A FURTHER COMMUNICATION ON THE TREATMENT OF GONORRHOEA BY KATAPHORESIS.¹

BY MAJOR A. T. FROST,
Royal Army Medical Corps.
Royal Herbert Hospital, Woolwich.

In November, 1923, I reported to this Section the trend of a line of research on a new arm in medicine in the treatment of gonorrhoea, by making use of the pressure of an electric current to bring the gonococci when deep in the tissues within the sphere of action of colloidal antiseptics, in contradistinction to the use of the rate of flow of a current of electricity to convey chemical antiseptics to the tissues.

The preliminary results of this new method of treatment, known as kataphoresis, were encouraging and were sufficiently definite to bring before you. At the first report some hundred cases were in hospital for an average of thirty days when treated by a negatively charged colloidal silver made electrically. It was anticipated that chemically prepared colloidal silver would act as well as the electrically made colloid. This expectation has been verified during the past year.

As practically no literature exists dealing with the use of kataphoresis in medicine a difficult and unlighted path has been travelled during the course of work of the past year. Many side-tracks were traversed, but these only led us into further darkness.

Gradually the period spent by patients under treatment for gonorrhoea in hospital increased till the time in hospital approached fifty days for the average case.

It was only in September of last year (1924) that the advice given by Sir William Leishman [2] at the meeting of this Section in November, 1923, could be carried out effectively. He advised the use of the microscope to elucidate the action of the treatment on the tissue cells and organisms. And we who have been working at the subject beg to acknowledge that any light which has come to us has been through following that advice.

The only change in the treatment up to the end of the year 1923 was the substitution of chemically made for electrically made silver colloid. In April, 1924, it was noted that the number of closed urethral follicles was

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¹ Paper read at Meeting of the War Section, Royal Society of Medicine, February 9, 1925, and published in the Proceedings of the Society.

Since reading the above paper it has been found that macrophages are much increased in the pus from the urethra after toxin kataphoresis. The macrophage can be seen engulfing injured leucocytes with their contained gonococci, which are also in various stages of disintegration within the macrophage.
more marked in those cases treated by kataphoresis than in cases in which this method of treatment had not been used. This condition was due to the use of a negatively charged colloid in contact with tissues which are themselves negatively charged; and by the driving of gonococci more deeply into the urethral mucous membrane increased exudation and reaction in the follicles were set up. This resulted from the necessary experimental variations of treatment which it was thought might improve the treatment. The colloid was changed by giving it a positive instead of a negative charge, so that the electric pressure would act towards the lumen of the urethra instead of driving organisms deeper into the tissues. This appeared to have been the means of reducing the number of closed follicles, but did not reduce the stay in hospital. At the same time an attempt was made to reduce the number of applications and also to diminish the time during which the colloid under electric pressure was applied to the urethra.

The method adopted by the middle of September, 1924, was that of applying a positive colloid for twenty minutes and of repeating it on four successive days. The results were not good. At this point a series of patients was taken, and during the treatment the movement of the colloid which was being applied to the patient was watched under dark-ground illumination, under exactly similar electrical conditions. As the current acted on the colloidal silver it was soon seen that the action was not a simple one, but the resultant of a combination of physical and electrical phenomena.

One of the earliest of these phenomena to be noted was a deposit on the end of the positive electrode in the urethral nozzle. This was found to be a mixture of precipitated colloid, pus-cells, and gonococci. Next it was demonstrated that, after a period of time depending on the amount of current and voltage employed, the route of the colloidal particles, which began at the positive pole within the nozzle and progressed towards the tissues of the urethra, as was intended, actually changed its direction, and that the stream of colloidal particles passed from the mucous membrane towards the positive pole and led to a deposit of cells and gonococci on the positive wire above mentioned. By the addition of suitable colloidal indicators, such as phenol red, to the silver colloid, the change in the amount of concentration of H and OH set free in the colloid by the action of the current on the water in which the silver was suspended was accurately measured.

