Original Articles.

THE PRESENT STATUS OF THE ANTISTREPTOCOCCIC SERUM.¹

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WHEN, in 1895, the news was spread broadcast that Marmorek, of the Pasteur Institute, had produced an effective serum for protection against streptococcus infections, public attention was forcibly called to the alleged solution of so important a problem. The fact that Marmorek reported not only laboratory experiments but clinical cases as well much heightened public interest, and clinicians on the continent at once began to try the new serum on patients.

Before considering the clinical application, however, it may be well to review briefly the laboratory data on the basis of which the treatment is advocated.

The real innovation in Marmorek's work was in the use of media containing serum of the horse or ass, or human serum, and the consequent possibility of dealing with highly virulent streptococcus cultures with some accuracy. For in these media the rapid loss of virulence occurring in ordinary streptococcus cultures was avoided, and it was possible, after raising a given culture to high virulence by passing it through a succession of animals, to keep it at a practically constant virulence in artificial media.

Marmorek used the horse or ass for immunization, which he carried out by successive injections of living pathogenic cultures in increasing dose and virulence. After a long period of immunization and a month's rest (to get rid of the toxic properties of the serum) these animals furnished a serum strong enough to protect rabbits against an otherwise fatal injection of streptococcus culture. He found 0.2 cubic centimetres (of one serum) injected eighteen hours before inoculation would protect a rabbit against ten times the fatal dose of streptococci.

If the serum is not injected till some time after the inoculation far larger doses are needed: with an original infection of ten times the fatal dose, one centimetre of serum will save the animal if injected within three hours; at five hours five centimetres are necessary; and six hours or more after inoculation with a highly virulent culture no amount of serum will check the infection. In case of less virulent cultures, the infection may be checked by serum injection even twenty-four to thirty hours after inoculation.

The weak point about all this is that the protection against increased dosage of streptococci by increasing dosage of serum is effective only up to a certain limit. This Marmorek admits, and says that with highly virulent cultures, injected in larger doses, death is the rule in spite of large injections of serum. What the limit is he does not state, but when we consider that he tested his serum against a coccus the fatal dose of which was one ten-millionth of a cubic centimetre, the whole matter, though legitimate, seems far removed from the conditions of infection to be met with clinically.

Marmorek's work, and especially his laboratory results, was, of course, soon tested.

Aronson and Petruschky, men of some authority, published rather discouraging articles on the subject. Aronson produced a serum by methods similar to Marmorek's, which protected rabbits up to a certain

limit, but on testing Marmorek's own serum he found it of very little if any power. This he was inclined to attribute to degeneration in the bottle, the more so since he found a serum of his own much weakened by three months' keeping.²

Petruschky experimented with Marmorek's own streptococcus culture, but did not succeed in increasing its virulence to nearly the point attained by Marmorek.³ On testing Marmorek's serum he utterly failed to demonstrate any protective powers, though he tried two samples. Nor did the "Lyon" brand seem any better.

Merieux and Niemann defended the "Lyon-Vaise" serum, which they found to have protective powers both against their own and against Marmorek's streptococcus. Marmorek's serum was also active against both cultures, but each serum acted best against the individual streptococcus culture used in the preparation of that particular serum.

Zenoni found the serum from the Pasteur Institute possessed of protective power against small dosage or against less highly virulent streptococci.

Courmont found Marmorek's serum of no avail against streptococci cultivated *direct* from erysipelas cases.

Van der Velde found immunization might protect against certain streptococci while of no avail against other streptococcus cultures.

Bornemann worked with a streptococcus obtained from Marmorek, of considerable virulence, against which he found the Paris serum only weakly active, though he tried three samples. A serum of his own, similarly made, proved more active. Schenck continued Bornemann's work, showing but little protective power for the serum.

Bordet found the serum efficacious.

Bullock, following Marmorek's methods, got a serum showing a moderate efficacy, as did also Bokenham.

