

p-aminohippuric acid were observed. However, when the acidosis was produced, by infusion of lactic acid (5 cases), a marked fall in all clearances was observed, coinciding with the appearance of methemoglobin in the urine. This observation makes it apparent that the renal failure was caused by the combined effect of acidosis and methemoglobin.

Summary. The infusion of crystalline methemoglobin into dogs acidified with ammonium chloride is followed by a fall in the effective renal plasma flow and the glomerular filtration rate of the dog. The dog may die in uremia on the third day following the infusion.

Infusions of metmyoglobin and hemoglobin into acidified animals, and of methemoglobin and hemoglobin into normal animals, fail to depress renal function. The renal lesions of acidified dogs infused with methemoglobin resemble those observed in cases of crush syndrome and blackwater fever.

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Excretion of Penicillin in Man.*

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Florey¹ has demonstrated that penicillin appears in the urine when administered to the experimental animal or to man. More recently Rammelkamp and Keefer² showed that 58% of penicillin administered by the intravenous route is excreted by the kidneys largely during the first hour after the injection. This rapid loss of penicillin in the urine is undesirable since frequent injections are required to maintain adequate concentrations in the blood during the treatment of infections. The fact that substances, such as diodrast, which are excreted by the renal tubules exhibit a similar rapidity of elimination suggested the possibility that penicillin is also excreted by the tubules in addition to being filtered through the glomeruli, and further that this portal of exit could be blocked and the elimination of penicillin decreased.

The present study was undertaken, therefore, to determine the mechanism of excretion of penicillin.

Methods. Penicillin[†] was used in the form of the sodium salt dissolved in 0.85% sodium chloride in a concentration of 1000 Florey units per cubic centimeter. All injections were made with this standard solution.

In one subject a constant intravenous infusion of penicillin was administered for a period of 5½ hours. The flow was adjusted so that 9600 Florey units per hour were delivered. The urine collected 30 minutes after institution of the constant drip of penicillin was discarded, thereafter hourly collections of urine were made. From the second to the fourth hours diodrast was given at the rate of 0.3 cc per minute after a priming dose of 10 cc.

The elimination of penicillin was studied in 5 subjects after a single injection of 5000 Florey units and again 24 hours later after the simultaneous injection of 5000 Florey

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¹ Florey, H. W., Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., and Jennings, M. A., *Lancet*, 1941, **2**, 177.

² Rammelkamp, C. H., and Keefer, C. S., *J. Clin. Invest.*, 1943, **22**, 425.

[†] Penicillin was supplied through the courtesy of Dr. George A. Harrop, Squibb Institute for Medical Research, New Brunswick, N.J.

EFFECT OF DIODRAST ON PENICILLIN EXCRETION

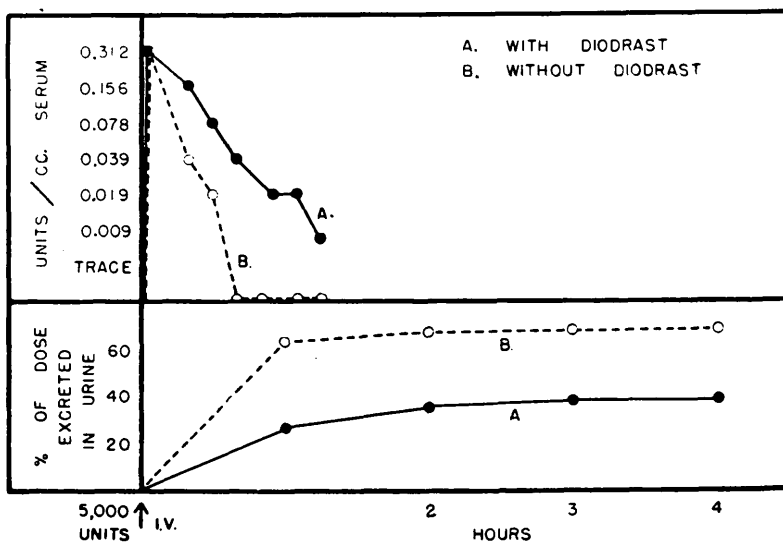


FIG. 1.

units and diodrast. On 2 occasions diodrast was given as a single injection of 30 cc just prior to the penicillin while in the remaining 3 instances 20 cc of diodrast was injected with the penicillin and 30 minutes later the administration of diodrast was repeated. Blood was withdrawn in sterile tubes at frequent intervals. Each subject ingested 400 cc of water every hour for 4 hours. Voided specimens of urine were collected in sterile containers at hourly intervals. The concentration of penicillin was then determined on each blood and urine sample using the method described previously.³ No effect of diodrast upon bactericidal activity of penicillin was observed.

