PERSONAL EXPERIENCE WITH NEOSTIGMINE THERAPY IN RHEUMATOID ARTHRITIS*

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Within the group of the chronic rheumatic diseases, rheumatoid arthritis and rheumatoid spondylitis undoubtedly constitute the most important syndromes from the medical standpoint, not only because of their symptomatology and evolution, but also because their aetiological agents are unknown and because they are, therefore, a difficult and complex therapeutic problem. No wonder, therefore, there is nowadays such a multiplicity of treatments, which vary according to the criteria and experience of each physician.

Clinicians have been working hard to find a therapeutic element which could really be relied upon in such affections, since researches into the aetiology are still yielding entirely negative results. Trommer and Cohen (1944), for instance, decided to experiment with neostigmine methylsulphate in a group of patients with various rheumatic affections, basing their decision on the fact that, from the point of view of muscle spasm and atrophy, there is a certain correlation between rheumatoid arthritis and anterior poliomyelitis, and also on the fact that in subacute and chronic poliomyelitis Kabat and Knapp (1943) reported encouraging results with the use of neostigmine, a drug that proved very efficient in the treatment of postoperative intestinal atony and of myasthenia gravis. In a preliminary paper these authors report the results registered in 19 patients, duly selected beforehand, in whom deformity, decrease of movement, and disability were present in a marked form, but with a minimum of demonstrable anatomical lesions. Thirteen of these patients, some of them with rheumatoid arthritis, responded favourably to the neostigmine therapy (subcutaneous injections, either daily, or every two or three to six days, according to the type of case). In 3 cases of rheumatoid arthritis with marked functional disability and invalidism the improvement led to functional recovery; and 2 of them, who had been confined to their beds for some time, were able to get up. In the 6 remaining patients, results were insignificant or completely negative. Trommer and Cohen state in their conclusions that neostigmine is the most efficient drug for muscular spasm in rheumatoid arthritis.

Later, Kabat (1944) used neostigmine in 53 selected patients with various affections (hemiplegia,

facial and cerebral paralysis, subacromial bursitis, and rheumatoid arthritis) complicated by chronic neuromuscular dysfunction, and in whom muscle pain, spasm, contracture, or partial paralysis were the main factors in the functional disability (cases in which the disability was devoid of an organic substratum). This group included 6 cases with chronic rheumatoid arthritis and 3 others with rheumatoid spondylitis, whose rheumatic complaints were of many years' standing, and who suffered also from severe disability. There were also 2 cases of rheumatoid arthritis in an acute stage. The first 9 patients (chronic cases) improved to some degree with the treatment, and Kabat noted a relief of pain, an improvement of motion, and an increase of the active muscular strength in the cases in which there was spasm, hypertony, or muscle pain. In the 2 cases in the acute stage the results were negative, so that the author considers the use of neostigmine in cases of rheumatoid arthritis with active inflammatory process to be contraindicated. Kabat states in his conclusions that the results are encouraging enough to warrant further investigation.

It was due to the results of Trommer and Cohen and of Kabat that we decided to experiment with neostigmine in a group of our own patients.

Clinical Material

We administered neostigmine to a group of 21 out-patients in our private practice as follows: 12 with rheumatoid arthritis, 7 with both rheumatoid spondylitis and rheumatoid arthritis, 1 with rheumatoid spondylitis, and 1 with cervical osteo-arthritis spondylitis. In these cases the rheumatic process had reached various stages of evolution. The patients were not specially selected for this type of study, but were chosen at random. However, the greatest care was taken as regards the accuracy of the diagnosis. The objective, articular conditions of all of them were favourable for experiment, for all of them (except 2, who were confined to bed), could move about spontaneously, without outside help.

Method

Each injection (subcutaneous) consisted of 2 c.cm. of a 1:2,000 solution of neostigmine (or prostigmine) methylsulphate. The injections were made twice daily, daily, or every two or three to four days according to the facilities which existed for seeing the patients. At

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the beginning we added $\frac{1}{4}$ mg. of neutral atropine sulphate in order to avoid the stimulus of neostigmine on the vagus. However, in view of the very disagreeable side-effects of atropine in the majority of our patients, we resorted to neostigmine alone, without ever noting any untoward manifestation of the drug.

When we started the present study, the greater part of our patients was already under our care, and a few only were about to start treatment. None of the patients, therefore, was given neostigmine alone, but always neostigmine associated with the basic therapy which had been prescribed according to the type of arthritis. During the period of the experiment we entirely gave up the use of analgesics.

Results

We administered a total of 260 ampoules. The results are described below.

