logic importance in the outbreak of Japanese B encephalitis which began on Okinawa during July 1945.

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The Absorption of Orally Administered Penicillin[1]

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In a previous communication (*7*), it was reported that when penicillin was administered orally to fasting subjects the concentrations attained in the blood and the range of urinary excretion were of the same order of magnitude whether the penicillin was presumably protected against destruction in the stomach by the use of oil, oil-beeswax, or an antacid, or whether it was ingested as the aqueous solution. Regardless of vehicle, it was necessary to administer approximately five times as much penicillin by the oral as by the intramuscular route to obtain comparable concentrations of penicillin in the blood. In no instance was more than 32 per cent of the ingested penicillin excreted in the urine during the 12 hours immediately following ingestion.

This low urinary excretion after oral administration is in striking contrast to the 70 to 100 per cent urinary excretion which Martin and Kirby (*9*) have demonstrated after single parenteral doses. In experiments which will be published elsewhere (*8*), there was no evidence that penicillin is destroyed in the portal circulation. Moreover, penicillin is not destroyed by whole blood *in vitro* when incubated at 37° C. for a four-hour period. It appears, therefore, that the quantitative difference between the urinary excretion of penicillin after parenteral injection and that observed after oral administration represents the penicillin which is not absorbed. Presumably the material which is not absorbed after oral administration is either destroyed or excreted in the alimentary tract.

As it appeared that the destruction of penicillin by the acid of the stomach was not an entirely satisfactory explanation of the fate of the larger part of the ingested material, an investigation of the absorption, excretion, and destruction of penicillin following oral administration has been conducted, and a preliminary report on certain of the observations is presented at this time.

A study of the urinary excretion of penicillin after both oral and intramuscular administration was made in six subjects with complete achlorhydria. Five of the subjects had pernicious anemia. On successive days, each subject received identical doses of penicillin by the oral and by the intramuscular route. Nine such experiments were performed, seven after 300,000-unit doses and two after 25,000-unit doses. The penicillin determinations were made by the Rammelkamp method of bio-assay (*10*). All subjects were in a fasting state when the penicillin was ingested and during the succeeding four hours.

The results are presented in Table 1. As may be seen, the amount of penicillin excreted in the urine (per cent of the total dose) ranged from 36 to 100 per cent following intramuscular administration, and usually was more than 60 per cent.[2] Following oral administration, the range of urinary excretion varied between 8 and 32 per cent. In the comparative studies in each individual, the differences are striking. The amounts of penicillin appearing in the urine of these achlorhydric subjects after oral administration were within exactly the same range as had been observed previously in normal subjects (*7*) and were definitely less than appeared after intramuscular administration.

TABLE 1

URINARY EXCRETION OF PENICILLIN FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION IN SUBJECTS WITH COMPLETE ACHLORHYDRIA

Subject	Penicillin dosage	Urinary excretion in per cent of total dose		Period of observation
	Units	Oral	Intramuscular	Hours
1	300,000	15		3
	300,000		46	5
	300,000	32	64	8
	25,000	19	100	8
2	300,000	28		8
	300,000		97	10
	25,000		36	8
3	300,000	21	68	4
	25,000	14	64	8
4	300,000	26	55	8
	25,000		52	8
5	300,000	10	96	8
6	300,000	27	73	24
7	300,000	8		3

Data on the urinary excretion of ingested penicillin obtained from the published reports and from our own observations are presented in Table 2. As may

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College.

[2] The difference between the values for the urinary excretion of penicillin in these experiments and the 70 to 100 per cent excretion noted by Martin and Kirby is presumably because fewer dilutions of a given specimen of urine were assayed in the present experiments.

be seen, the maximum urinary excretion (and hence absorption) of ingested penicillin which has been observed in the achlorhydric subjects and in normal subjects regardless of vehicle (*3, 4, 5, 7, 8, 12, 13*) is only 34 per cent. Although in one report (*6*) not included in the table, higher values were obtained, a extracted from the stools of subjects who had ingested single large doses of penicillin, but was not present in the stools of the same subjects after the intramuscular administration of penicillin. Since the amount of penicillin present in the stools represented only a small fraction of the ingested dose, it appeared probable that the majority of the material was destroyed in the intestinal tract.

