There is no need to enter in this paper upon a discussion of the sequelae of streptococcus infection. All we require to say is that the laryngeal variety is no less liable to them than the others.

Diagnosis

Apart from influenza and simple acute catarrh, this type of streptococcus laryngitis in its early stages may be mistaken for Ludwig's angina, laryngeal diphtheria, whooping-cough, and a foreign body impacted in the larynx.

In Ludwig's angina the grave constitutional prostration and the more massive and intense inflammatory swelling of the pharynx and larynx and sometimes of the cellular tissue of the neck ought to prevent any mistake. Laryngeal diphtheria, in turn, will be excluded by bacteriological examination, which should never be omitted. A streptococcal false membrane may form in the pharynx, as in one of our cases, but it differs from the diphtheritic membrane in colour, consistence, and attachment. In pertussis, which is not infrequent in elderly people, the early symptoms may resemble those of streptococcus laryngitis rather closely, as it occasionally commences with laryngeal congestion and some hoarseness. But the hoarseness is slight; there is no laryngeal oedema; and, as time passes, the cough becomes unmistakable. Finally, when confronted with a sporadic case of hoarseness, paroxysmal cough, and stridor, the possibility of a foreign body impacted in the larynx should not be forgotten, even although the patient may have no recollection of having swallowed one, or, as in certain types of neurosis, prefers to conceal the fact.

Under this heading we may mention that it is quite within the bounds of possibility for the oesophagus to be infected independently of the pharynx and larynx, with consequent hiccup and spasmodic stricture. Such cases are differentiated from organic stricture by x-ray examination or by direct oesophagoscopy.

Treatment

When swabs from the throat give a pure culture of streptococcus of whatever strain, a suitably large dose (20 to 40 c.cm.) of anti-streptococcus serum is the logical therapy. Even, indeed, when a culture shows other organisms as well as the streptococcus this may be regarded as the chief enemy, provided that the symptoms already described are clearly manifested. Naturally the earlier the remedy can be given the better. Sometimes the "scarlet" variety of the serum answers best; at other times the "polyvalent"; at other times again neither seems to have much effect. Our own experience of serum treatment, necessarily administered rather late, has not been very encouraging. It may clear up symptoms for the time being and yet fail to prevent a recurrence a few weeks later. There is no need for us to emphasize the necessity of guarding, as much as possible, against the onset of anaphylactic phenomena.

Apart from such specific treatment, the symptoms will require attention. The disturbing cough can be soothed by steam inhalations, and heroin, judiciously administered. An emergency tracheotomy will be required if dyspnoea becomes threatening, and preparations should be made for the operation before the necessity has actually arisen.

Acknowledgements.—In addition to expressing our deep indebtedness to Dr. F. P. Sturm for furnishing us with a clear and detailed account of epidemic streptococcus laryngitis as he saw it, we desire to offer our grateful thanks also to Messrs. W. A. Mill and W. M. Mollison and to Dr. F. H. Teale for their generous assistance in dealing with Case 1.

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PUERPERAL STREPTOCOCCAL SEPTICAEMIA

A REVIEW OF PREVENTIVE AND CURATIVE MEASURES

BY

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Puerperal septicaemia has been for many years the prime factor in the causation of "maternal mortality." The question, therefore, of its prevention and treatment constitutes a problem of first-rate practical importance to the nation. Broadly speaking, and from the point of view of incidence reduction, much can be achieved by the adoption of three main measures:

(a) Education of the public in the enormous importance of ante-natal clinics, the establishment of which makes it possible for septic foci and other abnormalities to be detected *early* in pregnancy, and timely advice imparted in the matter of raising general resistance to infection.

(b) Confinement in a properly equipped institution (hospital or nursing home), where the application of strict aseptic principles can be so much more readily facilitated, not alone at the birth itself, but also at all subsequent dressings, when sepsis may readily originate.

(c) Speedy isolation of all suspect cases to an "investigation" department, whereby risk of infection to other patients is reduced to a minimum, and a confirmatory diagnosis made possible in surroundings unattended by undue risks to the patient herself.