Paltauf has recently succeeded in showing some protection, more especially against the culture of streptococci used in preparing the serum used.

Dr. Williams, of the New York Board of Health Laboratory, has done work, not yet published, showing definite protection by serum in animals.

Certainly it seems that a passive immunization can be obtained which protects against certain streptococci up to a certain limit. A high degree of passive immunity has not yet been shown possible, and cure of infections well under way seems as yet hardly possible, even in the laboratory.

It remained, however, for Koch and Petruschky, in a recent article, to bring in a further element of doubt as to the clinical application of the serum. Marmorek assumed man to be more susceptible to streptococcus infection than any of the animals, but these investigators demonstrate clearly that virulence of a given culture for animals is no index of its action on man. In the course of a test series of inoculation with erysipelas in malignant disease they experimented with many cultures, and found it impossible to produce infection in man with several different cultures highly virulent for rabbits; among these was Marmorek's streptococcus culture. In one case a subcutaneous injection was given, in quantity of 5 centimetres, of a culture fatal to rabbits in the dose of one one-millionth centimetre: not even a local infection resulted. It

² This lack of permanency of the antistreptococcal serum has lately been confirmed by Dr. Park of the New York Board of Health.

³ Fatal dose one one-millionth vs. one one-hundred-millionth.

¹ Read at the Obstetrical Society of Boston, November 15, 1898.

is, then, questionable whether a serum like Marmorek's, protecting against a streptococcus not virulent to man, would be of great use against a clinical infection.

Further experiments by Petruschky bear directly on this. He finally succeeded in producing erysipelas by using cultures from human erysipelas and peritonitis, and in one patient could, with a certain culture, produce erysipelas regularly. Twenty-four hours before certain of these streptococcus inoculations, this patient received injections, in turn, of ten cubic centimetres of Marmorek's and of Aronson's serum, and of a serum made by Petruschky. None of these "protective" injections apparently hindered or modified the erysipelas which ensued.

Considering all these things, it must be admitted that the *a priori* case for the serum as a therapeutic agent in man is not as strong as might be desired, and some of the soundest critics have insisted that its place is still in the laboratory.

The serum has, however, been used clinically in a variety of conditions, most conspicuously often in puerperal fever. Marmorek himself reported 15 puerperal cases: 7 of these showed streptococci alone; of these all recovered. Five had staphylococci as well; of these 2 died. Three showed mixed streptococci and bacteria coli; all these died. The cases with pure streptococcus infection reacted promptly to the serum and did well in every way. The doses used varied from 15 centimetres upward. Bar and Tissier reported 12 cases, in 10 of which streptococci were demonstrated. There were streptococci alone in 7—4 died; streptococci with coli in 2—2 died; streptococci with pneumococci in 1, which recovered. Porak had 3 cases with 1 death, but took no cultures; in 1 case even the clinical diagnosis is not clear. Gaulard had 2 cases with 1 death; in one, serum and douches determined a rapid recovery; in the other, death occurred five days after the temperature reached normal.

At a meeting of the French Obstetrical Society, April 10, 1896, Charpentier spoke of 40 cases he had collected (including the above cases of Bar, Porak and Gaulard), with a mortality of 42.5 per cent., or, excluding those *in extremis* when treatment began, of 35 per cent. Of pure streptococcus infections there were 16 cases, of which 8 died; a mixture of streptococci with bacteria coli occurred 9 times with 4 deaths. Dubrisay reported a case which ended in recovery, but did not show clearly any effect from the serum. Bar was inclined to attribute some value to the serum, but in mild cases mainly; while Bué, Boissard and Budin, after having tried it, were still less in favor of its use. Charpentier thought its usefulness still to be demonstrated. Marmorek's advice to abstain from all other treatment in cases when the serum is indicated was strongly condemned and the consensus of opinion was in favor of relying mainly upon known surgical measures until further data are obtained.