TABLE 2

URINARY EXCRETION OF ORALLY ADMINISTERED PENICILLIN

Report	Dose (units penicillin)	Period of observation (hours)	No. of subjects	Vehicle	Protective agents	Per cent of total dose recovered	
						Average	Range
McDermott, Bunn, *et al.*	100,000–300,000	12–24	9		Absent	18.4	3–32
"	100,000–300,000	12–24	6	Magnesium trisilicate and amphogel	Present	16.5	6–29
"	100,000–300,000	12–24	16	Oil suspension of penicillin, alone or with beeswax or shellac	Present	9.9	2–21
Charney, *et al.*	25,000	6–8	25		Absent	12.8	4.2–23.3
"	25,000	6–8	18	1.4–7.0 grams trisodium citrate	Present	13.9–15.6	6.6–32.5
Free, *et al.*	100,000	6	4		Absent	20.2	8.8–33.6
"	100,000	6	3	10.0 grams $NaHCO_3$	Present	6.3	1.9–12.7
Heatley	15,000	7–8	3		Absent		4.2–15.5
"	27,500	7–8	1		Absent		13.3
"	15,000	7–8	3	Egg and $NaHCO_3$	Present	20.1	11.0–33.8
"	27,000	7–8	1	"	Present		18.0
Welch	100,000	7	10		Absent	6.7	Not stated
"	100,000	24	11	Amphogel adsorption	Present	13.6	5.5–27.3
"	100,000 in 4 divided doses		11	"	Present	7.2	1.2–15.0
Rammelkamp and Keefer	10,000	3	1		Absent		10.1
"	20,000	3½ (210 min.)	1		Absent		3.2
"	20,000	1½ (85 min.)	1	40 grams $NaHCO_3$	Present		5.3

repetition of the experiments (*5*) disclosed a maximum urinary excretion of only 33.8 per cent. A comparison of the extremes and the average values for the urinary excretion of penicillin ingested with and without acid neutralizing agents is of interest. With attempts at acid neutralization, the values for urinary excretion ranged from 3 to 33.6 per cent of the ingested dose, and the average values ranged from 6.7 to 20.2 per cent. Without attempts at acid neutralization, the values are from 1.9 to 32.5 per cent (extremes) and 6.3 to 20.1 per cent (averages). Thus, the range of urinary excretion of orally administered penicillin is of the same order of magnitude in subjects with achlorhydria as in normal subjects, regardless of whether attempts are made to neutralize the gastric acidity of the latter.

This suggests that the lower concentrations of penicillin which are attained in the blood and urine after oral, as compared with parenteral, administration are chiefly the result of a defect in absorption and not primarily due to penicillin lost by acid destruction. Presumably the penicillin which is not absorbed would be destroyed in the gastrointestinal tract or excreted in the stool.

In several experiments a variable amount of an antibacterial substance, presumably penicillin, was

Both in the cat and in man almost all of penicillin absorption occurs from the small intestine, and only minute amounts can be absorbed from the colon (*8*). Rammelkamp and Helm (*11*) have demonstrated that the incubation *in vitro* of penicillin with succus entericus (and with bile) caused no loss of activity. Therefore, it appeared probable that the destruction of a large part of the material which was neither absorbed nor excreted occurred distal to the duodenum, in the lower ileum or colon.

In the original report on the pharmacology of penicillin by Abraham, *et al.* (*2*), it was mentioned that feces inactivate penicillin, but no details were presented. Subsequently it was established (*1*) that a penicillinase could be extracted from *E. coli*. Since no information was available on the rate of the inactivation of penicillin by feces, known amounts of penicillin were incubated *in vitro* at 37° C. with emulsions of stool specimens from presumably normal individuals. The technique used for the assay of penicillin in feces is described elsewhere (*8*).