Further information was obtained during the experiments with the use of fifteen per cent gelatine to represent the tissues. The silver colloid was precipitated on the surface or edge of the gelatine at definite concentrations of H and OH-ions in the fluid, and the particles were redispersed at a higher concentration of these ions, following the known physical laws of colloidal chemistry.

These experiments were carried out under dark-ground illumination with gelatine fifteen per cent to represent the urethra in section, and were
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done to ascertain whether it was possible to cause the colloidal silver particle to penetrate into the tissues. The results were both interesting and suggestive of the possibilities of this form of treatment, for the silver could be seen first to be deposited on the surface of the gelatine, and then from this deposit a clear layer of undeposited colloid could be seen penetrating for a depth of two millimetres into the gelatine. The conditions as regards the colloid, the time, and the amperage and voltage necessary to bring about these results were carefully noted.

Patients were put under as nearly identical conditions in the circuit as in the experiment under the microscope, and the clinical results were noted. The experiments were carried on till the best results were obtained with the particular method under trial. It was considered that the colloidal metal used was of secondary importance compared with the conditions under which the electric pressure and current were applied, and with the acidity or alkalinity of the fluid in which the colloid was suspended.

The gonococcus was then put under test as to how it reacted under these conditions. It has been noted that a high degree of alkalinity resulted from the passage of the current through the urethra. The gonococci could be seen actually moving to the positive pole, which accounted for the concentration of cells and organisms on the tip of the wire in the urethral nozzle, and gonococci were seen dissolving in the fluid. Further, when the direction of the current was reversed and the movement was directed towards the surface of the gelatine, the organisms could be traced to the surface of the gelatine. Similarly the pus-cells became swollen and lysed with their contained gonococci. The leucocytes became twice or treble their original size before breaking up, their polymorphic nuclei changing into a round or oval contracted mass at the same time.

Owing to the brief time at disposal I propose to omit any record of the experimental work and confirmatory tests of the observed phenomena, also any detailed account of the stages which led up to our present position with regard to kataphoresis; but it is of interest to show some of the actual slides made during the early stages of the inquiry, which formed the basis upon which the further work developed.

The last point in the scheme laid out for investigation in 1923 was whether immunity could be obtained during the disease by adding the toxins of the gonococcus to the colloid in the hope of getting them conveyed into the tissues when adsorbed to the colloid. In the gelatine experiments solutions of the gonococcus protein were definitely seen to penetrate and become precipitated by the oppositely charged ions in the substance of the gelatine. For a year it had been the custom of Major Lambkin, the officer in charge of the treatment of gonorrhoea at the Royal Herbert Hospital, Woolwich, to use a solution of gonococci in distilled water —250,000,000 in each cubic centimetre—as a provocative test of cure. He finds that this method is the most active test, much more reliable than the injection of irritating chemicals such as silver nitrate or magnesium chloride.
At the laboratory various strengths of the proteins obtained from the gonococcus were used to protect the colloid, and also various fractions of the protein were used in an attempt to find one with the least toxic and highest immunity value. The first protein used was the endotoxin, ranging in strength from 30,000,000 to 160,000,000 organisms per cubic centimetre. This was excellent when used electrically as a provocative of pus and gonococci in an uncured case which had become dry. Other fractions tried were the alkali soluble fraction, the alcohol insoluble fraction, the mixture of the alkali soluble fractions of the *Gonococcus, Staphylococcus*, and of *Bacillus coli*, the two latter being added owing to the poor antigenic value of the gonococcus alone.

An increase of infiltration of the urethra was noted at this period (December, 1924, to January, 1925). This could be directly attributed to the introduction of the toxin into the urethra during the acute stage of the disease. There was also seen an increase in the number of cases suffering from posterior urethritis and epididymitis.

The method of application of the colloid and of the colloid protected with toxin was reviewed, and the whole method investigated with the aid of charts made for each case, showing the dose of toxin, type of toxin, time of application, and strength and pressure of the current used. These charts showed that those cases which received the weaker dose of toxin, and had a shorter time of application, did much better than those undergoing more active and stronger applications. The urethral infiltrations and closed follicles practically ceased, and the urethra began to look normal after a few applications of the colloidal silver.

