orally by mixing with powdered sugar and allowing the rats to eat it voluntarily. In almost all cases the complete amount was consumed within two days. The rats which received fluoride were supplied with potassium fluoride (KF) in the drinking water. A 24-hour pretreatment was given to all rats during which they were starved, and the experimental group supplied with the fluoride-containing drinking water. The arsenic-sugar mixture was then placed in individual cages and the rats were observed for the succeeding 10 days. No supplementary food was given until all rats had consumed their sugar supply. At the end of the fifth day the experimental rats were returned to ordinary tap water.

Nineteen rats were fed 30 mg As_2O_3, and of these only 3, or 16 per cent., were alive on the fifth day of the experiment. These same 3 rats lived through the remainder of the 10-day period.

Sixteen rats were fed 30 mg As_2O_3 and were supplied with drinking water containing 15 mg KF per 30 cc of water. All these animals were alive on the fifth day, and 14, or 88 per cent., were alive at the termination of the experiment.

Twelve rats were fed 30 mg As_2O_3 and were supplied with drinking water containing 30 mg KF per 30 cc of water. Of this group 2 rats died during the first 5 days, while the remaining 10, or 83 per cent., survived the experiment.

These results have been analyzed statistically, using the appropriate chi-square test at the .01 level of significance. The results of the two fluoride-treated groups do not differ significantly, but each of them is significantly different from the control group.

The mechanism of action of arsenic on protoplasm as suggested by Voegtlin[7] consists of an interference with normal functioning of glutathione in the oxidation-reduction processes in living tissues. The injection of a toxic dose of arsenic leads to cellular asphyxia, possibly due to a chemical reaction between reduced glutathione and arsenic to form a compound incapable of normal respiratory activity. Rosenthal and Voegtlin[1] showed that glutathione administration can protect rats against a lethal dose of arsenic, probably substituting for the amount tied up by arsenic. They found that feeding of fairly large amounts of glutamic acid and cystin, precursors of glutathione, will give considerable protection against a subsequent minimal lethal dose of arsenic.

It is suggested by Hogan and Eagle[8] that the systemic toxicity of arsenicals is primarily determined by the varying degree to which they are bound by, and thus block, essential functional groups in vital organs. These assertions are in accord with Ehrlich's thesis that chemotherapeutic agents in general can exert their therapeutic effect only if bound by the parasite, and that their toxic action is due to a similar combination with vital tissues of the host.

The chemical compounds which have been described as detoxicants for arsenicals presumably perform their function by a variety of methods. Organic acids, such as ascorbic and lactic acid, appear to exert their effect as detoxicants of neoarsphenamine by preventing its *in vivo* oxidation to highly toxic inorganic oxides.[4] It has been suggested that because p-aminobenzoic acid bears a similar structural relationship to arsanilic acid as it does to sulfanilamide an explanation of the mechanism of detoxication may be found which parallels the enzyme blockade theory.

The presence of fluoride in the tissues of an arsenic-fed animal must in some way prevent the binding of an essential substrate, such as the physiologically essential sulfhydryl groups. There may be formation of a compound of arsenic and fluorine which has less affinity for body tissues, or is less readily absorbed, so that the arsenic is bound and excreted before it can attack a vital system. The concept of reduced absorption is strengthened by the conclusions of Smith and Shaner,[9] who prevented death of guinea pigs fed a double lethal dose of fluoride by buffering with calcium carbonate.

JOHN C. FINERTY
UNIVERSITY OF MICHIGAN
JAMES D. GRACE
ANN ARBOR, MICH.

DEPRESSION OF LYMPHOCYTE CONTENT OF THORACIC DUCT LYMPH BY ADRENOCORTICOTROPHIC HORMONE

EXPERIMENTAL evidence available at the present time has demonstrated a reciprocal relationship between the adrenal cortical functional state and the weight of lymph and thymic tissue present in the body. Thus adrenalectomy has been shown to result in increase in weight of thymus and lymph nodes as compared with the normal control rat.[2] On the other hand, stimulation of the adrenal cortex by administration of adrenocorticotrophic hormone (ACTH) or the administration of adrenal cortical extracts has produced a rapid decrease in the weight of thymus and lymph nodes in the mouse and rat.[3, 4]

[7] C. Voegtlin, *Physiol. Rev.*, 5: 63, 1925.
[8] R. B. Hogan and H. Eagle, *Jour. Pharmacol. and Exp. Therap.*, 80: 93, 1944.
[9] R. R. Smith and E. O. Shaner, *Jour. Am. Dent. Asn.*, 31: 1483, 1944.

[1] Aided by grants from the Board of Research of the University of California and the Rockefeller Foundation of New York City.
[2] W. O. Reinhardt and R. O. Holmes, *Proc. Soc. Exp. Biol. and Med.*, 45: 267, 1940.
[3] T. F. Dougherty and A. White, *Proc. Soc. Exp. Biol. and Med.*, 53: 132, 1943.
[4] M. E. Simpson, Choh Hao Li, W. O. Reinhardt and Herbert M. Evans, *Proc. Soc. Exp. Biol. and Med.*, 54: 135, 1943.

