been the difference in the weight of the mice in the two groups. The animals of oxythiamine groups were not given the analogue until a varying number of days after the low-thiamine group had been started on the diet deficient in the vitamin. During this interval, the mice which later received oxythiamine were growing at a normal rate, while the vitamin-deficient animals were growing subnormally. The growth-rate differential resulted in a difference of about 3 g between the thiamine-deficient and the oxythiamine-fed animals at the time of inoculation, which may indicate a difference in the degree of deficiency not otherwise recognizable.

Summary. Mice from a genetically controlled colony and under controlled environmental conditions were used to examine the effect of oxythiamine, an inhibitory analogue of thiamine, on resistance against the Lansing strain of poliomyelitis.

A significant degree of protection was induced in all the groups on the oxythiamine as compared with those on the normal diet. This protection was not quite as marked as in the mice on the low-thiamine diet.

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Comparison of Penicillin G and A Biosynthetic Penicillin with Regard to Diffusion into Cerebrospinal Fluid.

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Under natural conditions *Penicillium notatum* or *Penicillium* chrysogenum produces a mixture of penicillins G, F, dihydro-F, K and X. The predominant form of the penicillin elaborated can be influenced by the addition of precursors to the nutritive media. Similarly, the addition of precursors that do not occur in nature has resulted in the formation of penicillins that do not occur naturally. Such penicillins are formed by reason of the ability of the mold to utilize these precursors and incorporate portions of them into the penicillin molecule.[1] Penicillins produced by the addition of precursors not occurring in nature may be referred to as biosynthetic penicillins. BT penicillin* is such a biosynthetic penicillin and will predominate if the precursor used is one containing the n-butylthiomethyl grouping in available form.

The widespread use of crystalline penicillin G (benzyl penicillin) has established the fact that many patients show the usual phenomena of drug sensitivity. In addition to the possible advantage of having a penicillin in which a substitution had been made for the benzyl group, it was thought that perhaps such a penicillin would have distinctive properties not possessed by benzyl penicillin. Preliminary observations made in animals suggested that BT penicillin might diffuse into the cerebrospinal fluid more readily than benzyl penicillin.[2] The investigation here reported was carried out to test this hypothesis.

Materials used. The water-soluble potassium salt of BT penicillin with a potency of 2900 units per mg was employed throughout. The material contained a small amount of penicillin G as a contaminant, for the media upon which the mold was grown during the preparation of this material contained naturally occurring precursors which permitted the formation of penicillin G. The sodium salt of crystalline penicillin G was used for comparison with the BT penicillin.

Patients studied. Eleven patients with central nervous system syphilis were investigated.

[1] Biosynthesis of Penicillins, *Science*, 1947, **106**, 503.

* n-butylthiomethyl penicillin supplied through the courtesy of Dr. N. P. Sullivan of Eli Lilly & Co.

[2] Sullivan, N. P., personal communication.

TABLE I.
Plasma Concentrations of Penicillin After Initial Intravenous Injection of 500,000 Units.

Patient	Age, yrs	Color	Sex	Penicillin G* Min. after injection 5	120	Penicillin BT† Min. after injection 5	30	120
BC	57	B	F	63.49‡	.992	34.56	4.32	.270
MW	35	W	F	46.08	.720	23.04	2.16	.180
RR	35	B	M	67.58	.248	34.56	5.74	.270
JS	43	B	M	70.92	1.08	23.04	2.88	.180
JO	52	W	M	46.08	.744	34.56	2.16	.360
McL	38	W	M	31.74	.496	17.18	2.16	.180
IJ	35	B	M	34.56	—§	17.18	2.16	.180
JM	44	W	M	23.81	.996	34.56	2.88	.360
HZ	63	W	M	63.49	1.98	39.94	3.74	.360
MK	41	W	F	31.74	1.49	34.56	6.66	.270
WW	61	W	M	63.49	1.49	64.51	13.31	1.66
		Avg		49.36	1.02	32.51	4.37	.388

* Sodium penicillin G in aqueous solution.
† n-butylthiomethyl penicillin in aqueous solution.
‡ Oxford units of penicillin per cc of plasma.
§ Specimen broken.

There was no impairment of general health and no evidence of inflammation of the meninges.