McKerron reports 3 cases with 1 death, in all of which there was some subjective improvement and a steadier pulse after the injections. Haultain had 2 cases with streptococci present in the discharge. One recovered rapidly; the other died at seven days. Durante and Siron report a case with streptococci present, which died at two weeks with extensive organic lesions due to the sepsis. Berthod, Ausset

and Rouzé, Chrobak and Ledrain all report single cases with apparently favorable results.

In most of the other cases on record the serum was obtained not from the Institute but from other sources which either drew on the Institute for supplies or made their own serum. In so far as Marmorek's methods were followed in the preparation of the serum the cases are included.⁴ This covers many English, some French and some American cases.

Stansby reports a case where the patient ten days after delivery was unconscious, with a temperature of 103° and a pulse of 140. After the serum injection she became conscious, and the temperature fell to 101°, the pulse to 92. The temperature rose later, but the patient remained conscious throughout, and ten days later was afebrile.

Groth had a case where streptococci were demonstrated in the blood two weeks after delivery, with a temperature of 105.8°. Serum injection, followed by a drop in the temperature; the patient was convalescent, however, only after six weeks.

Hastings reports a case where streptococci were present, where each injection was followed by an improvement in general condition with a fall in temperature.

Shaw, on the other hand, notes a case also shown to be a streptococcus infection, where each injection determined not a fall but a rise in temperature, though the patient recovered. Marx had five cases, all of which proved fatal, despite the use of serum.

Besides these there are at hand reports of 34 other cases, with 5 deaths, reported by twenty-five observers.⁶

Taking all cases in the list collected, we have a total of 107 cases with 34 deaths, a mortality of 31.7 per cent. Many of these cases were, of course, severe, and the treatment began late. The serum was in most cases given in doses varying from 10 to 30 cubic centimetres.

As to pyemia, endocarditis and other general sepsis cases, Marmorek reports a successful case of endocarditis of puerperal origin. Sainsbury had an endocarditis case where streptococci were present in the blood; treatment began late, and recovery was rather slow.

Wignhoff reported a streptococcus osteo-mylitis with streptococci in the blood, which recovered, but only after twelve weeks of fever. The dozens of serum injections had no obvious effect.

Coleman and Wakeling had a septic pneumonia with streptococci in the blood, which recovered; the effect of the serum was not obvious.

Thomson and Kemp note a case where the blood showed streptococci—a chronic endocarditis. He was treated with many serum injections, but without result, and finally died.

Low found streptococci in the blood of a child with otitis after scarlet fever; the case recovered under serum treatment.

Ballance and Abbott note a case of hemorrhagic septicemia, without cultures, remarkable for the prompt subjective improvement after the injections.

Butlin notes a case of streptococcus pyemia, fatal in spite of surgery and serum.

⁴ This applies to the "Lyon-Vaise" serum, to that of the British Institute of Preventive Medicine (Bullock), of Burroughs, Wellcome & Co. (Bokenham), of Gibber, of the Pasteur Vaccine Co., of Chicago, of Parke, Davis & Co., and probably to others.

⁶ Cases by Charrin and Roger, Denys and Leelel and others, where the serum used was prepared on different principles with different technique, are not included here.

Many cases⁶ of essentially local sepsis, from phlegmon to peritonitis, are reported with various results, but rarely with any indication of specific action of the serum. Pozzi, Chrobak, Weir and Gerster have used it in sepsis following operation. Senn advocates this use, but without personal experience, it seems. Cheyne and Boucheron have used the serum before operations as a preventive of probable sepsis, and advocate this use, as does Durham, but they give no convincing data.

In erysipelas the serum has often been used, but the only considerable series seems to be Marmorek's own. He treated 413 cases, with a mortality of 3.87 per cent. against a 5.12 per cent. mortality in a previous series in the same service treated without serum. In these cases he notes a definite improvement in general condition after five to twelve hours, often with a rapid fall of temperature and pulse, and an improvement in the local condition which was often rapid and permanent. He used doses of 5 to 20 cubic centimetres, with total amounts from 10 to 120 cubic centimetres. Rondot used the serum with similar results on a considerable number of erysipelas cases. Bokenham's results from injection in this class of cases were satisfactory. Gouin, Richardière, Chrobak, Polycoktoff and Magill note successful cases of its use.