As the majority of fatal cases are traceable to a strain of haemolytic streptococcus, I propose here to consider briefly the special preventive and curative measures that have been employed in the streptococcal variety of infection.

Vitamin Therapy

Prophylaxis.—As might be expected, the most important of the vitamins in relation to this condition is vitamin A, and its chief value lies in the sphere of prevention. By the exercise of its function to repair breaches in the lining mucous membranes it serves the useful purpose of fortifying local resistance, and the earlier it is employed in the period of pregnancy the more formidable is that resistance likely to be. The vitamin next in importance is vitamin D, which, by its utilization of calcium and phosphorus to meet the requirements of the body, contributes in no small measure to the maintenance of resistance generally. The main sources from which these vitamins may be derived are four in number—namely:

(a) The diet, which should include whole milk, wheaten whole-meal bread, butter, cheese, eggs, green vegetables, carrots, tomatoes, and fruit.

(b) Accessory vitamin foods.

(c) Vitamin concentrates, one of halibut-liver oil being particularly useful.

(d) Ultra-violet irradiation, whereby ergosterol in the subcutaneous fat is converted into vitamin D.

In the ante-natal ward of Belfast Infirmary the patients receive prophylactic vitamin therapy from all these sources, and among 162 normal deliveries of patients transferred from the ante-natal to the labour wards during the year 1934 there were only three septic cases. Rest and isolation from marital contact must, however, also be taken into consideration. In the same year, among 678 normal deliveries of patients admitted direct to the labour wards from outside hospital, the number of septic cases was 25. On standardizing these figures for purposes of comparison we find that among the patients confined from outside hospital the incidence of puerperal sepsis was twice as great as among those confined from the ante-natal ward. This result would very probably have been still more convincing had it not been for the fact that a large number of admissions to the ante-natal ward antedated the commencement of labour by little more than a week.

Curative.—Here chief reliance must be placed upon the employment of a selected potent vitamin concentrate in large therapeutic doses. It has to be borne in mind,

however, that vitamins usually require more time to demonstrate their undoubted value than can be afforded once an acute streptococcal infection has actually commenced. Hence vitamin therapy as a curative measure should be regarded as of supplementary value.

Drugs

Quinine is one of the older remedies employed for germicidal action in the treatment of septicaemia. Two considerations are of interest and importance in connexion with its use. The first is an observation by Cushny¹ that in many cases of septicaemia where successful results have been claimed from quinine therapy, the dose was far too small to be capable of acting either on temperature or on microbe. The second relates to the fact, mentioned by the same author,² that the micro-organisms of septic fever have been found to be much more resistant to the action of quinine outside the body than are the protozoa, which leads us to ask whether the blood and tissues are not liable to serious injury from the amount of quinine required to act upon the organisms contained in them. We gave this drug an extensive trial at Belfast Infirmary, with very disappointing results. The opinion formed was that quinine, administered in regularly repeated maximum *therapeutic* doses, was not a sufficiently potent germicide to check the activities of virulent haemolytic streptococci in the blood stream; and since massive doses expose the leucocytes and tissues to the risk of serious injury, the drug cannot be recommended in the treatment of this disease.

Disulphamine is one of the more recent preparations advocated for their antiseptic properties. It is held to promote hyperleucocytosis, principally of the polynuclear type, and is administered in the form of gelatin capsules (each containing $7\frac{1}{2}$ grains) dissolved in water. It is incompatible with alkalis. At Belfast Infirmary the preparation was given an extensive trial, but the results yielded were not convincing.

Collosol argentum, injected intramuscularly, is another preparation advocated for bactericidal action. At Belfast Infirmary there were some cases in which it seemed to do good, but, speaking generally, its usage did not meet with any uniform success.

Collosol iodine, in daily hypodermic injections of 1 c.cm., has been found of definite value in the treatment of rigors at Belfast Infirmary.

Mercurochrome, intravenously, has been advocated in recent years, but the results have fallen below expectations. *Perchloride* and *salicylate of mercury* have also been tried.

