central nervous system more readily in suckling than in older cotton rats. Although it is possible that the virus may behave differently in newborn cotton rats and mice, it is also possible that invasiveness from peripheral sites and multiplication within the central nervous system may depend on different mechanisms. It is perhaps noteworthy, in this respect, that it is generally agreed that poliomyelitis infection in human beings more commonly produces severe clinical disease in older individuals than in very young children, past the age of possible protection by placentally transmitted antibody.

Summary. The Lansing strain of poliomyelitis virus, unlike other neurotropic viruses in mice, produced the disease more readily and rapidly in mature mice than in newborn animals. The relative resistance of the newborn manifested itself by prolonged incubation periods and survival times after onset of paralysis in those inoculated with larger amounts of virus (170 LD_{50}), and by a failure to develop the disease following the intracerebral inoculation of smaller amounts (2-17 LD_{50}). The prolongation in incubation period was most marked in mice inoculated at 1, 2 and 3 days of age, was still definite but progressively less marked in those tested at 4 to 7 days of age, while suckling mice inoculated at 15 days of age exhibited incubation periods almost identical in their distribution with those of weaned, 21 to 35-day-old mice. The amount of intracerebrally inoculated virus required to initiate infection in newborn mice 1 to 3 days of age was 10 to 30 times greater than in 21- to 35-day-old mice. Although the incubation period was markedly prolonged in the newborn mice, the level of virus multiplication attained at the onset of paralysis was the same in the suckling as in the older mice. Mice becoming paralyzed during the first 14 days of life survived much longer (61% for 3 to 9 days) than the litter mates whose incubation periods were prolonged beyond 15 days of age (12% for 3 to 5 days). There was no evidence of inapparent infection in mice inoculated during the first week of life or subsequently, since the majority of surviving mice succumbed to a second inoculation of virus 35 to 80 days later.

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Conditioning, Through Stress, of the Action of Corticoids on Lymphoid Organs.* (17695)

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In vitro experiments concerning the action of corticoids on lymphocytes are at present inconclusive. While numerous investigators have suggested that gluco-corticoids have cytotoxic effects on lymphoid cells *in vitro* (1,2,3,7), other workers have found that total cortical extracts did not show this lympholytic action(4,5). The recent experiments of Hechter and Johnson(6) can perhaps explain the different effects of corticoids *in vitro* and *in vivo* on lymphoid cells. These investigators have found that total cortical extract is an effective lympholytic agent *in vitro* only in the presence of homogenates of lymphoid tis-

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1. Heilman, D. H., *Proc. Staff Meet. Mayo Clin.*, 1945, v20, 310.

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3. Hechter, O., and Stone, D., *Fed. Proc.*, 1948, v7, 52.

4. Dougherty, T. F., and White, A., *Am. J. Anat.*, 1945, v77, 81.

5. Robertson, J. S., *Nature*, 1948, v161, 814.

6. Hechter, O., and Johnson, S., *Endocrinology*, 1949, v45, 351.

7. Schrek, R., *Endocrinology*, 1949, v45, 317.

sue and their results suggest that the lymphoid tissue co-factor is perhaps enzymatic. The caryoclastic action of gluco-corticoids and stress on lymphoid organs *in vivo*, is well known. However, while Selye(8,9) has shown that adrenalectomy prevents the thymus caryoclasia caused by stress, we have obtained some preliminary data suggesting that even in the absence of the adrenals slight caryoclasia can occur in the lymph nodes. It seems therefore that the effects of stress on the lymphoid tissue cannot be totally explained by the secretion of corticoids. Consequently, we have performed the following experiment to obtain additional information concerning this question.

We have studied the influence of 3 stress-producing agents, cold, forced muscular exercise and 40% formaldehyde injections on the action of corticoids in the adrenalectomized rat.

The experimental animals, male piebald rats weighing 150-180 g were subdivided into 4 groups and treated as follows:

(1) The first group consisted of 9 rats, each of which received a single 0.2 cc injection of cortical extract (Upjohn lipo-adrenal cortex) 24 hours following adrenalectomy.

(2) The rats of the second group were similarly treated with 0.2 cc of the cortical extract 24 hours following adrenalectomy. Immediately after the injection, 6 of the animals were placed in the cold room (0°-5°C) for a period of 6 hours; 6 were subjected to forced exercise in a drum for the same period of time and the remaining 6 were given, within a 6 hour period, two 0.2 cc injections of 40% formaldehyde.

(3) A third group of 18 rats which likewise had undergone adrenalectomy 24 hours previously was subdivided into 3 equal groups and submitted to the same stresses as in (2) above but without the cortical extract pretreatment.

(4) A fourth group of 18 normal rats was similarly subdivided into 3 groups of 6 rats each and submitted to the same stresses also without hormone treatment.

All groups were sacrificed by chloroform inhalation 6 hours following either exposure to stress or injection of cortical extract. At autopsy, the thymus as well as a portion of the intestine with its Peyers patches were removed from the rats of each group. Alcohol-formal-acetic acid was used as the fixative and staining was done either with hematoxylin-eosin or with Feulgen's stain.

