Remarks

ON THE

TREATMENT OF TETANUS, DIPHTHERIA,
AND OTHER NEUROTROPIC DISEASES
BY THE METHOD OF PHYLAXIS

BY

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The interesting and suggestive work published by Dufour a few years ago on the value of chloroform anaesthesia in the treatment of tetanus has not, perhaps, attracted the attention it deserves. This has probably been due to its apparent lack of general application, although, as will be seen below, such is not really the case. Dufour¹ in 1925 showed that if anti-tetanic serum is administered under chloroform anaesthesia to a case of tetanus, unusually good results are obtained. This technique was originally adopted by Dufour in order to facilitate intrathecal injections, a procedure otherwise difficult of application in contracture, and especially if opisthotonos is present.

THE VALUE OF SEDATIVES IN THE TREATMENT OF
TETANUS

The suggestion of treating tetanus by inhalations of chloroform is not actually original, as Eschallier, house-physician to Velpeau, employed this method as far back as 1847. Chloral later came to be used for the same purpose, and was given by mouth, subcutaneously, or intravenously.

Oré, who first suggested the intravenous administration of chloral—a method which attracted much attention—did not favour giving the drug by mouth, not only because its action then became uncertain, but also because of the large doses necessary to produce an effect, and of the difficulty, if not the impossibility, of such large amounts being absorbed. He at first greatly preferred the subcutaneous route, but in 1872, as the result of his early experiments, abandoned this method. In 1875 he² returned to the subject, and came to the following conclusions:

“Chloral may be given subcutaneously in one of two ways—either in a weak or in a concentrated solution. If the weak solution is used, it is ineffective and therefore useless, while a concentrated solution produces abscesses and sloughs at the point of injection, with unpleasant and even dangerous consequences. These facts have been amply confirmed both by animal experiment and in the treatment of patients suffering from tetanus.”

RESULTS OF INTRAVENOUS CHLORAL

Oré therefore unhesitatingly recommended the direct injection of chloral into the veins. This new treatment was first used in November, 1872, and in February, 1873, on two patients suffering from tetanus. The first patient was given nine intravenous injections within the course of three days, receiving in all 28 grams of chloral hydrate. He died nine days later; but as he was moribund at the time of the first injection, therapeutic results could hardly be expected. The second patient was given a daily intravenous injection of 10 grams of chloral dissolved in 10 c.cm. of water for three consecutive days. He gradually began to improve, and within seventeen days (that is, twenty-four days from the onset of the disease) his convalescence was assured.

Oré was of the opinion that the continuous anaesthesia produced by chloral allowed time for the elimination of the “morbid element” of the disease. In this way the

disease became less virulent and passed into the more chronic and, therefore, more curable stage.

In spite of these striking results, and of many others obtained in the domain of general surgery, intravenous chloral anaesthesia was soon given up. So far as tetanus was concerned a cure was rarely obtained. Thus in Oré's book,³ published in 1877, out of eleven cases reported, only two survived. Moreover, the intravenous injection of chloral demanded a certain dexterity, as any effusion of the drug into the cellular tissue outside the vein was certain to give rise to an abscess. Even practised surgeons, such as Cruveilhier, Tillaux, and Lanelongue (of Bordeaux), recorded cases of coagulation of the blood, and of thrombosis and phlebitis following the use of this method.

RESULTS OF SUBCUTANEOUS CHLORAL

For some time, in spite of Oré's view, the subcutaneous route was preferred; but, although successes were reported by Lauri (1874), Salter, Ribelle, Bouchardat, Purefoy, and others, the method was soon abandoned. The use of concentrated solutions of chloral was almost invariably followed by abscess and sloughs, or by deep cellulitis. In 1900 I first suggested that isotonic solutions would possibly avoid these complications, and recommended the use of 5 grams of chloral dissolved in 250 c.cm. of distilled water. When first used in a case of tetanus the method worked perfectly, and no local complications were observed. Injections of anti-tetanic serum were given at the same time, but the doses employed were small (10 to 30 c.cm. daily), and were given subcutaneously. The results obtained in this case⁴ were comparable with those recorded by Oré. The attacks of contracture rapidly ceased, the patient slept quietly, and remained asleep for forty-eight hours. He then, however, had a further convulsive attack, and died within a few minutes, asphyxiated, before another injection of chloral could be given.

