whether peritoneal fluid response can be equated with febrile response.

Summary. Injection of certain bacterial polysaccharides into the peritoneal cavity of rats results in a local neutrophilia which can easily be determined and quantitated. Preliminary findings suggest the possibility of using this response to detect the presence of certain bacterial derivatives in solutions.

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Thyroiditis Resulting from Administration of Excess Iodine to Hamsters with Hyperplastic Goiters.* (25273)

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When physiological amounts of iodine are administered to hamsters which have hyperplastic goiters produced by an iodine-deficient diet(1), colloid rapidly accumulates in the follicles to bring about the morphological picture of colloid goiter. The suitability of the hamster for studies on the thyroid prompted us to investigate the effects of large amounts of iodine in order to reproduce, if possible, the state of *Jodbasedow.* It will be recalled that T. Kocher(2) introduced this term in 1910 to refer to the syndrome of clinical hyperthyroidism occurring in persons having endemic goiters to whom iodine had been administered. The only clear-cut example of this phenomenon in the experimental animal was reported by Webster and Chesney(3) 30 years ago when they administered large amounts of iodine to rabbits with hyperplastic goiters produced by a cabbage diet. Such animals lost weight, developed increased metabolic rates, and died; at autopsy their thyroid glands exhibited a patchy reaccumulation of colloid, but not true colloid goiter. When hamsters with hyperplastic iodine-deficient goiters were given large amounts of iodine, as will be reported herein, an inflammatory reaction developed in the gland, giving rise in a short time to the picture of sub-acute thyroiditis. It is the purpose of this communication to describe the evolution of this process in hyperplastic glands produced by iodine-deficiency or goitrogens(4).

