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Penicillin in the Cerebrospinal Fluid Following Parenteral Penicillin.

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(Introduced by L. E. Arnow).

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The desirability of attaining therapeutically significant concentrations of penicillin in the cerebrospinal fluid without the necessity of intrathecal injections is acknowledged. It is probable that some of the complications that have been noted following intrathecal injection of penicillin[1-9] can be assigned to the use of penicillin that was not as highly purified as that currently available and to the use of large doses of penicillin. Nevertheless, it would be advantageous if the procedure of lumbar puncture and the introduction of a foreign substance into the subarachnoid space could be avoided.

It is the consensus that penicillin is transported with difficulty across the tissue barrier between the blood and the cerebrospinal fluid, [10,11,12,14,15] and that inflammation of the meninges may favor passage of penicillin into the cerebrospinal fluid.[16-18] With few exceptions the schedules of penicillin dosage employed in the investigation of the permeability of the meninges with respect to penicillin have not maintained a penicillin plasma concentration high enough to cause diffusion of penicillin into the cerebrospinal fluid. There are reports of moderate doses of penicillin administered either intravenously or intramuscularly, occasionally giving assayable quantities of penicillin in the cerebrospinal fluid,[16-19] whereas, enormous doses of penicillin administered by continuous intravenous drip have produced detectable quantities of penicillin in the cerebrospinal fluid of all patients to whom they have been administered.[20-21] It is suggested, therefore, that penicillin can be recovered in the cerebrospinal fluid of every patient if an amount of penicillin is given to raise the diffusion pressure of penicillin in the plasma above the point at which the hematoencephalic barrier is capable of hindering the passage of the antibiotic into the cerebrospinal fluid. Since a few positive observations have been made following the parenteral adminis-

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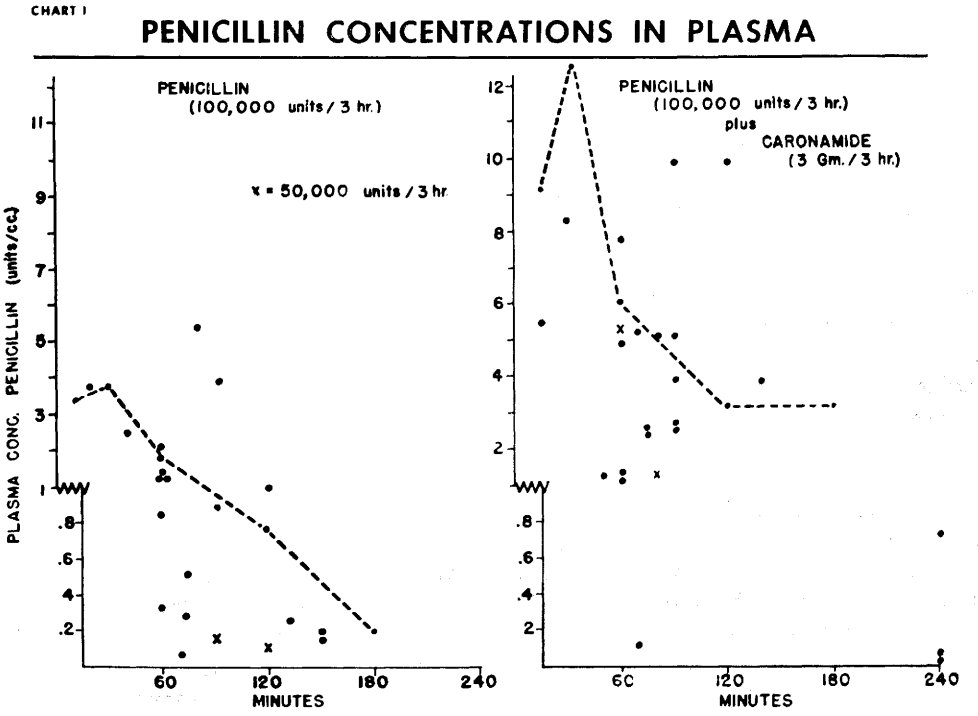
19 Dumoff-Stanley, E., Dowling, H. F., and Sweet, L. K., *J. Clin. Invest.*, 1946, **25**, 87.

