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Local Tissue Reaction to the Implantation of Crystals and Pellets of Estrogenic Hormone.

S. H. GEIST, R. I. WALTER AND U. J. SALMON.

From the Laboratories of the Mount Sinai Hospital, New York City.

Deanesley and Parkes,[1, 2] in a study of the various factors which influence the rate of absorption of sex hormones in animals, demonstrated that the subcutaneous implantation of the pure dry hormone was the most efficient mode of administration. In studies in the human, we have shown[3] that, by means of the subcutaneous implantation of crystals of a-estradiol benzoate, it was possible to prolong the period of effectiveness of the hormone. This was demonstrated by (a) the long period of clinical improvement, (b) the persistence of estrogenic effects on the vaginal smear and (c) the prolonged pituitary inhibition, in menopausal patients.[4] Subsequently, in an attempt to obtain more prolonged effects with the estrogenic substances, pellets of a-estradiol and a-estradiol benzoate were implanted subcutaneously.

One of the questions which immediately arose following the use of this procedure was, what effect the crystalline estrogens would have upon the contiguous subcutaneous tissues. It is our purpose, in this communication, to describe the local tissue reaction to the implanted estrogen crystals* and pellets.*

We have employed the implantation method in a series of 110 cases and from this series 14 patients (of whom 8 were spontaneous menopause, 4 surgical and 2 X-ray castrates), were selected for excision of the implanted hormone and surrounding tissues. Ten patients had been implanted with pellets (5 a-estradiol and 5 a-estradiol benzoate). All of these cases, before the implantation, had typical menopause symptoms and morphologic evidence of estrogen deficiency, as indicated by negative vaginal smears and biopsies of the vaginal mucosa and endometrium. The amount of hormone implanted varied from 15 to 50 mg. The individual pellets weighed

1 Deanesley, R., and Parkes, A. S., *Proc. Roy. Soc. B.*, 1937, **124**, 279.

2 Deanesley, R., and Parkes, A. S., *Lancet*, 1938, **2**, 606.

3 Salmon, U. J., Walter, R. I., and Geist, S. H., *Science*, 1939, **90**, 162.

4 Salmon, U. J., Geist, S. H., and Walter, R. I., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 424.

* For the crystals and pellets of a-estradiol and a-estradiol benzoate used in this investigation, we are indebted to Dr. E. Schwenk of the Schering Corporation, Bloomfield, N. J.

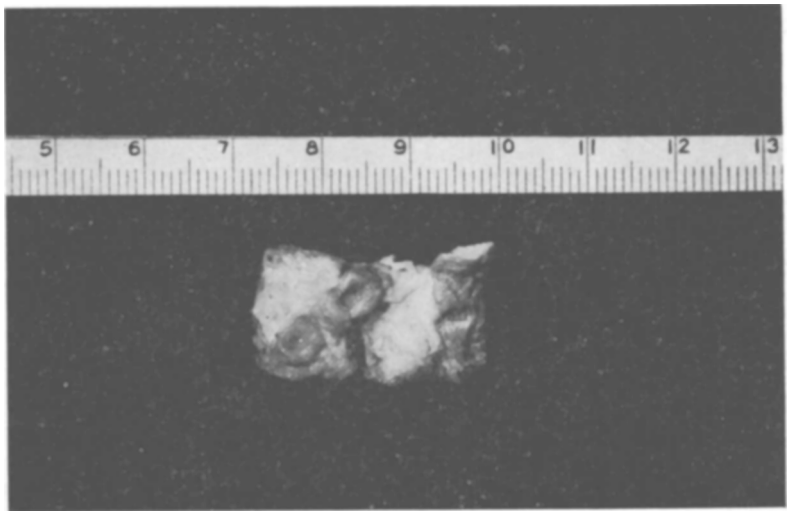

FIG. 1.
Case D.N. Natural size photograph of implantation site, excised 88 days after implantation of 2 pellets of a-estradiol benzoate, showing capsule formation.