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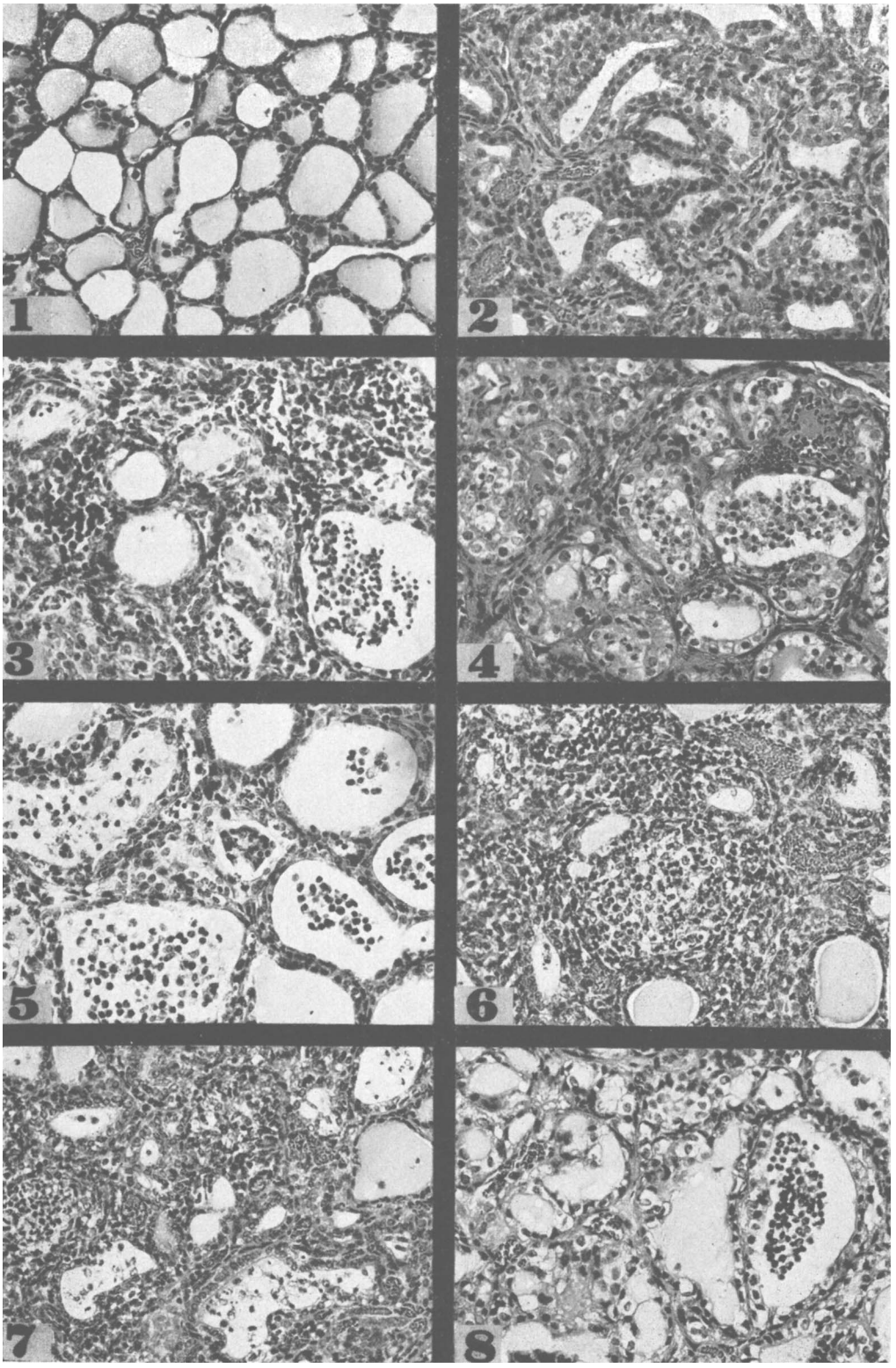
Materials and methods. A total of 28 hamsters weighing approximately 100 g were observed on 3 different diets: 1) an iodine-deficient ration composed of whole ground corn, 76; wheat gluten, 20; calcium carbonate, 2; and sodium chloride, 2; and 500 mg of a complete vitamin mixture per kilo. 2) thiouracil and 3) potassium thiocyanate, added to batches of the basal diet at levels of .3% and .5%, respectively. Sixteen animals were maintained on the iodine-deficient diet for periods up to 30 weeks. The thiouracil-containing diet was administered to 6 animals for 3-6 weeks, while potassium thiocyanate was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fed to 6 hamsters for a period of 5 weeks. When hyperplasia was well-established, excess iodine was administered as potassium iodide, 10 mg intraperitoneally per day, for periods up to 2 weeks. Six normal animals receiving this amount of iodide were also studied. Animals were killed serially during the period of iodine administration. Tissues were prepared for histological examination in routine manner.

Observations. Before describing alterations produced by excess iodine it will be advantageous to review the microscopic appearance of normal and hyperplastic glands, together with changes following administration of physiological amounts of iodine(1) or cessation of administration of goitrogens(4). The normal thyroid of the hamster is composed of colloid-filled follicles, averaging 45 μ in diameter and lined by flattened or low cuboidal cells. Adipose tissue is found within the gland; blood vessels are not prominent. No cellular infiltration is seen save an occasional mast cell. After hyperplasia, produced by either iodine deficiency(1) or a goitrogen(4), has developed, colloid disappears; blood vessels are more prominent and epithelial cells increase in size and number. In our experience no interstitial infiltration is seen under such circumstances. Following the introduction of physiological amounts of iodine or removal of the goitrogen from the diet colloid begins to reaccumulate in the follicle. The epithelial cells become more flattened; the follicle increases in size. Vascularity is decreased. No interstitial inflammatory reaction is found; an occasional mononuclear cell filled with fat may be present in the lumen of some follicles.

