

penicillin treatment concomitantly.

5. By the use of this method it has been noted that streptomycin is retained in the blood in effective therapeutic amounts for

relatively longer periods of time, thereby permitting more convenient spacing of injections. The clinical application of these studies will be made the subject of a subsequent report.

15573 P

Coccarboxylase and the Synthesis of Acetylcholine.

BRUNO MINZ. (Introduced by Robert Chambers.)

From the Laboratory of General Physiology, Paris University.

Biochemical studies of nerves under electrical stimulation or at rest have shown that acetylcholine, regarded for a long time only as a transmitter of nervous impulses at synaptic levels, is present in appreciable amounts in the nerve fiber itself.¹ We have proved that extracts from stimulated nerves produce a more intense action on the dorsal muscle of the leech than extracts from nerves at rest. This finding led us to consider the part played by acetylcholine in the phenomenon of nerve conduction. An analysis of the observed effects enabled us to reach the conclusion that excitation is followed not only by an increase in the amount of acetylcholine in nerves but also by the formation of an unknown substance appearing in the system and capable of sensitizing the reactive muscle. Further work has made clear analogies of action between this unknown substance and thiamin and has enabled us to prove that stimulated nerve liberates an amount of thiamin many times greater than that given off by the nerve at rest.¹ Since the amount of thiamin which sensitizes the muscle of the leech to acetylcholine is much smaller than that which would inactivate cholinesterase, we concluded that the vitamin plays a part in the synthesis of the chemical transmitter.

Thiamin is active in organisms in the form of thiamin pyrophosphate or cocarboxylase. Therefore, it seemed desirable to determine

whether this coenzyme may play a part in the synthesis of acetylcholine from choline.

A contracture of the dorsal muscle of the leech may be obtained with relatively high doses of choline. But contrary to the reaction produced by acetylcholine, this effect is not increased by eserine.^{2,3} If cocarboxylase is capable of transforming choline into acetylcholine, the mixture of both should exert an action on the muscle which is increased by eserine. Experiments have shown that cocarboxylase alone is without any effect on the leech muscle preparation whether treated with eserine or not. The coenzyme, however, increases the action on the muscle of a contracture-producing concentration of choline in the absence of eserine. This increase is even greater after the muscle has been treated with eserine. With threshold doses of choline, at which cocarboxylase has no visible effect, eserine has brought about a clear reinforcement. Thus, the muscle may aerobically and in the presence of cocarboxylase transform choline into an ester the action of which is increased by eserine. These are the biological properties of acetylcholine.

How may these facts be interpreted? We know that cocarboxylase intervenes at a particularly important level in the metabolism of carbohydrates. It catalyzes the decarboxylation of pyruvic acid so that acetic acid is produced. From the work of Banga, Ochoa and Peters^{4,5} it also appears that this de-

¹ Binet, L. A., and Minz, B., *C. R. Soc. de Biol.*, 1934, **115**, 1169; **116**, 107; *Arch. internat. physiol.*, 1936, **42**, 281; Minz, B., and Agid, R., *C. R. Arch. Soc.*, 1937, **205**, 576; Minz, B., *C. R. Soc. de Biol.*, 1938, **127**, 1251; 1939, **131**, 1156.

² Fühner, H., *Arch. f. exp. Path.*, 1918, **82**, 51.

³ Minz, B., *Arch. f. exp. Path.*, 1932, **168**, 292.

⁴ Banga, I., Ochoa, S., and Peters, R. A., *Biochem. J.*, 1939, **33**, 1980.

⁵ Ochoa, S., *J. Biol. Chem.*, 1941, **138**, 751.

carboxylation is associated with phosphorylation of adenylic acid to yield adenosine triphosphate. Nachmansohn and Machado⁶ have shown that adenosine triphosphate intensifies the activity of an enzyme system (choline acetylase) which produces the final

synthesis of the cholinergic transmitter. Our knowledge about this enzyme is still rudimentary, but if the enzyme should prove specific, the disintegration of pyruvic acid initiated by cocarboxylase should furnish the system with 2 important elements, *viz.*, acetic acid and adenosine triphosphate, concerned with the synthesis of acetylcholine from choline.

⁶ Nachmansohn, D., and Machado, A. L., *J. Neurophysiol.*, 1943, **6**, 397.

15574

Effect of Pemphigus Serum on the Behavior of Rats.

DAVID I. MACHT AND MARION C. INSLEY.

From the Department of Pharmacology, Laboratories of the Sinai Hospital, Baltimore.

Macht and Pels,¹ by employing special phytopharmacological methods have demonstrated the presence of a toxic substance in the blood of pemphigus patients. This toxic reaction is not given by other dermatoses so that the phytopharmacological test has been found useful in establishing the diagnosis of pemphigus at an early stage and in doubtful cases.²⁻⁴ More recently, Macht and Ostro have extended our knowledge concerning this substance and have employed the test in evaluating therapeutic procedures employed in treating this disease.⁵ From these experiments it was evident that pemphigus is not a simple dermatosis but is primarily a constitutional or systemic disease or a form of toxemia. Concomitant with the characteristic skin eruptions the patient exhibits profound disturbances of a systemic nature, the most prominent symptoms of which come from the nervous system. This has been noted already 50 years ago by Payne⁶ who, in his classical

lecture on pemphigus, stated:

"If any system of the body is affected besides the skin it seems to be the nervous system rather than any other. Obscure symptoms of nervous depression are sometimes recognized before the eruption begins, and in the severer forms the cerebral nervous system—or at least the brain—is evidently profoundly affected, as is shown by delirium and nervous prostration."

In order to investigate further the effects of this toxic substance in pemphigus serum on the nervous system the present writer undertook experiments on the behavior of white rats by 3 kinds of experimental psychological methods. First, a study was made on the behavior of the rats in Watson's circular maze. While views differ as to the complete significance of the process through which the rats undergo the learning of the maze problem, it is generally agreed that such a performance involves not only a response to the proprio-sensitive stimuli but also a *choice* reaction or faculty of *discrimination*, which the rats exhibit under the urge of hunger. A second series of experiments was made on rats which have been trained to walk a tightly stretched rope 8 feet long from one platform to another on which food had been placed. This performance involves a delicate neuro-muscular coordination. In the third series of experiments, rats were trained to climb a tightly stretched per-

¹ Macht, D. I., and Pels, I. R., *Proc. Soc. Exp. Biol. and Med.*, 1927, **25**, 237.

² Pels, I. R., and Macht, D. I., *Arch. Dermat. and Syph.*, 1929, **19**, 640.

³ Pels, I. R., and Macht, D. I., *Arch. Dermat. and Syph.*, 1931, **23**, 601.

⁴ Pels, I. R., and Macht, D. I., *Arch. Dermat. and Syph.*, 1934, **29**, 206.

⁵ Macht, D. I., and Ostro, M., *Urologic and Cutaneous Rev.*, 1946, **19**, 271.

⁶ Payne, J. F., *Lancet*, 1893, **2**, 421.