FIBROSITIS AND β -DIETHYLAMINOETHYL DEHYDROCHOLATE

BY

HARRY COKE

This paper describes the origin and purpose of a new therapeutic substance which has been used experimentally upon rheumatic fibrositis. The aetiology of fibrositis is still unknown, although numerous advances have been recorded during recent years (Copeman, 1944; Herz, 1945). Treatment is therefore still essentially empirical, but the results so obtained are of value in formulating hypotheses on which to base further experiments. The purpose of this paper is, therefore, not only to put forward a personal experience of a new drug for possible specific treatment, but to record preliminary results which may help towards the establishment of a pharmaco-chemical base line for further research.

Preliminary

The known methods of treating fibrositis were surveyed, and the action of procaine was then especially considered. The value of the local injection of this substance into fibrositic myalgic areas has been recorded for some years (Kellgren, 1938; Bier, 1908). The exact pharmacological action has not yet been established. It has been regarded as effective against the rheumatic lesion because of the local anaesthetic action, which breaks a vicious circle of pain and spasm. After full consideration, however, it seemed open to question whether the local anaesthesia was not purely a secondary effect, having no permanent therapeutic value beyond the temporary relief of pain just so long as the anaesthesia lasts; and the more prolonged therapeutic effect due to an entirely different pharmacological action of the procaine hydrochloride molecule. It seemed inadvisable, owing to the toxicity of this substance, to direct a general procainization by intravenous administration. Recently generalized anaesthesia by a slow continuous drip intravenous technique has been recorded as successful in cases of extensive burns (Gordon, 1943), generalized eczema (Greene, 1946), jaundice pruritus (Hewer, 1945), post-herpetic pain (Ravina, 1945), and asthma (Pérez, 1944).

Procaine is the salt of an ester of a substituted amino alcohol and p-amino-benzoic acid. A series of cases were treated, both orally, and by subcutaneous injection of p-amino-benzoic acid—which is relatively non-toxic. This was without

the slightest effect upon the rheumatic element. The other half of the procaine molecule—diethylaminoethanol—is a component of many therapeutic substances. It appeared probable, therefore, that in the esterified diethylaminoethanol the primary value of procaine for fibrositis might be found. A general effect, comparable to that of procaine locally, might be possible if this active radicle could be esterified with an acid radicle other than p-amino-benzoic acid (thus forming a less toxic ester), the second radicle being such as might make the whole more effectively operative upon the rheumatic lesion than the inert p-amino-benzoic acid.

As a result of an entirely separate investigation, an impairment of hepatic function was found in many cases of fibrositis. It was seen that in fibrositic anxiety states, in toxic sub-jaundice and in the prevalent over-ingestion of carbohydrates, the dysfunction was more pronounced. This suggested that a strong cholagogue might relieve both the hepatic dysfunction and the associated fibrositis. To this end a series of cases were treated with 3-7-12-triketocholanic acid (Dehydrocholin B.D.H.). It was found that, although this had little effect in righting the particular hepatic dysfunction, it had a remarkably beneficial effect upon many cases in the relief of their fibrositic symptomatology. Unfortunately this improvement was only temporary. It appeared probable, therefore, that the combined action of dehydrocholin and procaine might be useful for the treatment of generalized fibrositis. For this purpose dialkylaminoalkyl esters of dehydrocholic acid were envisaged; the β -diethylaminoethyl ester was prepared, and water-soluble salts were submitted to clinical trial. Difficulty was at first experienced in preparing solutions of the salts which were stable enough for storage over long periods.

The necessary toxicity tests have been carried out, and show that the minimum lethal dose of the hydrochloride of the above substance, when given intraperitoneally into white mice, is over 1,000 mg. per kg. of body weight. Intravenously it is much more toxic, the minimum lethal dose in mice being about one-tenth of this figure.

Extensive pharmacological investigations are being undertaken and will be reported in due course. The present report deals with the preliminary clinical trials and their assessment.

Clinical Administration

Patients were treated by subcutaneous or intramuscular injection of amounts varying from 5 to 25 mg. The clinical response was most marked in those patients in whom the fibrositic element was dominant. This was very evident when articular and non-articular rheumatism were present in the same individual. The cases treated may be divided into two groups.

1. *β -Diethylaminoethyl Dehydrocholate and Vaccine Injections.*—In the first place—and an unexpected effect—the β -diethylaminoethyl ester was determined as an activator of the physiological response to a vaccine. The administration of a dose of bacterial vaccine has an incontrovertible physiological effect, entirely divorced from any subsequent and controversial therapeutic effect. That is to say, the injection in a sufficient dose of bacterial organisms will give rise to a set of conditions that are well known, and that are recognized within the term “reaction.” If a dose of vaccine which alone was insufficient to produce a clinical or physiological reaction was given with a dose of the β -diethylaminoethyl ester (5 mg.), there was then again a typical reaction—this reaction being similar in every respect to that obtained with a larger reactional dose of the vaccine alone. As a corollary there are a number of people who are relatively insensitive to vaccine injections; if they are given a few doses of the β -diethylaminoethyl ester, followed later by the same vaccine injections, they are then found to be sensitized and to give typical reactions. This feature is recorded briefly as of physiological interest.

