growth essentials. The "narcotic" hypothesis gives no expectation of mutual specificity between their effects. Such does, however, exist (Table II) and is readily

TABLE II

SPECIFICITY OF ANTIBACTERIAL AGENTS

Organism and reference to conditions of testing	Addenda		Growth
	Inhibitor, *M*	Metabolite, *M*	
Strep. haem.[1]	0	0	+
Bact. coli[8]	sulfanilamide, 3×10^{-4}	0	0
	"	*p*-aminobenzoate, 10^{-7}	+
	"	pantothenate[11], 10^{-7} to 10^{-4}	0
	"	nicotinamide[11], 10^{-7} to 10^{-4}	0
Staph. aureus[9]	0	0	+
	pyridine-3-sulphonamide, 10^{-2}	0	0
	"	*p*-aminobenzoate, 10^{-7} to 10^{-4}	0
	"	pantothenate, 10^{-7} to 10^{-4}	0
	"	nicotinamide[11], 10^{-5}	+
Strep. haem.[7]	0	0	+
Diplococcus pneumoniae[10]	pantoyltaurine, 10^{-4}	0	0
C. diphtheriae[10]	"	*p*-aminobenzoate, 10^{-7} to 10^{-4}	0
	"	pantothenate[11], 10^{-6}	+
	"	nicotinamide[11], 10^{-7} to 10^{-4}	0

explained in terms of competitive enzyme inhibition. Thus the inhibition by pyridine-3-sulfonamide is unaffected by the presence of *p*-aminobenzoic acid or pantothenic acid, but is antagonized by a definite fraction of its concentration of nicotinic acid. Pantothenic acid, but not nicotinic or *p*-aminobenzoic acids, reverses the inhibition due to pantoyltaurine.

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THE EFFECT OF INSULIN SHOCK ON LEARNING IN THE WHITE RAT

SINCE its introduction by Sakel, insulin shock has been successfully used in the treatment of certain cases of dementia praecox and allied psychiatric and psychoneurotic conditions to bring about a remission of the symptoms which in certain cases has lasted indefinitely. There has been, as yet, no agreement as to the theory of its action, although there is no doubt that a cerebral anoxia is produced, with which the therapeutic effect is associated and upon which it is probably dependent. It occurred to one of us that the psychopathological symptoms might be regarded as recently formed habits of response, with younger and metabolically more unstable synaptic patterns of neuronal associations involved. If this were true, the more recently formed habit pattern should be more easily broken up, because of the effects of the cerebral anoxia. It was decided to test this hypothesis by observing the effect of insulin shock on habit formations in the experimental animal.

This is a preliminary report of a study involving the effect of insulin shock on habits of varying degrees of stability and age in the white rat. Exploratory observation established a tentative optimum dosage as one unit of insulin per 12 grams of body weight. In the exploratory group of animals, this medication caused a state of lethargy and/or coma lasting about two hours with a latent period of approximately 40 minutes. In almost half of the cases, there occurred severe convulsive seizures in which movements of the head region were particularly pronounced. All animals seemed to be normal within eight hours after injection.

Two mazes differing in complexity and type constituted the bases for the learning situations. The first group of animals began on a multiple-unit, elevated T maze. When this had been mastered to a criterion of 9 perfect runs in a sequence of 10 trials, 100 additional runs were made. Upon completion of this overlearning, training was begun on a linear arrangement of the Warner-Warden multiple-unit alley maze. The same criterion of learning was used, but the additional overlearning was omitted. During the learning of the alley maze no practise was given on the elevated maze. As soon as an animal had learned both mazes it was given 20 trials on each maze separately. Any animal making more than two errors in this stage was discarded. Following the test period, each rat was injected with the appropriate dose of insulin. Twenty-four hours after injection, the animal was again given 20 trials on each maze. A similar procedure was followed for the second group except that training was begun on the alley maze and the elevated maze habit was made the younger and less well-established habit. All rats were males.

The results are given in the appended table. It will be noted that, because of the rotation of groups, the first six animals who began their training on the elevated maze are found in the lower right side of the table, when the newer or alley habit is considered. That is, rat No. 1 began on the elevated maze and continued on the alley maze, whereas rat No. 7 reversed this procedure.

