and pregnant guinea pig uterus were stimulated by both the amine and epinephrine, while the nonpregnant cat uterus was stimulated by the amine but relaxed by epinephrine, thus again resembling tyramine and ephedrine. Bronchi constricted from histamine and pilocarpine were not effectively relaxed by phenylethanolamine or ephedrine, while epinephrine caused relaxation; additional tests are necessary. Administered subcutaneously and intravenously, phenylethanolamine was less effective than epinephrine, about as effective as tyramine, but more effective than ephedrine in preventing the experimental edema of paraphenylenediamine and equally as effective as epinephrine in dionine chemosis, but ineffective (also tyramine and ephedrine) against mustard oil chemosis and dermatitis. Local application of 1% concentrations in the nose of human subjects shrank congested nasal mucosae and turbinates promptly without objectionable irritation, the effects persisting 2 to 3 hours, thus resembling ephedrine.

Provisionally, the pharmacological actions of phenylethanolamine resemble those of tyramine and ephedrine more than epinephrine. Further tests are being made experimentally and clinically.

[1] Alles, G. A., *J. Pharm. Exp. Therap.*, 1927, xxxii, 121.

[2] Chen, K. K., *J. Pharm. Exp. Therap.*, 1926, xxvii, 61.

[3] Tainter, M. L., and Chang, D. K., *J. Pharm. Exp. Therap.*, 1927, xxx, 193.

[4] De Eds, F., and Butt, E. M., PROC. SOC. EXP. BIOL. AND MED., 1927, xxiv, 800.

3812

Excretion, Distribution and Fate of Bismuth Under Clinical Conditions.

H. G. MEHRTENS, P. J. HANZLIK AND D. C. MARSHALL.

From the Neurological Division of the Department of Medicine and the Department of Pharmacology, Stanford University School of Medicine.

The object of this study is to determine the limitations and usefulness, and, if possible, to establish better control, of bismuth therapy in syphilis by quantitative studies of the excretion of bismuth in urine and feces, its distribution in body fluids and organs, influence of various conditions on mobilization of stored bismuth, relationship of bismuth concentration and dosage to therapeutic efficiency, toxicity, etc., in human subjects, both convalescent and syphilitic. The plan includes also a study of various agents and

conditions in experimental syphilis. Although the program of work is not yet completed, we desire to record certain results that have been obtained to date with 3 preparations, namely, metallic bismuth in suspension, potassium bismuth tartrate and bismuth salicylate used in single and multiple therapeutic doses by intramuscular injection.

Briefly summarized, the main results are as follows: With all preparations, urinary excretion, using Leonard's method[1] slightly modified and adapted to our material, is prompt, occurring on the second day after administration; the peak of excretion is reached at the end of about 12 days and then the excretion falls steadily but continues over long periods (weeks or months). The rapidity and quantity of bismuth excretion in urine appeared to be greatest with the tartrate (55% end of 53 days after 0.11 gm. Bi), probably less with the salicylate (uncompleted results) and least with the metal (24% end of 32 days after 1.2 gm. Bi.), while the order for duration is reversed. Increasing doses increase the excretion. The feces contain very little or only traces of bismuth, the incomplete excretion, therefore, being presumably due to storage in the body. This stored bismuth may be mobilized by certain conditions, for sudden marked increases in excretion have been demonstrated during attacks of gastric crises and of fever. External application of heat ("baking") to the whole body caused a moderate increase in urinary excretion. It would seem that the stored bismuth could be drawn upon for medication of the patient without the need of further administrations of bismuth. Other pyrogenic and various agents are being tried. Provisionally, bismuth acts as a diuretic without demonstrable injury to the kidney as indicated by the absence of albumin, casts, etc., but these features require further testing under controlled conditions.

Except for 12 cases of "bismuth-line" and 4 cases of mild stomatitis, no evidence of toxicity from metallic bismuth have been encountered among 100 individuals receiving a total of 1,500 injections, the highest number of injections in one individual being 131, equal to 26.2 gms. of bismuth in 18 months, the next highest being 119 injections (23.8 gm. Bi.) during the same period; nor after a total of 33 doses of the tartrate and 82 doses of the metal together (total 15 gm. Bi.) in 27 months and after 4 doses (0.3 gm.) of the salicylate. Hence, even with the supposed, considerable stores of bismuth in the body after these preparations, the danger of toxicity seems to be practically negligible.

Our results on distribution are too few to warrant a statement,

but we have detected bismuth in cerebrospinal fluid and blood 10 months after administration of bismuth and expect to find it in all organs, but especially in the usual organs for storage of heavy metals. We are indebted to Dr. Frederick Proescher of the Agnew State Hospital for assistance in securing a portion of the materials used in the study. The work is being continued.

[1] Leonard, *J. Pharm. Exp. Therap.*, 1926, xxviii, 81.

3813

Comparative Electrocardiography of Cardiac Drugs With Reference to Emesis from, and Distribution of, Digitalis.

W. DOCK, A. B. STOCKTON, D. A. WOOD AND P. J. HANZLIK.

From the Departments of Medicine and of Pharmacology, Stanford University School of Medicine.

Electrocardiographic studies of pigeons were made with the idea of comparing the emetic and cardiac actions of digitalis, since emesis is a prominent action of the drug in pigeons, and the emetic assay method appears to predict the therapeutic dosage for slowing of the heart in man. Using tinctures of the drug injected intravenously, one-fourth the minimum emetic dose of digitalis caused a 10% slowing of the rate, and one-half the dose a 20% decrease in auricular rate and an A-V block in some pigeons. A single minimum emetic dose, causing emesis in 10 minutes, produced heart block or marked slowing in 1 to 5 minutes and 3 times the emetic dose produced all the effects in 10 to 15 seconds. The cardiac slowing was always preceded by a short period of acceleration which was due only partly to the injection fluid. On the other hand, veratrum and aconite, which also affect the heart through the vagus mechanism but do not cause emesis in pigeons, caused an immediate but brief slowing followed by tachycardia, either auricular or ventricular in origin, and in the case of veratrum there was, in addition, a curious waxing and waning of electrical complexes in cycles, 20 to 30 beats long. That the cardiac changes after digitalis and the slowing of veratrum were of vagal origin was shown by the fact that the effects were prevented and abolished by atropine and vagotomy. The effects were not altered by previous injection of ergotoxine, which by itself slowed the pulse through paralysis of the accelerator nerves, although epinephrine, in large doses, still caused a marked and pro-