Eusol, given intravenously in normal saline, has not proved a success, while *flavine* can claim no better results. Many drugs of germicidal repute fail in the treatment of this condition because the maximum dose that can be permitted is insufficient to cope with the virulence of the infection.

Arsenic is of value in the treatment of the associated anaemia. Lord Horder³ recommends it in the form of sodium cacodylate intramuscularly, and often combines with it *nucleic acid*, a stimulant to leucocytosis.

The Glycerin Treatment

Prophylaxis.—Treatment consists in the injection of sterile glycerin into the cavity of the uterus, following labour, in all cases attended with suspicion. Glycerin is possessed of well-known healing properties, as a result of which its employment in the manner indicated induces a much more ready recovery of normal healthy tone in the raw inner uterine surface. It is therefore of decided value as a prophylactic expedient.

Curative.—By its action in promoting a free flow of lymph from the uterine wall into the uterine cavity, the glycerin treatment produces a "lavage à retro" through which infecting bacteria are washed away. In addition, the lymph itself possesses bactericidal properties. In view of the virulence by which streptococcal infections are commonly characterized, however, and of the fact that the treatment is purely local in its action, glycerin

therapy, to be of material benefit as a curative measure, must necessarily be employed at the outset of the infective process; otherwise the local defence may well be overcome before the treatment can be afforded a fair trial, in which event its role must be considered as of purely supplementary value.

Vaccines

Prophylaxis.—Stock vaccines are, in my experience, of decided value in the preventive campaign against puerperal streptococcal septicaemia, particularly when there are a large number of patients to be immunized. At Belfast Infirmary we once had an epidemic among patients who had had perfectly normal confinements and who had not been examined per vaginam. Exhaustive investigations failed to disclose any external cause for the outbreak. It was therefore promptly decided to take throat swabs from all the lying-in patients, numbering sixty, with the interesting result that fifty-two of them demonstrated the *Streptococcus haemolyticus*, a pure culture being obtained in several instances. A stock vaccine was then prepared (1 c.cm. = 5,000,000 cocci), and each of the "positive" patients received an initial dose of 1 minim, followed, after an interval of five days, by a second dose of 2 minims. The adoption of this procedure was followed by the speedy termination of the epidemic, only one of the patients so immunized developing puerperal pyrexia.

Curative.—When it comes to the question of curative treatment by vaccines, however, the outlook is generally not at all so bright, though exceptional cases undoubtedly occur showing good results. An autogenous vaccine is here to be preferred to a stock, though this involves the disadvantage of having to wait until it is prepared. To bridge the difficulty the temporary employment of an appropriate stock vaccine has been advised. We gave autogenous vaccines an extensive trial at hospital, with very disappointing results. One has to bear in mind that a formidable degree of exotoxaemia is frequently of early and rapid development in these cases, and that if the tissues are to be preserved from its deadly effects speedy neutralization becomes imperative. Having regard, therefore, to the nature and virulence of the infective process in this condition, and to the results already referred to, one does not feel disposed to advocate vaccine therapy as an exclusive method of treatment in this condition. The judicious employment of a vaccine along with appropriate serum treatment affords much greater likelihood of success.

Anti-streptococcal Sera

These belong to the anti-bacterial class, their purpose being to destroy in the blood stream the organisms against which they are specially prepared. They are divided into two main varieties—polyvalent and univalent. The idea of introducing a polyvalent, or multivalent, serum is based on the fact that streptococci exist in groups, and a serum prepared against any one group is not by any means specific in respect of antibody for another group. The experiment, however, has not proved a success. In this condition our attention is confined to one group of streptococci, and it the most virulent of them all; and, apart altogether from the question of antibody content, a polyvalent serum is, at the best, only in part directed against it. At Belfast Infirmary we gave this variety the test of a very fair and extensive trial, but met with extremely disappointing results.