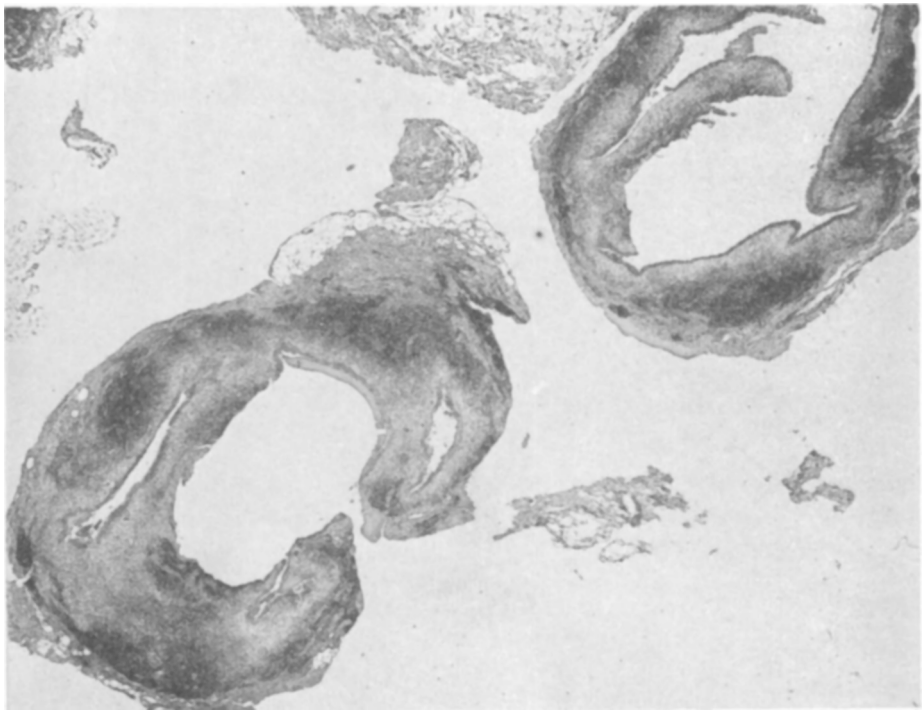

FIG. 2.
Case D.N. Cross section through capsules (× 10).

15 to 25 mg. Four patients were implanted with crystals of a-estradiol and a-estradiol benzoate, varying in weight from 10 to 23 mg. The implantation sites were excised under local (1% novocaine) anesthesia, at periods varying from 23 to 238 days after the implantation. An ample elliptical incision was made over the site of implantation in order to include the skin and surrounding tissues. The pellets were removed and the excised tissue was fixed in 10% formalin. Serial sections were made and stained with hematoxylin and eosin. In none of the cases implanted with crystals were we able to find any gross evidence of the crystals at the time of excision.

It was noted that a fairly uniform tissue reaction occurred in each case. The pellets were completely surrounded by a fibrous capsule which varied in thickness depending upon the duration of implantation. The pellets retained their original shape and consistency and, although intimately adherent to the capsule, could be easily shelled out. The subcutaneous tissues showed a typical foreign body reac-

