

THE ALLEGED EFFECT OF ACETYLCHOLINE ON IMMOBILIZED JOINTS

BY

A. M. HARVEY, M.D. Baltimore

(From the National Institute for Medical Research, Hampstead, London)

Neuburger and Scholl (1937a) have recently claimed that acetylcholine, given by subcutaneous injection, relieves or prevents the ankylosis and muscular atrophy which normally follow the immobilization of the limbs of experimental animals. In their experiments the knee-joint and ankle-joint of one hind limb in each of twenty rabbits were immobilized by means of a plaster bandage several layers thick, which extended from the great trochanter of the femur to the toes. The ten animals which served as controls showed ankylosis and a high grade of muscular atrophy after three to four weeks of continuous immobilization. The remaining ten animals received 10 mg. of acetylcholine subcutaneously every second day, until a course of eleven to fourteen injections had been made, when the plaster was removed. All the joints were found to be entirely free to passive movement; in active motion there was a slight sparing of the previously immobilized extremity, but this disappeared after a few hours. The muscles of the leg seemed fully normal and did not differ from those of the other hind limb.

In a more recent report Neuburger and Scholl (1937b) have extended their observations. A group of twelve rabbits were treated in the same manner, but the dose for injection ranged from 0.1 to 10 mg. It was found that the dose of 10 mg. gave the best results, and no effect was observed with doses below 3 mg. Six more controls were studied with this group, and all showed ankylosis when the casts were removed. Atropine did not counteract the beneficial effect. When prostigmin and atropine were given before each injection of the acetylcholine a dose of 3 mg. was found to be sufficient to prevent the ankylosis and atrophy. The authors state that, because of the similar action of acetylcholine and histamine on the blood vessels of the rabbit, the latter drug was given to a series of eight animals prepared in the same fashion: 1.5 mg. of histamine hydrochloride was administered subcutaneously every two days to a total of fourteen injections. A beneficial action was reported, but it was not so good as that obtained with the acetylcholine. In view of the practical importance of this suggested new action of acetylcholine it was thought advisable to repeat these experiments, following as closely as possible the technique for immobilizing the limb described by Neuburger and Scholl.

Twelve rabbits of different sexes, each weighing between 2 and 3 kg., were used. As in Neuburger and Scholl's experiments, the right hind limb was firmly wrapped in a bandage impregnated with plaster, six yards in length and one inch wide, extending from the greater trochanter of the femur to the toes. The animals quickly became accustomed to the cast, and, by using it as a crutch, were able to get about quite easily. They were allowed to run about freely in a small room.

Of these rabbits seven were used as controls. Two received a subcutaneous injection of 1 c.cm. of 0.9 per cent. saline each second day, and the other five the same quantity of a "dummy" solution, containing the same

amounts of choline and sodium acetate as would be liberated by the hydrolytic decomposition of 10 mg. of acetylcholine. The five remaining rabbits were given 10 mg. of acetylcholine in 1 c.cm. of saline solution each second day. The injections were made beneath the skin covering the shoulder-blades. Some respiratory distress and collapse was observed to follow the acetylcholine injections, but the animals recovered rapidly, and in their general behaviour closely resembled the controls. All of the animals received from twelve to fourteen injections over a period of about four weeks, at the end of which time the casts were removed.

After the casts had been in position for some time they showed in practically all cases a tendency to become a little loose. The muscular atrophy resulting from the immobilization, which is one of the effects described by Neuburger and Scholl in their controls, makes it inevitable that the fixation should thus become less perfect with the progress of the experiment. This loss of complete immobility in the later stages must be encountered if the cast is initially applied as closely as is possible without impairment of the circulation in the leg and foot. In my series it affected equally the rabbits treated with acetylcholine and the controls. When the animals were finally anaesthetized with ether and examined more thoroughly, before being killed under the anaesthetic for further study, the opportunity was taken to examine the circulation in the neighbourhood of the joints by incising the tissues. In all cases free bleeding followed the incisions, showing that the circulation had been well maintained.

The results of the plaster fixation were the same in all the rabbits, whether treated with acetylcholine or with either of the control solutions. All showed changes of the kind observed by Neuburger and Scholl in their control rabbits, and none revealed any trace of the amelioration or prevention of these effects which they attributed to treatment with acetylcholine. In every case there was limitation of movement both at the knee-joint and the ankle-joint, and this limitation persisted under deep anaesthesia with ether. When, under the terminal anaesthesia, strong force was applied to produce flexion of these joints, crepitations were felt, and a snap, as of adhesions being broken, was often audible. In spite of the not quite perfect immobilization of some of the limbs the muscles in every case showed a pronounced atrophy of disuse, being very much smaller than the corresponding muscles in the other normal leg. All these effects were present, and without perceptible difference in degree, in the rabbits treated with acetylcholine as in the two groups of controls.

I am unable to suggest any explanation of the contrast between my negative results and those reported by Neuburger and Scholl, in which they describe a prevention by acetylcholine of the effects of immobilization so definite that they are able to study it quantitatively with graded dosage. I have thought it desirable to record my completely negative experience, since Neuburger and Scholl's publications may well lead to an application of this method in surgical practice. My own experiments suggest no likelihood of its success.

Summary

Neuburger and Scholl have recently reported that acetylcholine prevented the ankylosis and muscular atrophy normally resulting from the immobilization of the hind-limb joints of rabbits.

