essential. Vitamin B has been shown to restore appetite in such animals.[1] The effect of the products on the flow of pancreatic juice and bile was noted in anesthetized dogs in which the pylorus was ligated to prevent secretion due to discharge of acid chyme from the stomach, and the gall bladder bile was prevented from discharging by ligation of the cystic duct. Normal dogs and dogs fed a diet lacking vitamin B were used. It is planned to experiment upon polyneuritic dogs as well. Fresh secretin solutions prepared by the usual method were injected as a control.

Except in the case of tomato juice, all of these products gave negative results. The secretin solutions, however, in comparatively small amounts always produced a characteristic and vigorous flow.

72 (1654)

Theoretical considerations bearing upon the chemotherapy of arsenical compounds.

By GEORGE W. RAIZISS, JAY F. SCHAMBERG and JOHN A. KOLMER.

[*From the Dermatological Research Laboratories, Philadelphia, Pa.*]

Chemotherapy is essentially the study of the toxic and therapeutic properties of chemical compounds. Its main purpose is to establish the maximum tolerated and minimum curative doses. The numerical value representing the ratio of these two doses is the chemotherapeutic index. Chemical compounds possessing the highest chemotherapeutic indices in experimental infection are usually the best adapted for the treatment of disease in man.

Ehrlich, Bertheim and Hata[2] were the first to engage in systematic chemotherapeutic work, in the course of which numerous new chemical bodies were synthesized. They were all derivatives of one certain compound called atoxyl, selected because it was the only organic arsenical known at that time which possessed trypanocidal properties, although to a very small degree. The changes in the chemical constitution of atoxyl led finally to the

[1] Karr: *Jour. Biol. Chem.*, 1920, xliv, 255.

[2] Ehrlich, P., and Hata, S. "Die Experimentelle Chemetherapie der Spirillesen."

elaboration of a derivative many times more powerful in the cure of protozoön infection. At present, a considerable amount of work is being performed along the lines established by Ehrlich and numerous organic arsenicals have been prepared, still, the synthesis of new chemical compounds merely for the purpose of testing their toxic and therapeutic properties and thereby finding the best drug for the treatment of disease will not advance the science of chemotherapy beyond mere empiricism.

Is it impossible to find a relationship between certain atomic groupings and toxicity or curative effect? Once the influence of these various groups upon the parasite or the animal body is appraised the synthesis of new compounds will assume a more rational course. Some very valuable findings have already been made in this direction by Ehrlich who discovered the remarkable trypanocidal and spirillocidal effects of the arseno group (As = As) when attached to the nuclear carbon atom.

Our attention has been attracted to the influence of the amino group upon toxicity and therapeutic effect when present in organic arseno compounds. We confined our study to the derivatives of 3, 3′ diamino -4, 4′ dihydroxy arsenobenzene, the dihydrochloride of which is the important remedy in syphilis known as salvarsan or arsphenamine. When this substance is converted into other compounds containing various substituents in the amino group, the toxicity and curative properties are influenced to such an extent as to lead to the assumption that the amino group is as vitally essential as the arseno group. As an illustration, let us consider a condensation product of arsphenamine with sodium formaldehyde sulphoxylate known as neoarsphenamine. As described in the patent papers and also in the work of Raiziss and Falkov,[1] it is evident that substitution took place completely in one amino group and partially in the second. The work of Schamberg, Kolmer and Raiziss[2] and also Roth[3] show that the average maximum tolerated dose of this compound is 0.254 milligrams per kilo of body weight, whereas that

[1] *Journal Biol. Chem.*, March, 1921.

[2] Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W., *Amer. Jour. of Med. Sci.*, clx, No. 188.

[3] Roth, G. B., *Archiv. Dermat. and Syph.*, II, No. 3, 301.

of arsphenamine is 100 milligrams. Considering the arsenic contents of these two substances, 50 milligrams of arsenic in the form of neoarsphenamine is tolerated as compared to 30 milligrams in the form of arsphenamine. Here it is evident that a change in the amino group resulted in the reduction of the toxicity amounting to about 40 per cent. The minimum therapeutic dose, however, was increased from 23 milligrams to 40 milligrams or in terms of arsenic from 6.9 milligrams to 8.0 milligram, *i.e.*, the curative power decreased 16 per cent. In the 3, 5:3′, 5′—tetraamino 4, 4′—dihydroxyarsenobenzene[1] we have a derivative which contains two more amino groups than arsphenamine. The maximum tolerated dose established by us is equal to seventy milligrams per kilo or in terms of arsenic 18.2 milligrams, an increase in toxicity of 39 per cent. The therapeutic effect remains as with arsphenamine. We also prepared 4, 4′—dihydroxyarsenobenzene —3, 3′—diaminoacetic acid, 4, 4′—dihydroxyarsenobenzene—3, 3′—alpha diaminopropionic acid, 4, 4′—dihydroxyarsenobenzene—3, 3′ alpha diaminobutyric acid, 4, 4′—dihydroxyarsenobenzene—3, 3′ alpha diaminovaleric acid. All of the above compounds are derivatives of arsphenamine in which both amino groups contain fatty acid substituents. In each case we observed a considerable reduction in the toxicity as well as therapeutic effect. We may conclude, therefore, that the toxicity as well as the curative power of organic arseno compounds is dependent to a considerable extent upon the fact as to whether the amino groups are free or substituted.

73 (1655)

Refractometric studies with the sera of syphilitic patients under arsphenamin and neo-arsphenamin treatment.

By KEIICHI TOKUDA.

[*From the Dermatological Research Laboratories and the Wistar Institute of Anatomy and Biology, Philadelphia, Pa.*]

Refractometric studies were made by the writer upon thirty-two cases of *untreated* syphilis and the following observations were made:

[1] Raiziss, G. W., and Gavron, J. L., *Jour. Am. Chem. Soc.*