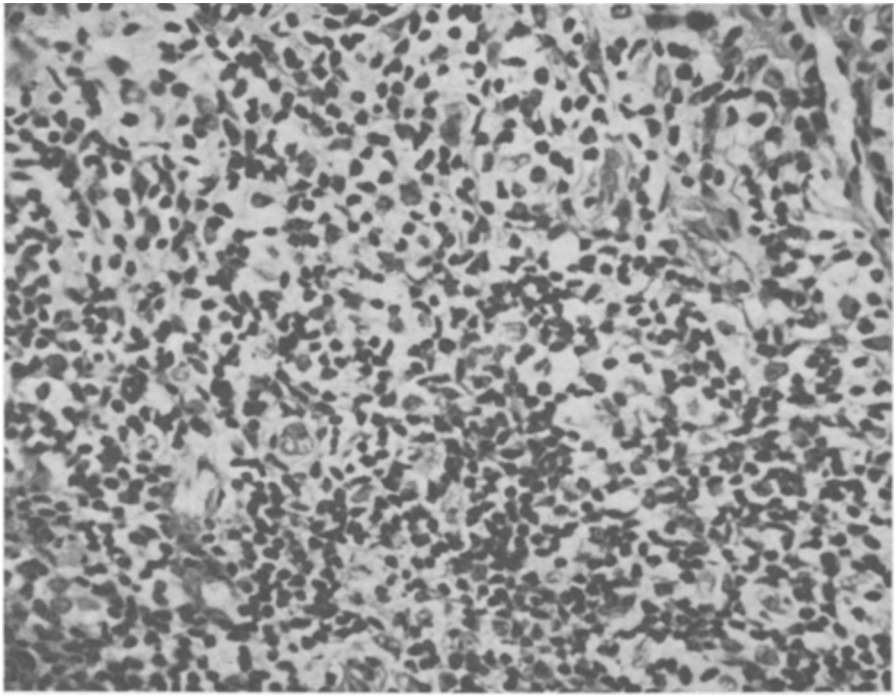

FIG. 3.

Case D.N. Section through middle layer of capsule showing round cells and giant cells (× 400).

tion. Each of the capsules showed essentially the same histologic picture. The protocol of a typical case is presented here.

This patient (D.N.) was implanted in the subcutaneous tissue of the right thigh with 2 pellets of a-estradiol benzoate (total weight, 50 mg) and the implant-site was removed 88 days later. Fig. 1 is a natural size photograph demonstrating the gross appearance of 2 capsules after removal of both pellets. Fig. 2 is a low power magnification of a cross section of the capsules illustrated in Fig. 1, showing the sharply demarcated character and thickness of the capsules. The significance of the thickness of the capsules will be discussed later.

The capsule consists of 3 more or less distinct layers surrounding a central cavity. The inner layer adjacent to the cavity consists of 2 zones: (a) an inner zone which is composed of 1 to 3 layers of cells which are elongated, narrow and eosinophilic and contain irregular nuclei which have no uniform cell position; and (b) an hyalinized connective tissue zone containing scattered lymphocytes, leucocytes

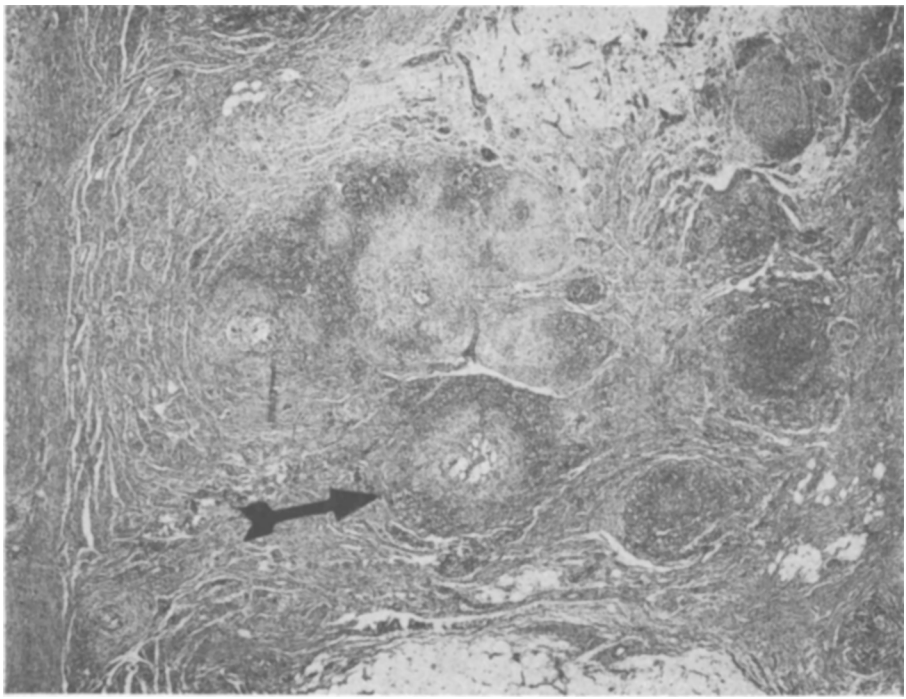

FIG. 4.