At the time of writing this paper the method in use is first to wash out the urethra with lime water of a strength of 0·2 per cent, and afterwards to remove the salts with distilled water. Next the bladder is filled with silver colloid of a strength of 1 in 32,000 silver, with N/300 NaOH added, equal to 0·13 gramme of NaOH per litre of colloid. Then the patient sits on a pad of copper gauze well wrapped in lint, the pad fitting into the hollow of the perineum, and the penis is bandaged up to the tip with a one-inch bandage, which is then soaked in water. The negative pole is attached to the perineal pad by soldering the wire to the copper gauze. The positive pole is led into the colloid by means of a wire which ends just at the tip of the special flanged nozzle which carries the colloid to the urethra. Means are adopted in the circuit to vary polarity when required.

The colloid itself in the glass funnel consists of a 1 in 32,000 silver colloid, chemically made by means of placing in a litre measure eighty cubic centimetres of a one per cent solution of silver nitrate, and adding N/1 ammonia solution until just a faint haze is left. The litre is made up with triply distilled water. Another litre measure is filled with triply distilled water to which 100 cubic centimetres of tannic acid are added of a strength of 1·3 gramme to the litre. The two are mixed with constant rotation of the bottles used. The colloid is made positive by means of positively
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charged H-ions—many methods of effecting this without precipitation of the colloid are available. Lastly, a small quantity of gonococcal endotoxin of an equivalent strength of half a million organisms per cubic centimetre is added to the colloid.

The patient (whom we have left seated on the negative pad with his bladder filled with negative colloid) now inserts the nozzle into his meatus, and when his urethra is full of colloid, the current at a pressure of 112 volts is turned on in the main circuit including the potentiometer.

An accessory resistance of Eureka wire is inserted in a lamp socket so that the potential drop of the main circuit is 112 volts, made up of a potential drop of 12 volts in the lamp socket-resistance and 100 volts in the potentiometer.

By means of the sliding contact of the potentiometer the pressure is slowly increased in the patient's circuit from zero to 100 volts and allowed to act for ten minutes. The current is then reversed and the direction of the colloid particles for the next ten minutes is from the inside of the urethra towards the pad, through the tissues, carrying in colloid and endotoxin. In the first instance, for the first ten minutes, the negatively charged gonococci are attracted out of the tissues into the lumen of the urethra, and, as has been mentioned, can be recovered from the tip of the positive wire inside the nozzle.

This process is repeated for two or three days, and if successful the case dries up and the treatment is not repeated unless failure to clear up the case is indicated by continuance of gonococci in daily smears from the urethra. When the patient is reported as having a dry urethra for five or six days, the next stage of the treatment is in the form of a test of cure. If the urethroscopic examination of the urethra shows it to be clear of inflammation, and the vesicles and prostate are found normal, and if the case is clear for six days after what is really producing a negative phase in the urethra—namely, the injection of endotoxin-protected colloid electrically applied—the case is declared cured. This test is carried out as follows: The preliminary preparation is the same as before, and the kataphoresis stage comes next. Then a small ten-cubic-centimetre funnel, with a similar electrical attachment to that used in kataphoresis, is filled with endotoxin-protected colloid, each cubic centimetre of which contains the equivalent of twenty or thirty million gonococci. This is introduced into the urethra by means of the special flanged nozzle, and the current slowly applied. The amperage and voltage and the strength of endotoxin-protected colloid must be watched and not exceeded, otherwise too big a reaction may occur, especially if the case is not cured. If the case is cured no reaction occurs. The amperage should not exceed three-fifths of a milliampere; the voltage should be kept below twenty. The time of application which is found to be best is one and a half minutes, as application for a longer time than this is liable to produce more reaction and infiltration in uncured cases, and delay in final cure.
The foregoing record is a brief account of the position of this research up to the present date.

