

any evidence of liver tumor. Whether coincidental or not, the influence of the liquid skim milk diet on the resolving of hepatomas and other related disturbances is worthy of investigation.

Conclusions. The urinary excretion of galactose in the young rat is lower than that

of the adult animal when a supplemented skim milk diet is fed.

On such a diet, adult rats, with hepatoma induced by azo dyes, excrete a lower percentage of galactose in the urine than do normal adult rats.

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A Method for Producing Sustained High Penicillin Levels in the Blood.

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(Introduced by Gregory Schwartzman.)

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Improvement in antibiotic therapy may be expected if high penicillin levels could be maintained in the blood stream and tissues for prolonged periods. The required period of therapy may perhaps thereby be shortened and infections due to exceptionally resistant organisms may more readily be brought under control. Furthermore, high, sustained penicillin blood levels may result in tissue saturation and greater penetration of the drug into foci of infection.¹

To date, efforts to achieve prolonged levels consisted in the employment of two methods, (a) the use of oil, wax and other menstrea to delay absorption of penicillin introduced into a local depot and (b) the use of drugs capable of delaying the ordinarily rapid excretion of penicillin through the kidneys, *i.e.* para-aminohippuric acid,² and caronamide.³ Caronamide (4'-carboxyphenylmethanesulphonanilide) has been shown by Beyer⁴ to have an inhibitory effect on the renal tubular excretion of penicillin. In addition, attempts have been made to obtain high levels by continuous intravenous drip and by the

periodic administration of large "booster" doses of the antibiotic. The dose and speed of injection have been limited under the continuous intravenous method because of thrombo-phlebitis.

In this study, we have achieved sustained and unusually high levels of penicillin in the blood stream by the periodic intravenous injection of large doses of crystalline penicillin* when caronamide† was used as an adjuvant to block rapid excretion through the kidney.

Initially it was planned to obtain high intracardiac levels of penicillin by introducing the drug through an intracardiac catheter passed into the right ventricle or pulmonary artery. Preliminary experiments on dogs demonstrated, however, that the levels‡ in the aorta achieved by rapid injection of equally large doses of penicillin in concen-

* Sodium and calcium salts of crystalline penicillin kindly supplied by Schenley Laboratories, Inc.

† Kindly supplied by Sharp and Dohme, Inc.

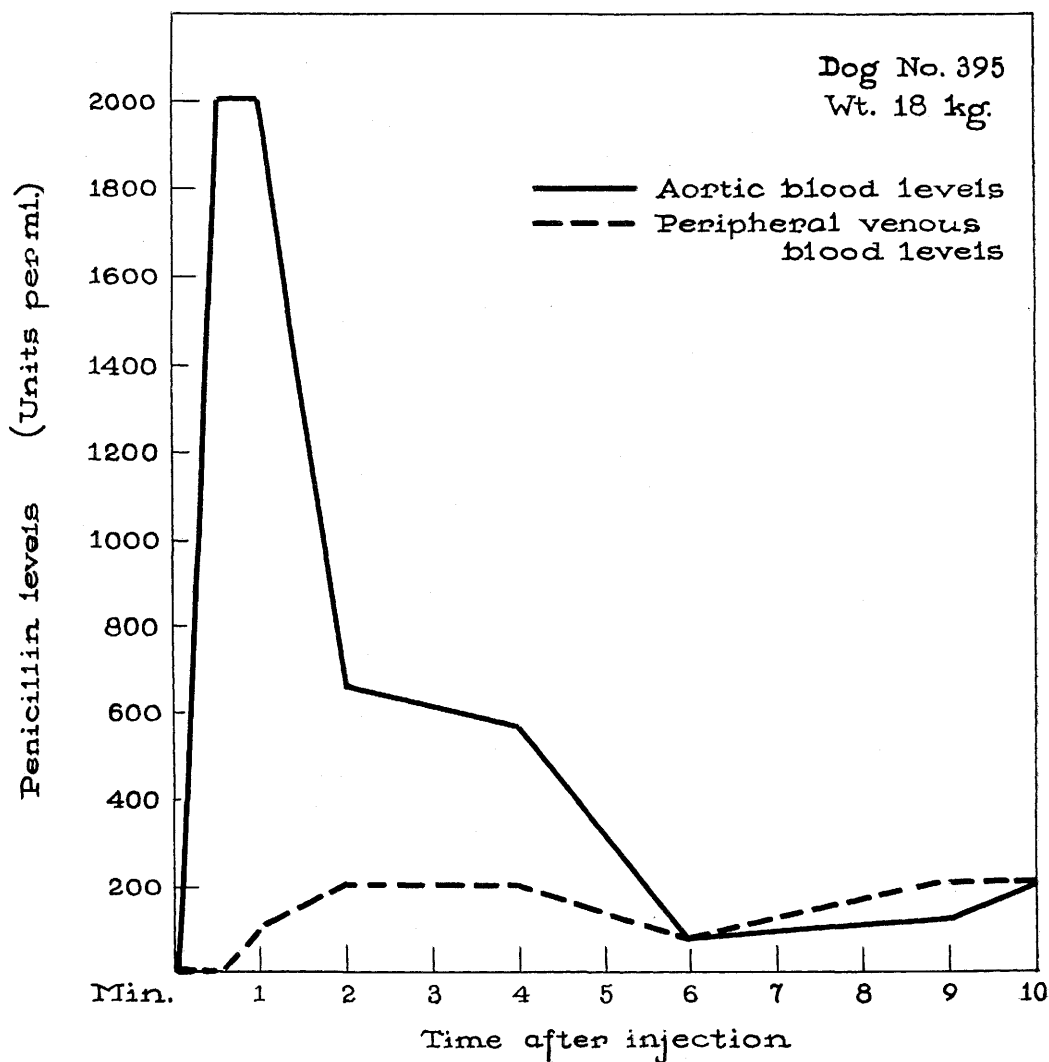
‡ The method of penicillin assay employed is a broth tube dilution method using *Staphylococcus aureus* H as the test organism and fresh meat extract broth as the medium. The minimal concentration of the standard penicillin required to inhibit the inoculum of 5×10^2 *Staphylococcus aureus* H cells was 0.02 units per ml. The standard penicillin was obtained from the U. S. Department of Agriculture. All titrations of serum levels were accompanied by and compared with this standard.