It might be expected that such pronounced changes in the wide-spread lymphatic system would result in definite and marked changes in the blood leucocyte picture, particularly as regards the lymphocytic elements. Such a change has been demonstrated experimentally in the mouse, rat and dog.[5, 6] Injection of ACTH or adrenal cortical extracts into these forms has resulted in the production of an absolute lymphopenia.

The mechanism of production of this lymphopenia has been of sufficient interest to stimulate the following experimental approach. Single doses of pure ACTH (1–6 mg dose levels) were injected (by subcutaneous and intraperitoneal routes) into normal and adrenalectomized adult female rats of the Long-Evans strain. The hormone (in amounts of 6 mg per cc) was dissolved in a phosphate buffer solution of pH 7.4. To measure the flow of thoracic duct lymphocytes into the blood stream, the common lymph sac, into which empties the thoracic duct in the rat, was cannulated[7] intermittently, before and after injection of the various hormone preparations. The animals were anesthetized by intraperitoneal injection of a 1 per cent. solution of sodium pentobarbital. Leucocyte counts were carried out on thoracic duct lymph specimens at intervals of 30 to 60 minutes for a number of hours preceding and following administration of ACTH.[8]

The results of the experiments obtained to date justify the following conclusions. Administration of ACTH by either the subcutaneous or intraperitoneal route produced a rapid decrease in the number of lymphocytes in the thoracic duct lymph. This reduction occurred within 15 to 30 minutes, was usually more than a 50 per cent. reduction in the pre-existing cell count, and persisted in most rats for the duration of the experiment (4 to 10 hours). Administration of ACTH to the adrenalectomized animal did not produce a comparable effect. Subcutaneous injection of pure growth[9] and lactogenic[10] in similar dose levels failed to imitate the action of ACTH. The buffer solution and the anesthetic agent employed produced no demonstrable effect on the lymphocyte level of the thoracic duct lymph. There were no changes in the rate of flow of the lymph which could account for changes in the lymphocyte level in the thoracic duct.

It is apparent from the results of these experiments that stimulation of the adrenal cortex by the administration of ACTH produces a rapid and persisting fall in the number of lymphocytes entering the blood stream, probably as the result of decreased outpouring of these cells from the thymus and lymph nodes. This change can, it is felt, account in a large measure for the lymphopenia of absolute proportions in the blood stream of the rat following injection of ACTH. Further experiments must clarify the fate of the lymphocyte circulating in the blood stream. A direct experiment to demonstrate the effect of the adrenal cortex on lymphocyte production would consist in the collection of lymph from the isolated lymph node with intact artery and vein in the living animal before and after administration of ACTH or adrenal cortical extract. It will be of further intense interest to determine which of the substances present in the adrenal cortex are responsible for this rather dramatic effect on the lymphocyte level of thoracic duct lymph. The technique of measuring the fall in lymphocytes in thoracic duct lymph may further prove to be a sensitive indicator for the assay of ACTH or adrenal cortical substances.

It may be generalized that the lymphocyte level of the circulating blood is under direct adrenal cortical control. Such a generalization should divert attention to the role of the anterior pituitary and adrenal cortex in various disease states accompanied by hitherto inexplicable relative and absolute lymphopenias or lymphocytosis. To the knowledge of the writers, this is the first direct experimental demonstration using pure anterior pituitary hormones of the control of entry of a white blood cell into the circulating blood stream.

This is a preliminary communication.

WILLIAM O. REINHARDT
CHOH HAO LI
DIVISION OF ANATOMY AND INSTITUTE OF EXPERIMENTAL BIOLOGY,
UNIVERSITY OF CALIFORNIA, BERKELEY

[5] T. F. Dougherty and A. White, SCIENCE, 98: 367, 1943.
[6] W. O. Reinhardt, H. Aron and Choh Hao Li, *Proc. Soc. Exp. Biol. and Med.*, 57: 19, 1944.
[7] W. O. Reinhardt, "Rate of Flow and Cell Count of Rat Thoracic Duct Lymph." To be published.
[8] Choh Hao Li, M. E. Simpson and H. M. Evans, SCIENCE, 96: 450, 1942.
[9] Choh Hao Li and H. M. Evans, SCIENCE, 99: 183, 1944.
[10] Choh Hao Li, M. E. Simpson and H. M. Evans, *Jour. Biol. Chem.*, 146: 627, 1942.

SUSCEPTIBILITY OF HAMSTERS TO CLOSTRIDIUM CHAUVEI

IN experimental work with *Cl. chauvei* where clinical infection is necessary, guinea pigs are generally employed. In comparison to cattle where the basic infection occurs naturally, an immensely larger dose of the infecting agent, on a basis of body weight, is necessary. Berg[1] notes that guinea pigs are comparatively insusceptible to blackleg and quotes Nitta's statement that it required as much culture to kill guinea pigs as calves. He also states that Graub and Zschokke found it took twice as much to kill guinea pigs as calves and sheep.

Considerable work with one strain of *Cl. chauvei* disclosed that 0.3 cc of a 48-hour Hibler culture injected

[1] W. N. Berg., *Jour. Am. Vet. Med. Asn.*, 607–622, 1922.