Rheumatoid arthritis groups.—In the rheumatoid arthritis group, 9 patients were in the evolutionary phase of the affection, and 3 in its terminal stage. In 7 of the 9 cases in the evolutionary stage there was an immediate relief of the articular pain, followed by an improvement of active movement; this improvement lasted from a few hours, in the case of least duration, to 48 hours in the cases of greatest duration. In 5 of those patients, however, we noted an irregular and inconstant action of the drug, for in 3 cases the first injections produced a favourable effect, reducing the intensity of the pain, whereas after the succeeding injections we noted an exacerbation of the pain, very accentuated in 1 case, and this led us to discontinue the administration of the drug. In the 2 remaining patients, neostigmine produced a relief of the articular pain and an improvement of active movement until the twentieth ampoule, but the next ampoule in 1 case, and the following 5 in the other, did not produce any result, so that we discontinued the experiment. In the last 2 cases in the evolutionary period results were entirely negative.

Of the 3 cases in the terminal stage, the first was a patient whose hands and feet only were affected, with flexion of two fingers of the right hand due to muscle contracture, and in whom the first injection of neostigmine produced a relief of pain and an improvement of movement, followed, however, by an intensification of symptoms after the sixth ampoule. In the second case, a patient with total rigidity of the lower limbs, who was consequently compelled to stay in bed but who did not have articular ankylosis, the administration of 16 ampoules did not produce any result. And yet this was the only case of our series in which arthritis was in its inactive stage, as could be recognized by the normal values of the sedimentation rate and by the absence of joint swelling. The third case was a patient who had to stay in bed, principally because of involvement of the knees, which were in mid-flexion and painful, with functional disability. The rheumatic process, although without joint inflammation, was decidedly active, the sedimentation rate being 125 mm. at the end of the first hour. The administration of 2 ampoules of neostigmine per day did not produce any results.

Rheumatoid spondylitis and arthritis.—Of the 7 patients with both rheumatoid spondylitis and arthritis, we noted in 2 cases a slight decrease of the articular pain and a corresponding improvement of the active movement, which lasted for several hours. In 1 case there were favourable results after the first ampoule, but none whatsoever after 20 more ampoules. In the fourth case there was slight improvement after the injections (25 in all), followed by an intensification of the whole symptomatology. In the 3 last cases entirely negative results were observed.

Advanced rheumatoid spondylitis.—A patient with rheumatoid spondylitis in its terminal spondylitic stage showed constant relief after the 21 ampoules she was given. Immediately after the injection of the drug the radiating pains in the inguinal regions disappeared, with consequent greater facility in walking. The discontinuation of neostigmine was followed by an intensification of pain.

Osteo-arthritic spondylitis.—We tried neostigmine in 1 case of cervical osteo-arthritic spondylitis with pain in the trapezius muscles. No results, however, were noted after 2 injections.

In 8 of the cases in which neostigmine therapy had been followed by a relief of pain, we injected later on atropine only, in order to determine whether the sedative action obtained could be due to that alkaloid. The results of the 22 ampoules administered, however, were entirely negative.

Modification of the sedimentation rate due to the administration of neostigmine could not be discovered in any of the 20 cases of rheumatoid arthritis or rheumatoid spondylitis.

Comment

In 20 cases of rheumatoid arthritis and spondylitis submitted by us to the neostigmine therapy, we observed favourable results in 13, but such results were not regular, even in temporary relief of pain. In some patients there was marked improvement after the first injections, whereas the following ampoules produced entirely negative or even harmful results. In the 7 remaining cases (rheumatoid arthritis and spondylitis) and in one more case (osteo-arthritic spondylitis), the results were negative.

In the cases in which the action of neostigmine was favourable, such action was characterized by only temporary relief of pain, followed by an improvement of proportional duration in the joint function. In 5 of those 13 cases there was increase of pain during the period of administration of neostigmine, and in 2 other cases relief was felt after the first injections only, whereas the subsequent ampoules did not produce any result.

In none of the cases did we observe any objective action of the drug on the general or articular condition or on the sedimentation rate. And we must point out that we never administered neostigmine alone, but that we always associated it with the basic therapy commonly used in other patients. Neostigmine being a supposedly anti-spasmodic drug, it could not be expected to produce a real,

positive effect on rheumatoid arthritis or spondylitis. Because of the absence of any objective action of neostigmine upon our patients, and of the irregularity and inconstancy of its subjective effect in rheumatoid arthritis and spondylitis, we did not find it necessary to extend the treatment to a larger number of cases. Nor did we prolong the observation period, lest the effect of the basic treatment could be attributed to neostigmine, thus rendering possible an over-estimation of the real results of the drug.

Summary and Conclusions

In a group of 20 patients with rheumatoid arthritis and spondylitis in various stages of evolution

who were submitted to neostigmine methylsulphate therapy, the drug proved to have an inconstant and irregular effect on the symptomatology of pain and on the range of movement in the 13 cases which were benefited in various degrees. Neostigmine had no objective effect on either the general or articular conditions or on the sedimentation rate. In 1 case of cervical osteo-arthritic spondylitis the results were negative.

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