After administration of large amounts of iodine to hamsters which have been on an iodine-deficient diet, the earliest change appears after 24 hours. This consists of the presence of polymorphonuclear leukocytes in the lumens of the follicles. At the beginning, only an occasional structure is involved; however, after several days many contain cellular exudate. Such follicles are usually devoid of colloid. Cells which doubtless represent desquamated thyroid epithelial structures are found among the leukocytes. At this early stage, while the blood vessels are still prominent as a result of the preceding hyperplasia, leukocytes are found adherent to capillary walls as though they were making their way through these structures. Relatively little interstitial infiltration is present at this time, however. Those follicles which are free of leukocytes contain a pale-staining eosinophilic material and have increased somewhat in diameter. It is difficult to find necrotic epithelial cells, though an occasional cell with a pyknotic nucleus is made out. At the end of a week the cellular infiltration within the follicles is more extensive. Such collections are made up of polymorphonuclears and round cells. A definite interstitial infiltration is found between the follicles at this time; the cells composing this exudate are primarily mononuclear, *i.e.*, lymphocytes together with an occasional plasma cell. By now the blood vessels are less prominent in a fashion similar to the decrease in vascularity seen after physiological amounts of iodine. The follicles have increased in size, yet not nearly to the diameter which would have been expected as a result of the administration of physiological amounts of the element. Some are even devoid of colloid at this time. At the end of 2 weeks the acute inflammatory reaction within the follicles has disappeared; a more chronic though less intense form in which mononuclear cells predominate is found. A moderate inter-

All sections stained with H. and E. All $\times 200$.

FIG. 1. Normal; clear areas are fat.

FIG. 2. Hyperplasia after 28 wk on iodine-deficient diet; note increase in number and size of cells and granular material in lumens of follicles. This is control for animals shown in Fig. 3-7.

FIG. 3. Two days after excess iodine administration to animal with hyperplasia shown in Fig. 2; note leukocytes within follicles, absence of colloid and interstitial infiltration.

FIG. 4. Four days after excess iodine administration.

FIG. 5. Six days after excess iodine administration.

FIG. 6 and 7. Ten days after excess iodine administration.

FIG. 8. Six days after administration of excess iodine to animal which had hyperplasia resulting from potassium thiocyanate administration. Follicles have not accumulated excess colloid; note cells within follicle.

stial inflammatory reaction remains. The change has been followed for 2 weeks at which time the inflammatory reaction is still present.

Hyperplasia can be produced in the hamster by a goitrogen such as thiouracil(4); moreover, the follicles fill up with colloid when the drug is removed from the diet. The effect of large amounts of iodine on hyperplastic glands produced when thiouracil and potassium thiocyanate are fed with the iodine-deficient diet, was therefore studied. When 10 mg doses of potassium iodide are given to animals receiving thiouracil, the cellular infiltration of the follicles and interstitial tissues appeared to be identical with that described in iodine-deficient hamsters. The follicles, moreover, do not contain as much colloid as those from animals which have received physiological amounts of iodine. Since colloid cysts are seen more commonly in thiouracil-treated animals than in those on an iodine-deficient ration before realimentation with iodine, the lack of involution was not as uniform in this group as in the preceding one.

When excessive amounts of iodide are administered to hamsters with hyperplastic glands produced by potassium thiocyanate administration, polymorphonuclear leukocytes soon appear within the lumens of the follicles and in the course of a week cellular infiltration is found in the interstitial tissues as well. The increase in size of the follicles as a result of colloid accumulation is not as great as that seen when physiological amounts of iodine are administered.

Discussion. The original intent of these experiments was to produce a syndrome analogous to *Jodbasedow* by administration of large amounts of iodine to hamsters with hyperplastic thyroid glands which had developed as a result of iodine deficiency. We hoped to repeat Webster and Chesney's observation(3) on the response of rabbits with cabbage goiter to administration of excess iodine. Although no metabolic studies were performed on the animals herein reported, the hamsters did not lose weight or die in the manner of Webster and Chesney's rabbits. The pathogenesis of alteration which has been described in the hamster thyroids, that is, a form of thyroiditis, cannot be explained, though the lesions deserve some comment.

