COMMENTS ON THE USE OF PYRAZINAMIDE

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In science there is a tendency to attempt simple explanations of complex phenomena. Renal physiology is no exception. For example, in measuring the net renal tubular secretion of a substance such as *p*-aminohippurate (PAH) as a function of either plasma PAH or the total PAH load to the kidney, an unknown amount of carrier-mediated PAH reabsorption occurs concomitantly (1). Yet such bidirectional transport often is conveniently ignored when transport occurs largely in one direction. In the case of uric acid in man, however, the recognition of its bidirectional transport is necessary for an adequate evaluation of renal urate handling. Although more urate is reabsorbed than is secreted, the existence of urate secretion appears mandatory if urate is to be eliminated at rates sufficient to establish homeostasis and to avoid hyperuricemia (2).

Pyrazinamide has been utilized extensively to delineate the importance of each unidirectional component of urate transport. The "pyrazinamide suppression test," which measures the maximum decrement in urate excretion following pyrazinamide, was originated in this author's institution (3) and adopted by several others. The assumption underlying the test is that the antiuricosuric effect following pyrazinamide occurs secondary to inhibition of the tubular secretion of urate. Subsequent pharmacologic studies in man and animals by Weiner and Tinker (4) have upheld this assumption. The ultimate effects of pyrazinamide on renal transport systems are mediated by a metabolite, pyrazinoic acid. This compound appears to inhibit urate transport bidirectionally. Like many agents that affect urate transport, pyrazinoic acid mainly inhibits urate secretion at low plasma levels, but becomes significantly uricosuric at very high plasma concentrations (4,5). This "paradoxical effect" of pyrazinoate virtually rules out any possibility that the antiuricosuric state following pyrazinamide may derive from accelerated urate reabsorption. Furthermore the administration of pyrazinamide probably results in quite selective secretory inhibition. Limited observations in man indicate that only very low plasma pyrazinoate concentrations result from the oral administration of a large dose of pyrazinamide (4). Thus, following pyrazinamide administration, the low levels of metabolite ensure a predominantly antisecretory action, probably with only very minimal inhibition of urate reabsorption. Furthermore this antisecretory effect following pyrazinamide is extremely stable in a quantitative sense for many hours (6); this stability allows the use of the "pyrazinamide effect" in prolonged clearance

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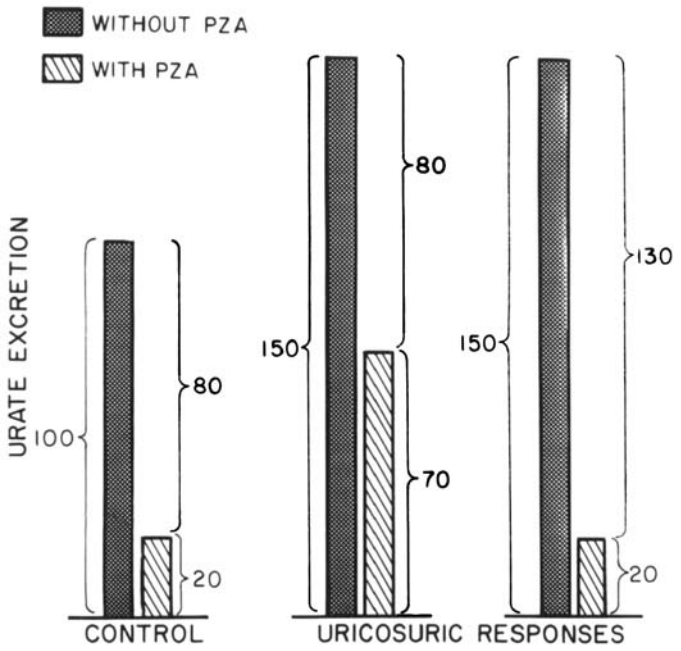

