

amounts of 4-amino-1-naphthoic acid were toxic for the chick embryo even at the level of the minimal effectual dosage, but some of the embryos survived sufficiently long at levels well above the minimal dosage so that they could be examined for rickettsiae. For example, when a 0.5 mg dosage of paba was used (minimal effectual dosage = 0.25 mg), an equimolecular amount of 4-amino-1-naphthoic acid killed all of the embryos within 2-4 days. But smears from these embryos contained as many rickettsiae as the controls, whereas no rickettsiae were seen in smears from paba-treated embryos of the same age. It seems clear, therefore, that 4-amino-1-naphthoic acid does not appreciably affect the growth of rickettsiae.

These data all indicate that practically any possible modification of the paba molecule will diminish, and possibly even destroy, its inhibitory activity on rickettsiae. Such a high degree of specificity is usually associated with activity on an enzyme system, and leads one to speculate that the blocking of such a system by paba may be responsible for the inhibition of rickettsial growth.

Summary. 1. The maximal dosage of p-

aminobenzoic acid for the chick embryo (2 mg) is effective in inhibiting the growth of rickettsiae of the spotted fever group in the following order of magnitude: Rocky Mountain s. f. > Brazilian s. f. > Colombian s. f. > South African tick f. > fièvre boutonneuse. There was much more inhibition of the American group than of the African spotted fevers.

2. p-Aminobenzoic acid was about twice as effective on Rocky Mountain spotted fever infection (46% survivors) as on either epidemic or murine typhus (20% and 26% survivors, respectively).

3. p-Aminobenzoic acid did not appreciably inhibit the growth of the agents of "Q" fever, tsutsugamushi, lymphogranuloma venereum, or psittacosis.

4. Studies on the mode of action of p-aminobenzoic acid indicate that not only must the amino and carboxyl groups remain intact and in the para position with respect to one another, but the total size of the molecule must not be altered, if the inhibitory properties are to be retained. Such a high degree of specificity suggests that paba may be acting on an enzyme system.

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Synaptic Transmission of the Muscles in Arthritis.*

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Thomsen, Altamirano and Luco¹ studied some aspects of the mechanism of synaptic transmission in muscles whose tendons had been cut, thus approaching the general problem of a possible synaptic perturbation by changes in the effector.

Lippmann and Selig² gave experimental

proof to the clinical observation that muscles of diseased joints undergo a process of atrophy. These results suggested the idea that an experimentally produced arthritis might also cause changes in the neuromuscular transmission. In this paper we report some experiments that were carried out with that idea in mind.

Procedure and Methods. The experiments were performed on cats. The arthritis was produced by injecting about 0.1 cc of 3%, 5%, or 10% silver nitrate under anesthesia by ether or nembutal. The tibio-tarsal joint was

* Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

¹ Thomsen, P., Altamirano, M., and Luco, J. V., *Medicina* (Buenos Aires), 1942, **3**, 67.

² Lippmann, R. K., and Selig, S., *Surg. Gynec. Obstet.*, 1928, **47**, 512.

selected in all experiments, and the silver nitrate was injected into the articular cavity through the skin.

The study of the synaptic conditions was performed with the soleus and tibialis anticus muscles from 3 to 17 days following the onset of arthritis, by anesthetizing the cats intraperitoneally with nembutal (Abbott) in a dose of 0.033 g per kg of body weight dissolved in 1 cc of 25% urethane. A cannula was inserted in the trachea in order to apply artificial respiration when necessary. For the recording of muscular contraction the tibia was fixed by drills, and the tendon was attached to the short arm of a lever pulling on rubber bands. The sciatic nerve was isolated, sectioned, and silver electrodes were applied; it was stimulated by condenser discharges controlled by electronic valves. Curare (Merck) and Prostigmine (Roche) were injected intravenously.

Results. The injection of silver nitrate into the joint caused in every case articular lesions of different intensity, ranging from congestion of the articular cartilage to necrosis and caries of the bone. Sometimes, and especially when using 10% silver nitrate, the inflammatory process caused a rupture of the capsule and a spread to peri-articular areas. These lesions resulted in an abnormal gait from immobilization of the tibio-tarsal joint, and the animals would not use their inflamed limb or would use it discreetly. This spontaneous immobilization had a tendency towards flexion.

Both the soleus and tibialis anticus on the side of the arthritis, showed a definite loss of weight when compared with their homologues of the opposite leg.

Synaptic transmission in these muscles was studied by indirect stimulation at various frequencies, by controlling the post-tetanic potentiation and by observing the action of some drugs with synaptic effect.