A univalent *Streptococcus haemolyticus* serum is, in comparison with the polyvalent type, certainly to be preferred, because it is entirely concerned with the group of streptococci involved in this disease. Both types, however, are possessed of common failings. To begin with, although each is primarily designed to destroy streptococci in the blood stream, neither is prepared to deal effectively with the condition of exotoxaemia which very frequently precedes, and always accompanies, the septicæmic condition; and it is, after all, the toxin that does chief damage. If either type of serum were sufficiently concentrated in respect of antibody against haemolytic streptococci to overcome the septicaemia—assuming early

and generous dosage—additional toxin formation would then be controlled, though there would still remain the existing degree of toxæmia to be neutralized if its serious ill effects were to be avoided in time. Here again, however, we are doomed to disappointment, for, in the words of a very eminent authority⁴ in reference to anti-bacterial sera, "by none of the methods yet employed have these sera been produced with a sufficiently rich content of antibody to lead to any uniformly good results."

Antitoxin Sera

Streptococcus antitoxin (scarlatina), more commonly known as anti-scarlatinal serum, constitutes, in my experience, the most effective method of treatment at our disposal to-day. Its usage is based on the fact that the streptococcus of scarlatina and that of puerperal streptococcal sepsis belong to the same bacteriological group, the haemolytic group, and produce an identical toxin, the Dick toxin. Hence, from this consideration alone, a serum prepared to neutralize the toxin of scarlet fever would naturally be expected to exercise the same effect upon that produced in the puerperal infection. In practice this is found to be the case, the serum acting as a neutralizer of exotoxins formed by haemolytic streptococci in the body.

Prophylaxis.—The chief indications for a prophylactic dose of anti-scarlatinal serum are: (1) marked anaemia; (2) the presence of a septic focus or foci; and (3) manipulative intervention on any large scale. The most suitable dose for prophylactic purposes is 10 c.cm. intramuscularly, immediately following the third stage of labour. In the presence of a septic focus, for example, a dose of serum at this point will be found instrumental in reinforcing a depleted resistance by neutralizing toxins that are being absorbed. I have seen several patients in hospital who appeared likely candidates for sepsis. They were all given a prophylactic dose of this antitoxin following the third stage, and in none of them did sepsis develop. As examples I may cite:

(a) Macerated hydrocephalic monster; foetus very foul; placenta decomposed. Prophylactic dose of anti-scarlatinal serum immediately after third stage. Temperature remained normal and puerperium was quite uneventful.

(b) Patient suffering from tonsillitis, stomatitis, and other lesions of the mouth. Confinement quite normal. Prophylactic dose of anti-scarlatinal serum immediately following third stage. Puerperium quite normal.

(c) Manipulative case.—Umbilical cord doubly twisted around child's neck; quick manipulation necessary to effect release; third stage complicated by retention of large portion of chorion, necessitating manual removal. Intrauterine douche given, followed immediately by prophylactic dose of anti-scarlatinal serum. Puerperium quite normal.

(d) Manipulative case.—Transverse presentation, with hand and foot presenting. Considerable manipulation necessary to carry out bipolar podalic version. Prophylactic dose of anti-scarlatinal serum immediately after third stage. On the first three evenings following, the respective temperatures read 100°, 99.6°, and 99° F. Subsequently temperature became normal, and no signs of any description appertaining to sepsis ensued.

Prevention of Anaphylactic Shock.—Prior to administering a dose of serum it is imperative to ascertain whether or not the patient requires to be desensitized, and to act accordingly. Thus, with a history of one or other of the specific fevers or, apart from that, of a previous dose of serum at an interval of ten or more days, the following skin test should be carried out:

"A small quantity, say 0.25 c.cm., of normal horse serum (or antitoxin) is injected intradermally or rubbed into a scarified surface. There occurs, if anaphylaxis—or a toxic idiosyncrasy to horse substance—exists, an urticarial patch sometimes progressing to a vesicular eruption with a surrounding area of erythema. This occurs usually within half an hour, but is occasionally delayed. If anaphylaxis be demonstrated, the patient should be desensitized."⁵

Curative.—The moment "puerperal pyrexia" is diagnosed, a dose of 60 c.cm. anti-scarlatinal serum should be administered without waiting for the result of the routine investigations. So many of these cases subsequently prove to be of streptococcal origin that the adoption of this

procedure often ensures not only the saving of a patient's life, but also a very material shortening of the duration of illness. The serum should be given slowly and by the intramuscular route. At this early stage neutralization of toxins is much more readily achieved, with consequent benefits of far-reaching import to the patient. These include the preservation from irreparable damage of the cardiac muscle and other tissues for which haemolytic streptococci have a special affinity. Furthermore, the work of the leucocytes in augmenting local resistance, and ingesting streptococci which may be encountered in the circulation, is thereby prevented from being undermined by an exogenous poisoning of the vital body tissues. In the more severe cases a repeat dose of 30 c.cm. should be given after twenty-four hours.