Fig 1. *Diagrammatic representation of pyrazinamide suppressibility or nonsuppressibility of uricosuric responses. Under normal circumstances with a urate excretion rate of 100 U, 80 U are suppressible by pyrazinamide (left). After inhibition of reabsorption the urate excretion increases to 150 U, giving a net uricosuric response of 50 U (middle and right). If the uricosuric response is completely nonsuppressible (middle), treatment with pyrazinamide would decrease the urate excretion by only 80 U, leaving a nonsuppressible excretion rate of 70 U (ie 50 U greater than the control with PZA). If the response is completely suppressible by pyrazinamide (right), the residual nonsuppressible urate excretion after pyrazinamide would be the same as control circumstances.*

studies. Although a recently published treatise on renal physiology has termed the pyrazinamide suppression test a "pyrazinoate suppression test" (7) because pyrazinoate is the renally active metabolite, that term is somewhat misleading. Probably the fact that the test is performed with pyrazinamide rather than pyrazinoate is responsible for the very stable antisecretory effect obtained.

It is generally agreed that the low levels of urate excretion remaining after pyrazinamide administration reflect changes in renal urate handling that have largely resulted from secretory inhibition (2,8). Indeed the difference between the filtered urate and urate excretion, following pyrazinamide, is a minimal estimate of urate reabsorption. In most circumstances studied to date this computed reabsorption rate is almost as great as the filtered load. However it is conceivable that urate reabsorption following pyrazinamide could be *greater than* the amount of urate filtered if secretory inhibition were incomplete. In that case urate reabsorption would approximate the sum of the filtered load plus the residual secretion rate, because the urine after pyrazinamide is virtually free of urate.

Originally the decrement in urate excretion produced by pyrazinamide was taken as an estimate of tubular secretion of urate (3). However several converging lines of evidence have suggested that an unknown portion of the secreted urate is reabsorbed within nephrons (9–11). The pyrazinamide-induced decrement in urate excretion probably substantially underestimates the true tubular secretion of urate intrarenally. Thus it seems more reasonable to refer to the pyrazinamide-induced decrement as the "pyrazinamide-suppressible urate excretion." By analogy the component of excretion remaining during maximal pyrazinamide action could be designated the "nonsuppressible urate excretion," because it is not suppressible after pyrazinamide.

Much of the evidence for post-secretory reabsorption of urate in man was derived from experiments utilizing more than one pharmacologic agent (9,10). Specifically, either the effect of pyrazinamide pretreatment on the response to a uricosuric agent was studied (9), or the pyrazinamide-induced decrement in urate excretion was measured while a uricosuric response was in progress (10). In Figure 1 (left) the normal response of urate excretion to pyrazinamide is shown diagrammatically (3). If baseline urate excretion is 100 U, the pyrazinamide-suppressible fraction is 80 U and 20 U of excretion remain after pyrazinamide as the nonsuppressible urate excretion. Classically, uricosuric agents would have been expected to yield the response shown in the center of Figure 1 if reabsorption and secretion were functionally separate. In Figure 1 (center) the total urate excretion after the uricosuric agent is 150 U, giving a net uricosuric response of 50 U. Yet the pyrazinamide-suppressible portion of the urate excretion remains the same at 80 U. The entire 50-U uricosuric response is contained within the nonsuppressible component of the urate excretion. On the other hand several uricosuric agents have yielded responses as in the right panel of Figure 1. Again total urate excretion after the uricosuric agent is 150 U, giving a net uricosuric response of 50 U. Yet the entire 50-U response now lies within the pyrazinamide-suppressi-

