The plasma ultrafiltrate of the blood of a cystinuric patient (S.P.)[3] contained 1.13 mg. % of cystine, a value slightly higher than our average normal value, but, we believe, within the upper limit of the range of values for normal human blood. To this subject, 5.6 gm. of methionine were administered in 2 equal portions at the morning and midday meals. The plasma ultrafiltrate of a sample of blood withdrawn at 3:45 P. M. contained 0.92 mg. % of cystine. It may be noted that, while the isolation of cystine from cystinuric blood has been claimed,[4, 5] no quantitative data have been reported.

It should be noted that no attempt was made to determine the possible presence of cysteine in these ultrafiltrates. The values reported represent "total" cystine, *i. e.*, values obtained by the application of the Sullivan procedure to the ultrafiltrates after reduction with cyanide.

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9281

Effect of Various Sterols on Thymus in the Adrenalectomized Rat.

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It has been pointed out that when an organism is seriously injured by an acute, non-specific, nocuous agent, a characteristic syndrome occurs, which consists of a rapid involution of the thymus and lymphatic system, oedema formation, with fluid in the pleural and abdominal cavities, loss of muscle tone, fall in body temperature, lung hemorrhages, and ulcers in the digestive tract. This syndrome has been given the name "Alarm Reaction".[1]

It has been shown further,[2] that, while adrenalectomy facilitates

[3] Lewis, H. B., Brown, B. H., and White, F. R., *J. Biol. Chem.*, 1936, **114**, 171.

[4] Demoulière, A., *La Cystinurie*, 1911, *Thèse pour le Doctorat en Médecine. Faculté de Médecine de Paris.*

[5] Müller, A., *Wien. med. Woch.*, 1911, **61**, 2364, 2488.

[1] Selye, H., *Endocrinology*, 1937, **21**, 169.

[2] Selye, H., *Br. J. Exp. Path.*, 1936, **17**, 234.

the production of all other symptoms of this "Alarm Reaction", it prevents the thymus involution. Physiological NaCl solution given to the animals restores their resistance to damaging influences, but does not enable the thymus to involute. Adrenaline is without effect both on the resistance of rats and on the ability of the thymus gland to respond to toxic stimuli. In animals maintained with very large doses of cortin slight involution will occur. This may be due to small amounts of some contaminating substance present in the cortin, or to the cortin itself. The only other substance which was found to be active in causing thymus involution following bilateral adrenalectomy was oestrone.[3]

The following investigations were carried out in order to determine whether the thymus of adrenalectomized rats would involute following the administration of sterol substances other than oestrone and at the same time to study the toxicity of these substances in such animals.

Rats varying in age from 40 to 162 days were used, 5 to 8 rats in each series with an equal number of controls. They were given standard Purina food and normal saline. Adrenalectomy was performed in one stage under ether anesthesia. Following a 24-hour rest period injections were begun.

The substances investigated were: 1. oestrone; 2. oestradiol; 3. pregnandiol; 4. dehydroandrosterone acetate; 5. cholestenone; 6. cholestenone acetate; 7. cholesterol; 8. progesterone; 9. androstenediol; 10. testosterone; and 11. testosterone propionate.* These compounds were administered in oil solution by daily subcutaneous injections. All the animals were autopsied for evidences of the alarm reaction, and the weights of the thymus, spleen and lymph nodes recorded. Survival was used as the criterion of toxicity.

Eight male rats were given 100 gamma of oestrone daily for 10 days. By that time half of the animals died. The remainder and the control animals were killed and autopsied. The oestrone produced a decided decrease in the size of the thymus, spleen and lymph glands.

Thymus Weights. Rats given oestrone: 256, 151, 293, 153, 185, 350, 237, 143; average 221. Controls: 580, 512, 514, 366, 460, 378, 495; average 472.

A group of seven 80-day-old females resisted the same dose of oestrone for 14 days. The thymus was even more markedly invo-

[3] Selye, H., Harlow, C. M., Collip, J. B., *Endokrinologie,* 1936, **14**, Heft 1/2.

* The authors are indebted to the Schering Corporation, who through the courtesy of Dr. E. Schwenk, kindly supplied most of these compounds.

luted, the average weight being 81 mg., the control rats averaging 322 mg.

