FORMIC ACID IN THE TREATMENT OF DIPHTHERIA.

ORIGINAL COMMUNICATIONS.

THE THERAPEUTIC VALUE OF FORMIC ACID IN THE TREATMENT OF DIPHTHERIA.

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For some years after the introduction of antitoxin the percentage case mortality rate of diphtheria gradually declined, as the doses of serum administered became larger. Latterly, however, the death-rate has tended to remain more or less stationary, no doubt because we have reached the limit beyond which no improvement can be expected by increasing the dosage of serum. The mortality from the disease is still serious enough to make it necessary for us to do all in our power to supplement the action of the serum by the use of some suitable treatment, and indeed there are few who are accustomed to rely solely upon the use of antitoxin. Stimulation by alcohol, the systematic use of iron, of strychnine, or of various cardiac tonics, have all their supporters, and the value of some general tonic treatment may be said to be universally admitted. In this paper we propose to give our experience of a drug which has hitherto been but little employed in medicine, and never, to our knowledge, in the treatment of diphtheria.

Formic acid, as is well known, occurs in nature in the bodies of ants, in the hairs and other parts of certain caterpillars, and in stinging nettles. Its stimulant properties have been known for centuries. The Arabs were accustomed, before commencing any particularly long and arduous journey, to administer a decoction of ants' eggs to their horses, believing that their powers of endurance were thereby markedly increased. Preparations containing formic acid have also been long used as remedies, being greatly esteemed for their supposed tonic, diuretic, and aphrodisiac properties. Huchard has pointed out that there are, in the pharmacopoeias of the seventeenth and eighteenth centuries, references pointing to the value of such preparations in dropsy, chronic skin eruptions, and paralysis, and adds that formic acid itself has remained official in Switzerland and Germany. Garrigue, in 1902, claimed that the drug was useful in infectious and chronic diseases, and even had hopes of influencing favourably the course of tuberculosis and cancer by its administration.

It was not, however, till 1903 that Clément made a really scientific investigation of the properties of the acid, and reported the results of his experiments in a communication read before the Société Nationale de Médicine de Lyon. He found that formic acid is a powerful stimulant of striped muscle, and is in its tonic action closely allied to kola, cocoa, and caffeine. The internal administration of the substance is very efficacious in dispelling sensations of fatigue and in increasing muscular power as estimated
by the ergograph and dynamometer. In the same year Krull noted marked improvement in chronic kidney conditions with albuminuria after the subcutaneous injection of formic acid, in solution from 1–1000 to 1–100,000, according to the age of the patient. Provided no advanced cardiac disease existed, he found that nutrition was improved, albuminuria diminished, and diuresis increased. In 1904, Clément reported further experiments corroborating his previous statements regarding the increase of muscular force after the administration of the drug, and he also obtained good results in the treatment of two cases of muscular tremor.

The results of Clément were confirmed in almost every particular by Huchard in 1905. This observer, however, appears to have worked chiefly with formate of soda. He came to the conclusion that there is no doubt about the action of the drug in increasing muscular force, and suggests that the presence of formic acid in the bodies of ants may have much to do with their remarkable strength. There is equally no doubt about the diuretic properties of this substance, which, moreover, has practically no toxic qualities. Huchard has used it in neurasthenia, post-influenzal conditions, infectious diseases, dilatation of the heart, and senile weakness, and appears satisfied with the results obtained. But later in the same year he found it necessary to protest against the use of this remedy as a sort of universal panacea, and advised that its employment should be restricted to those cases in which there is an indication for tonic and diuretic treatment.

Considering that the asthenia, so characteristic of diphtheria, might be favourably influenced by the use of formic acid, one of us (Croom) treated with this substance one hundred cases of that disease admitted to the Edinburgh City Hospital in the early months of 1906. His results, published in the October number of this Journal, were sufficiently encouraging to warrant a more prolonged trial. Accordingly, during the remainder of the year, all cases of diphtheria admitted to the hospital were systematically treated with formic acid.