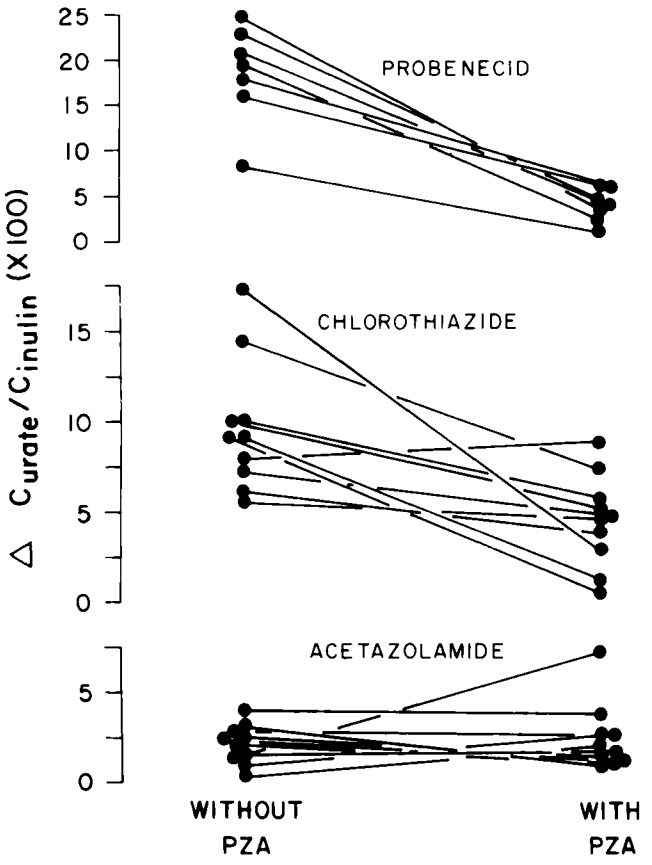

Fig 2. *Uricosuric responses to probenecid, chlorothiazide (9), and acetazolamide (12), expressed as the change in urate clearance (Δ C_{urate}/C_{inulin}). Each normal participant was studied, both without and with PZA pretreatment. Uricosuric responses to probenecid and chlorothiazide were significantly depressed by PZA. The smaller uricosuric responses to acetazolamide were not affected by PZA.*

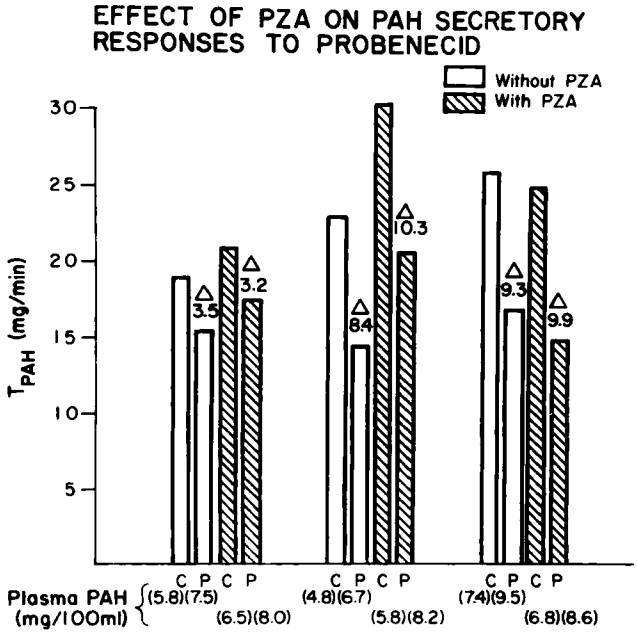

Fig 3. *Failure of pyrazinamide to affect the inhibitory effect of probenecid on* p*-aminohippurate (PAH) secretion (T_{PAH}) in 3 of the probenecid-treated subjects of Figure 2. Control values (C) for T_{PAH} and values after probenecid (P) are diagrammed for the paired studies without and with PZA pretreatment. In each experiment plasma PAH was elevated continuously in a concentration range in which T_{PAH} normally varies directly with plasma PAH. PZA pretreatment did not diminish baseline T_{PAH} and did not appreciably affect the probenecid-induced decrement in T_{PAH} in any of the subjects (13).*

ble fraction. The nonsuppressible urate excretion is exactly the same as that during the control studies (without a uricosuric agent). Stated differently, in Figure 1 (right) pyrazinamide treatment completely obliterates the uricosuric response, whereas in Figure 1 (center) pyrazinamide treatment has no effect whatsoever on the uricosuric response (considered as the *incremental* response).

In studies in the author's laboratory (9) both probenecid and chlorothiazide showed markedly diminished uricosuric responses when subjects were pretreated with pyrazinamide (Figure 2). Whereas the increase in urate clearance after probenecid ranged from 10 to 25% of the glomerular filtration rate (GFR) in the studies without pyrazinamide, the response was less than 10% of the GFR after pyrazinamide. In contrast to probenecid and chlorothiazide, pyrazinamide did not affect the uricosuric response to acetazolamide (12). However the possibility existed that pyrazinamide (or pyrazinoate generated) could have interfered with the renal actions of probenecid and chlorothiazide on a pharmacologic level. In the case of chlorothiazide some circumstantial evidence against this possibility was derived from observations that the natriurectic and phosphaturic responses to chlorothiazide were not affected by pyrazinamide pretreatment (9). Analogous evidence related to probenecid was more difficult to come by because this agent has little effect on cation or inorganic phosphate reabsorption. In order to examine the renal effects of probenecid after pyrazinamide, the inhibitory effect of probenecid on net PAH secretion was examined in 3 of the 7 probenecid study pairs depicted in Figure 2 (13). These effects of probenecid on PAH secretion are summarized in Figure 3. In each person baseline PAH secretion was never less