A. Stimulation at Various Frequencies. Rosenblueth and Cannon³ found that the indirect stimulation of a muscle at various frequencies produces a series of rises and falls in tension called stages 1, 2, 3a, 3b, and 3c. The

study of these stages in our experimental animals showed that, in 29 of 34 cases the stages 3a and 3c were more marked in the muscles of the arthritic side than in those of the normal side. Fig. 1 and 2.

B. Post-tetanic Effects. In all the experiments in which we studied this effect, we found that it was present with practically the same intensity on the muscles of both sides.

C. Curare. The action of curare was studied at low frequencies. In this way it was easier to detect differences in the muscles. In

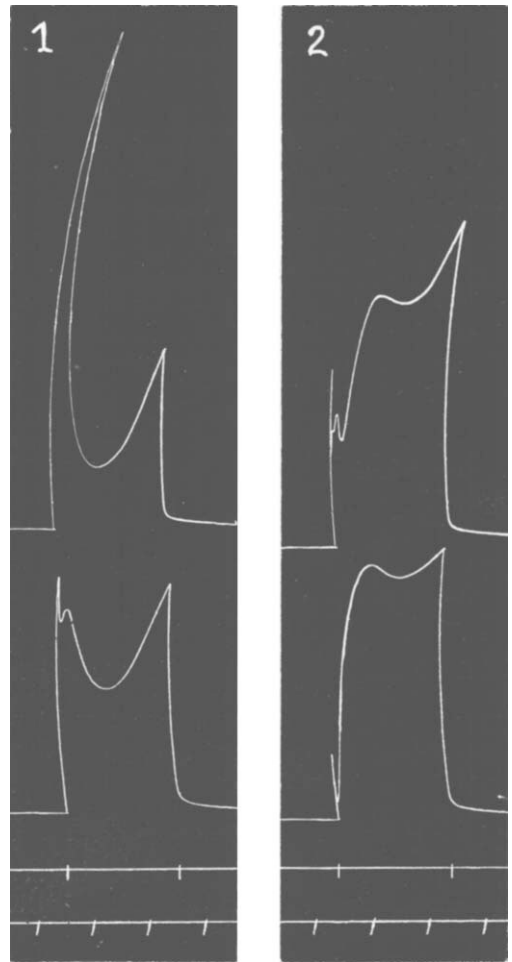


FIG. 1 AND 2.

Arthritis of 11 days (5% silver nitrate).

Upper tracing: normal soleus.

Lower tracing: arthritic soleus.

Upper marks: stimulation.

Lower marks: time in minutes.

Fig. 1. Indirect stimulation at 200 per sec.

Fig. 2. Indirect stimulation at 350 per sec.

³ Rosenblueth, A., and Cannon, W. B., *Am. J. Physiol.*, 1939, **128**, 31.

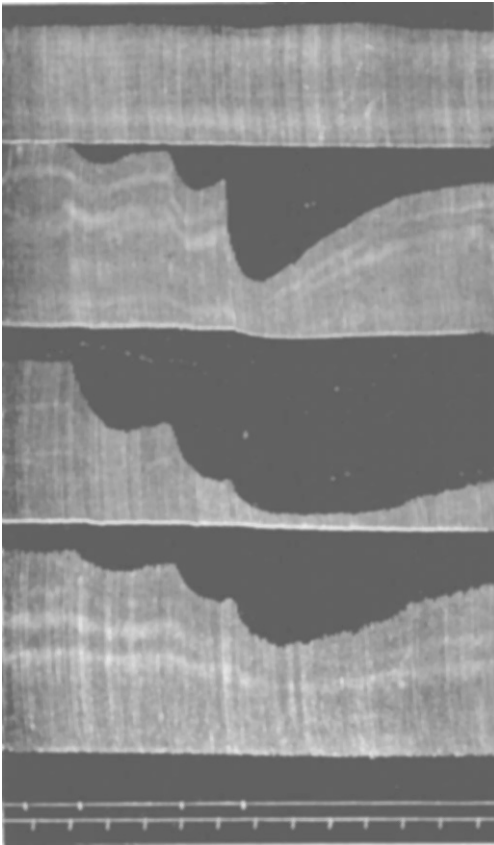


FIG. 3.

Effect of Curare on Arthritic Muscles.

Arthritis of 13 days (5% silver nitrate).

From the top the tracings are: arthritic tibialis, normal tibialis, normal soleus, and arthritic soleus.

Upper marks: doses of curare.

Lower marks: time in min.

nine experiments performed we found that the atrophic muscles were much more resistant to the effects of curare than were those of the normal limb. Fig. 3.

D. Prostigmine. In this series we also used stimuli of low frequencies. This drug produced a greater potentiating effect in the normal and a greater depressing effect in the muscles of the arthritic limb.