Anaphylactic Precautions.—If the initial dose of serum has been administered reasonably early in the disease, it is decidedly the exception for a patient to need a further dose at so great an interval as ten days. Such an exception would, of course, necessitate due observance of the anaphylactic precautions already discussed. It should also be borne in mind that this idiopathic phenomenon may occur with a third dose of serum if administered at an interval of more than ten days from the first dose.

Value of Anti-scarlatinal Serum

Evidence in support of the claim that anti-scarlatinal serum constitutes the most potent form of treatment at our disposal to-day may fittingly be considered here. One is not unmindful of the fact that cases sometimes occur where recovery takes place spontaneously. An attempt should therefore be made to allay any possible doubts that attribution of satisfactory results to this serum bears full justification. To begin with, a Dick test will decide as to the presence of streptococcus antitoxin in the body; and the fact that cases are recorded showing spontaneous recovery is explained by the knowledge that in certain patients' blood this antitoxin already exists in considerable quantity, in some instances of a sufficiency to neutralize the exotoxins that issue into the circulation. Hence the value of anti-scarlatinal serum, itself a *Streptococcus haemolyticus* antitoxin, at once becomes apparent in the treatment of the disease, where its administration will serve either to compensate for antitoxin deficiency or to augment the quantity present. The more antitoxin, the less toxæmia.

From the clinical standpoint the value of the treatment can conveniently be determined by making a comparison of the "pre-serum" condition with the "post-serum" condition of a series of patients injected reasonably early in the disease. With patients who are at all severely ill before serum injection, it is highly improbable that the quantity of streptococcus antitoxin in the blood is great; and when, twenty-four hours after early serum administration, they show a definite and generally progressive change for the better, as was the rule in my experience, the efficacy of the treatment is measured.

At Belfast Infirmary during the year 1930—the first complete year in which we used this serum as a routine measure—the total number of cases of puerperal sepsis admitted to the isolation department was twenty-seven, of which number twenty-two were found to be suffering from puerperal haemolytic streptococcal sepsis. These latter all received the anti-scarlatinal serum treatment (Parke, Davis and Co.), and no fewer than twenty-one of them made a good recovery—a percentage recovery rate of 95.45. The chief reason for this very satisfactory result lay in the fact that the majority of the cases were embraced by the intern epidemic already referred to, which meant that they were immediately accessible to prompt treatment.

During the succeeding four years the results with this method, among patients received in reasonable time, have been such as to justify completely the spirit of optimism which prevailed at the end of the first year's trial. During the twelve months ending March 31st, 1935, no fewer than eighty-three cases received the anti-scarlatinal serum treatment at Belfast Infirmary; the large majority of these were confined outside hospital, many

of them being severely ill for several days prior to admission. Despite this handicap, however, there were sixty-eight recoveries, representing a percentage recovery rate of 81.92, a figure which might well have been exceeded under more favourable circumstances.

It cannot be too strongly emphasized that *early administration* and *generous dosage* are factors of supreme importance, and that if these essentials are observed a very material reduction in the number of deaths from this disease may confidently be expected. Opinions based upon indifferent results from fourth- and fifth-day administrations are of little value, since failure in such instances is primarily due to lateness and, it may be, to too small dosage. A late initial dose gives attacking haemolytic streptococci greater time and opportunity to invade the circulation, multiply at a rapid pace therein, and freely elaborate their toxins. In these circumstances the phagocytic value of the leucocytes, of which the polymorphonuclears play a leading part, becomes negated by the steadily increasing army of invaders. The blood stream

then becomes so drenched with toxins that neutralization of them is impracticable; and even if it were not so the deadly effect of these toxins is by this time imprinted upon the tissues of the unfortunate patient.

