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THE EFFECT OF TETRAETHYL AMMONIUM BROMIDE ON DYSBASIA ARTERIOSCLEROTICA

BY

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Since *Acheson* and *Moe* in 1945 demonstrated the specific action of tetraethyl ammonium bromide in blocking the autonomic ganglia, they and other workers (*Lyons et al.* and *Berry et al.*) have published the results of further investigations into the effects of this substance on various disorders of the vascular and autonomic nervous systems.

The best results of its use have been obtained in the treatment of peripheral vascular disorders, since, according to publications by *Berry* and his associates, this substance produces a temporary vasodilatation, which is just as marked as that which follows sympathectomy. Injected intravenously it should be an unfailing diagnostic test and, in addition, it is reported to have a good therapeutic action, even in advanced cases of vascular disorders.

In Sweden, *Larsson* and *Frisk*, and later *Ejrup*, have published results of research in this field.

Larsson and *Frisk* used big doses, 6-7 ml., intravenously, and up to 16 ml. intramuscularly, given at one injection, without secondary effects. In four cases they found, contrary to *Berry*, that peripheral procain block of the tibial nerve and spinal anaesthesia both had better results than tetraethyl ammonium bromide.

Ejrup has pointed out the importance of giving the injection slowly, at about 1 ml. per minute.

In normal individuals, as far as is known, tetraethyl am-

[1] In collaboration with Hagbart Starklint.

monium bromide always produces vasodilatation and a quick rise in the skin temperature of the extremities.

Slaughter, Brown and *Wakim* demonstrated plethysmographically that the blood flow in the extremitites increased after the administration of 3 ml. doses of tetraethyl ammonium bromide. In normal individuals there was an average increase of 100 % in the upper and 135 % in the lower extremities.

During the last 18 months experiments have been carried out at the Copenhagen Orthopaedic Hospital, Dept. 2, to determine the action of tetraethyl ammonium bromide in patients with peripheral vascular disorders and posttraumatic dystrophy, and—as control—in a few patients with non-vascular disorders. A preliminary report of these experiments was given by Dr. Starklint at the meeting of the Orthopaedisk Selskab in Copenhagen in January, 1948.

The preparation used ("Etylon") is a 10 % solution of tetraethyl ammonium bromide.[1]

The following technique was used in the so-called "Etylon test". The lower extremities of the patient were exposed to room temperature for half an hour, after which up to 5 ml. of Etylon were injected intravenously slowly over two to three minutes, with careful observation of the blood pressure and pulse rate, and temperature-readings from the big toe, the dorsum of the foot and the leg. A vasodilatation test by *Gibbon* and *Landis'* method and other examinations necessary for establishing a diagnosis had been carried out previously.

Etylon was also given therapeutically by intramuscular injection. First 6-8 ml. and then 3×10 ml. injections were given at intervals of a week. Experience showed this dosage to be too small and too infrequent, and in the past 12 months two injections have been given per week. We are now giving the injections every second day in increasing doses, but 1 0ml. was the standard dose in the cases reported in this paper.

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[1] The Danish pharmaceutical manufacturers "Pharmacia", who make the solution under the name of "Ethylon" have kindly supplied the necessary quantity of the material.

The secondary effects most frequently observed were a metallic taste and dryness in the mouth, slight dizziness, a fall in blood pressure, a rise in pulse rate and transient accomodation pareses. Considerable falls of blood pressure were seen in only two cases. One rose again spontaneously. The other, which fell from 210 to 50 mm. Hg. rose again immediately after a subcutaneous injection of 0.5 ml. adrenaline. The patient only felt slightly dizzy and clinically did not appear to be on the verge of collapse.

According to the literature temporary paresis of the intestine and bladder are other possible secondary effects.

The action on the vessels is felt as transient paraesthesiae in the extremities, followed by numbness and a "cool sensation" in the hands and feet, and, within 5 minutes, a sensation of warmth, which is accompanied by a rise in the skin temperature of the extremities. This paper will show that we, like *Larsson* and *Frisk* found that tetraethyl ammonium bromide has an undoubted effect and is of diagnostic, as well as therapeutic, value. Probably its most important use will be in vascular disorders in which the spastic element is predominant. However, the number of patients whom we have treated has not been large enough to prove this, and the pathological pictures have been so various that we have not wanted to include many of them in this paper. But it has been among this type of patient—in whom vasospasm predominated—that we have observed the most encouraging effects of tetraethyl ammonium bromide.

We shall only deal here with patients with the signs and symptoms of intermittent claudication of arteriosclerotic origin.

A summary of the results obtained is given below.