I have, on several occasions since, had recourse to subcutaneous injections of isotonic chloral for the treatment of tetanus, but obtained my most interesting results in 1915, during the war. While with the 5/68 Ambulance Service, of a great number of wounded I had occasion to treat eight cases of tetanus—three at Tusey, near Vaucouleurs, and five at Toul: three of these patients recovered. Acting on the advice of G. Canuyt, who was pharmacist to the ambulance, and who unfortunately died later in the Flying Corps, I used a 1 per cent. solution of chloral, which, though a little more concentrated than the isotonic solution, caused no unpleasant local symptoms whatsoever. Two to three injections were given daily, making a total of 5 grams of chloral in the twenty-four hours. As the condition improved the dose was diminished, until the patient was taking 4, 3, 2, and 1 gram or less daily. In the case of R. G., which ended in complete recovery, chloral was given for the whole period between April 15th and May 14th, 1915. In the case of P., who also recovered, chloral was given from March 13th to March 30th, 1915, beginning with a daily dose of 5 grams, and ending with a dose of 0.5 gram. I often combined the treatment with a little morphine (1/8 to 1/4 grain in the twenty-four hours), and with subcutaneous injections of anti-tetanic serum in doses of 10 to 30 c.cm. daily. Occasionally the serum was given intravenously, but never in larger doses than 10 c.cm. Although the treatment failed in five of our cases, complete muscular relaxation was obtained, life was definitely prolonged some four to eight days, and death at least was rendered peaceful and free from the agony of body and mind that otherwise is almost invariably present. Moreover, these patients were already gravely ill with septicaemia (two had had amputations performed under very bad conditions) before developing tetanus.

INTRODUCTION OF CHLOROFORM INTO TREATMENT

We now know that the doses of anti-tetanic serum used were too small. Much larger doses are now given (Etienne and Benech have injected as much as two to three litres). We have also since learned, in cases of necessity, to employ the subarachnoid route, with the result that the mortality rate of tetanus has definitely diminished.

Certain patients were nevertheless found to be refractory to this intensive treatment, and, solely with a view to facilitating intraspinal injection of serum, certain observers again had recourse to chloroform anaesthesia. Remarkable results were sometimes obtained, which were assumed to be due to the anti-tetanic serum, until Dufour raised the question as to whether the chloroform itself might not have some beneficial action in tetanus. On investigation this seemed indeed to be the case, but for some time nothing further was done. These facts, however, demand an explanation, and it is with this aspect of the problem that I now propose to deal.

PHYLACTIC ACTION OF CHLOROFORM

Billard, the late professor of physiology at Clermont-Ferrand, was the first to give an original and convincing explanation of the value of chloroform anaesthesia in tetanus. Certain other workers had already attacked the problem, but none had envisaged it so completely or had seen in it an expression of a universal law. It was Billard who first established this conception, and who, after innumerable experiments, first described the phenomenon of "phylaxis."

With regard to this matter, Billard⁵ wrote as follows:

"Profoundly convinced of the essential importance of lipoids in the production of phylactic phenomena, I wondered whether anaesthetics generally, which had already been shown by Nicloux to have an affinity for the central nervous system, and in particular, whether chloroform, which had enabled Overton to establish the existence of lipoids, did not have the power of so modifying lipid equilibrium *in vivo* as to render animals either more sensitive or more refractory to neurotoxins."

EXPERIMENTAL EVIDENCE

Experiments with guinea-pigs in this direction gave the following results: (1) The injection into a guinea-pig of a lethal dose of tetanus toxin produced no reaction if the animal had been anaesthetized for about three minutes, twelve to fifteen minutes before the injection. An anaesthetized guinea-pig is therefore refractory to tetanus toxin (Billard). (2) If the lethal dose of toxin is given some ten to fifteen minutes before the chloroform anaesthesia, the animal dies more rapidly than by the injection alone. Therefore chloroform anaesthesia administered subsequently to the toxin increases the virulence of the toxin. (3) If, in the second example, an injection of anti-tetanic serum is given either just before or just after the chloroform anaesthesia, the amount of serum used being 0.5 c.cm. per 100 grams of weight, the animal survives. It follows, therefore, that anti-tetanic serum administered just before or during chloroform anaesthesia has the effect, as in the first case, of nullifying the action of tetanus toxin.