The present report will deal only with comparisons in terms of total errors during the pre-post-shock test

[7] H. McIlwain, *Brit. Jour. Exp. Path.*, 20: 330, 1939.
[8] P. Fildes, *ibid.*, 19: 239, 1938.
[9] H. McIlwain, *ibid.*, 21: 136, 1940.
[10] H. McIlwain, *ibid.*, in press; summarized in *Chem. Ind.*, 61: 96, 1942.
[11] Low concentrations of these compounds are in some cases necessary for growth, and were then present in the inhibited cultures; further quantities (those quoted) were necessary for reversal.

periods and on the learning of new and old habits. The means for the various groups are as follows:

Older habits

Elevated maze, pre-shock, .33, post-shock, 6.0
Alley maze, pre-shock, .83, post-shock, 4.83

Newer habits

Elevated maze, pre-shock, .50, post-shock, 11.00
Alley maze, pre-shock, .50, post-shock, 15.33

The conclusions from the above results seem to point to a more severe impairment of the newer and less overtrained habits. This statement is bolstered by the small size of the differences between the various habits during the pre-shock test period. Using Fisher's T test to determine the significance of the obtained differences we find that neither of the comparisons between the pre-shock tests are of statistical reliability. The P values for these differences are between .7 and .9.

The P values for the comparisons between the new and old habits in terms of post-shock differences are .075 for the elevated maze and less than .01 for the alley maze. In other words, the insulin shock seems definitely to impair the learning of a recently acquired alley maze habit and probably to impair the learning of a recently acquired elevated maze habit. No definite impairment can be found for the learning of older habits either on the elevated or alley maze.

TABLE I

EFFECT OF INSULIN SHOCK ON ERROR SCORES OF RATS

Elevated maze (old habit)			Alley maze (old habit)		
Subject number	Pre-shock errors	Post-shock errors	Subject number	Pre-shock errors	Post shock errors
1	0	8	7	1	3
2	1	6	8	1	6
3	1	9	9	1	4
4	0	5	10	0	4
5	0	5	11	2	10
6	0	3	12	0	2
(new habit)			(new habit)		
7	0	5	1	1	10
8	1	15	2	0	12
9	0	6	3	1	11
10	0	18	4	0	24
11	0	12	5	0	16
12	2	10	6	1	19

Each entry under "errors" represents the sum of 20 trials.

In the psychiatric conditions in which insulin shock has been employed, the symptoms are relatively recent cerebral manifestations as compared with the behavior acquired during the pre-morbid phases of the individual's development. These results with the experimental animal would seem to confirm our hypothesis of their relative susceptibility to metabolic shock applied to the cerebral patterns behind them. We are continuing our experiments and shall carry out similar ones with metrazol shock and electro-shock which also produce their therapeutic effects by the production of a cerebral anoxia.

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TOXIN FORMATION BY CERATOSTOMELLA ULMI

SINCE the discovery of the Dutch elm disease, caused by *Ceratostomella ulmi* (Schwarz) Buisman, in 1919, gums and tyloses have been observed commonly plugging xylem vessels of affected elm trees.[1,2] It has been assumed that wilting and decline of diseased elms are entirely the result of a "drouth" reaction, caused directly by the plugging of the vessels.

In the case of many vascular diseases of plants the concept that wilting and necrosis result primarily from plugging of xylem elements with hyphae, gums and tyloses has been largely replaced during the past twenty years by evidence that a toxin is the primary disease factor. Many of the fungi causing this type of disease, as well as other pathogenic fungi, have been shown to produce toxic substances which, on being transported upward in the vessels, can cause symptom appearance considerably in advance of the pathogen. Linden, Zenneck and Gunther[3] and Clinton and McCormick[4] have speculated that the symptoms produced by *Ceratostomella ulmi* might be the result of toxin production, but these authors did not present experimental evidence.

As the result of experiments begun here in 1940 it has been found that *C. ulmi* in culture produces a soluble toxic substance which is evidently the primary factor in the production of Dutch elm disease symptoms. This toxin is produced when the fungus is grown on a liquid nutrient solution containing yeast extract in addition to other nutrients. The fungus grows very poorly on the standard liquid synthetic media, but good mat formation is obtained when essential growth factors are provided by adding yeast extract, as in the following solution: KH_2PO_4 1.5 g., $MgSO_4 \cdot 7H_2O$ 1.0 g., $FeCl_3$ 0.01 g., asparagin 2.0 g., dextrose 30 g., Bacto yeast extract 2 g. and distilled water 1,000 cc.

Toxicity is tested by filtering off the fungus, after 12 to 25 days growth on the nutrient solution, injecting the sterile filtrate into small American elm trees, and testing its effect on various plant cuttings. When the toxin was freed of the fungus by Berkefeld filtra-

[1] M. G. Schwarz, *Meded. Phytop. Labor. Willie Comm. Scholt. Baarn*, 5: 74 pp., December, 1922.
[2] C. J. Buisman, *Tijdschr. Nederl. Heidemaatsch.*, 40: 338–345, October, 1928.
[3] G. V. Linden, L. Zenneck and Gunther, *Centralbl. Bakt. Abt.* II, 69: 340–351, February 28, 1927.
[4] G. P. Clinton and F. A. McCormick, *Conn. Agr. Expt. Sta. Bull.*, 389: 697–752, October, 1936.