Pregnandiol in daily doses of 100 gamma for 12 days had no toxic action and did not alter the thymus gland of 7 male rats. Daily doses of one mg. of pregnandiol for 17 days were also without effect in a series of 8 females.

Because of the similarity in structure between the 2 sterols, pregnandiol and oestrone, it was thought possible that pretreatment with the apparently inert pregnandiol would increase the resistance of the adrenalectomized rats to oestrone by stimulating the same detoxifying mechanism. The opposite was found to be the case. Seven rats were pretreated with pregnandiol, 100 gamma daily for 10 days. Seven control rats received injections of oil during this period. Following adrenalectomy the pregnandiol was discontinued and both groups were given 100 gamma oestrone daily, with the result that 5 of the pretreated group died after 7 injections of oestrone. Only one of the non-pretreated group died in the same period. Pretreatment of 8 males with larger doses of pregnandiol (750 gamma daily for 15 days) gave similar results. Removal of the uterus and ovaries prior to adrenalectomy did not alter the resistance of the rats to oestrone, provided sufficient time was allowed for recovery from the first operation.

In a series of six 54-day-old female rats oestradiol proved to be toxic in daily doses of 100 gamma for 10 days and caused a significant decrease in thymus weight—241 mg. compared with 325 mg. for the control animals.

Cholestenone, cholestenone acetate and dehydroandrosterone acetate were each used in 2 mg. doses on six 47-day-old females. Six cholesterol-treated animals served as controls. None of these substances caused thymus involution. Dehydroandrosterone acetate was the only one of the group which had any appreciable toxic action in the doses used. It also had some sex stimulating activity as shown by positive vaginal smears and uterine oestrus.

Progesterone, 100 gamma daily, resulted in death of 4 out of 7 male rats after 7 injections, whereas 7 females of the same age withstood 15 injections. The thymus gland was not altered.

Androstenediol (100 gamma daily) produced no thymus involution and 4 of the 8 rats died in 15 days.

Testosterone in the same dose also gave negative results in 16 animals. Five hundred gamma doses used on 5 rats for 16 days gave an average thymus weight of 258 mg. compared with 317 mg. for the control animals. As the difference was of questionable significance another group of 6 was treated with one mg. doses of

testosterone propionate for 14 days, with marked effect. The thymus decreased from an average of 327 mg. to 160 mg.

We conclude that thymus involution occurs in adrenalectomized rats following the administration of substances other than oestrone. Both oestradiol and testosterone were effective. None of the sexually inert substances caused any thymus change. This suggests a relationship between the sex stimulating property of the sterols and the thymus effect, but the amount necessary to cause thymus involution is many times that required for the physiological effect. The toxicity of the sterols in adrenalectomized rats also appears to run parallel with their physiological activity.

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Serum Sodium in Relation to Liver Damage and Hyperthyroidism.*

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The liver of patients with severe hyperthyroidism has shown impairment of function and marked pathological changes.[1] In a search for the cause of thyroid crisis, we were unable to find any definite relation between impairment of liver function, as measured by blood bilirubin and bromsulphalein dye retention, and the degree of postoperative reaction, the latter being of the same nature and in its severe form, true thyroid crisis.[2]

Our attention was then drawn to a publication by Schneider[3] concerning a marked disturbance of serum sodium in relation to liver damage and hyperthyroidism. This investigator has shown experimentally in guinea pigs that daily injections of the thyrotropic hormone from the anterior lobe of the pituitary gland or injections of thyroxine reduce serum and liver sodium below one-half of its normal value, while potassium and chlorides are not significantly

* This investigation was assisted by a grant from the Horace H. Rackham School of Graduate Studies.

1 Weller, C. V., *Ann. Int. Med.*, 1933, **7**, 543.

2 Maddock, W. G., Coller, F. A., and Pedersen, S., *West. J. Surg.*, 1936, **44**, 513.

3 Schneider, E., *Internat. Clin.*, 1934, **2**, 87. Schneider, E., Widmann, E., *Deutsche Z. f. Chir.*, 1933, **241**, 15, 778; *Z. f. d. ges. exp. Med.*, 1933, **90**, 45. Schneider, E., *Klin. Wchnschr.*, 1933, **12**, 1708.