The above experiments relate to tetanus, but Billard's work suggests that similar conclusions might be drawn with regard to other toxins which have a special affinity for the nervous system, and particularly to diphtheria. Under similar experimental conditions identical results were obtained in cases of poisoning by sparteine and by the venene of the viper; here chloroform anaesthesia gave the same successful results as with tetanus toxin.

THEORETICAL CONSIDERATIONS

Billard was of the opinion that the beneficial action of chloroform was an example of what he called "phylaxis." The preliminary anaesthesia by chloroform impregnated the lipoids of the nervous system in such a way as to render it impossible for the toxins mentioned above to become fixed. In other words, chloroform acted as a protective or phylactic agent (*φύλασσις*, protection). This phylactic property has not the same force when neurotropic toxins are already fixed in the nerve centres. Chloroform, because of its affinity for lipoids, does indeed displace toxins already fixed to the lipoids of the nerve cells, and exercises, therefore, its phylactic action; but as the body is by this time considerably weakened, it cannot, alone, manufacture the antibodies necessary for its defence. The nervous system, by fixing these toxins in its own substance, serves to limit and neutralize their action. When, because of the greater affinity of chloroform for lipoids, these toxins are set free, it is in a body incapable of further resistance. The problem becomes quite different, however, if an antitoxin, in the form of a serum, is supplied at the same time. The toxins in circulation are at once neutralized, and the infection is cured.

In conclusion, it would seem that, when a patient is gravely ill from some neurotoxin such as tetanus or diphtheria, the best method of phylaxis is to inject large doses of antitoxin under chloroform anaesthesia.

TECHNIQUE AND RESULTS

Tetanus.—As we have seen above, the earliest cases reported were those of Dufour and his pupils, who applied the method in the treatment of tetanus. Similar cases have since been published by Ravina, Archambault and Friedman, Teissier and Coste, Bernard (of Lille), Pagniez, Guillaïn and de Sèze, by Brulé and Lenègre, Maurice Villaret, and Haguenau.

We have personally treated five cases of tetanus in children by the phylactic method of chloroform anaesthesia in our wards at the Clinique Médicale des Enfants. Three of the children recovered. I have also treated two other cases in men with complete success. In two cases in children the contractures gradually disappeared, the patient lost his pain and trismus, and became quiet and drowsy; life was prolonged, but death finally ensued. In other words, the disease ran the same course as it has been observed to do when chloral is given in large doses.

Nevertheless, we are convinced that this method will give still better results if it is practised according to the following rules, although we must admit we have not always followed them ourselves. (1) The injections of anti-tetanic serum should be given either immediately before or during chloroform anaesthesia. When utilizing the intraspinal route, subcutaneous injections of 50, 80, or 100 c.cm. should also be given from the start. In fulminating cases the serum should be given intramuscularly or even intravenously. The treatment should end with a subarachnoid injection of 10 to 30 c.cm., according to the severity of the case. It is sometimes necessary to repeat the treatment a second time within the twenty-four hours, but as a rule it need only be given once daily. (2) The mistake that is most frequently made is to postpone the phylactic treatment too long, to give it in the last and final resort. It should, on the contrary, be commenced at the onset of the disease, before the nervous system is too much involved, and when the body has some power of resistance still left.

Diphtheria.—The nervous sequelae of diphtheria, which have long been described, have of late years become increasingly and unusually severe. Hitherto the phylactic

method of chloroform anaesthesia has not been applied to diphtheria, in spite of the suggestive experiments of Billard in this connexion. Since February, 1930, we have tried the method in six cases, four without any success. We must frankly admit, however, that the treatment was applied only when the patients were *in extremis*, so that no really satisfactory conclusions can be drawn from these cases.

It is absolutely necessary to intervene early if the method is to be applied at all. As soon as nervous complications begin to appear chloroform anaesthesia should be at once combined with the administration of large doses of anti-diphtheritic serum, following the same technique as for tetanus, and giving the serum subcutaneously, intramuscularly, or even, in the hypertoxic cases, intravenously. The intraspinal route might also be employed, although this, to our knowledge, has not yet been tried in diphtheria. Such are the general indications which we advise, and which we shall ourselves follow in the future.