Method of study. Each patient was observed during both periods of the study and each served as his own control. Following a single intravenous injection of 500,000 units of crystalline penicillin G (injection time 5-15 seconds), blood specimens were obtained at 5 and 120 minutes and a specimen of cerebrospinal fluid was obtained from the lumbar subarachnoid space at 120 minutes. These specimens were submitted for penicillin assay by a modification of the Rammelkamp serial dilution method. After an interval of no less than 3 days and no more than 7 days the patient received a single intravenous injection of 500,000 units of BT penicillin and thereafter blood specimens were obtained at 5, 30 and 120 minutes and a cerebrospinal fluid specimen was obtained at the end of 120 minutes. These specimens were likewise assayed for their penicillin content.

Results. The results are presented in Tables I and II. In Table I it may be observed that the average penicillin plasma concentrations resulting from the intravenous injection of 500,000 units of penicillin G were 49.36 units per cc at 5 minutes and 1.02 units per cc at 120 minutes. Following the administration of 500,000 units of BT penicillin, plasma concentrations were 32.51 units per cc at 5 minutes and 0.388 unit per cc at 120 minutes. The difference between the plasma concentrations observed at 5 minutes following the use of the two penicillins is not significant since the difference represents only a one tube difference in the Rammelkamp serial dilution method.[3] The difference between 1.02 units per cc and 0.388 unit per cc observed at the end of 120 minutes represents a difference of 4 tubes in the Rammelkamp assay and is therefore significant, but the difference is not great enough to postulate any essential difference in rate of elimination of the two penicillins. In Table II it may be observed that, at 120 minutes after the injection of penicillin G, 8 of 11 patients showed assayable quantities of penicillin in the cerebrospinal fluid whereas only 4 of 11 patients showed penicillin in the cerebrospinal fluid following the injection of BT penicillin. These results are barely significant statistically ($p = 0.057$). The difference in actual penicillin concentration observed, that between 0.032 following penicillin G and 0.01 following BT penicillin, is statistically significant ($p = 0.02$–0.05).

Summary. BT penicillin (n-butylthiomethyl penicillin) gave no evidences of toxicity, either immediate or delayed, following the

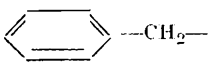
[3] Miller, A. K., and Boger, W. P., *Am. J. Clin. Path.*, 1948, **18**, 421.

TABLE II.
Penicillin in Cerebrospinal Fluid Two Hours After Initial Intravenous Injection of 500,000 Units.

Patient	Age, yrs	Color	Sex	Penicillin G*	Penicillin BT†
BC	57	B	F	.045	.0
MW	35	W	F	.0	.0
RR	35	B	M	.031	.0
JS	43	B	M	.045	.0
JO	52	W	M	.0	.045
McL	38	W	M	.0	.0
IJ	35	B	M	.023	.022
JM	44	W	M	.031	.0
HZ	63	W	M	.045	.0
MK	41	W	F	.090	.022
NW	61	W	M	.045	.022
			Avg	.032	.010

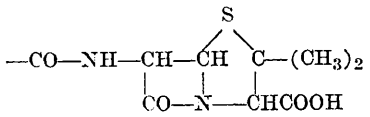
* Sodium penicillin G in aqueous solution.
† n-butylthiomethyl penicillin in aqueous solution.
‡ Oxford units of penicillin per cc of cerebrospinal fluid.
§ Any penicillin concentration less than 0.022 unit per cc has been regarded as zero.

Formula of R



Benzyl or G

Penicillin Nucleus



$CH_3—CH_2—CH_2—CH_2—S—CH_2—$
n-Butylthiomethyl or BT

Structural comparison of the two penicillins employed in this study.

intravenous injection of 500,000 units in 11 patients. From the work here reported it appears that BT penicillin does not diffuse into the cerebrospinal fluid as readily as benzyl penicillin and plasma concentrations resulting from its use are essentially the same as those following the use of benzyl penicillin.

The authors wish to express their indebtedness to Doctors Harvey Bartle, Robert Bookhammer, Raphael Durante, Herbert Freed, and Anthony Frignito for their kindness in allowing us to study patients on their psychiatric services at the Philadelphia General Hospital; to Miss Barbara V. Prey for penicillin assays here reported, and to Mr. Joseph L. Ciminera for the statistical analysis of data.

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Effect of Necrosin on Spontaneous Tumors in Mice.

VALY MENKIN.

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The pattern of injury with inflammation has recently been found by the writer to be referable to the liberation of a toxic substance by injured cells.[1] This substance is located in or at least it is associated with the euglobulin fraction of exudates of dogs and of man. It has been termed necrosin. Recent as yet

* Aided (in part) by a grant from the National Advisory Cancer Council.

[1] Menkin, Valy, *Arch. Path.*, 1943, **36**, 269.