The results of five representative experiments are presented in Fig. 1. As may be seen, 80 to 100 per cent of the penicillin was inactivated by incubation

with emulsion of stool for 24 hours. No inactivation was demonstrable in one experiment which was conducted for only four hours. In general, the rate of inactivation varied, but considerable destruction had

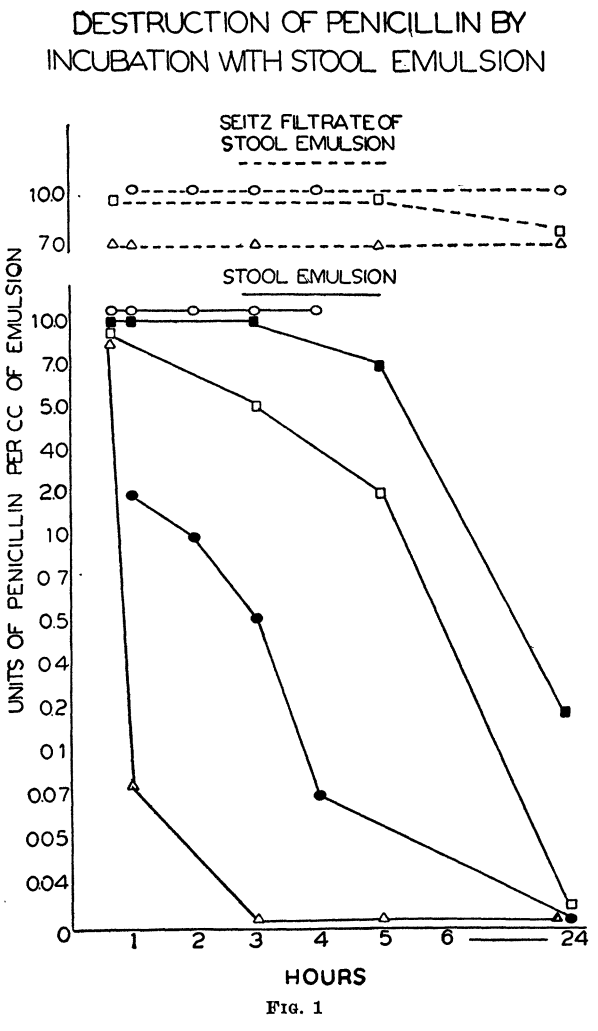

FIG. 1

usually occurred by the end of the third hour of incubation. When emulsions of stool were passed through a Seitz filter prior to incubation with penicillin, little or no destruction of the penicillin occurred, although unfiltered specimens from the same emulsion destroyed penicillin.

Thus, there are two mechanisms for the destruction of penicillin in the alimentary tract: the secretion of acid in the stomach and some agent, presumably bacterial, in the intestine. It is impossible to determine in an individual case the relative proportions of an ingested dose of penicillin which are destroyed by these respective mechanisms. One operates before, the other after, the penicillin has reached the site of greatest absorption, the duodenum (*8*). Of greater importance, however, is the fact that even if destruction by acid does not occur at all, because of achlorhydria, successful neutralization, or the normal fluctuations of gastric acidity, the greatest absorption which has been noted is only 34 per cent of the ingested dose. The penicillin which is not absorbed is eventually destroyed by the action of the second mechanism or is excreted in the feces.

It appears, therefore, that the maximal benefit which is attainable from protecting the penicillin against acid destruction is limited to the difference between the amount of absorption which occurs in the absence of such protection and the maximal absorption which has been noted when acid destruction is not a factor. As the theoretical advantage of protection of all of the material against acid is so largely counterbalanced by the fact that no more than a third of the ingested dose is absorbed in any event, it would seem that no penicillin preparation for oral use which is based solely on the principle of protection against acid will prove to be significantly superior to penicillin alone.

Furthermore, in the presence of maximum absorption approximately three times as much penicillin is required by the oral as by the intramuscular route to produce comparable penicillin concentrations in the blood. Since maximum absorption does not generally occur, the usual ratio of oral to intramuscular dosage will be in the neighborhood of 5:1.

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Effect of Penicillin on Growth of *Alcaligenes fecalis*

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The literature contained no information on the effect of penicillin on *Alcaligenes fecalis* previous to a recent paper by Altemeier (*1*), who reported the marked susceptibility of five strains to penicillin. In