Owing to the numerous factors involved in this work, and the difficulty of judging by immediate observation on a few cases the effects of small changes in the method of application—for example, the difference of half a minute in applying the test of cure—it may take years of work to obtain what is essential, a fixed method of treatment. The basal fact with regard to the method consists in a definite control of the disease being possible in so far that gonococci can be taken out of the tissues and ducts of the urethra; that the protein of the gonococcus can be driven into the tissues, and probably, by analogy, deposited within the tissues as a precipitate.

In discussing the results, it must be emphasized that disease external to the urethral canal is at present outside the scope of kataphoresis. It is only in the acute cases and in those in which the patients suffer from chronic anterior urethritis that hope of success is predicted. The figures might be divided into three groups for comparison. The first group comprises 107 cases treated without any knowledge of the principles which govern kataphoresis, with an average time of thirty days in hospital, reported to this Section in November, 1923. The results were good. But the conditions under which the colloid was made were constantly changing, and the resulting colloid was variable in strength and in size of colloidal particle. It also tended to produce chronic folliculitis towards the beginning of the second period, and therefore it was abandoned.

The second period, from May to December, 1924, was a period of retrogression owing to the number of cases which failed to clear up under an average of fifty-three days in hospital. This period was one of frequent change of the method of application. The principal method consisted in the use of a positive instead of a negatively charged colloid. It is now recognized that the principal cause of failure was too long application of the current, which has been remedied in the third period. The number of cases treated in the second series was 191.

Since September 30, 156 cases have been treated up to date and the patients were 39·3 days in hospital. The first two months were devoted to experimental work, as has been briefly detailed. Definite lengthening of the period in hospital resulted from using for immunity the strong toxin-protected colloid which is now only used as a test of cure. These cases developed infiltrations which took a long time to clear up, and the method of treatment has not been continued. However, within the last few weeks a modification has been tried by adding the equivalent of 500,000 gonococci per cubic centimetre of silver colloid in the treatment. It was observed by this method, and first noted when using the stronger toxin-protected colloid, that on the fourth to the sixth day after treatment had been given, all pus-cells were degenerated and appeared to be lysed. As the time was too long for any direct action of the treatment, it is suggested that an autolysin is developed in the tissues which is either a
direct or indirect result of the introduction of the toxin by kataphoresis. This is shown by the charts, and is indicated by an interrupted line in the curve of epithelium to pus ratio. During this cell-disintegration no gonococci can be detected, but on the return of gonococci in the pus, the unchanged cells reappear, while in cured cases there is a decline in pus to the stage in which epithelial cells only are found.

The cases under this period were thirty in number, and the patients were in hospital 31.2 days for each case.

This paper is not intended to be a report of a completed method, but a progress report with its findings, brought up to date, showing the possibilities of a new method. There are numerous facts which have yet to be elucidated, and not the least of these is the maximum dose of the various factors. Selected typical examples of the various results obtained are plotted, the charts showing the factors used in the treatment.

It is suggested that the future line of work should consist in fixing the voltage, amperage and time of application at their finest limits; in finding the best type of antigen and its dose, and as part of this latter, in determining a method of growing the gonococcus so that there is a fixed strength of toxin used in this form of treatment, which is of much more importance than in the preparation of vaccines.

Control of the electric supply of direct current has been very little changed since the publication of my previous paper on this subject. The change has consisted in an attempt to render cheaper the means of regulating the current. The direct current of 112 volts is brought on to a board through a plug and a 5-ampere fuse to a switch which allows the current to pass through a resistance which regulates, as described above, the potential drop to exactly 100 volts maximum pressure from which the current passes to the potentiometer and back to the negative pole of the main. From each end of the potentiometer the current is tapped, so that the patient receives a gradient of voltage regulated from zero to 100 volts. A milliammeter is in this circuit to show the rate of flow. This is the simplest form of switchboard. It has been working, without giving any trouble, for the past six or eight months. All the wiring is on the front of the board and none at the back, so that there is no difficulty in tracing the circuit. Neither has the method of wiring the room for treatment been altered.

