

other respects this lesion resembles those previously described. This is the first aneurysm that has been observed in this series, but the possibility was suggested by the fragmentation and disintegration of elastic tissue seen in previous lesions.¹

Thus the observations with uranium nitrate have been confirmed with mercuric chloride. Experiments are now in progress to determine whether the heavy metal as such or the renal insufficiency following the administration of the heavy metal is the essential factor in the production of these experimental arterial lesions. The other two factors apparently concerned in their production are diet and plasma alteration.

Summary. Mercuric chloride can be substituted for uranium nitrate in the production of necrotizing arterial lesions in dogs. An aneurysm developing on the basis of one of these lesions is described for the first time.

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Epithelial Hyperplasia of Hassall's Bodies of Thymus Gland Induced by Methylcholanthrene.

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The histogenesis and functions of the thymus gland are still imperfectly understood. Uncertainty exists concerning the essential nature of Hassall's bodies, the thymic reticulum, and the thymic lymphoid cells. The rôle of the thymus as a gland of internal secretion, and as a source of lymphocytes is also not clear.

During experiments designed to induce tumors in the thymus with a cancerogenic hydrocarbon observations were made which give support to the idea that Hassall's bodies are epithelial and not endothelial, and that some of the thymic reticulum may be epithelial in nature.

Procedure. Cylindrical pellets consisting of 10 mg of methylcholanthrene plus 10 mg of cholesterol and measuring approximately 1.75 mm in diameter and 8-10 mm in length were¹ implanted into the thymus gland of young guinea pigs of both sexes by open surgical operation.

Animals were sacrificed at 7, 14, 21, and 28 days and irregularly at

¹ Shear, M. J., *Am. J. Cancer*, 1936, **26**, 322.

other earlier and later time intervals. The left lobe of thymus which contained the pellet was fixed in Zenker's solution or in formalin, as was the corresponding right unoperated lobe. They were embedded in paraffin after which sub-serial sections were cut. The sections were stained by hematoxylin and eosin, by Mallory's aniline blue method, and in critical instances also by Dr. George Gomori with his modification of Mallory's phosphotungstic acid-hematoxylin method² to demonstrate intercellular bridges. Thus the pellet space could be studied at numerous levels to be sure that the representative cellular reactions were seen. The pellets themselves were dissolved away by the alcohol and the xylol used in making the preparations.

Results. Fibrous encapsulation of the pellets, which were apparently unchanged in size, was already present at 7 days and subsequently the connective tissue became more mature and abundant. There was a leukocytic reaction to the pellets as well as sometimes a foreign body giant cell reaction.

The changes in the thymic tissue consisted of acute degeneration of the thymic lymphocytes, irregular areas of hyperplasia of thymic reticulum, and hyperplasia of Hassall's bodies all in the region within about 0.5 to 2.0 mm of the pellets, epithelialization of the pellet space, and epithelial cyst formation.

The hyperplasia of Hassall's bodies was seen as early as the 7th day. They enlarged and their centers became cystic, the cysts containing cell debris including the centers of the old Hassall's bodies.

Most remarkable was the epithelialization, by a stratified squamous type of epithelium, of the pellet space. This was first seen at 14 days. Its origin in one case, studied in serial section, and illustrated in Fig. 2, was from a Hassall's body which sent an epithelial stalk toward the pellet space and, reaching it, spread to line the space. In other animals this relationship was not seen, and the possibility is not excluded that the epithelium came from other thymic cells.

The encapsulated space occupied by the pellet sometimes enlarged up to 1 cm in the first month. This additional space contained fluid, leukocytes and cell debris. In other instances similar cyst-like spaces were found in close proximity to the pellet space and communicating with it through a small opening revealed by serial sections. In still other instances no such connection was seen and the impression given was that the cysts were enlarged Hassall's bodies.

A marked hyperplasia of cells was sometimes seen in the regions near the pellet in which the small, dark thymic cells had disappeared. These cells were large, plump spindle to polyhedral with a large

² Gomori, G., *Am. J. Path.*, 1941, **17**, 395.