Their experiments have been repeated, but no differences between the control and treated animals, as described by these authors, could be demonstrated.

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REFERENCES

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GLASGOW EXPERIENCE OF INCREASED DYSENTERY PREVALENCE

BY

E. BLOCH, M.A., M.B., Ch.B., D.P.H.

Public Health Department, Glasgow

During the past three years the annual number of dysentery cases registered in Glasgow has been increasing and has become relatively high. During the second half of 1937, too, the city, with 203 cases, shared in the reported country-wide increase in prevalence. I attempt here a brief review of some aspects of the prevalence of dysentery during these years and on previous occasions of raised incidence.

Annual Incidence

Dysentery became notifiable in 1919, when 117 cases were registered. During the nine years thereafter the annual number of notifications was small, often being less than twenty. In more recent years the number has been increasing, and has exceeded a hundred again on five occasions—namely, 1929, 119; 1932, 136; 1935, 135; 1936, 239; 1937, 272. The annual average over the whole period 1919-37 was 81.4.

OTHER DIARRHOEAL DISEASES

There has not been any apparent regular association between increased prevalence of dysentery and that of other diarrhoeal diseases. It is true that in 1919 and 1932 an increased number of deaths from diarrhoea were registered, that in 1935 enteric and paratyphoid fevers were more prevalent than usual, and that 1936 was a high year both for paratyphoid cases and for deaths from diarrhoea. On the other hand, deaths from diarrhoea were more numerous than usual in 1920, 1921, and 1926; also, the incidence of enteric fever was relatively high in 1920, and that of paratyphoid B fever in 1927, 1930, and 1933.

Seasonal Incidence

Reports from various sources regarding the seasonal incidence of dysentery differ widely. The years under special review here might be regarded as revealing some resemblance between the seasonal incidence of dysentery and that of the other diarrhoeal diseases. Deaths from diarrhoea and enteritis are highest in either the third or the fourth quarter of the year. Enteric infections are most frequent in the third quarter. Paratyphoid infections are less regular in this respect than typhoid; and, indeed, a large outbreak of paratyphoid B comprising 159 cases in Glasgow and forty-one other cases in neighbour-

ing county areas occurred in the spring of 1936. The total seasonal incidence of dysentery during the past three years was as follows:

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
Home Infections ..	41	65	136	106	348
Institutional Infections..	116	13	59	110	298
Total	157	78	195	216	646

If it is held that the true seasonal tendency of the disease is obscured in the figures with respect to institutional cases by reason of special opportunities for spread, then dysenteric infections would appear to be most frequent in the third quarter, as suggested by the figures regarding cases infected at home. From the following list it will also be noted that of fifteen outbreaks of dysentery the numbers commencing in each quarter of the year were respectively 4, 0, 8, and 3. Of twelve institutional outbreaks included in the list the quarterly distribution of the onset was 4, 0, 5, and 3.

Outbreaks

The outbreaks recorded up to the end of 1936 and those now falling to be recorded for 1937 were as follows:

Date	Outbreak
1928: Aug.-Sept. ..	7 fatal institutional cases among infants. 2 positive Sonne. Reported by Hay (1930)
1929: Aug.-Nov. ..	51 cases and carriers in group of overcrowded tenements. 35 positive Flexner, including 9 symptomless persons. No common source detected. 93 other cases of enteritis investigated
1930	5 of 10 institutional cases positive Sonne
1933: January ..	Small Flexner Z institutional outbreak
Aug.-Sept. ..	Small Sonne institutional outbreak affecting children
August ..	7 children positive Sonne of 12 cases which sickened 1-3 days after consumption of suspected ice-cream
1934: March-April ..	5 of 13 institutional cases positive Sonne
1936: January only ..	60 positive Flexner (X or Z) of 104 cases in large Poor Law institution, including 20 positive food workers. Total inmates, excluding staff, 1,343. 23 patients sickened in first 5 days after eating suspected meat pies on January 1; then 29, 27, and 24 in successive weeks. 10 aged patients died
September ..	9 positive Sonne cases associated with ice-cream—2 in family of vendor and 7 cases sickening 1 to 2 days after consumption
Sept.-Nov. ..	13 positive Sonne and 2 Flexner in children's institution
1937: Jan.-March.	23 young children and 2 nurses notified from large general hospital; Sonne and Flexner W, X, and Z. Again:
Aug.-Sept. ..	23 young children and 2 adults notified from this institution, Sonne and Flexner W, X, and Y. Total cases notified in 1937 from this institution, 60, mainly Flexner; several of the foci untraced
September ..	9 men notified as cases of Flexner dysentery from ward in large general hospital, which later housed the big outbreak described below
Oct. 21-Nov. 4	Fever hospital staff outbreak affecting one doctor and 34 nurses, with 14 positive Sonne. Cases sickening on successive days—1, 2, 2, 2, 3, 5, 5, 3, 4, 1, 2, 1, 0, 2. Possibly due to fresh fruit eaten October 20. Controlled by removing cases from nurses' home to special ward
Nov.-Jan., 1938	5 positive Sonne of 11 cases among staff and female patients in large mental institution. First case, missed, inmate of old standing. Good isolation accommodation. Notifications in 1938 figures
Nov.-Jan., 1938	94 cases and 12 carriers in large general institution with 86 positive, of whom 78 were positive Sonne. Described below. 42 cases included in 1937 figures. 386 other persons investigated, including 114 with loose motions. Total persons examined, 492