First, these experiments show that the effects produced by physiological amounts of iodine on the hyperplastic gland are different from those resulting from massive doses. We have now studied the thyroid glands of over a 100 hamsters which have developed colloid goiters resulting from the involution of hyperplasia produced by either iodine deficiency(1) or administration of several different goitrogens(4). In each case the follicles become distended with large amounts of colloid. More important, no inflammatory reaction within the follicles has been seen, nor is there evidence of interstitial cellular infiltration. In contrast, when large amounts of iodine are administered, as in these experiments, not nearly as much colloid accumulates in the follicles; the inflammatory reaction which develops has been described above. To our knowledge a lesion such as this has not heretofore been produced in the thyroid gland in an experimental animal by administration of large amounts of iodine. The development of painful swelling of the thyroid gland, called by some "iodine thyroiditis," has been mentioned from time to time in the human and is said to result from excessive iodine administration(5). Histological studies of such glands have not been reported. However, one sometimes sees an intrafollicular cellular infiltration in the thyroid glands of patients with Graves disease to whom iodine has been administered pre-operatively. When large amounts of iodine are given to normal animals, no prominent change in basal metabolic rate has been detected(6), though a decrease in uptake of I^{131} has been reported (7). In our own experience no morphological alterations occur after administration of large amounts of iodine to normal hamsters. Some observations may be cited to indicate that iodine has certain known, as well as doubtless unknown, actions on the activity of the thyroid epithelial cells, particularly when administered in excessive amounts(8). For instance, iodide appears to interfere with the action of TSH on the thyroid gland of hypophysectomized rats, since the hyperplasia produced by thyrotropic hormone in such animals is decreased by large

amounts of potassium iodide. Moreover, iodine decreases the inactivation of TSH by thyroid tissue *in vitro*.

An inflammatory reaction in the thyroid glands of experimental animals has been produced by several technics; the most striking alterations follow radiation or auto-immunization procedures. Treatment of rats with appropriate amounts of I^{131}(9) leads to damage of thyroid epithelial cells and an inflammatory reaction not unlike the changes described above. So, too, the descriptions of auto-immune thyroiditis in several species(10) are certainly reminescent of the alterations we have observed here, so much so that we are currently attempting to produce thyroiditis in hamsters by injection of homologous thyroid tissue with an adjuvant and are examining the sera of animals with iodine thyroiditis for antibody to thyroglobulin. We are unable to explain the pathogenesis of the changes described herein. Certain possibilities such as the deleterious effects of accumulation of large amounts of iodine in a depleted gland, or production of excessive amounts of thyroid-active materials within the gland come to mind. Further study of this problem may help to understand the phenomena of *Jodbasedow*(2) and "iodine thyroiditis"(5) in man.

Summary. Administration of large amounts of iodine to hamsters which have hyperplastic goiters produced by an iodine-deficient diet or by a goitrogen results in a morphologic response which is different from that encountered when iodine is given in physiological amounts. An acute inflammatory reaction and a diminution of the accumulation of colloid are found, neither of which has been observed in animals treated with smaller amounts of iodine.

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Synthesis, Cytopathogenicity, and Modification of Avian Encephalomyelitis Virus (AEV) in Chick Kidney Cell Culture.* (25274)

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Multiplication of AEV in minced whole chicken embryo tissue culture has been reported(1). Owing to the low titer obtained the method is of limited value. This communication reports successful propagation of the virus in monolayer chick kidney cell culture, cytopathogenic changes produced in the cell culture, and modification of virulence of the virus for chicks.

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Materials and methods. Virus. The seed virus was the brain homogenate from 6th chicken embryo passage. It had previously undergone 16 passages in chicks, after being received as the 135th chick-brain passage virus.† The titer of the virus was 10^{-5}/0.05 ml when inoculated intracerebrally into chicks. *Cell culture.* Monolayer chick kidney cell culture was prepared from 1-week-old chicks (2). *Passage of virus.* The growth medium (2) was replaced by 0.1 ml virus and 0.9 ml growth medium containing 0.07% sodium bicarbonate. Serial passage was made every 3