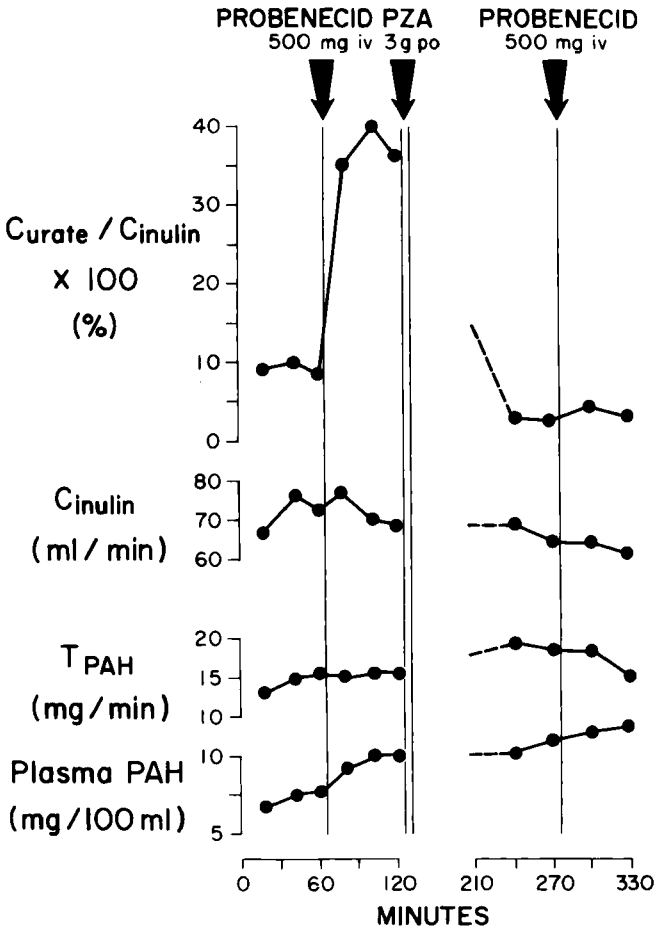

Fig 4. *Obliteration of uricosuric response to probenecid by pyrazinamide (PZA) and lack of any relationship to T_{PAH} in a 51-year-old man with tophaceous gout. This patient demonstrated no inhibitory effect of probenecid on T_{PAH} but manifested a brisk initial uricosuric response to probenecid. After pyrazinamide there was essentially no uricosuric response to probenecid.*

after pyrazinamide pretreatment. Furthermore the decrement in PAH secretion following injection of probenecid was not different in the pretreatment studies, in comparison to the previous studies in the same persons without pyrazinamide.

On the other hand probenecid may produce a large uricosuric response in some persons without altering PAH secretion as illustrated in Figure 4, a study performed in a 51-year-old man with gout and some renal functional impairment. When probenecid was administered initially, no change in PAH secretion occurred. Pyrazinamide administration was followed by the usual decrease in urate clearance, which was maximal after 1 hour. The administration of a second dose of probenecid again resulted in no clear-cut decrease in PAH secretion as well as in no uricosuric response to probenecid. The results of this particular study seem similar to the combined effects of pyrazinoate and probenecid in the chimpanzee (14,15), but different from the 7 subjects of Figure 2, in whom there was a small but significant uricosuric response to probenecid following pyrazinamide.

