dose is multiplied to remove the variation due to weight. The correction factor, therefore, is 1/a weight^b. There are numerous instances in which dose of drug is proportional to a power of body weight(2,3,9-11). If the value of (b) is unity, then a direct proportionality exists and the customary mg/kg correction is proper(12,13). If (b) is zero, then the correction factor becomes unity and dose is independent of body weight. This is illustrated by the data of ANTU in albino rats for which it can be shown that $Y = 0.98 \text{ weight}^{0.03 \pm 0.06}$.

Summary. The toxicity of alpha-naphthyl thiourea for both wild pigmented and laboratory albino rats, when expressed as a dose per animal, appears to be constant over a wide age and weight range. The use of the customary mg/kg correction for body weight introduces marked systemic variation. The requirements for a proper correction factor of dose for weight of animal are considered and it is suggested that this factor should minimize variation in effective dose between groups of animals of different weights and make corrected dose independent of body weight.

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Effect of Phenylbutazone (Butazolidin) on Renal Excretion of P-Aminohippurate and Thiosulfate in the Dog.* (20506)

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This study of the effect of phenylbutazone‡ on the renal tubular transport of p-aminohippurate (PAH) and thiosulfate was prompted by a report that the drug produced a striking diminution in the serum uric acid of patients with gout(1). It seemed possible, therefore, that the drug might be a uricosuric agent. If so, it would be of interest to determine whether it resembles p-(di-n-propylsulfamyl)-benzoic acid (Benemid), which blocks PAH but not thiosulfate transport, or 4'Carboxyphenylmethanesulfonanilide (Caronamide) which blocks both PAH and thiosulfate(2). Subsequent reports as to the uricosuric activity of phenylbutazone are conflicting. One group of investigators states that there is "no marked increase in urinary excretion of urates"(3) while another believes that the drug "usually increases urinary excretion of urates"(4). Phenylbutazone has also been said to inhibit

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TABLE I. Effect of Butazone and Sodium Acetate on Tm PAH and T thio.

Exp.	Sex	Drug*	Clearance period	C_{Cr}	C_{thio}/C_{Cr}	T_{thio}† (mg/min.)	C_{PAH}/C_{Cr}‡	Tm PAH (mg/min.)
A	♂	None	1, 2	26	1.17	1.6	1.42	7.0
		Butazone	3	11	1.28	1.2	.98	.5
		"	4	18	1.38	2.7	1.09	2.2
B	♀	None	1, 2	46			1.45	5.8
		Butazone	3, 4	42			1.07	1.8
		Butazone & acetate	5, 6	43			1.18	5.9

* Prime: 50 mg/kg. Sustain: 50 mg/kg/hr.

† T_{thio} (tubular transport) is used rather than Tm because tubular resorption may occur concomitantly with secretion. Therefore, T_{thio} is not necessarily a maximum.

‡ PAH considered 92% filterable.

the excretion of p-aminosalicylic acid(5).

It has previously been shown that a rapid infusion of isotonic acetate increases the renal secretion of PAH(6) and is capable of reversing the inhibition of tubular transport caused by Caronamide(7). It was found in this study that phenylbutazone did block PAH transport; therefore, the effect of Na acetate on this inhibition was investigated.

Methods. All experiments were performed on anaesthetized dogs, 5 males and 3 females. Male dogs were chosen because of their ability to secrete much larger amounts of thiosulfate than normal females. The dogs were fasted for 18 hours. During this period, water was allowed as desired. After the intravenous injection of an initial priming dose of creatinine, thiosulfate and PAH, these substances were continuously infused at a rate appropriate for the maintenance of the desired serum levels. The level was around 20-30 mg/100 cc in the case of thiosulfate and creatinine and 50 mg/100 cc for PAH. Clearance periods of 20 minutes were used after an initial equilibration time of 30 minutes. Urine was collected by means of an indwelling catheter and the bladder flushed with 15 cc of distilled water at the end of each period. Blood samples were drawn from the jugular vein at the midpoint of each clearance period without correction for kidney to bladder delay. After 2 control periods, a priming dose of Phenylbutazone (50 mg kg) was given intravenously and subsequently the drug was incorporated into the sustaining infusion (50 mg/kg/hr). Na acetate was given as an isotonic solution at the rate of 10 cc/min. Creatinine was determined by the method of Folin and Wu(8); PAH by the method of Smith *et al.*(9); and thiosulfate by the method of Gilman, Philips, and Koelle (10) with the modification of Elliott and Scott (11) for analysis in the presence of PAH.