Experience convinces me that to avoid such disastrous consequences as these, the *early* and *generous* employment of anti-scarlatinal serum may be relied upon with every confidence.

I desire to acknowledge my indebtedness to Mr. T. S. S. Holmes, M.Ch., F.R.C.S., and to Dr. T. Howard Crozier, B.Sc., M.R.C.P., for permission to carry out these investigations.

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PRINCIPLES OF RADIOLOGICAL TREATMENT AND THEIR BEARING ON HOSPITAL X-RAY ORGANIZATION

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The Position Attained in Radium Therapy

The position to-day in Great Britain is that for a country of its size and population the general level of treatment of malignant disease by radium compares not unfavourably with any other. The excellent results at such a centre as l'Institut du Radium in Paris are not a reliable guide to the general level of attainment throughout France; the same remark is not so applicable in the case of Sweden, for the Radiumhemmet at Stockholm is able to control, to a great extent, the form of treatment of a large percentage of the patients who require radium treatment throughout the country. But the small Swedish population and the relatively large economic resources on which the Radiumhemmet can rely combine to make a system that, while serving them extremely well, is not one which could be applied in general. Even with our much bigger population we shall very soon be in the position that we need not fear a comparison of statistics.

Our present position in radium therapy is mainly due to the medical groups or individuals by whom the treatment has been given, but there have been three contributory factors which have played an important part in the development of this form of treatment. First, there is the service rendered by the Medical Research Council in 1921 in forming research centres throughout the country, their main functions being to explore the possible ways of using radium in the treatment of malignant disease. Periodic reports issued under the heading "Medical Uses of Radium" have been prepared by the Radiology Committee of the Council under the chairmanship of Sir Cuthbert Wallace; these reports have discussed the development of technique, the advances in our knowledge of radium reactions, the importance of pathological as well as clinical diagnosis, and finally they have exhibited comparable statistics relating to several sites of cancer.

Secondly, there are the services rendered by the National Radium Commission since 1929 in ensuring that

the large quantity of radium put at its disposal by the National Radium Trust is, in the words of its Charter, administered so as:

"to make arrangements for the proper custody, equitable distribution, and full use of the radium which may from time to time be the property of the Trust with the object of promoting the treatment of the sick throughout Great Britain and the advancement of knowledge of the best methods of rendering such treatment and of securing due economy in the use of radium for the purposes of such treatment. . . ."

The chief steps taken by the Radium Commission were the concentration, so far as possible, of such work at the chief university medical centres, the exploration of the facilities not only for radium but for all the ancillary services, and the requirement of guarantees from all participating National Centres that methods of treatment (selected and agreed upon by the medical members of each centre) should be carried out for long enough to enable their value to be determined statistically. Five-year figures from the Radium Commission cannot appear until next year, but a "Preliminary Report on Radium Treatment in Cancer of Certain Sites" has recently been published, and this is to be followed by similar publications.

The prestige of British physicists in the domain of radio-activity has contributed to the advance of radium therapy. The work of men like Lord Rutherford leaves its mark on the whole field of science, but it also has a distinctive effect upon the nation's science. As a consequence, knowledge of radio-activity became widespread here at a time when this could not be said of many other countries, and thus developments of technique were made very much more easily. An instance which comes to mind is the technical advance in the use of radon, which was initiated by the late Professor Joly so long ago as 1914.

It is submitted that the Medical Research Council and the National Radium Commission have been largely contributory to advances in radium therapy, and that the lack of similar supporting and co-ordinating help is now being felt in the domain of x-ray therapy.

Facts and Tendencies in X-Ray Therapy

It is probably true to say that up to the year 1920 x-ray treatment developed chiefly in the light of clinical experience, and from the technical side the exponents of it received the amount of support from manufacturers of apparatus which they asked for; the voltage and output of x-ray tubes were increased by gradual stages.