Steele used the antistreptococcic serum in a case of erysipelas neonatorum, and reports a rapid recovery, but Comby notes three such cases so treated — all of which died; and both of Bar and Tissier's cases in infants were likewise fatal.

The treatment of pseudo-membranous angina with streptococci has not been a success, according to Sevestre; and the series of broncho-pneumonias in children treated by Marmorek in Comby's wards is said to have shown, at one time, 16 cases with 16 deaths (Lutaud).

Scarlet fever has been treated with the antistreptococcic serum, partly because the streptococcus has been suspected as the infective agent, and partly because streptococci are so frequent in the complications of the disease. Marmorek treated 96 cases with doses of 10–30 cubic centimetres of serum in totals up to 80 cubic centimetres; the mortality is stated by Comby as 8.3 per cent. Baginsky reports 48 cases, with a mortality of 16 per cent. Polycoktoff notes 17 cases with 8 deaths.

Josias had in two series a mortality of 2.08 and 5.3 per cent. respectively; those treated without serum showed a mortality of 5.8 per cent. These are, in part, the same cases reported by Marmorek.

Marmorek frankly admits that the serum has little or no effect on the scarlet fever itself, but finds a favorable influence on the complications, especially nephritis and adenitis. Baginsky, with a much worse series, is more impressed with the value of the treatment.

With so large a number of clinical cases on record, it would seem possible to draw some conclusions, but unfortunately many of the cases are not so presented as to be of any particular value, and such conclusions as can be drawn must be mainly negative. Before drawing conclusions as to the value of any remedy one must either see its effect in disease ordinarily running a definite typical course, or there must be a decided drop in a heavy mortality, or else an opportunity to compare long series of cases with and without the

given treatment under otherwise like surroundings. In the present case the first two conditions are in no way fulfilled, the third only apparently; apart from Marmorek's own cases, a large proportion of the cases of all sorts have been reported in ones or twos by different observers. This is, at best, a poor way of getting statistics, and here especially unfortunate, since these are just the sort of cases where the personal equation should enter in as little as may be. This criticism applies to all the series recorded, with the exception of the scarlet fever cases. This scarlet fever series we can set aside; the case is not proven, and is, at best, not really relevant. Nor is much to be made out of the cases of local and post-operative sepsis; serum and surgery are too hopelessly mixed.

The cases of general infection, puerperal fever and erysipelas are more directly available.

In the series of cases of general sepsis there are some in which the diagnosis is not quite satisfactory; others, on the other hand, of recovery which is surprising under the conditions actually shown. Cases recovering after streptococci were found in the blood are surely striking, but it must not be lost sight of that the clinical course of these cases was not unusual,⁷ the happy result not always very directly attributable to the serum, and that such recoveries are not entirely unknown where no serum-therapy has been employed.⁸

In the puerperal cases the difficulties are: (1) the cases are mainly isolated observations by different observers; (2) many cases reported are without any bacteriological evidence; (3) the course of puerperal fever is most varied, the prognosis notoriously uncertain; (4) many of the reported cases were efficiently treated surgically as well as by serum.

It is hard to draw just conclusions under these circumstances. The mortality, 32.3 per cent., cannot be called low, even granting that the series includes many desperate cases. It is perhaps not fair to compare this with any ordinary series of cases of puerperal sepsis, but certainly on such figures as a basis there can be no talk of any considerable reduction of mortality.

In individual cases the use of the serum would seem to have helped definitely, but these are more than counterbalanced by cases of streptococcus infection alone where no effect whatever is to be attributed to the serum. The irregularity of course in puerperal fever, the difficulty of distinguishing the results of other treatment from those of the serum, cannot be too clearly borne in mind.