In undertaking this method of treatment, our main object was to note its effect on the occurrence of heart failure and of post-diphtheritic paralysis. It was considered that a substance, reputed to have such a marked tonic effect on muscle, might to some extent act as a prophylactic to that most dreaded of all the sequelle of diphtheria, cardiac failure. Moreover, it should in some degree prevent those forms of paralysis in which the muscle rather than the nerve plays the most prominent part, as, it has been suggested, is the case in palatal paralysis. Further, it was hoped that the patients would benefit by the improvement in nutrition, which is so much insisted on by the French observers. Lastly, it was not unreasonable to suppose that albuminuria might not occur so frequently in cases treated by a drug, which, in contrast to adrenalin and strychnine, has no marked action in increasing the blood pressure.
It is exceedingly difficult to estimate the value of any particular drug in the treatment of diphtheria. Some cases react so much better than others to serum treatment, and afford examples sometimes of such astounding recoveries, that it is impossible to attribute a quite unexpected change for the better in a desperate case to any new remedy which may be undergoing trial. Two cases, similar apparently in all respects, may be admitted; both may appear quite hopeless, and both receive equal doses of serum. Yet, while one improves from the first, the other may as steadily progress to a fatal termination. If the former has been treated with any new remedy, it would none the less be entirely unsafe to attribute its recovery to that cause. Differences of immunity and resistance, differences in the association of the infecting micro-organisms, may be, and probably are, quite sufficient to account for that result. It seems to us safer to rely on broad results than to depend too much on the impressions which have been left by individual cases.

Here again we are confronted by the difficulty that we are compelled to take as our standard of comparison the statistics of the hospital in previous years, and the question at once arises whether diphtheria was more or less severe in type last year than it has been previously. This we can only judge from our personal impressions and from the average amount of antitoxin given to each patient in each year. The type of diphtheria in Edinburgh has recently been mild. For four years preceding the one under discussion there has been practically no change in the mortality rate, which has remained between 7 and 8 per cent. In 1905 it was exactly 8 per cent. During the year 1906 there was no obvious change of type, and the average amount of antitoxin given was the same. We have no reason to believe that the disease was in any way less severe.

The routine treatment of diphtheria at the hospital in previous years has been the systematic administration of small doses of strychnine to all cases. This, we are aware, raises another difficulty, as although strychnine is approved of by many outstanding authorities, other competent physicians object to its employment. Whether they would carry their objections so far as to suggest that the mere withdrawal of strychnine from the routine treatment would account for any improvement subsequently noted, we are not prepared to say. One of us, however, has been gradually led to adopt this systematic use of strychnine after long experience of cases treated by various methods, and is convinced that it has hitherto given by far the most satisfactory results.

The formic acid which during 1906 was given systematically to all patients instead of strychnine was administered in the form of a 25 per cent. aqueous solution. Of this, doses varying from 5 to 20 minims were given in water every four hours. The dosage was graduated more by the severity of the case than by the age.
of the patient. As a rule, no immediate effect on the pulse was noted. Our experience was the same as that of the French writers, that forty-eight hours' administration is necessary before any change is observed. This change would appear to be rather a negative than a positive one, that is to say, that a large proportion of the severe cases did not show the irregularity and weakening of the pulse which would be naturally expected as the disease progresses, although it is only fair to say that in many instances the character of the pulse was much improved. Broadly speaking, less irregularity of strength and rhythm was observed than is usual. The general nutrition of the patients appeared benefited, and the most striking feature of the cases was the way in which their colour improved. Even in patients suffering from the most profound toxaemia, who were admitted pale, with lips almost purple, a natural and healthy colour rapidly returned to the lips and cheeks, and, most curious fact of all, this colour seemed to be maintained to the last even when a fatal termination ensued. This was especially commented on by nurses with large experience of diphtheria. The drug was easily taken, and caused no tendency to sickness. Indeed, it could be given with no bad effects to patients, who could tolerate nothing else by the mouth except iced brandy. The diuretic effect we found to be disappointing, and we are not inclined to lay stress on this property of the acid. In this respect, then, we cannot confirm the observations of Clément and Huchard.

As regards the broad statistical results, we have made a comparison between the two years 1905 and 1906 in the subjoined table, omitting from the latter year fifty cases which were not treated with formic acid and of which the percentage mortality was 8, the paralysis rate being 6 per cent.:—

| Year | No. of Cases | Percentage Deaths | Percentage Fatal Heart Failures | Percentage Paralysis | Percentage Albuminuria |
|------|--------------|-------------------|--------------------------------|---------------------|-----------------------|
| 1905 | 507          | 8.0               | 3.07                           | 9.09                | 23.7                  |
| 1906 | 412          | 6.2               | 1.94                           | 2.9                 | 15.7                  |

If the forty-eight hour death-rate is deducted, there is not much difference in the results. In 1905 the rate is 6.8, in 1906 4.6 per cent. A somewhat larger percentage of cases, then, was admitted in a hopeless condition in 1906 than in the previous year.