Results. In the first group, it was found that 6 hours after the injection of the cortical extract, the lympholytic effect was hardly manifest. Areas of pyknosis were few and,

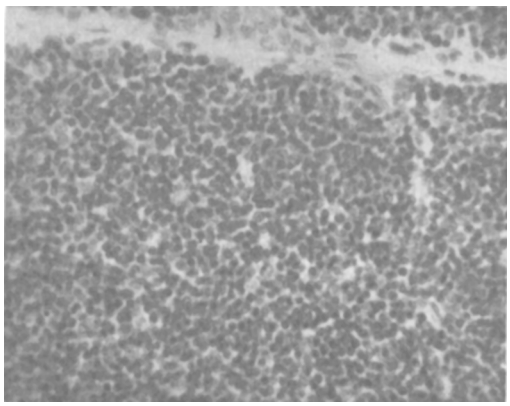

FIG. 1.
Thymus of an adrenalectomized rat treated with 0.2 ml of lipoadrenal cortex extract (Upjohn). The absence of caryoclasia of the thymocytes can be clearly seen.

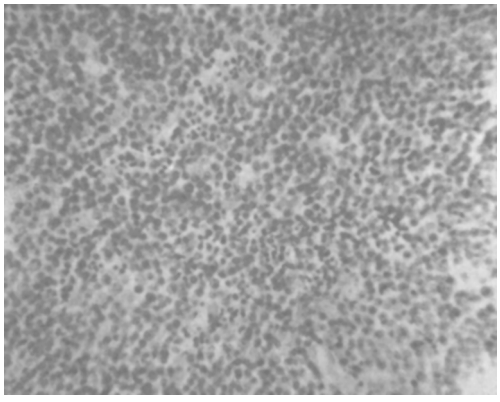

FIG. 2.
Similar section of thymus from an adrenalectomized rat treated with the same dose of cortical extract but exposed to muscular exercise. Note the development of confluent areas of caryoclasia of thymocytes.

8. Selye, H., *Brit. J. exp. Path.*, 1936, v17, 234.
9. Seyle, H., *Endocrinology*, 1937, v21, 169.

in most of the animals, the thymus and Peyers' patches were entirely normal in appearance.

In the second group where the effect of stress was added to the action of the same dose of corticoids, extensive caryoclasia had taken place in the thymus and in the germinal centers of the Peyers' patches. In both tissues, massive and often confluent areas of pyknosis could be observed, their aspect remaining the same despite the type of stress to which the animals had been subjected.

In the third group, thymus caryoclasia was inhibited by the adrenalectomy, yet a very few areas of pyknosis could be observed in the Peyers' patches.

In the fourth group the classical picture of caryoclasia was observed in both lymphoid organs of the normal rats subjected to stress. It was noted however, that the caryoclasia was often less pronounced than it was in the second group of animals, particularly in those subjected to forced muscular exercise.

Comments. These experiments show that the influence of corticoids on the lymphoid system may be conditioned by non-specific stress. They militate in favor of the view that these hormones act on the lymphoid cells by some indirect means as well as imply that some conditioning factors related to the stress (enzymes?) influence this action.

Summary. The combined action of a small dose of cortical extract and non-specific stress of moderate intensity has a well marked caryoclastic effect on the lymphoid system of adrenalectomized rats, whilst the same dose of extract given to adrenalectomized, non-stressed rats, produces a negligible effect.

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Demethylation of C^{14}-Labelled Codeine in the Rat.* (17696)

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The demethylation of codeine has been postulated by Sanfillipo(1) on the basis of the presence of typical morphine withdrawal symptoms in dogs after the prolonged administration of codeine. More direct evidence was obtained by Bernheim's *in vitro* studies which showed that codeine after incubation with rat liver slices gave rise to a phenolic-OH compound, presumably morphine (2). Since Bernheim has also shown that morphine itself is oxidized at an appreciable rate, the extent to which demethylation occurs is presumably greater than that indicated by quantitative tests for residual morphine. Our experiments with radiocodeine (codeine*) now establish by direct evidence that codeine is demethylated in rats at the 3-position. The present studies were initiated by the observation that $C^{14}O_2$ rapidly appeared in the expired air of rats after administration of codeine labelled with C^{14} in the methoxy group. The present data include measurements of $C^{14}O_2$ output *in vivo* and analyses of tissues for $C^{14}O_2$-$HC^{14}O_3^-$ concentrations in addition to studies on the ability of various tissues to demethylate codeine* *in vitro*.

Methods. The animals used were adult, male and female albino rats of the Slonaker-Wistar strain maintained on a diet of Friskies dog food and tap water. The codeine* was synthesized by Chang, *et al.*(3), and had a specific activity of 0.9 microcuries/mg. The

* Supported, in part, by a grant from the National Institutes of Health, Bethesda, Md.

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2. Bernheim, F., and Bernheim, M. L. C., *J. Pharm. and Exp. Therap.*, 1944, v81, 374.

3. Chang, F. N-H., Oneto, J. F., Sah, P. P. T., Tolbert, B. M., and Rapoport, H., to be published in *J. Org. Chem.*