2. *β -Diethylaminoethyl Dehydrocholate used alone.*—Investigations covered a wide field, and the results can be alluded to only briefly. In the absence of any specific biochemical pathology upon which to gauge results, these are necessarily subjective. Deep local injections, as in the present use of procaine, show β -diethylaminoethyl dehydrocholate to have a similar effect. It soon became evident that, unlike procaine, the effect was a general one. Thus, the treatment of a local condition at the elbow joint with the substance was followed by disappearance of fibrositic pain in the knee. An injection in the arm was followed by a flare-up of an old osteomyelitic sinus in the sacrum; and similar distal effects were noted. Thus it appears that a subcutaneous injection, given usually in the upper arm, has a general effect. This suggested also that there was nothing to be gained by injection at the site of pain. Nevertheless, many patients were treated by intramuscular injections more or less in the area of pain. The clinical impression was gained that, although there was a general response, it was more concentrated and therapeutically more effective adjacent to the site of injection. This opinion has not been confirmed by all the physicians making therapeutic trials.

The β -diethylaminoethyl ester has been given in the presence of many possible complicating features without any ill-effect—cardiac disease, diabetes,

asthma, thyrotoxicosis, infective foci, etc. In general, doses of 5 to 10 mg. subcutaneously once a week have been employed. But it has been observed that, while increasing benefit may follow the first three or four doses of the ester, there may, after subsequent doses, be a relapse: in other words, general stimulation may easily be overdone. This is important, because the persistence of injections during this overstimulated or negative phase may lead to a general deterioration and worsening of the disease. A similar effect was noted and emphasized with the A.C.S. (antireticular cytotoxic serum) stimulation of the physiological system of the connective tissue (Bogomoletz, 1942). Experiments suggest that this saturated stage, which is clinically easily recognizable, may be reached after six weekly injections. After the first three doses of the ester intervals between them should be lengthened in order to avoid provoking such a negative phase—a phase which may last two, three, or more weeks before it is possible to give another dose producing a positive therapeutic effect. Naturally all cases do not respond satisfactorily. Greater clinical experience of administration, and investigations into the pharmacological action of this and related substances, may lead to improved results. The two tables record the general results in 100 unselected cases, 52 of which were treated with nothing but β -diethylaminoethyl ester, as described.

TABLE 1
ONE HUNDRED CASES TREATED WITH β -DIETHYLAMINOETHYL DEHYDROCHOLATE ALONE OR IN COMBINATION WITH OTHER METHODS

	All cases	Non-articular rheumatism (N.A.R.)	N.A.R. with arthritis: result on N.A.R.
Symptom free ..	26	23	3
Greatly improved ..	24	17	7
Some improvement ..	26	12	14
No change ..	22	18	4
Detrimental effect ..	2	0	2
	76%	74%	80%

TABLE 2
FIFTY-TWO CASES TREATED WITH β -DIETHYLAMINOETHYL DEHYDROCHOLATE ALONE

Symptom free ..	20*
Greatly improved ..	14*
Some improvement ..	5
No change ..	13
Detrimental ..	0
	75%

Conclusions

It is too early yet to arrive at any definite conclusion about the therapeutic value of the β -diethylaminoethyl ester. But the clinical results so far obtained are sufficiently encouraging to warrant further clinical trials, and also—after full pharmacological assay—investigation of related substances. The common factor of both the ester and procaine is probably a pharmacological radicle of basic importance in the construction of therapeutic drugs

* Two of these cases had a preliminary medication with the anterior pituitary adrenocortical hormone (corticotrophin) kindly supplied by the Organon Laboratories.

active on the rheumatic fibrositic lesion. On such a pharmaco-chemical base line it is possible to build further, and to direct research on similar chemical analogues.

Summary

Treatment of fibrositis by a new drug— β -diethyl-aminoethyl dehydrocholate—is described.

Of 100 cases analysed, 52 were treated with β -diethylaminoethyl dehydrocholate alone. In these 52 cases, 39 (75%) showed degrees of improvement from slight to symptom-free states.

It was observed that, when the substance was given with doses of vaccine, the former (*a*) activated non-reacting doses, (*b*) caused reaction in relatively insensitive individuals.

I wish to record my sincere thanks to Roche Products, Ltd., for their chemical collaboration and for the ample supply of material for these clinical investigations, which they supplied under their serial research number S/42.

REFERENCES

- Bier, A. (1908). *Verhandl. d. deutsch. Gesellsch. Chir. Berlin.*, 37, 204.
 Bogomoletz, A.A. (1942). *Rep. Conf. Acad. Sci. Ukrainian S.S.R.*
 Copeman, W. S. C., and Ackerman, W. L. (1944). *Quart. J. Med.*, N.S., 13, 37.
 Gordon, R. A. (1943). *Canad. med. Ass. J.*, 49, 478.
 Greene, R. (1946). Personal communication.
 Herz, R. (1945). *J. Amer. med. Ass.*, 128, 921.
 Hower, C. L. (1945). *British Encyclopaedia of Medical Practice*, Suppt., p. 32. London.
 Kellgren, J. H. (1938). *Clin. Sci.*, 3, 175.
 Pérez, J. P. (1944). *Rev. Clin. Española*, 12, 191.
 Ravina, A. (1945). *Presse méd.*, 53, 124.