

reason that there are many organs in the body which are affected contemporaneously. The action must be limited to the organ which we are studying. The observations of the German experimenters is open to the objection that they do not confine their observations to single organs. In Prof. Wilcox's paper we had a study directed to one question, does strophanthus act as a stimulant to the heart muscle or through its effect on the blood vessels? I may recall some experiments which I made with digitalis when a student with Dr. H. Newell Martin in the laboratory of Johns Hopkins University, in order to determine the effects on the heart. The heart of a frog was isolated from all surrounding structures, including nerves and blood vessels. The heart was then placed on a warm stage, and connected with two reservoirs of defibrinated blood, in one of which the medicament was placed. By this means we could study the effect on the heart tissues by comparing its action when the pure blood was supplied with its action when the digitalis was introduced. These experiments were repeated too often and studied too closely to admit of error; they forced us to the conclusion that after the administration of digitalis the effects on the heart are due not to any action upon the wall of the heart, but entirely to its influence upon the nerves and blood vessels. This was followed by another line of experiment to study the action upon the blood vessels. In this experiment the mesentery of the living frog was placed on the stage of the microscope and immersed in warm salt solution, so as to keep the stage wet during observation. It was noticed that as soon as the drug was introduced into the circulation, there was a contraction of the blood vessels like that observed after administering ergot. I merely mention this to show the importance of confining our observations to one organ in studying the effects of a remedy.

Prof. WILCOX—I would be remiss in my duty if I did not record my appreciation of the value of the work which Dr. E. M. Houghton of Detroit has done and also my gratification that the results of laboratory investigation confirm the observations made in clinical medicine. I may say with regard to the suggestion of Professor Remington that the tincture furnished by Parke, Davis & Co. is satisfactory and no bad results follow its use, whereas the official tincture is unsatisfactory because of great variations in strength. I desire particularly to call attention to the necessity of having these preparations standardized. The crude drug varies in their percentage of strophanthin from 1.726 to 3.372, so that, according to their source, they should not only be standardized by chemic means but also by physiologic methods, if we wish to get good results from their use. Finally, I call attention to one other point: Before you get the full effect of digitalis when administered by the mouth, some forty-eight hours must elapse; but you can get the same results at once from the hypodermatic injection of one two-hundred and fortieth of a grain of strophanthin in about twenty minutes because of the great solubility of the latter.

Dr. E. M. HOUGHTON of Detroit—Before this investigation is complete, a very large amount of work must be done before we decide upon all the factors which must be taken into consideration in establishing the physiologic effects of strophanthus. I trust that during the coming year this work will be carried on and I will endeavor to do my part, especially in the line of physiologic investigation.

OBSERVATIONS IN THE USE OF DIPHThERIA ANTITOXIN, WITH SPECIAL REFERENCE TO ITS USE IN MALIGNANT CASES.

Presented to the Section on Materia Medica, Pharmacy and Therapeutics, at the Forty-eighth Annual Meeting of the American Medical Association, held at Philadelphia, Pa., June 1-4, 1897.

BY ALEXANDER McALISTER, M.D.

CAMDEN, N. J.

In bringing this subject before you it is my purpose to confine myself to those features of the disease which demonstrate the rationale of the serum treatment, as now recommended by all leading clinicians.

The development of the bacillus of Löffler in a susceptible individual constitutes diphtheria in its primary form. The seat of development, a local lesion, is usually the mucous surface of the respiratory tract, but may be any mucous surface or flesh wound of the body. The medium of infection is atmospheric air,

and the portions of the body most exposed are the tonsils because of their structure, function and situation. It is important in this connection to recall the anatomy of the tonsils. They are racemose glands, covered with reduplications of the oral mucous membrane. Their inner surface presents from twelve to fifteen orifices leading into small recesses, from which numerous follicles branch out into the substance of the gland. The orifices, recesses and follicles are lined with a continuation of the pharyngeal mucous membrane. The viscid secretions which serve as a lubricant invite to the folds of the tonsils the diphtheria bacillus; when once within these folds in a susceptible person, they not only rapidly develop, but in so doing produce toxins of most astounding virulence. In their development *per se*, they constitute the local lesion of diphtheria; as their toxic products are absorbed and carried by the circulation to every part of the system they produce indirectly the constitutional lesion of diphtheria. The pseudomembrane is always present and more or less extensive, but this does not constitute the essential lesion. The latter is the acute degenerative cell change particularly affecting the mucous membrane underlying the local lesion, but showing a marked predilection for the cardiac muscles, the kidneys, the peripheral nervous system and the lymphatic glands. In necropsies of malignant cases this cell destruction is shown in extensive localized necroses in these organs.