Case L.S. Excised tissue 236 days after the implantation of 10 mg of a-estradiol crystals (× 20). Note tubercle-like nodules.

and some large, pale-staining cells with oval nuclei. The nuclei of these large cells have a well-defined chromatin content, the cells resembling phagocytes. The middle layer (Fig. 3) is a slightly wider area, which is supported by an hyalinized connective tissue substratum and is infiltrated by many closely packed, small, round cells (lymphocytes and plasma cells), fibroblasts, occasional leucocytes, and a scattering of giant cells. The outer layer consists of a relatively narrow band of hyalinized fibrous tissue which contains some dilated lymphatic vessels. The surrounding fat tissue shows slight edema and contains a few lymphocytes and giant cells. The skin overlying the implanted pellets is normal.

On excision of the crystalline implantation sites, no macroscopic capsule could be seen. On cut section one could, however, discern multiple, pin-point, grayish-white areas distributed throughout the subcutaneous fat tissue.

Fig. 4 is a low power photograph of a cross section of an im-

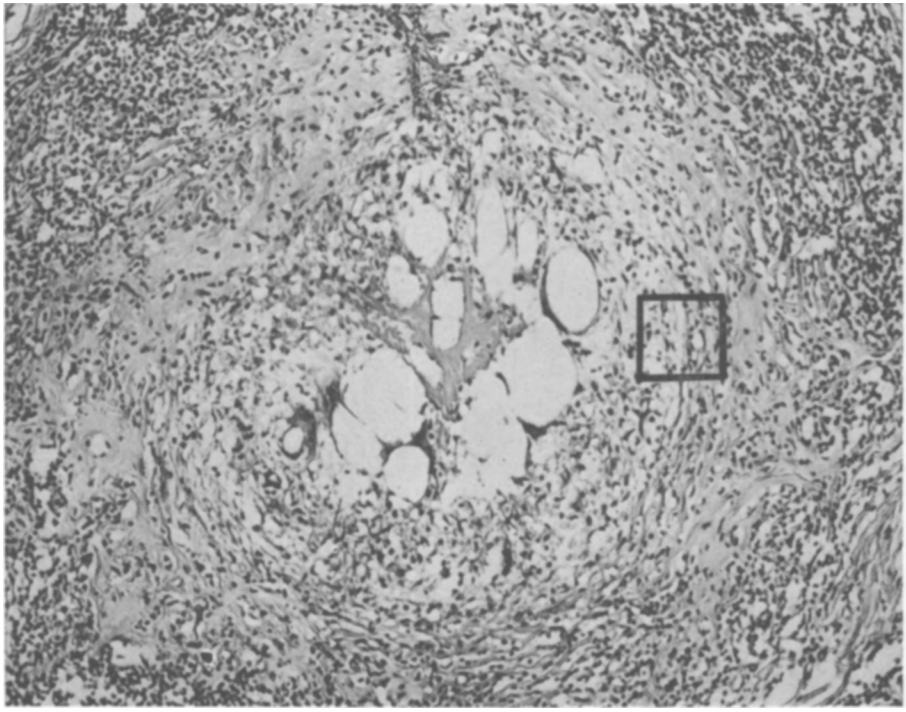

FIG. 5.