Arteriosclerotic intermittent claudication	12	patients
Improvement in claudication	8	„
Disappearance in coldness of feet	4	„
Objective improvement in the appearance of the feet	3	„

Reflex vasodilatation and rise in skin temperature	more than 2° C	8	„
	„ „ 4° C	5	„
	„ „ 8° C	3	„

Twelve patients, including two women, all with advanced and confirmed arteriosclerosis have been fairly easy to compare. We have not included any patients who were having any other treatment at the same time as the tetraethyl ammonium bromide injections. The exclusion of these cases from the paper, and of patients with pangrenous lesions from the treatment, accounts for the small number of cases reported.

The ages of the patients varied from 43 to 63. Seven cases were examined well over twelve months, three only four months and two between six and twelve months after treatment.

After treatment with tetraethyl ammonium bromide the claudication has noticeably improved in eight of the 12 cases, and very noticeably in 4 of these 8.

It must be admitted that our best criterion of a favourable effect on the vascular disorder is the subjective improvement in the patient's dysbasia. All the patients treated have given satisfactory information on the distances they have been able to walk before feeling cramps in the calf, or pain or tiredness in their legs. We have come to the conclusion that, in future, a standardised walking test with a definite pace rate, controlled by a metronome and performed under experienced supervision, should be adopted since tests of function, such as the *Lewis* test, with or without resistance and with or without elevation, and the *Moskowicz* test, give results which vary too much with different examiners.

But it is worth noting that in the patients who reported improvement in their dysbasia definite objective signs of an increased blood-flow in the lower extremities were found.

Certainly some importance may be ascribed to the patients' statements that they do not suffer so much from cold feet, since this symptom causes great discomfort, and its disap-

pearance is sure to be noticed. The 8 patients whose dysbasia improved had all suffered from cold feet. One noticed an improvement in this symptom and—what is more encouraging—in 4 the symptoms disappeared altogether. In 2 it remained unchanged, while one patient only complained of it after treatment.

We have not ventured to attach too great an importance to the reports of the appearance of the feet at the follow-up examination—again on account of changes in the examiners. Nor did it seem justifiable to place much emphasis on the results of palpation of the arterial pulsation of the feet. However, in 3 patients the changes were convincing and there was also considerable improvement in the results of the *Lewis* function test, and in the postural colour changes, such as pallor of the skin with elevation, and rubor with dependence, of the feet.

Only 1 of the 12 arteriosclerotic cases suffered from pain at rest, and this was unaltered after treatment. Pain at rest often develops after acute arterial occlusion, of which none of our patients showed any evidence.

The vasodilatation test of *Bibbon* and *Landis* makes possible more objective comparisons. In this test the patient holds his hands in water kept at 44° C. and the temperature of his feet is recorded. Before the test his lower extremities are exposed to room temperature, which was always about 20° C.

Of the 8 patients who improved as a result of the treatment, 7 showed a rise in skin temperature of between 2 and 9° C., compared with the maximum temperature previously obtained on the more severely affected foot. In 4 patients the rise was more than 6° C., and in 2 the vasodilatation reflex was more brisk, giving a steeper curve. Out of the 4 patients whose condition showed considerable improvement, as already mentioned, 3 gave rises of 8°, 8°, and 9°, respectively, compared with the maximum temperature measured on the more affected foot before treatment.

As was expected the oscillometer showed no increase in the oscillations. All the 12 patients with arteriosclerosis had

small oscillometric indices for the lower part of the leg, and small oscillations in the upper part of the leg and the thigh. A few patients rises of about 1 in the index, but, as repeated measurements are necessary, and the readings may vary if the cuff is not applied at exactly the same level each time, no conclusions could be drawn.

In 6 of the 12 cases there were small decreases in the oscillometric index; in the other 6 there was no change, which, to say the least, suggests that the organic changes in the vessels were not reduced.

On the other hand, 2 patients, who had improvement in their dysbasia had rather bigger oscillations before treatment than the rest—3 and 2.5 respectively on the lower part of the more affected leg—which might have been considered a good prognostic sign for treatment, whether with procain block or tetraethylammonium bromide. But 2 other patients who showed marked improvement had oscillations of 0 and 1 both before and after treatment, which shows that it is not possible to draw from the oscillometric findings any conclusions on the relative proportions of vasoospasm and organic changes in the vessels.

We mention this point particularly, since it is not necessary to assume that the action of the substance on the autonomic nervous system is exclusively a relief of vasospasm. The interruption of reflex arcs through the autonomic ganglia may be of importance also in other ways in patients with peripheral vascular disorders.

The number of unfavourable oscillometric findings before and after treatment with tetraethyl ammonium bromide, including the 8 cases whose condition improved, supports the view that oscillometry is not a satisfactory objective measurement of the condition and of the function in the lower extremities, though it may be useful for a rough localisation of an obstruction in a big artery. This agrees with the opinion of *Allen, Barker* and *Hines,* who, in their book on peripheral vascular diseases, almost condemn oscillometry as a method

of examination, and do not attach any importance to it as a control test.