Discussion. The results reported here about the behavior of the synapsis under indirect stimulations at various frequencies, show that there is a difference between the normal muscle and the arthritic muscle, and that there are similarities between the arthritic muscle and the tenotomized and immobilized muscles. In

the last 3 conditions, stages 3a and 3c are greater, there is a larger development of tension than in the normal when compared with stage 1. Normal, fatigued muscle (Thomsen and Luco⁴) responds similarly to the above ones.

Thomsen and Luco⁴ have attributed, hypothetically, the synaptic changes in tenotomized and immobilized muscles to an exaggeration of the postural reflexes that would bring about a state of synaptic fatigue and, therefore, a state similar to the fourth experimental stage.

In the case of arthritis there is a spontaneous immobilization of muscles from pain and the same hypothesis is applicable. This reasoning would explain the similar results obtained in all these cases with stimulations at various frequencies. Besides, the resistance to the effects of curare is more marked in tenotomized, immobilized, arthritic, and fatigued muscles, than in normal ones.

In regard to prostigmine, both the arthritic and tenotomized muscles (Luco and Thomsen⁵) show that, with the same dosage and frequency, the potentiating effects are more marked in the normal and the depressive effects more marked in the altered muscles. This has been explained in the tenotomized muscle as due to its greater sensibility to acetylcholine, in such a way that prostigmine brings about a paralytic level rather quickly (Rosenblueth and Morison⁶). This would also explain the greater resistance to the effects of curare of the muscles in all the conditions mentioned above.

As a result of exaggeration of reflexes or some other cause, there could be a common denominator that would explain the similarity of the synapsis in the normal muscle fatigued by intense stimulation, and in the tenotomized, immobilized, and arthritic muscles. It could be that this common factor is a functional alteration, chemical or physico-chemical, of the excitable mechanism of the effector.

⁴ Thomsen, P., and Luco, J. V., *J. Neurophysiol.*, 1944, **7**, 245.

⁵ Luco, J. V., and Thomsen, P., in press.

⁶ Rosenblueth, A., and Morison, R. S., *Am. J. Physiol.*, 1937, **119**, 236.

In support of this hypothesis we have the results of Eccles and O'Connor⁷ who have localized the effects of curare and eserine in relation with the action potentials of the terminal plate. As these potentials may not be entirely localized to the histological terminal plate (Feng⁸), it would not be surprising that a chemical or physico-chemical change of the effector might modify the effect of these drugs.

The fact that the arthritic muscle shows a post-tetanic effect and the tenotomized muscle usually does not, may mean that in the latter the synaptic alteration is quantitatively greater.

⁷ Eccles, J. C., and O'Connor, W. C., *J. Physiol.*, 1939, **77**, 44.

⁸ Feng, T. P., *Biol. Symposia*, The Jaques Cattell Press, Lancaster, Pa., 1941, **3**, 121.

Summary. We have studied in cats the effect of an atrophy of the soleus and tibialis anticus, caused by an arthritis of the tibio-tarsal joint, on some aspects of the synaptic transmission in those muscles.

1. The third stage of the neuromuscular transmission is different in the normal and arthritic muscles. Section A, fig. 1 and 2.

2. The atrophic muscle is more resistant to curarization. Section C, fig. 3.

3. Prostigmine, with the same dosage and frequency of stimulation, produces less potentiation and more depression in the arthritic than in normal muscles.

4. The synaptic behavior of the arthritic muscle is similar to the behavior of the tenotomized, immobilized, and fatigued (4th stage) muscles. The possible significance of such similarity is discussed.

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Billroth I, Gastric Resection: Extent Necessary to Protect Against Histamine-Provoked Ulcer.*

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It has been shown in this clinic that a short afferent duodenal loop is an important component of a satisfactory operation when gastric resection on the Billroth II plan of operation is applied to ulcer.¹ It has been shown also that another criterion of a successful operation for ulcer is an extensive gastric resection

(75%).^{2,3} Inasmuch as the short afferent duodenojejunal loop is so important, the question arose whether it would be equally as satisfactory to sacrifice less stomach (25 or 50%), but to effect gastrointestinal continuity by end to end suture between the stomach and the duodenum by the Billroth I operation. It is the purpose of this report to indicate our observations and experiences with this plan of procedure on the dog, and to note whether the Billroth I plan of performing gastric resection will protect against the histamine-in-beeswax provoked ulcer with excision of less stomach tissue than in the Billroth II operation.

Method. These experiments were carried

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¹ Merendino, K. A., Lannin, B. C., Kolouch, F., Jr., Baronofsky, I., Litow, S. S., and Wangenstein, O. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1945, **58**, 226.

² Wangenstein, O. H., and Lannin, B. G., *Arch. Surg.*, 1942, **44**, 489.

³ Lannin, B. G., Hay, L. J., Judd, E. S., Jr., and Wangenstein, O. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1944, **56**, 231.