In a proportion of cases, however, there does appear, apparently as a definite result of the use of the serum, a marked improvement in subjective condition, in the pulse, and often in the temperature. This is by no means constant, and apparently bears little if any relation to the general course of the infection, but it seems definite and must mean something.

In the erysipelas cases, again, the mortality figures are not convincing, for, as Therese points out, the ordinary mortality varies from 1 to 5 or 6 per cent., while Marmorek's figure was nearly 4 per cent.

Here again there appears the same improvement in subjective condition, pulse and temperature following injections, but more often in this erysipelas series,

⁶ Marmorek, Rondot, Crossing and Webber, Boake, Pearse, Lockwood, Lillienthal, Cook, Heatherley, Weir, Grandin, Johnson, Vinberg.

⁷ For example, Wignhoff's case with a three months' run of fever. ⁸ Potruschky, *Zeitschr. f. Hygiene*, xvii, p. 59, and Bernhelm, *Jahrb. f. Kinderh'k.*, 1896, xlii, 208, report ten such cases of their own.

and often accompanied by a rapid improvement in the local process. This is noted by Rondot as well as by Marmorek. Unfortunately, even here, Petruschky's experiments with inoculation erysipelas and serum must make us a little conservative in interpreting the clinical notes.

Probably no one will now contend that the anti-streptococcic serum is, broadly speaking, effective against streptococcus infections. Beyond a doubt, a certain degree of passive protection is possible in the laboratory, and probably something of the sort is possible in man. There seems, in view of recent work, no ground for drawing sharp distinctions between alleged species of streptococci, and, though it would be a mistake to assume too close a parallel between the conditions of infection in man and in animals, yet probably a serum really effective in protecting rabbits against streptococci would afford some aid to the human organism in its struggle against a like infection. It is likely enough that this is the explanation of the temporary relief of symptoms so often noted. It does not seem that this represents a strong action against the infection, but it is something, and in many cases a very little may turn the tide.

This seems reason enough to give the serum further trial — as a symptomatic treatment if no more. There seems to be no good reason against its use. Urticaria, erythema, joint pains, etc., are of not uncommon occurrence, but of no great moment. Abscesses at the point of injection, sometimes containing streptococci, are not rare, and would indicate care in using a bacteriologically tested serum. Buc and Thomson have thought the serum a cause of albuminuria, but this must be either unusual or slight, judging by reports.

If the serum is to be used in earnest, it should be used in considerable doses. Probably in many cases the dosage has been too small. To protect a rabbit against a ten times fatal dose needed 0.2 centimetres of Marmorek's serum; this is one seven-thousandth the body weight, corresponding to about 10 centimetres in man. The potency of different makes of serum varies, and they seem to lose notably by keeping. Hence, while there are no accurate data for dosage in man, yet the problem is not to protect against an infection, but to cope with an infection in full swing, and that with a serum of doubtful efficacy; the needed dose will probably be large, if anything is to be accomplished. The limit of dosage must vary, but the untoward effects above noted are not frequent, and plenty of cases have borne 25 cubic centimetre doses. In one case a total of 1,030 cubic centimetres was given, though this in a case of some duration; there were no ill effects beyond a slight erythema.

There seems, then, some reason for continuing the use of the serum in cases of demonstrated streptococcus infection; care is needful in selecting the serum to be used; it should be used, if at all, in considerable amount; and, above all, until more evidence of its power is forthcoming, it should be used as an adjunct only, and never to supplant or modify other treatment of the case.