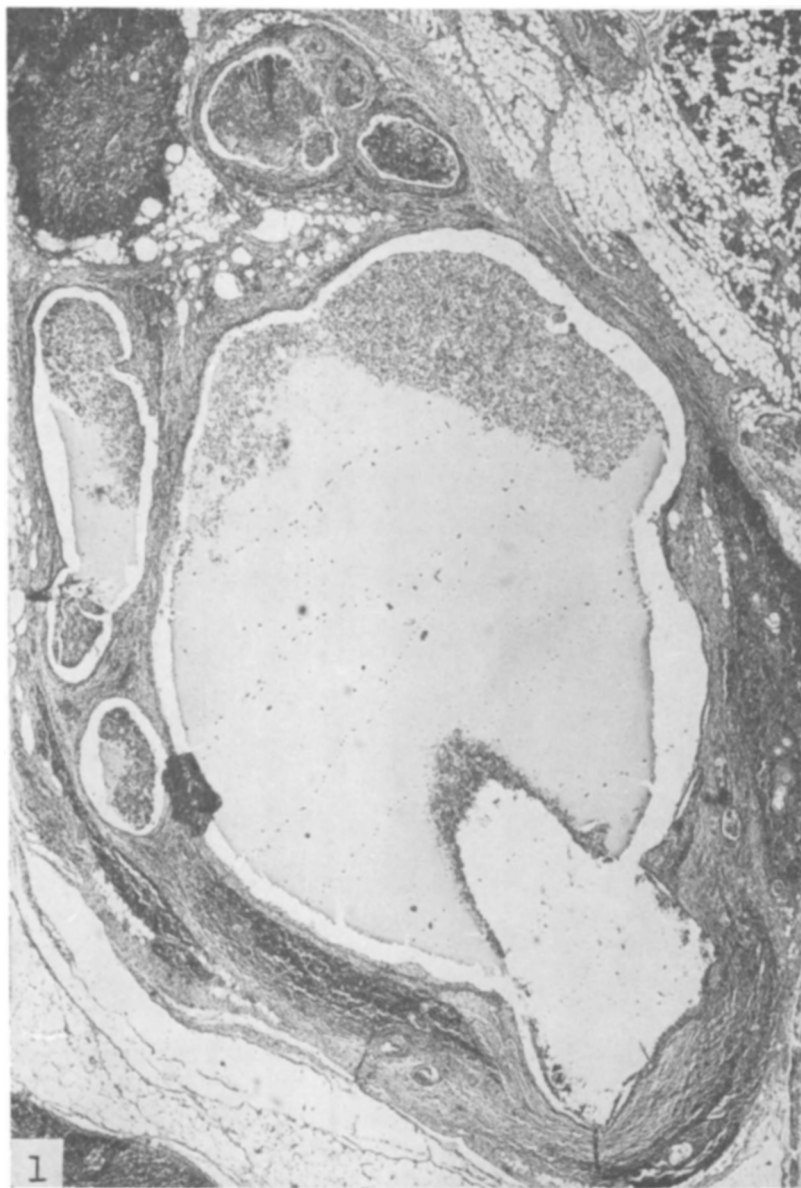


FIG. 1.

($\times 25$) The pellet has been dissolved from the lower right. Its space is enlarged and is lined by stratified squamous epithelium. At the left and above are independent squamous cysts resembling enlarged forms of Fig. 3.

oval nucleus. Such regions showed a marked paucity of intercellular fibrils, and they sometimes merged gradually with definite

stratified squamous epithelium lining the pellet space. These cells appear to have had their origin from thymic reticulum, and they appear to be forming squamous epithelium.

Epithelial proliferation seemed to take place at a slow rate after the first month, some keratinized material slowly accumulating in the cysts. After about one year palpable masses were present which sometimes grew rapidly. These were true tumors and will be described elsewhere.

Controls. Controls were studied to establish the normal structure of the thymus for guinea pigs having the same age, sex, environment, and operative procedure. They consisted (a) of guinea pigs who were implanted with pellets of the same size but composed of 20 mg of cholesterol, (b) of guinea pigs with pellets of methylcholanthrene and cholesterol implanted in other tissues and organs also located in the neck (salivary glands, muscle, adipose tissue, and lymph nodes), and (c) of the contralateral, unimplanted thymic lobes from the experimental animals.