¹ Gerber, I. E., Schwartzman, G., and Baehr, G., *J. A. M. A.*, 1946, **130**, 761.

² Beyer, K. H., Flippin, H. F., Verwey, W. F., and Woodward, R., *J. A. M. A.*, 1944, **126**, 1007.

³ Crosson, J. W., Boger, W. P., Shaw, C. C., and Miller, A. K., *J. A. M. A.*, 1947, **134**, 1528.

⁴ Beyer, K. H., *Science*, 1947, **105**, 94.



GRAPH 1.
500,000 units crystalline penicillin dissolved in 5 cc distilled water injected rapidly into right brachial vein through an 18-gauge needle.

trated solution into the brachial vein were as great as those that could be obtained by introducing the penicillin directly into the right side of the heart. In the animals, in addition to extremely high levels in the aorta immediately following injection there were found unusually elevated peripheral blood levels. No untoward manifestations supervened when one million units of crystalline penicillin, dissolved in 5 cc of distilled water, were injected as rapidly as possible through a large (18 gauge) needle into the brachial vein of a dog weighing 18 kg (55,600 units/kg). A continuous electro-

cardiogram taken before, during and following the injection failed to show any alterations in rate, rhythm, or contour of the complexes.

Following these preliminary experiments, the method was applied to patients. The first patient received one million and the second, 2 million units of crystalline penicillin, dissolved in 5 cc of distilled water. The solutions were injected rapidly into the right antecubital vein through a 15-gauge needle, the injection being completed within 5 seconds. No clinical or electrocardiographic abnormalities were noted.

The levels of penicillin in the aortic blood,

TABLE I.
Effect of Caronamide upon Penicillin Blood Levels in Units per ml in Patients Receiving a Single Large Dose of Crystalline Penicillin (One Million Units).

Time after inj.	Rapid Intravenous Injection								Intramuscular inj.	
	Patient 1		Patient 2		Patient 3		Patient 4		No caronamide	With caronamide
	No caronamide	With caronamide	No caronamide	With caronamide	No caronamide	With caronamide	No caronamide	With caronamide		
1 min.	112	152	88	152	136	160	—	—	—	—
3 "	132	152	112	152	152	160	—	—	—	—
5 "	120	136	112	136	128	144	32	32	32	32
10 "	104	88	—	112	88	136	32	40	32	40
15 "	64	72	40	72	56	96	40	40	40	40
20 "	—	—	—	—	—	—	40	48	40	48
30 "	40	56	32	48	32	80	32	48	32	48
1 hr	16	48	16	40	8	48	24	48	24	48
2 "	5.7	13	6.6	20	4.4	20	10	20	10	20
3 "	2	10	2	13	0.8	13	4.4	13	4.4	13

obtained from the descending aortic arch during operation, in a human subject weighing 58 kg were determined. At 1, 3, 5, and 10 minutes following rapid injection into the left antecubital vein of one million units of crystalline penicillin (17,300 units per kg) dissolved in 5 cc of distilled water the levels were found to be 480.0, 346.0, 320.0 and 106.6 units per ml respectively.