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SOME OVERLOOKED CAUSES OF COUGH.¹

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RIEDEL says "the intensity of paroxysms of cough is in no way immediately dependent upon the extent or intensity of the local alterations, so that we cannot form any definite conclusions from the nature and severity of the cough as to the seat and extent of the pathological alterations." This statement may well serve as the text for a paper dealing with extra-thoracic causes of cough. In a general way there are two kinds of cough: in one the explosive effort is attended by the dislodgment of some material within the air passages; with this we have nothing to do. In the other, sometimes called a useless cough, there is no expectoration. It may be tormenting, persistent and painful, but it is not attended by any systemic disturbance. Some of the causes of this latter will claim our attention. This kind of a cough is essentially chronic, since it depends upon a persistent lesion and, although worse in winter, it often persists throughout the year. You will readily understand from the foregoing that I do not propose any panacea for cough as ordinarily met with, nor advise that the chest be less thoroughly investigated in any case of cough; but I shall try to emphasize the fact that there are causes of cough outside the thoracic cavity.

The reflex cough, excited by the presence of a foreign body within the external auditory canal, is noteworthy for other reasons than that of being a mere pathological oddity, as each of you may know from experience if a probe has been passed into your ear, thus demonstrating the peculiar sensitiveness of a part of the canal. The irritation of other branches of the pneumogastric nerve may give rise to cough, and in this connection Dr. Leaming's facetious remark upon the nerve may well have place: "The pneumogastric

is a chummy, friendly nerve. It is the source of all our friendships. We dine together, drink together, smoke together by its influence, and in an assembly of people a cough will immediately be answered by coughs through the hall." Prof. W. H. Thompson enumerates fourteen kinds of useless cough, but I am especially interested in only such as are dependent upon some abnormality of the upper air passages.

Beginning with the nose, the subject of reflex cough due to irritation within its passages has been studied for some time. Such a cough is almost invariably set up when the nasal mucous membrane is touched with a probe, or when even a bland spray is used in the nose for the first time. It were easy to wax eloquent over adenoids and faucial tonsils as a cause of cough; but I forbear, for individually and collectively during the last three years we have exhaustively discussed this subject.

That follicular pharyngitis—really lymphoid tissue on the posterior wall of the pharynx—may be a cause of persistent cough has been well shown by Dr. Mayer, who reported twenty such cases, and devised a special instrument to remove the redundant tissue. A relaxed and elongated uvula occasionally causes an annoying tickling and a cough; but this usually innocent bit of tissue has been so sinned against that one hesitates to refer to it in this connection. "Our good daily paper" for a long time bore the advertisement of a man who named nine kinds of palate catarrh, against which he warned the public and for which he had the cure. I have seen cases in which he has amputated the uvula, short, as a step in the treatment but not the relief of the patient.

Dr. McCoy has investigated a nocturnal cough of children which he considers due to the drainage of mucus and saliva toward the larynx while the child lies upon its back—a sudden paroxysm of cough following the entrance of the fluid into the upper part of the larynx.

The most common of the, so to speak, outside causes of persistent cough is the presence of lymphoid tissue and varices at the base of the tongue, and since this is the most important I shall confine myself to its consideration. The foregoing causes should, however, be in mind when searching for the source of a persistent cough which does not yield to the usual treatment.

The entrance to the pharynx is surrounded by a ring of lymphoid tissue, which is made up of adenoids in the naso-pharynx, the faucial tonsils upon either side of the throat, and completed by a more or less irregular mass of lymphoid tissue upon the base of the tongue. Although to the eye these various aggregations of tissue seem somewhat unlike, they all belong histologically to the same class—lymphoid. That at the base of the tongue is sometimes spoken of as the lingual tonsil. It extends from near the circumvallate papillae toward and into the glosso-epiglottic fossa. It is separated into two lateral halves, being divided in the median line by the central glosso-epiglottic ligament. The degree of hypertrophy of course varies, and it never reaches the large proportions observed so often in the faucial tonsils. I recall one case in which, upon drawing the tongue forward, two large masses presented upon either side of the base of the tongue, and stood up to such a height that a mirror was unnecessary for examination of their upper and anterior surfaces. Usually the hypertrophy does not exceed three-eighths of an inch in thickness

¹ Read before the Springfield Medical Club, December 14, 1898.