It is usual, in estimating the great advantages of the antitoxin treatment, to lay stress on the laryngeal and operative death-rates, as these refer to a class of cases more fixed, so to speak, in type. The general improvement noted above is confirmed in an interesting manner by our figures. The death-rate of all
laryngeal cases in 1905 was 18 per cent. In 1906 it had fallen to 16 per cent. Of the cases subjected to tracheotomy or intubation, the mortality in 1905 was 35.28 per cent. In the following year only 25.7 per cent. died, although a smaller percentage of the total laryngeal cases were operated upon.

We are well aware that a fall of little under 2 per cent. in the mortality rate cannot be claimed as a striking success, and may be readily explained by other causes than the addition of formic acid to the routine treatment. Still, looked at from another point of view, it is a reduction of the existing rate by, roughly speaking, a quarter. It is, moreover, interesting that no fluctuation in the rate has been observed in Edinburgh for the last four years, and it is most curious that its first marked variation should coincide with a complete change of treatment.

As regards the heart failures, we only include the cases which suffered from such classical symptoms as cardiac vomiting, pain, and syncope. The reduction of the fatality from this cause is very slight, and, we must confess, is disappointing. Still, we have observed patients who suffered from all these symptoms, and who appeared certainly doomed, rally in a way which has not previously been noticed in our wards, and we attribute the fall in the death-rate from this cause, small as it is, to the four or five patients who survived these attacks. We think it possible that the use of formic acid either limited the degeneration of the cardiac muscle, or acted beneficially upon its undamaged fibres. It is also possible that, as we had hoped before commencing this treatment, the blood pressure not being raised, the work of the heart was rendered easier.

The most interesting and surprising of our results is the extraordinary decrease in the amount of paralysis. This rate has varied more in recent years than the death-rate. In 1902 and 1903 it was 17 per cent., in 1904 somewhat over 12 per cent., while it fell to 9.09 in 1905. But in 1906 it was only 2.9 per cent., and throughout the year it was difficult to find cases to demonstrate this complication to the students attending the hospital. The small amount of it cannot be possibly attributed to slight cases being missed. If, on the other hand, we assume that the diminution of paralysis is really due to treatment with formic acid, the interesting point is raised why a muscular tonic should have such a surprising result on a lesion usually regarded as primarily of nervous origin. It is true that the post-diphtheritic muscular weakness is more a paresis than a complete paralysis.

It appears that only certain of the nerve fibres are affected in the degenerative process of the peripheral nerves. Are we to suppose that those muscular fibres, whose nerve supply is unimpaired, are so stimulated by the formic acid as to be able to carry on the work previously performed by the whole
muscle? Or is it possible that the general improvement in nutrition so affects the nerves that the tendency to degeneration of their fibres is lessened? Or may we not assume that the muscle is primarily affected in some forms of paralysis, as is admitted to be the case with the cardiac muscle, and, as Rolleston has suggested, probably with the palatal muscle also?

As regards albuminuria, the observations of others had led us to believe that this complication might also occur less frequently. It is, however, extremely difficult to explain satisfactorily why this should be, and we will content ourselves by stating the fact that its percentage incidence was very materially reduced.

The most obvious criticism of these results is to assume that the type of diphtheria was milder in 1906, and that this is particularly evidenced by the small amount of albuminuria and paralysis. We have already pointed out that, judging by the average amount of serum administered, the cases appeared as severe as those of the previous twelve months. The antitoxin dosage has always been determined by the same individual acting on more or less fixed principles, and for economical reasons the dose given is very seldom more than is absolutely necessary. The greatest care has been taken to exclude from these statistics all cases which could not fairly be called "clinical" diphtheria. Of 585 admissions to the wards, 123 have not been included. Many of these had the bacillus of diphtheria present in their throats either before, or at the moment of, admission. The mild type of diphtheria which has recently been present in Edinburgh makes the estimation of differences in death and complication rates very difficult. When a death-rate is only 8 per cent., and one-quarter even of these deaths occur within forty-eight hours of admission, there is not much room for any striking improvement in the percentage mortality.

Our only conclusion is that the results obtained are distinctly encouraging, particularly in relation to the occurrence of cardiac failure and paralysis. Formic acid is at least an admirable tonic, and we think it may be used in the treatment of diphtheria with safety, and to the great advantage of the patient. We are continuing our observations, and we trust that, by giving the drug to every alternate case only which enters our wards, we may secure a safer standard of comparison for its merits, and so avoid the fallacy raised by a possible change of type in the severity of the disease.

PRINCIPAL REFERENCES.

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