Diphtheria is a self-limited disease which tends toward a fatal issue. For reasons which are not now fully understood, the rapidity with which symptoms appear and the membrane spreads, or the course of the disease is run after infection, varies considerably in different persons. Next to the importance of an early diagnosis stands the question of malignancy. Formerly a malignant case of diphtheria was one that terminated fatally; but with the advent of our present superior methods of the serum treatment many cases once properly so classed recover. Malignancy now refers to the severity of a case rather than to its termination, depending on the seat and extent of the pseudomembrane and the virulence of the infection.

While the former may be ascertained by inspection we have as yet no means of knowing the latter in advance of its dire effects. The virulence of diphtheria toxins is nowhere more forcefully demonstrated than in a case of the disease in which a comparatively small number of bacilli situated in a mere speck of pseudomembrane produce a high degree of toxemia almost from the first. In such cases the bacilli of the infection are especially virulent and determine the malignancy of the resulting disease. In cases attended by extensive formation of pseudomembrane the malignancy of the disease is due to the rapidity of absorption of toxins from the local lesion or to the mechanical impediment they cause to the respiratory function. The rapidity of absorption on the other hand, depends on the particular understructure of the affected membrane. In laryngeal diphtheria the pseudomembrane is often quite extensive, yet because of the underlying membrane it is not so tough as elsewhere, and the absorption of the toxins and the resulting toxemia do not form an element of danger. On the other hand, because of the structure of the larynx and trachea and their abundant nerve supply, the immediate danger is from stenosis, spasm, cyanosis and asphyxia. Such cases show comparatively little toxemia and are generally not followed by the usual sequelæ. Glandular

enlargement, albuminuria and sthenic symptoms are wanting, and in necropsies of cases that die early, localized areas of parenchymatous degeneration in the heart and kidneys are not observed.

The opposite, however, is true where the local lesion is situated on the pharyngeal mucous membrane. Here the resisting basement membrane is displaced by glandular structure, vascular sinuses, erectile tissue and the like, and absorption takes place very rapidly. A fibrous network is situated around and among the above structures, and connects the mucous membrane to the periosteum. The glands are composed of tortuous tubules with many sinuses and oblong offshoots, all favoring rapid absorption. This applies especially to the rhinopharynx and nares where the hypersecretion which attends all acute inflammations of these parts makes the field all the more favorable to the thrifty development of the bacillus of Löffler. Vascular engorgement and accumulation of nasal secretions alike facilitate, the one in the formation of a specially dense membrane and the other in making the colony of bacilli specially thrifty. Such cases run a comparatively short acute course, and if they do not terminate fatally are followed by a train of sequelæ and attended by complications.

Barring any immediate danger from asphyxia, which is now readily met by intubation, the highest consideration in the question of treatment should always be the nature and degree of toxemia present. The danger now confronting the serum treatment of diphtheria, greater than any other, is that it be applied generally upon an empirical basis. To obviate this it is of importance that the question of malignancy and the degree of toxemia of each case be carefully studied. A scientific remedy requires to be employed scientifically. In a certain sense each case is a law unto itself. It is not sufficient to say that antitoxin must be administered during the first two, three or four days of the disease. It is possible that any case may speedily change in type and prove fatal within twenty-four hours. At times a case will run this short course when the pseudomembrane has the most innocent appearance and occupies only one or two recesses of a tonsil. If the infection could be early recognized and treated in its incipency, nothing in the remedial art would be easier than the cure of every case of diphtheria with one moderate dose of antitoxin. But cases must be treated as they are found, and alas, many are not found until the disease has made serious inroads by damaging vital organs or arousing latent disease. "The prognosis of any case of diphtheria is always doubtful, since the mildest case may become severe and the severe may improve. The prognosis is especially grave among children and in proportion to their youth; sucklings, however, are rarely affected. The progress is more severe among patients debilitated by previous disease or faulty hygienic surroundings. The outlook in the individual is worse as the disease becomes septic or gangrenous, since mixed infection there exists." (Wood's "Practice of Medicine," 1897, fol. 172.)