20 Schwemlein, G. X., Barton, R. L., Bauer, T. J., Loewe, L., Bundesen, H. N., and Craig, R. M., *J.A.M.A.*, 1946, **130**, 340.

21 Peters, E. E., and Barton, R. L., *Am. J. Syph., Gonorrhea and Venereal Diseases*, 1947, **31**, 522.

CHART 1



tration of 100,000 units of penicillin[16-18] and a group of our patients were receiving this dose every third hour routinely, the following study was made of the penicillin concentrations in the plasma and cerebrospinal fluid.

Patients Studied. Twenty-six patients suffering from central nervous system syphilis (paresis) were treated with 100,000 units of penicillin intramuscularly every third hour for a period of 12½ days. These patients were not selected in any way and they were all in good general health.

Method of Study. One hundred thousand units of penicillin in aqueous solution was administered intramuscularly every third hour for 5 days. Upon the completion of this period of therapy blood and cerebrospinal specimens were obtained simultaneously, the time interval between the last injection of penicillin and the obtaining of samples being accurately noted. Thereafter, the patients continued on the same schedule of penicillin therapy and were given, in addition 3 g of caronamide* orally every 3 hours for an additional 5 days, and then blood and cerebrospinal fluid specimens were again drawn simultaneously. Specimens obtained at the end of the first period were submitted for penicillin assay and those obtained after the second period for both penicillin and caronamide estimations. In 3 patients the period of caronamide therapy preceded that in which penicillin alone was given, and in 2 patients the penicillin dosage administered was 50,000 units every 3 hours rather than 100,000 units. Penicillin in the plasma and cerebrospinal fluid was estimated by a modification of the Rammelkamp serial dilution method making use of a standardized strain of a Group A hemolytic streptococcus as the test organism. Caronamide estimations were done by the Ziegler method.[22]

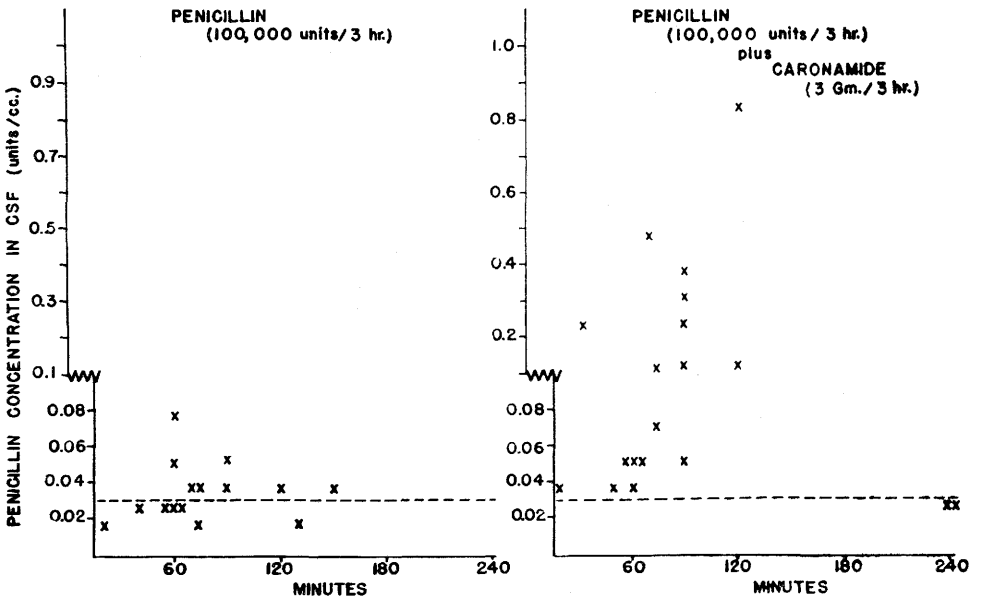
Results. The results obtained from this study are presented in Charts 1 and 2, and Table I. Following the 5 days of penicillin therapy alone, 15 of 23 patients showed assayable quantities of penicillin in the cerebrospinal fluid. The range of concentrations

* Caronamide (4'-carboxyphenylmethanesulfonanilide) used in this investigation was supplied through the courtesy of Sharp & Dohme, Inc.