Similar changes were not seen under any of these conditions. Epithelialization of the space occupied by the pellet was seen only in implants into the salivary gland as previously reported.³ The inflammatory reaction and the fibrous response appeared to be quantitatively less when cholesterol alone was used.

Comment. These hyperplasias are of interest because they precede neoplasias and the latter are generally considered to be difficult to produce in guinea pigs, especially epithelial tumors.^{4, 5} Methylcholanthrene, like some other chemical cancerogens can have destructive actions on cells and it is also of interest that the concentration required to induce the epithelial proliferation was approximately the same as that capable of destroying the small thymic lymphocyte-like cells.

The new cells produced in Hassall's bodies, in the cyst linings, and in the lining of the pellet spaces are stratified squamous epithelium as is shown by their general morphology, intercellular bridges, and the formation of keratohyaline. Whether they represent the process of hyperplasia or of metaplasia, they indicate that Hassall's bodies are epithelial.

Ross and Korenchevosky⁶ have reported epithelial hyperplasia and

³ Steiner, Paul E., *Third International Cancer Congress*, page 138, Sept., 1939.

⁴ Warren, Shields, and Gates, Olive, *Cancer Research*, 1941, **1**, 65.

⁵ Shimkin, Michael B., and Mider, G. Burroughs, *J. Nat. Canc. Inst.*, 1941, **1**, 707.

⁶ Ross, M. A., and Korenchevosky, V., *J. Path. and Bact.*, 1941, **52**, 349.



FIG. 2. ($\times 50$) Pellet space partly lined by stratified squamous epithelium and connected with a Hassall's body. Fourteen days after implantation.

FIG. 3. ($\times 50$) Hyperplastic Hassall's body showing beginning cyst formation at 14 days in an area devoid of small thymic lymphocytes.

FIG. 4. ($\times 120$) Hyperplastic Hassall's body with hazy margin at seven days.

FIG. 5. ($\times 850$) Intercellular bridges in the epithelium lining a pellet space.

cyst formation, not dissimilar to those reported here, in the thymus of rats injected with female hormones. Some of the cancerogens are estrogenic, but Gardner reports⁷ that methylcholanthrene in 10 mg

⁷ Gardner, W. U., personal communication.

amounts is not, so that in these experiments methylcholanthrene apparently exerted its effects as a growth promoter other than as an estrogen.

Summary. Methylcholanthrene pellets implanted into the thymus gland of young guinea pigs induced hyperplasia of Hassall's bodies and of the thymic reticulum near the pellet, squamous epithelialization of the pellet space, small epithelial cysts, and degeneration of the small thymocytes. These new epithelia show intercellular bridges and keratohyaline formation, and since they arise from Hassall's bodies they show the epithelial nature of the latter.

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Influence of Sex on Resistance to Intraperitoneal Inoculation of Sarcoma in Mice.

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Previous studies performed in this laboratory have shown clearly that adult male mice are more susceptible than females to intradermal inoculation of sarcoma S 37, as evidenced by the greater incidence of takes and the lower incidence of spontaneous regression of the cutaneous tumors produced in males.¹

Experiments reported in this paper were carried out to determine whether this difference in resistance between males and females is demonstrable only following intradermal inoculation of sarcoma or whether a similar sex difference can be demonstrated following implantation of this tumor by another route such as the intraperitoneal route of inoculation.

Experimental. Groups of male and female mice were inoculated intraperitoneally with equal doses of cell suspensions of sarcoma S 37. Tumor-cell suspensions, varying in concentration from 1 to 20%, were prepared in the usual manner¹ and injected with a tuberculin syringe and a 27-gauge needle. Sexually mature male and virgin female mice of the albino E. S. strain² were used throughout this study. These animals were 2 to 3 months old and weighed 18 to 24 g.

Eighteen of the 209 males and 51 of the 224 females did not react to the inoculation. The remaining 191 males and 173 females de-

¹ Gross, L., *Proc. Soc. Exp. Biol. and Med.*, 1941, **47**, 273.

² Gross, L., *Cancer Research*, 1941, **1**, 880.