Encephalomyelitis and Poliomyelitis.—The phylactic method of chloroform anaesthesia might, by analogy, be used in encephalitis and poliomyelitis, but it would be necessary to have at our disposal corresponding specific serums. As far as poliomyelitis is concerned, Petit's anti-poliomyelitis serum might well be employed in this way, and may possibly give far better results than those obtained hitherto.

Against encephalomyelitis there is, as yet, no specific serum, but it is interesting to note that urotropine, which was quickly found to have a favourable therapeutic effect in this condition, probably acts in the same phylactic way as chloroform. Urotropine becomes decomposed in the tissues and gives rise to formaldehyde, which displaces the toxins from the nerve centres and becomes fixed to the lipoids of the cells. Billard's experiments with urotropine suggest this conclusion. As with chloroform, similar results were obtained; if urotropine is injected into a guinea-pig some fifteen minutes after the administration of a toxin (tetanus anatoxin), the animal dies more rapidly. But toxins differ among themselves, and it is possible that if the toxins of encephalitis were liberated in the blood stream, the body would be better able to deal with them than when they are fixed in the central nervous system.

Other Indications.—Although so far we have only discussed the more common neurotropic diseases, it is evident that the phylactic method might quite well be applied to other infections having a particular affinity for the nervous system. Among these are certain cases of influenza, typhoid fever, herpes zoster, varicella,⁶ typhus, sleeping sickness, and of poisoning by strychnine, phalline, snake bite, the botulinus bacillus, curare, etc.

CONCLUSIONS

For purposes of simplification we have confined our attention to the use of chloroform alone as a phylactic agent, though, as we have seen, urotropine may act in the same way. We must add, however, that Billard, in experiments of the highest ingenuity, has shown that sparteine sulphate, gardenal, and especially certain mineral waters, possess the power of similarly protecting the nerve centres. Further research may discover yet other phylactic substances. Although Billard considered his discovery of phylaxis to be of theoretical interest only, it has nevertheless been shown by later workers to have practical implications of the highest order, and to offer therapeutic possibilities of the greatest value.

This short memoir, which Professor Achard⁷ read for the first time at the Académie de Médecine of Paris, is written solely with a view to giving an indication of the results that can be achieved by phylaxis, of showing that we have now in our hands a method of wide application,

capable in the future of leading to considerable advances in the treatment of the neurotropic diseases.

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DIAGNOSIS OF DRUNKENNESS FROM THE EXCRETION OF ALCOHOL

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As part of a more extensive study we have carried out a number of experiments on the excretion of alcohol by human subjects. In all these experiments the excretion both by the lungs and by the kidneys was measured, and the condition of the subjects with respect to intoxication was observed by various psychological tests and by the routine methods of examination used by police surgeons. It seemed to us desirable, in view of the fact that estimation of alcohol in the breath¹ and urine² has been recommended as a test of drunkenness, that our experiments should be separately reported, especially as they do not support the use of this method of diagnosis.

The subjects of our experiments were all young, healthy men, and were all light or moderate drinkers. The experiments all commenced at about the same time, three hours after a light lunch. Except in one or two cases when gin was used, the alcohol was given in the form of whisky, the same brand being used throughout, and was diluted with an equal volume of soda-water. Drinking-water or soda-water was allowed during the experiment. Samples of air and urine were collected before the alcohol was ingested and periodically afterwards. Psychological and routine tests were made at regular intervals, the examination, in a number of experiments, being carried out by a police surgeon, Dr. Cameron, to whom our thanks are due.

For the estimation of alcohol in the expired air, the subjects blew air through a solution of potassium bichromate and sulphuric acid, the delivery tube being terminated by a disk of Jena sinter glass in order to ensure the formation of small bubbles, and consequently the complete absorption of alcohol. The air then passed through a flow meter placed with a dial facing the subject, who was instructed to stop when the required volume of air—usually five litres—had passed through. Control experiments with air saturated with alcohol vapour showed that at the rate of blowing adopted the alcohol was completely absorbed. The amount of alcohol absorbed and oxidized by the bichromate was determined, as usual, by the addition of potassium iodide in excess and titration with sodium thiosulphate. The quantities and concentrations of the solutions used were those recommended by Southgate³ for the estimation of alcohol in urine. The analysis of the urine was carried out by the method and with the apparatus described by Southgate.