22 Ziegler, C., and Sprague, J. M., *J. Lab. and Clin. Med.*, 1948, **33**, 96.

CHART II

PENICILLIN CONCENTRATIONS IN CEREBROSPINAL FLUID



found was from 0.019 to 0.052 units of penicillin per cc. Following a period of 5 days therapy with the same doses of intramuscular penicillin and 24 g of oral caronamide per day, 20 of 25 patients showed detectable quantities of penicillin in the cerebrospinal fluid. The range of concentrations was from 0.026 to 2.5 units per cc. Comparison of penicillin concentrations in plasma and cerebrospinal fluid in the two periods of study indicates the enhancement effect of caronamide (Charts 1 and 2).

The estimations of caronamide in the plasma showed that concentrations ranging from 1.2 to 110 mg per 100 cc were obtained in this group of patients. Despite the broad range of caronamide concentrations in the plasma, the compound was detected in the cerebrospinal fluid in significant quantities in only 2 cases (Table I).

Discussion. Inasmuch as the largest group of patients heretofore reported in whom detectable amounts of penicillin were found in the cerebrospinal fluid received from 10 to 25 million units of penicillin by continuous intravenous drip over a period of 24 hours,[20] and lesser doses, except in occasional cases, had failed to show penetration of penicillin into the cerebrospinal fluid, the results of this study are of interest. The individuals studied were regarded as having no inflammation of the meninges, for in no case was the cell count in the cerebrospinal fluid higher than 25 cells per cc. There are precedents for considering patients suffering from general paresis as having a "normal" blood brain barrier,[13,16,17] and it has been shown that the meninges of such "normal" patients are less permeable to the passage of fluorescein than patients suffering from meningitis.[23]

The concentrations of penicillin that were obtained in the cerebrospinal fluid in this study may be regarded as therapeutically significant inasmuch as 0.03 units per cc "is adequate to sterilize actively growing cultures of almost all strains of gonococcus, Group A hemolytic streptococcus, and pneumococcus and most strains of alpha hemolytic streptococcus, about half of the strains of meningococcus, and a somewhat smaller proportion of strains of pathogenic staphylococci."[14] Penicillin concentrations in the cerebrospinal fluid

[23] Lange, K., Schwimmer, D., Boyd, L. J., *Am. J. Med. Sci.*, 1946, **211**, 611.

TABLE I

Concentrations of Caronamide in Plasma and Cerebrospinal Fluid (CSF)

	Time (Min.) after last dose of caronamide							
	30	60	70	75	80	90	120	240
Plasma Concentrations of Caronamide mg./100 cc.	71	110[a]	59[c]	10[d]	21	41[c]	57[c]	1.2[d]
	59	48		77[c]		48	34	
		36					82	
		51[c]						
		58						
		87[b]						
		9[d]						
		57						
		63[c]						
AVERAGES	65	57	59	43	21	44	57	1.2

a—Caronamide concentration in CSF was 48 mg./100 cc

b—Caronamide concentration in CSF was 4.5 mg./100 cc.

c—Caronamide concentration in CSF was "a trace" (less than 1 mg./100 cc.)

