, before this occurred all signs and symptoms of a gonococcal infection had disappeared.

Pyrexia

Analysis of the temperature charts of sixty in-patients separates naturally into three groups; two types of pyrexia confirming the specific reaction of the antitoxin, and a third apyrexial class.

(a) A specific pyrexial reaction rising progressively (Fig. 1) as the injections proceed, but dropping to normal directly

FIG. 1.—An uncomplicated gonococcal urethritis.
G = Gonococcus antitoxin 2 c.cm.

FIG. 2.—An acute gonorrhoeal urethritis complicated by prostatitis, a right-sided vesiculitis, and a right-sided epididymo-orchitis.

G = Gonococcus antitoxin 2 c.cm.

the administration of the antitoxin ceases, and remaining normal (except for serum thermal reactions), occurred in forty-four patients.

(b) A specific pyrexia falling (Fig. 2) after the first injection gradually and progressively, as the injections proceed, to normal, and remaining normal (except for serum thermal reactions), occurred in twelve cases.

(c) The temperature remained normal during the administration of the injections in four cases.

At this point the cause of these reactions may be discussed. Several possibilities emerge. One, that the gono-

coccus is a delicate organism easily destroyed, possibly with the liberation of toxin. If this is the explanation then the patient may be experiencing a toxæmia as the result of auto-inoculation, further doses resulting in a complete neutralization. Or the gonococcus antitoxin may possess some residual toxin which, circulating in the serum of the horses, is contained in the antitoxin.

It may be that some of the reactions are due to impurities in the toxin used in the preparation of the antitoxin. I have been unable to obtain evidence that the reactions are due to protein in the antitoxin. In order to demonstrate this point a series of controls were carried out on in-patients in the same ward under identical conditions, first with a natural horse serum, and secondly with a concentrated horse serum of the same concentration as the concentrated gonococcus antitoxin. In no instance did the serum influence the infection or the patient, nor was there any evidence of pyrexia or other reaction. These controls were also important in demonstrating that the effects which were obtained with the antitoxin were presumably specific and not to be ascribed to "protein shock." Again, variations in the type or strain of gonococcus may affect these reactions, and patients may vary in reaction to the antitoxin according to the resistance they may possess individually against the infection. Possibly the patients in group (a) have a poorer resistance than those in group (b). It has to be admitted that it is not yet possible to explain all the different phenomena and types of reaction that have occurred; but clinically it seems certain that an active as well as a passive immunity is established.

Discussion

At the time of writing a total of 789 injections have been administered to 178 cases. Early in the investigation 3,090 c.cm. of unconcentrated gonococcal antitoxin, and later 452 c.cm. of concentrated gonococcal antitoxin, have been given intramuscularly or deep-subcutaneously. Hitherto I have hesitated to give the antitoxin intravenously, but more satisfactory results should be obtained by this route. The results obtained with the concentrated antitoxin have been, if anything, better than those treated with the unconcentrated product.

When treating out-patients it was essential to avoid reactions so far as possible, and more recently the dosage has been restricted to 1 c.cm. of the concentrated product daily. Patients have received 1 c.cm. each day over the period of a fortnight, and clinically appeared to be cured. Obviously the term "cured" cannot be employed until the patients have been subjected to exhaustive clinical and laboratory tests. There is always the disadvantage that the out-patient may not follow the instructions which have been given to him, so that in many ways the use of the antitoxin in the out-patient department is a more severe test than when the patient is in hospital under supervision. Treatment is further complicated by the varying resistance of the patients to the infection, which may, for instance, be good, medium, or poor, so that it is not possible to be definite in regard to dosage. Various schemes of dosage have been on trial, and although in one case as much as 100 c.cm. of the unconcentrated antitoxin was administered, my limited experience indicates that too large a dose is a mistake. It is better to give small doses regularly than large doses occasionally. In most cases the best results seem to be obtained when the injections are given daily in small doses of 1 to 2 c.cm. of the concentrated antitoxin, not increasing the dose as the injections proceed, but maintaining it at the same level, and continuing until the patient has improved

clinically—that is, until the discharge ceases, pyrexia is not provoked, and complications, such as an arthritic effusion, disappear.

The requisite dosage may vary according to the individual resistance of the patient to the infection. Patients may be separated into three groups accordingly: (a) good, (b) medium, and (c) poor resistance. Probably (a) require a very small total dosage, recovery is remarkably rapid—two injections may be sufficient to enable the patient to effect a cure; (b) require the daily repetition of small doses over a longer period than (a); (c) require larger doses over a longer period still than (a) or (b).

The more acute the case the greater the necessity for the antitoxin. Delay in administering the serum renders the prognosis less satisfactory. Given early in arthritis the effect is rapid; administered later there is temporary improvement and then a tendency to relapse, necessitating further treatment.

Vaccines and sera hitherto produced are declared to be useful mostly in the chronic or only in the acute stages; seldom or never are they recommended for both types of case. These preliminary trials seem to indicate that this antitoxin affects both acute and chronic cases favourably. It may be that further refinements will be possible in the production, and perhaps the method of evaluating the product may be improved, but the fact remains that this experimental gonococcus antitoxin would appear to be the most valuable remedy which has yet been forthcoming since gonorrhoea was subject to scientific investigation.

Summary

1. In this preliminary report the results obtained with this experimental gonococcus antitoxin have been distinctly encouraging.

2. Acute and chronic cases, complicated and uncomplicated, respond equally well, which is in marked distinction to other biological preparations hitherto available.

3. Reactions and results indicate that this antitoxin possesses specific therapeutic properties; properly regulated controls confirm this.

4. Clinical evidence suggests that active as well as passive immunity is established.

5. Sufficient data are available to indicate that a remedy for the treatment of gonorrhoea has been evolved which offers considerable promise.

I wish to extend my thanks to Professor E. Mellanby for initiating this research; to Dr. Mervyn Gordon for his expert advice, particularly from the serological aspect; to Sir Frederick Menzies for his encouragement and kindness in allocating hospital accommodation, and to members of his staff for their co-operation; to Professor de Wesselow for valuable assistance in the later stages of the investigation, and for help from members of the staff at St. Thomas's Hospital; to Dr. N. S. Ferry and Dr. Stanley White of the Parke Davis Laboratories, to whom acknowledgement is made in the paper; and finally to Parke, Davis and Co. for their courtesy and ready acquiescence in placing their resources at my disposal.

REFERENCES

- Anwyl-Davies, T. (1935). *The Treatment of Venereal Diseases in General Practice*, Bale, London.
 Clark, L. T., Ferry, N. S., and Steele, A. H. (1931). *J. Immunol.*, **21**, 233.
 de Christmas, J. (1897). *Ann. Inst. Pasteur*, **11**, 609.
 Gordon, M. H. (1918). *British Medical Journal*, **2**, 335.
 — (1920). Cerebro-spinal Fever. Medical Research Committee, Special Report Series, No. 50, London.
 Herrold, R. D. (1925). *J. Amer. med. Ass.*, **84**, 361.
 — and Hoffman, S. J. (1930). *Ven. Dis. Inf.*, **11**, 397.
 — and Traut, E. F. (1927). *J. Infect. Dis.*, **40**, 619.
 Minet, H., and Debains, E. (1923). *J. Urol.*, **16**, 390.