The test of cure by introducing gonotoxin-protected silver colloid electrically into the urethra requires no elaborate apparatus. All that is required is a four-six-cell secondary battery with a milliammeter in the circuit, and the small funnel and rubber tubing ending in a nozzle in which there is a wire connexion to the positive pole of the battery. The pad is connected to the negative pole. The current loss is inappreciable, and it is only ten to twelve volts at two-fifths of a millampere for ninety seconds per case. This, as I have mentioned, only fails in complicated cases with infection of the prostate or vesicles or post-urethra. A vaccine test is combined with the urethral test to limit these failures. The relapses amounted to sixteen
per cent, however, in spite of the tests during the past year, in which an unusually high number of complicated cases occurred. But they should not occur from this onwards.

In conclusion, I wish to acknowledge the careful and very laborious research work of Captain J. Lyn Dimond, by which the biochemical and electrical facts were elucidated and repeatedly confirmed, and form the subject of this paper. Also, I have to thank Major E. C. Lambkin, D.S.O., for his clinical insight and control of all the cases under this form of treatment which kept it from straying too far into wrong paths of inquiry.

DISCUSSION.

Captain F. CARMENOW DOBLE, R.A.M.C., asked whether this treatment had been tried in the case of women. Diathermy, the great rival of this new method, had recently had excellent results in the treatment of gonorrhœal infections of the cervix in women and of the prostate in men. He asked whether the amount of penetration of the colloid particles had been worked out by experiment on raw meat, such as a beef-steak.

Squadron-Leader MONTGOMERY said that the treatment and cure of gonorrhœa had always been so unsatisfactory that any new method was much appreciated. In his later results Major Frost had brought down the number of days under treatment to thirty-one. This was a great advance. At the R.A.F. Hospital, Halton, the treatment was that of the old Rochester Row routine method of irrigations by pot. permang., and had resulted in the last thirty-four cases in an average of fifty-five days under treatment. The number of relapses was not as high as twelve per cent. Would the number of relapses (sixteen per cent) in Major Frost’s series be accounted for by the fact that the colloid silver failed to penetrate the crypts and follicles or the patches of infiltrated mucous membrane where the infection lurked?

In reply, Major FROST said that he was not impressed by the action of diathermy on the anterior urethra, but that arrangements were under consideration for cases of prostatic and vesicular infection to be treated by diathermy. Relapses were principally due to prostatic and vesicular infections for which no action could be brought to bear by kataphoresis at present.

In the test for cure, using gonococcal antigen, the toxin is obtained by adding distilled water to the organisms. The injection is made into the lumen of the urethra, two or three cubic centimetres, and held in by pressure for twenty minutes. Each cubic centimetre is equivalent to 250 million organisms. This is the method, in use for a year, referred to in the paper.

The question of antiserum had been considered but was not tried owing to the animals available being small. In gonorrhœa the polymorphonuclear cell is looked on with suspicion. It has been noted that pus containing mostly free organisms gives primary cultures more rarely
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than pus in which the gonococci are all within the pus cells. Further, the growth is more profuse the longer the pus is rubbed on the surface of the medium. It is thought that the pus-cell has to be broken up to get the organisms in contact with the medium.

Captain J. Lyn Dimond has sent the following additional information:

The following change has been made in the treatment in order to avoid running into the bladder an alkaline solution which occasionally may pass back into the urethra and cause local burns due to the high conductivity of the alkaline colloid allowing a dangerous amount of current to pass through it into the tissues of the patient. As the alkaline colloid is exactly similar in appearance to the non-conducting colloid used for kataphoresis, there was also a real danger that it might be used for kataphoresis with consequent danger to the patient.

So soon as the patient reaches hospital he is put on a barley water diet and given bicarbonate of soda solution until the pH of his urine reaches 8.0. To control this, the patient's urine has the pH estimated daily and so soon as a pH of 8.0 is reached kataphoretic treatment is applied.

In addition to producing the right chemical and electrical conditions required for satisfactory kataphoresis, there is a definite diminution of pain, congestion and irritation of the local lesions which permit of a much more satisfactory application of kataphoretic methods than in the very acute early stages, when the patient's urine is highly acid and of low pH.

REFERENCES.