The peripheral venous blood levels were then studied in human subjects under the following conditions: one million units of crystalline penicillin dissolved in 5 cc of distilled water were injected rapidly into 3 patients prior to and, again later, following the administration of caronamide. For comparison the same dose was given intramuscularly in a control patient, also preceding and following caronamide administration. The results are given in Table I. In all patients receiving caronamide the dose employed was 4 g orally every 3 hours day and night starting 24 hours before antibiotic therapy and continuing throughout the period of observation.

As may be seen from Table I, a very high blood level still persisted one hour after each injection, especially when the patient was receiving caronamide. The peak level in the venous blood from the opposite arm was reached within the first 3 minutes and was equally high in patients under caronamide therapy and without it. There was a progressive fall during the 3 hours of observation, the most precipitous drop occurring during the first 30 minutes. At the 3-hour period the level in the patients receiving caronamide was 5 to 15 times higher than in the same patients without caronamide.

It was thought that the high level still present at the end of the first hour could be maintained or exceeded if the intravenous injection of the same dose was repeated hourly. Table II shows the levels achieved in 3 patients receiving rapid intravenous injections of one million units of penicillin hourly for 10 hours. Two of these patients received caronamide and one did not. Table II also shows the blood levels found after administration of the same total dose (10 million units in 10 hours) by slow intravenous drip in a

TABLE II.
Peripheral Blood Penicillin Levels in Units per ml After the Administration of 10 Million Units of Crystalline Penicillin in 10 Hours.

Time	One million units of crystalline penicillin, dissolved in 5 cc distilled water, rapidly inj. into right antecubital vein, hourly, for 10 hrs			Ten million units of crystalline penicillin, dissolved in one L. physiological saline, administered by slow intravenous drip in 10 hrs		
	Patient 5 Caronamide	6 Caronamide	7 No caronamide	Time, hr	8 Caronamide	9 No caronamide
After 1st injection:						
3 min.	184	184	120	1	27	20
5 "	160	120	80	2	96	32
30 "	96	88	24	3	96	48
55 "	64	64	8	4	104	40
				5	112	48
After 5th inj.:				6	120	40
3 min.	224	228	128	7	136	32
5 "	208	176	96	8	128	—
30 "	104	144	24	9	128	48
55 "	72	96	—	10	136	56
				10½	128	
After 10th inj.:						
3 min.	280	256	120			
5 "	280	240	64			
30 "	232	240	56			
55 "	208	200	16			
24 hr after start	13	5.7	0.5	24 hr after start	8	<.05

patient treated with caronamide and in one, in the absence of the drug.

No toxic effects were noted in any of the cases studied. Bleeding and coagulation times and clot retraction remained normal.

It is apparent from these experiments that higher peak levels are obtained and that higher interim levels are maintained by the hourly rapid injection of a concentrated solution of crystalline penicillin than by giving the same amount of the antibiotic during the same period by means of the usual slow continuous method of intravenous administration. In addition, a summation effect is indicated by the levels recorded after the first, fifth and tenth injections in patients No. 5 and 6 who received caronamide. This indicates that the repeated hourly intravenous injection of such large amounts either still further reduced the renal excretion rate or resulted in tissue saturation so that the fall of blood level by movement of the penicillin into the tissues was reduced.

The high levels of penicillin in the peripheral blood, just described, are the result of the hourly and rapid intravenous administration of extremely high dosage in combin-

ation with inhibition of renal excretion by caronamide. The intraaortic peak levels are many times higher than those in the peripheral blood when the antibiotic is injected rapidly in concentrated solution. It is believed that even higher sustained levels could be safely achieved by larger single doses.

Studies are now in progress to determine the effect of such high sustained levels in the peripheral blood and high aortic levels of penicillin upon the rapid sterilization of the vegetations in bacterial endocarditis and upon other acute and chronic local and general infections caused by refractory microorganisms. It is also important to determine the effectiveness of this method in shortening the duration of therapy in these diseases and, perhaps, reducing the total amount of penicillin required.

Summary. A method for obtaining high sustained blood levels of penicillin is described. This consists in repeated large intravenous doses of crystalline penicillin, injected rapidly, in patients receiving caronamide. Clinical applications are suggested.

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