d—These caronamide concentrations are far below those obtained in the other patients in this study and cannot be correlated with previous experience. There is some likelihood that patients did not receive scheduled medication

indicated in Table I as <0.026 and <0.039 have been regarded as zero values in determining the number of patients showing a significant amount of antibiotic in the cerebrospinal fluid. Actually, these patients may have had quantities of penicillin in the cerebrospinal fluid that were undetectable by the method of penicillin assay employed. Since the patients studied in this investigation had been and were being treated with malaria and the Kettering hypertherm, it was of importance to determine whether these circumstances favored the retention of penicillin in the circulation. In Chart 1 the plasma concentrations of penicillin obtained in this group of patients have been plotted against values that were obtained in a group of normal individuals following the administration of 125,000 units of penicillin in a control and a caronamide modified period. The fact that the plasma concentrations obtained in this group of patients fell, in the main, below those obtained on normal subjects (left side, Chart 1) clearly indicates that the group did not deviate markedly from previously studied normal groups of patients with respect to the rapidity with which penicillin was excreted. The higher plasma concentrations obtained during the periods of caronamide administration compare favorably with the enhancement effect of caronamide (right side, Chart 1) observed in previously studied normal patients. The increase of penicillin plasma concentrations by 2- to 7-fold[24,25] by the co-administration of caronamide and penicillin was confirmed.

In Chart 2 the concentrations of penicillin observed in the cerebrospinal fluid in the control and in the caronamide modified periods have been plotted and the tendency to higher values following the administration of caronamide is clearly indicated. It is noteworthy that the concentrations of penicillin in the cerebrospinal fluid observed in this study following the administration of 800,000 units of penicillin per day, are of the same

[24] Crosson, J. William, Boger, William P., Shaw, Christopher, C., and Miller, A. Kathrine, *J.A.M.A.*, 1947, **134**, 1528.

[25] Boger, William P., and Baker, Richard M., PROC. SOC. EXP. BIOL. AND MED., 1947, **66**, 1.

magnitude as those obtained following the administration of 20 to 25 million units by continuous intravenous drip over a 24-hour period.[20] In this preliminary investigation repeated sampling of the plasma and the cerebrospinal fluid following the administration of a single penicillin dose in order to determine the measure to which plasma and cerebrospinal fluid penicillin concentrations can be correlated, was not done, and it should be emphasized that the cerebrospinal fluid concentrations (Chart 2) are not a direct reflection of the concentration of penicillin found in the plasma at the time that the specimens were simultaneously obtained in this study. Since penicillin probably gains access to the cerebrospinal fluid through the choroid plexuses and a measurable time is required for penicillin in the ventricular cerebrospinal fluid to diffuse into the lumbar cerebrospinal fluid,[19] the distribution of penicillin between plasma and cerebrospinal fluid was probably determined by much higher levels of penicillin in the plasma than those observed at the times when specimens were obtained. Repeated samplings of blood and cerebrospinal fluid following a given dose of intramuscular penicillin are being done at the present time in an effort to determine a more exact plasma-cerebrospinal fluid penicillin concentration relationship, and the results will be the subject of a subsequent report.

Plasma penicillin concentrations above 0.156 units for as long as 4 hours with a peak concentration during that 4 hour period up to 10 to 20 units of penicillin per cc have resulted in a concentration of at least 0.02 units per cc in the cerebrospinal fluid.[15] These results were observed in 5 patients, all of whom received at least 300,000 units of penicillin intramuscularly and 100,000 units intravenously. These peak concentrations correspond closely to the concentrations that were maintained for 24 hours by the continuous intravenous administration of from 10 to 25 million units of penicillin, and that resulted in measurable quantities of penicillin in the cerebrospinal fluid.[20,21] Lesser doses of penicillin, 15,000 to 20,000 units, either intramuscularly or intravenously,[12] 30,000 units intramuscularly[13] and 20,000 to 60,000 units intramuscularly[14] cannot be expected to give such peak concentrations for even a short period of time and these levels of dosage have not given assayable quantities of penicillin in the cerebrospinal fluid. One group of investigators[17] has indicated rather high levels in the cerebrospinal fluid following intravenous doses of 20,000 to 40,000 units, but some question has been raised about the reliability of the Foster turbidometric method of penicillin assay. A single injection of 100,000 units intravenously in a case of meningitis resulted in detectable quantities of penicillin in the cerebrospinal fluid within 2 hours,[18] and such an injection can be assumed to have given a concentration of penicillin in the plasma above 10 units per cc for only a few minutes, and above 5 units for approximately 30 minutes.[26] Five hundred thousand units given intravenously resulted in 0.039 units per cc in the cerebrospinal fluid at the end of 2 hours and such a dose resulted in plasma concentrations from 87 to 10 units over a period of 30 minutes and above 1.5 units throughout the 2-hour period prior to the sampling of the cerebrospinal fluid.[26]