Results. When penicillin was administered to a normal subject by a constant intravenous drip delivering 9600 Florey units per hour, the excretion of the material by the kidneys was depressed by the addition of diodrast to the infusion. In this subject control periods of one hour both before and after the simultaneous injection of penicillin and diodrast showed excretion of 4530 and 3931 Florey units, respectively. During the 2-hour period of penicillin-diodrast administration, only 1087 Florey units were excreted each hour. This suggested that diodrast depressed the excretion

of penicillin and, therefore, 5 additional subjects were studied after single injections of penicillin and penicillin-diodrast solutions.

In the 5 subjects who received 5000 Florey units and 24 hours later a second injection of 5000 Florey units and 30 to 40 cc of diodrast, the serum concentrations showed that the level of penicillin remained elevated to a greater height and for a longer period of time when diodrast was injected simultaneously. Fig. 1 shows the results obtained in Subject 6. In this instance, one minute after the injection of penicillin or penicillin-diodrast the serum contained 0.312 Florey unit per cubic centimeter. Penicillin disappeared from the circulating blood within 40 minutes after 5000 Florey units of penicillin, whereas the injection of penicillin-diodrast resulted in the maintenance of a significant level of penicillin in the serum for 75 minutes. In the remaining 4 subjects (Nos. 2, 3, 4, 5) the serum concentrations of penicillin were invariably higher and remained elevated for a longer period of time when diodrast was injected simultaneously with the penicillin.

The excretion of penicillin in the urine was greatly depressed by the injection of diodrast. As demonstrated in Fig. 1, 69% of the administered dose of penicillin was excreted in the urine within 4 hours while the total excretion

³ Rammelkamp, C. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1942, **51**, 95.

TABLE I.
Effect of Diodrast on Penicillin Excretion in Normal Subjects. Intravenous Injection of Penicillin in 5000 Florey Units.

Case	Diodrast, cc	% of penicillin excreted in urine per hour*			
		1	2	3	4
2	30	16	31	34	34
	0	40	47	48	48
3	30	32	37	39	39
	0	56	58	59	59
4	40†	19	24	25	26
	0	62	65	66	67
5	40†	17	24	25	25
	0	38	41	43	43
6	40†	27	35	36	36
	0	63	67	68	69

* Cumulative excretion.

† Initial injection of 20 cc of diodrast followed in 30 minutes by a second injection of 20 cc.

of penicillin when diodrast was given simultaneously amounted only to 36%. Most of the penicillin was excreted within the first hour after its injection on every occasion (Table I), and this was true both with and without the addition of diodrast. The average excretion of penicillin during the first hour in all subjects when diodrast was not given was 51.8% and after 4 hours was 57.2%. In contrast, when diodrast was given simultaneously, the average excretion during the first hour fell to 22.2%, and during the 4-hour period to 32%.

Discussion. Smith and his co-workers⁴ have shown that there is mutual depression of the diodrast, hippuran, and phenol red clearances when these substances are given simultaneously, and more recently a similar relation between diodrast and other pyridone derivatives has been demonstrated.⁵ When these substances are given simultaneously, there is a marked depression of all clearances but diodrast, which is lowered to only a slight extent. This phenomenon of mutual depression of tubular excretion is attributed to a

competition for elimination through a common tubular mechanism. Since penicillin elimination is decreased in the presence of diodrast, it is probable that it is excreted by the tubules, perhaps largely by the same mechanism responsible for tubular excretion of diodrast and the other substances depressed by it. This may imply the presence of common chemical groups or common physico-chemical properties. It also suggests the possibility that elimination of penicillin may be decreased during clinical use, thus maintaining adequate blood levels, by simultaneous administration of substances which block its excretion or that structure of penicillin may be altered in such a way as to produce this effect.

Of considerable interest is the fact that the total amount of penicillin excreted after diodrast-penicillin administration averaged only 32%, whereas 57.2% was excreted after the injection of penicillin alone. This suggests that penicillin is destroyed or inactivated within the body to a greater extent following diodrast administration and confirms the previous suggestion² that the degree of "inactivation" of penicillin is related to the time of exposure within the body.

Conclusion. The excretion of penicillin in man may be partially blocked by the simultaneous administration of diodrast.

⁴ Smith, H. W., Goldring, W., and Chasis, H., *J. Clin. Invest.*, 1938, **18**, 263.

⁵ Finkelstein, N., Aliminos, L., and Smith, H. W., *Am. J. Physiol.*, 1941, **133**, 276.