In my own practice I have found it advantageous to distinguish between early and late cases in the question of dosage and supplementary treatment. This is not based on an estimate of the hours or days the disease has probably continued, but on the progress it has made. Though somewhat arbitrary, it seems to me the best classification that can be made for the purpose. A thorough clinical examination of

the patient will generally suffice to determine to which class a particular case belongs.

Early cases will require only the initial dose of antitoxin, 1,000 units. The disease is promptly arrested and its natural course cut short. In such cases the patient is generally found quite well on the third or fourth day, and no sequelæ or complications will be observed. The conditions found are as nearly those of experimental diphtheria as is possible in clinical practice and accordingly the full specific powers of the remedy are obtained. In a series of early cases the physician's work becomes a matter of simple routine. He administers the requisite dose of antitoxin, orders a mild aperient and directs that the nose and throat be kept clean with a mild antiseptic or alkalin. Other remedies are not needed, and frequently it is difficult to keep the little patient in bed. If one will review his work as compared with his experience in the disease before the introduction of antitoxin, he is tempted to pronounce such cases of mild type and probably so conclude that many of the cases would have recovered without specific treatment. Bearing in mind, however, the gravity of any diphtheritic infection and the natural tendency of the disease, it is safe to declare that of a given number of cases treated with antitoxin early, less than 1 per cent. would have terminated in complete recovery within four days if treated otherwise; while according to the best pre-antitoxin statistics, between 25 and 30 per cent. would have died. On the other hand the 70 to 75 per cent. that would have recovered would have run courses ranging from ten days to three weeks and been attended by both sequelæ and complications. This applies to all cases treated early whether the type of the disease is pharyngeal or laryngeal. Cases treated early with antitoxin are universally mild because treated early; and remain mild because treated scientifically and specifically.

Late cases usually require more than one dose of antitoxin. The conditions to be met are graver and less easily appreciated than in early cases. In addition to the primary lesion there is the secondary or constitutional lesion. The pathologic condition from being purely local has become widely disseminated throughout many and important organs of the body. The toxins absorbed from the pseudomembrane have caused the essential lesion of the disease or scattered centers of cell necrosis. From these centers arises a new element of danger. The way in which this is caused is clearly indicated in the following from Louis Fisher: "If large quantities of this so-called membrane-toxin are absorbed into the system through neglected or delayed treatment, these toxins transform the albuminoid bodies of the tissues and cause tissue poisons or tissue toxins. These tissue toxins can be classed as those that belong to digested proteids, and those that are not proteid substances. The first is an albumose; the second is an organic acid. Albumoses have a specific action on the human organism; when present in large quantities they produce fever, and if allowed to act for any length of time they produce paralysis. In very large quantities they produce great exhaustion and also fatty degeneration of the heart and kidneys. It is in these cases that antitoxin at times fail, owing to the presence of poisons other than those peculiar to pseudomembrane, and which are by-products of degenerative changes in the tissues."

In late cases then the condition is that of primary

diphtheria for which antitoxin is fully specific, plus the damage already done and its grave constitutional results. The cases seen late are frequently of mixed infection, streptococci or other pathogenic organisms having followed upon the diphtheritic infection.

The local lesion soon becomes gangrenous and the constitutional condition, that of approaching pyemia. To this must be added in a certain percentage of cases the effects of pre-existing disease, either manifest or latent. While it is now largely conceded that antitoxin exerts specific power in neutralizing the membrane toxins and arresting the primary infecting process, it is not known to have such action against the tissue toxins, and certainly will not restore the integrity of damaged organs. In these cases the danger from the disease *per se*, is not so great as that from the damage already sustained by vital organs. The former is much more promptly amenable to treatment than the latter.