The tissue barriers between the cerebrospinal fluid and blood prevent the free exchange of penicillin between the plasma and the cerebrospinal fluid, but they are not impermeable to penicillin. It can be anticipated that there will be individual differences both in the concentration of penicillin that must be achieved in the plasma and the duration of time over which this concentration must obtain, to cause diffusion of penicillin into the cerebrospinal fluid, but it should be possible to obtain with regularity therapeutically significant concentrations of penicillin in the cerebrospinal fluid following parenterally administered penicillin. From data reported in the literature and from the results of this study, there is reason to believe that a plasma concentration of 10 units per cc maintained for less than 4 and possibly less than 2 hours is sufficient to cause measurable amounts of antibiotic to appear in the cerebrospinal fluid. The rapidity with which penicillin can be made to appear in the cerebrospinal fluid is

[26] Boger, William P., Unpublished data.

of great importance in the therapy of meningitis, and it is suggested that intermittent intravenous injection of penicillin may most promptly establish the circumstances favoring diffusion of penicillin into the cerebrospinal fluid.

In this investigation the use of oral caronamide to produce an inhibition of excretion of penicillin by the renal tubules resulted in increased penicillin plasma concentrations and, in the measure that it did so, contributed to the finding of larger quantities of penicillin in the cerebrospinal fluid. The failure of caronamide to pass freely into the cerebrospinal fluid in the majority of patients is another evidence that there is a hindrance of the free interchange of dissolved substances between the blood and the cerebrospinal fluid. The passage of caronamide into the cerebrospinal fluid when excessively high concentrations of caronamide were obtained in the plasma suggests that the barrier is only relatively impermeable.

Although the plasma concentrations of caronamide observed in this study were in excess of the 20 to 40 mg per 100 cc that have been shown to be effective in inhibiting the excretion of penicillin,[27] the only toxic symptoms were nausea and vomiting in 5 patients, and in only 2 patients was it necessary to discontinue administration of the drug.

Conclusions. Therapeutically significant quantities of penicillin (above 0.03 units per cc) have been observed in the cerebrospinal fluid following the intermittent intramuscular injection of 100,000 units of penicillin in aqueous solution. Caronamide increased the plasma levels of penicillin resulting from the administration of this dose of penicillin and thereby increased the amounts of penicillin found in the cerebrospinal fluid. Caronamide itself enters the cerebrospinal fluid only at excessively high plasma concentrations (87 to 110 mg per 100 cc).

The authors wish to express their indebtedness to the Chiefs of the Neurological Services at the Philadelphia General Hospital for their kindness in granting permission to study patients on their services, to Grace Schuchardt for caronamide determinations, and to Elizabeth Hughes and June E. Heckman for penicillin assays.

[27] Boger, William P., Trans. and Studies College of Physicians of Phila., 1947, **15**, 104.

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Influence of Dietary Lipids on Experimental Tuberculosis.*

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Experiments are recorded in the literature in which it has been demonstrated that the administration of certain of the lipids may result in an enhancement of experimental tuberculosis while the administration of other of these compounds may result in a retardation of the progress of the infection.

Weigert[1] conducted feeding experiments, using guinea pigs, and concluded that the tuberculous processes generalized more rapidly in animals fed a strict carbohydrate diet than in those receiving an added liberal amount of milk fat.

Troteanu[2] administered cod-liver oil directly into the stomach of guinea pigs and noted an enhancement of the progress of tuberculosis following the inoculation of the animals intraperitoneally with 1 mg of bovine

* This paper represents a portion of the dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, St. Louis University.

[1] Weigert, R., *Berl. Klin. Wechen.*, 1907, **44**, 1209.

[2] Troteanu, V. C., *Comp. Rend. Biol.*, 1929, **102**, 141.