Recent evidence suggests that urate and PAH are secreted via at least two different transport mechanisms in both the chimpanzee (14) and man (16). Thus the fact that pyrazinamide does not suppress the inhibitory effect of probenecid on PAH secretion may be irrelevant to the possibility that it may counteract the inhibitory action of probenecid on urate reabsorption. Although it seems likely that pyrazinoate itself is secreted via the PAH transport system (4,5), it presently is unknown whether pyrazinoate secretion also occurs via the urate secretory system. In the chimpanzee probenecid, like PAH, markedly reduces the clearance of pyrazinoate, although chlorothiazide and salicylate do not (5). Thus, especially in the case of probenecid, interaction with pyrazinamide or pyrazinoate at a pharmacologic level could have accounted for the results in Figure 2.

Another consideration is the possibility that probenecid itself may inhibit urate secretion. Because of the intense uricosuric potency of the compound, a convincing antiuricosuric action of probenecid at low doses has not been readily demonstrable. Recently Fanelli and coworkers have provided indirect evidence of an inhibitory action of probenecid on urate secretion in the chimpanzee (11). They demonstrated that treatment of the chimpanzee with probenecid prevented the net secretory response to mersalyl that is usually observed in that species. That finding was consistent with the possibility that probenecid could have inhibited the tubular secretion of urate, but also could have been explained as a manifestation of a diminished action of mersalyl on the kidney in the presence of probenecid. At least in some of the experiments, however, the mersalyl-induced increases in sodium and mercury excretion were similar to values in animals not treated with probenecid, a result suggesting that marsalyl exerted its full effect.

More direct evidence for an inhibitory action of probenecid on urate secretion occurred in a patient studied by Simkin (17). That patient had a defect in urate reabsorption manifested by urate clearances much greater than the GFR. The adminis-

tration of probenecid decreased urate clearance and abolished net urate secretion. Thus it would appear that an antisecretory action of probenecid was unmasked without a second pharmacologic agent being present because of an extensive inborn defect in urate reabsorption. If the doses of probenecid utilized in Figure 2 (approximately 10 mg/kg) are sufficient to inhibit urate secretion in man, the diminished uricosuric response to probenecid after pyrazinamide, as compared to the studies without pyrazinamide, must have occurred on the basis of pharmacologic interaction. Urate secretion then would have been inhibited during both studies, although possibly more completely during the second.

In summary, studies of renal urate handling employing several pharmacologic agents may be fraught with interpretative hazards because drug-drug interaction may occur. If such studies are performed it would seem desirable to measure the characteristics of renal handling of each pharmacologic agent in the presence of the others. Although there are drawbacks in employing pharmacologic agents to examine renal urate handling, such studies can continue to provide useful information. The capability to suppress selectively the tubular secretion of urate can provide evidence for the relative importance of tubular secretion in maintaining renal urate homeostasis under a wide variety of clinical and physiologic conditions. Thus, although large transtubular flux rates for urate make quantitative estimations of bidirectional transport parameters impossible at this time, studies utilizing pharmacologic agents—especially pyrazinamide—have played a crucial role in achieving the present state of knowledge.

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From the collection of Gerald Rodnan, MD

Extract (colored impression) from *Sketches of Wit and Humour* by H. Heath (fl. 1824–42). Published by S. Gans, London.

"My dear Friend do'nt drink that filty stuff, its yr greatest enemy!"
"But you know we are commanded to love our enemies so here goes!"

Note the grog-blossom nose on the drunkard, whose flannel-wrapped leg rests on a gout stool. "Patience and flannel" were recommended for fits of the gout until well into the nineteenth century.

> "In the happy moment of mirth and conviviality, and the mad career of dissipation, an epicure, or a voluptuary, little dreams of the gout; which hangs over his head, like the sword of Damocles, and threatens his destruction.
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> Amid the joys of wine, and the shouts of the Bacchanals, the still voice of reason is not heard; the sober dictates of discretion are disregarded; and the friendly warnings of the physician are either totally forgotten, or treated with ridicule and contempt . . .
>
> When Prometheus animated his image of clay with fire stolen from heaven, he did not understand the process of distillation; otherwise he would have known, that the posterity of man whom he created, would pay dearly for the theft . . .
>
> . . . for it is an unquestionable truth, that a man who indulges himself in the liberal use of alcohol, under any form, has not only the vulture perpetually gnawing his liver, but is also, in general, tortured with the gout."
>
> —John Ring, *A Treatise on the Gout*, London, 1811