In treatment every feature must be kept in view. As early as possible the primary infecting process must be removed. It is impossible to form an adequate estimate of the number of antitoxic units required to accomplish this. The symptoms hyperemia, stupor, coma, or certain physical signs, the appearance, condition and extent of the pseudomembrane, the rapidity of spread may indicate a high degree of toxemia and mark the case as one of great malignancy, but all these form no basis for estimation. The condition must be met by special dosage. In these severe cases give 2,000 units of antitoxin and repeat the dose in eight to ten hours if the desired effects are not obtained. The full neutralizing effects of a dose of antitoxin are secured on absorption of the serum and within ten hours. To wait a longer time before repeating the dose is to expose the tissues of the body to further damage from the unneutralized toxins. Too much importance can not be attached to the use of concentrated serum. The smaller bulk is more promptly absorbed and results can be confidently expected in a much shorter time than when weak serums are employed. When this rule is followed I find comparatively few late cases require more than two doses. Late cases are always to be regarded as in imminent danger. Any undue effort or excitement on the part of the patient may induce cardiac paralysis. The patient's strength must be husbanded by quiet, the recumbent posture and nutritious food. To tax the heart as little as possible I have the foot of the bed slightly elevated. To these measures must be added, in many cases, cardiac and general tonics and stimulants. Such cases always run a more prolonged course and are often attended by complications and sequelæ. Though the disease proper is cured by the entire removal of the primary infecting process, the damage already sustained is sufficient to carry the disease process through a fixed course with the above named results.

Since introducing the serum treatment of diphtheria into my practice in January, 1895, I have employed it in sixty cases with a loss of five. In all these cases, excepting a few seen in consultation with other physicians, the diagnosis was confirmed by laboratory culture. They embrace all types and all degrees of malignancy and include a number of cases seen quite late in the disease. My earliest experience was with the French product, but since a most excellent antitoxin has been furnished by a reliable Philadelphia firm I have used this exclusively. My first eighteen

cases were treated in the West Jersey Orphanage and all recovered. These have been under my observation ever since and are in perfect health to this day. My results with the treatment have been entirely satisfactory in every particular, so that my former dread of meeting diphtheria cases has entirely left me. My only anxiety now is to see the cases reasonably early.

When I hear a physician question the value of antitoxin in the prevention and cure of diphtheria, or what is more in the face of the volume of testimonies now in its favor openly oppose antitoxin, my conclusions are that he has never used it or seen it used; or if the contrary is true, that a reliable product was not employed or was employed improperly. Antitoxin is not employed scientifically when the physician delays in order to first know whether the patient will most likely die without it, or to have his diagnosis confirmed by a culture before inaugurating the serum treatment; or when employed it is given in too small doses and at too long intervals.

582 Federal St.

STREPTOCOCCIC INFECTION AND MAR-MOREK'S SERUM.

Presented to the Section on Materia Medica, Pharmacy and Therapeutics at the Forty-eighth Annual Meeting of the American Medical Association held at Philadelphia, June 1-4, 1897.

BY GEO. W. COX, M.D.

CHICAGO.

The study of bacteriology during the past few years has developed many interesting facts, not alone to the scientist, whose labors and interests are confined to the laboratory, but also to the clinician, whose work it is to practically apply the knowledge furnished him by the former. It would be difficult to name any one branch of the subject which could justly claim precedence if viewed merely in its scientific aspect, for all are of absorbing interest in this regard; but in the matter of practical application and tangible results it may be safely asserted that the study of the streptococcus microbe stands first in the list. It is the most widely distributed of any of the members of its class; it is more variable in its morphologic development than any of the others; it is unique in the matter of biologic characteristics, and it is decidedly the most far-reaching in its pathogenic effects. Unlike any of its congeners its mere presence does not signify a single specific operation, but may be the harbinger of one of several conditions that vary widely in their effects on living tissues. Thus the microbe is found alone or associated with other micro-organisms in such diseases as erysipelas, puerperal septicemia, diphtheria, scarlatina, bronchitis, bronchopneumonia, septic wounds, gangrene, salpingitis, otitis, appendicitis and many others, as well as on the mucous surface of the natural orifices of the body in individuals who appear to be free from disease of any kind.

The very fact of the presence of this germ in such a large number of diseases and conditions of dissimilar character makes it difficult to attribute to it any certain and fixed pathology; while on the other hand this seeming conflict of testimony readily accounts for the wide diversity of opinion that exists between various observers as to its nature and effects.

It does not come within the scope of this paper to treat of the history, morphology, biologic characteristics and pathogenesis of this germ, for these are all