Results and discussion. The initial priming dose of phenylbutazone produced a clear-cut fall in the ratio C_{PAH}/C_{Cr} in all the dogs studied. In 6 experiments the clearance ratios of the control period as compared to that of the experimental period fell as follows: 1) 1.52 to 1.06 2) 1.28 to 0.88 3) 1.49 to 0.94 4) 1.42 to 0.98 5) 1.45 to 1.07 and 6) 1.86 to 1.13. Occasionally there was a small rise in TmPAH (averaging less than 2 mg/min) during the second period after the priming solution was given. This occurred despite the sustaining dose of drug. A representative experiment is shown in Table I, Exp. A. The data indicate that phenylbutazone inhibits the tubular transport of PAH.

Secretion of thiosulfate in excess of filtration and concomitant resorption continued unchanged or slightly increased. Thus, in dogs, phenylbutazone blocks the secretion of the organic acid, PAH, but not that of the inorganic anion, thiosulfate. In this, it resembles Benemid as well as 2,4 dinitrophenol and dehydroacetate(2). Unlike Caronamide, the drug does not affect thiosulfate secretion.

In 2 experiments a rapid infusion (10 cc/min) of approximately physiological concentrations of $NaHCO_3$ and NaCl was given throughout the control and first 2 phenylbutazone periods. Following this, isotonic Na acetate was substituted for 2 periods. In one dog, the initial TmPAH averaged 15.5 mg/min and dropped to 6.4 mg/min after phenylbutazone. During the simultaneous infusion

of acetate (4 mEq/kg/hr), the TmPAH rose from 6.4 mg/min to 12.3 mg/min. In another animal, the control Tm was 5.8 mg/min. It dropped to 1.8 mg/min after phenylbutazone was given and rose to 5.9 mg/min after the administration of Na acetate (8.9 mEq/kg/hr). (See Table I, Exp. B). Thus, it would seem that the rapid intravenous infusion of Na acetate will partially or wholly reverse phenylbutazone inhibition of TmPAH as measured by clearance studies. It has previously been shown to reverse Caronamide inhibition.

In the first experiment, intravenous phenylbutazone (200 mg/kg) caused marked hyperventilation, hemolysis, coma and terminal bloody diarrhea. A subsequent reduction in dose to 50 mg/kg in the priming solution and 50 mg/kg/hr in the sustaining solution was well tolerated in 2 experiments. In 2 other dogs, this dose caused hyperventilation followed by coma. Autopsy of 2 dogs was unrevealing as to the cause of death. The remaining animals were sacrificed immediately after the experiment.

Summary. Phenylbutazone blocks PAH transport but does not affect thiosulfate excretion. The inhibition of TmPAH by phenylbutazone is reversible by the simultaneous infusion of isotonic Na acetate.

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Mosaic Photography in the Demonstration of Human Synapses (*Boutons terminaux*).* (20507)

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The objective demonstration of human cerebral synapses has long been thought to be of considerable interest and importance. However, at the high magnifications required (approximately 2000 x) it has been difficult, in one photomicrograph, to show a convincing number of synapses. As a result, drawings have usually been resorted to, and photographic proofs of the size and distribution of the *Boutons terminaux* have been wanting.

The branching nature of nerve cells has also served to make difficult the picturing, in any single photograph, of the synapses on the dendrites. In many instances the number and location of synapses on the dendrites may be more important that on the "cell body," narrowly interpreted.

The thickness of frozen section of nervous tissue for silver staining (approximately 15 μ) allows one to follow the dendrites great distances, at times. Thinner sections are not very practical since metallic stains make them brittle and since nerve cell processes

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