In patients with other disorders whom we have treated with tetraethylammonium bromide, sympathetic block or spinal anaesthesia, we have found that the oscillometric index did not rise with effective treatment, and in some cases it was even reduced.

Whether a rise in the skin temperature can be taken as indication of an improved blood-flow through the arterio-venous shunt, or whether there is also an improved blood-flow in the muscles, we have not been able to determine from our investigations; but certainly the reduction of the patients' pain suggests it.

Finally, we should like to report 2 further cases of arterio-sclerotic intermittent claudication. Both showed marked improvement. They were prescribed a protective regimen at the same time as they received the tetraethyl ammonium bromide.

One patient was an official weigher and measurer, aged 58 years. He had worn only carpet-slippers for 7 years, had suffered from cold feet, and before treatment could walk only a few metres. After the second injection of tetraethyl ammonium bromide (6 ml. intramuscularly) he was able to walk well over 3 kilometres in ordinary leather shoes. He no longer suffered from cold feet. A vasodilatation test (see above) showed a stisfactory rise in the skin temperature of his feet, while the oscillometric index showed no improvement after treatment and later the oscillations tended to diminish. One year after treatment he is still satisfied with the result and able to work. (Fig. 1).

The other patient was an infant-school teacher (female), aged 58 years, who before treatment could not walk many steps without cramp in her left calf. Her feet were also cold. 8 months after treatment with tetraethyl ammonium bromide (6 ml. rising to 10 ml.—altogether 10 injections) she is able to walk for an hour provided she does not walk too fast.

The vasodilatation test shows a satisfactory rise in the skin temperature of both feet (Fig. 2). The room temperature

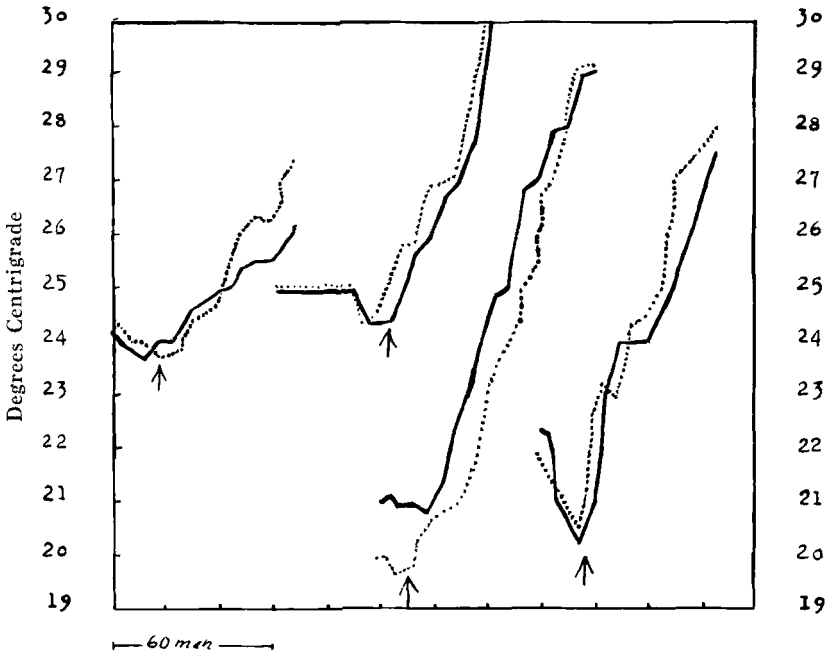

Fig. 1.

Vasodilatation after immersion of hands (indicated by arrow) in warm water. Man aged 54 years with obliterative arteriosclerosis. Skin temperatures of first toe on both sides, — before, 5 days, 3 months and 12 months after treatment (from left).

was higher (22° C.) at the follow-up examination and an attempt was made to cool the feet with a ventilating fan. The maximum value of the oscillations measured on the lower part of the leg was about 3, both before and after treatment.

We have had to prescribe a protective regimen after treatment. This has amounted mainly to general prudence regarding the feet, warm footwear which does not pinch, elevation and postural exercises, and hot and cold bathing, or Hauffe baths.

It would have been desirable, and perhaps also justifiable, to have treated a number of patients with tetraethyl ammonium bromide alone. We think that the substance is a therapeutic victory, and that its effect has been convincing in

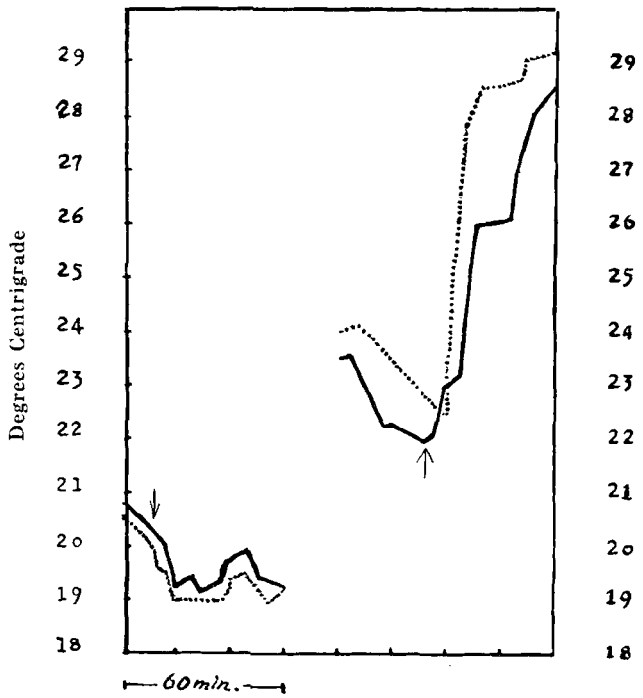

Fig. 2.

Vasodilatation after immersion of hands (indicated by arrow) in warm water. Woman aged 58 years with obliterative arteriosclerosis. Skin temperatures before and after treatment.

several of the patients mentioned. We expect that for some time its use will prove disappointing in many patients in whom the organic changes are more advanced and the spastic element less—in other words, in cases where the reserves of blood supply are small.

On the other hand, this criterium cannot be considered to be universally applicable, since some of our patients felt definite improvement though there was no objective evidence of increased blood-flow through the extremities.

We have encountered no real disadvantages of the dosage which we used, and the patients have felt no discomfort or anxiety with the treatment. On the contrary, some felt re-

markable relief and a pleasant sense of warmth in their legs, even when there was no improvement in the clinical picture.

Most of the patients were out-patients during the final part of the treatment. After injection they were kept in a horizontal position for 30 minutes; they were then allowed to sit up, and we made sure that there was no fall in blood-pressure.

We do not possess any data for comparison with the cases described here, but we think that if the results obtained with tetraethyl ammonium bromide are viewed against the background of lumbar sympathectomy, which is, after all, a comparatively serious operation, they call for further investigation and use of the substance.

SUMMARY

12 cases of advanced, well investigated, intermittent claudication of arteriosclerotic origin treated with tetraethyl ammonium bromide are reported.

The dysbasia diminished noticeably in 8 patients, and in 4 there was a remarkable subjective improvement following the treatment. The oscillometric index remained unchanged, but other objective indications of improvement were found, especially an increase in the rise in skin temperature in responce to a vasodilatation reflex. The significance of the objective findings are discussed. The results have been encouraging, and call for further investigation and therapeutic use of this substance.

RESUME

Communication de 12 cas de malades souffrant de dysbasie avancée et vérifiée, d'origine artériosclérotique traités au tétraéthylammoniumbromide.

Les symptômes dysbasiques ont nettement diminué chez 8 malades et chez 4 on a constaté une sensible amélioration subjective après le traitement.

L'indice oscillométrique ne montrait aucune modification. Par contre, à l'aide d'autres mesures de contrôle, on a constaté une meilleure élévation de la température de la peau à l'épreuve des réflexes vasomoteurs.

L'importance des trouvailles objectives est discutée. Les résultats obtenus ont été si encourageants qu'ils engagent à poursuivre les expériences et à continuer l'administration thérapeutique du produit utilisé.

ZUSAMMENFASSUNG

Es wird über 12 Patienten berichtet, die alle eine sicher verifizierte arteriosklerotische Dysbasia hatten und mit Tetraäthylammoniumbromid behandelt wurden.

Die Dysbasiebeschwerden nahmen bei 8 deutlich ab, und bei den übrigen 4 kann es nach der Behandlung zu einer sehr wesentlichen subjektiven Besserung.

Der oszillometrische Index zeigte keine Besserung, dagegen fanden sich andere objektive Kriterien einer Besserung, in erster Linie eine erhöhte Temperatursteigerung bei der vasomotorischen Reflexprüfung.

Die Bedeutung der objektiven Befunde wird erörtert.

Trotz des Fehlens eines Kontrollmaterials findet man die Ergebnisse so ermutigend, dass sie zu weiterer Untersuchung und Behandlung mit dem Stoffe auffordern.

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DISCUSSION

S. Kiær.

A. Langenskiöld: Tetraethylammonium bromide (Astra) has been used by Dr. Bj. Lindström in the IIIrd Department of Surgery of the Helsingfors University since Dec. 1947. Experience has shown that T.E.A.B. therapy is no substitute for sympathectomy in thromboangitis obliterans. In a case of severe phantom limb pain following disarticulation of the humerus T.E.A.B. had a good effect for 5-6 hours after its injection. The same effect was obtained with a paravertebral injection of novocain. Complete relief was obtained by cervicothoracic sympathectomy.