Case L.S. Higher magnification (× 100) of single nodule indicated by arrow in Fig. 4.

plantation site removed from patient L.S. who had been implanted 236 days previously with 10 mg of a-estradiol crystals. One can clearly see in this section at least 14 minute discrete, conglomerations of cells, which have the appearance of small tubercles. With higher magnification (Fig. 5), the resemblance of these accumulations of cells to foreign body tubercles becomes even closer.

These tubercles consist of a central core of tissue containing several cavities of variable size, which are delimited by fine connective tissue septa. The latter contain many irregular nuclei which vary considerably in size and shape. Some of the nuclei are giant sized and no separate cell margins can be identified. This central core is surrounded by a zone of hyalinized tissue which contains numerous irregularly shaped cells with large vacuoles and a scattering of foreign body giant cells (Fig. 6).

Surrounding the above described central structure are 3 layers of cells which resemble, in miniature, the 3 layers of cells which make up the gross capsule previously described.

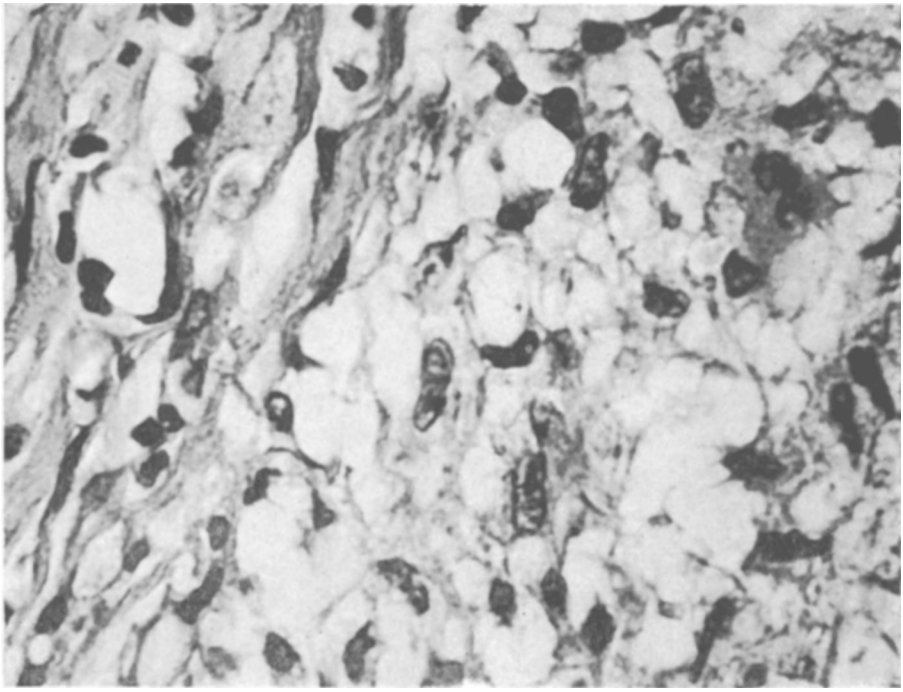

FIG. 6.
Case L.S. High power magnification (× 1200) of boxed-in area of Fig. 5 showing large multi-nucleated vacuolated cells.

Summary and Conclusions.

The local tissue response to implanted crystals and pellets is a typical non-specific foreign body reaction. Following the implantation of crystals of a-estradiol and a-estradiol benzoate, the tissue surrounding the crystals responds by the formation of tiny nodules. In contrast to this type of reaction, a thick avascular capsule forms about the pellets of the implanted hormone. It is important to note that the epidermis overlying the implants showed no evidence of cellular atypism and, similarly, in no instance did the subcutaneous tissues in contact with, and adjacent to, the implanted hormone show any abnormal cellular proliferation.

A significant observation which emerges from this study is the probable effect that the thick avascular capsule has on the absorption rate of the estrogenic substances employed. It was noted that the crystals had a strikingly more prolonged therapeutic and physiologic effect than the pellets composed of the same estrogenic substance and of comparable weight. It would appear, therefore, that the capsule might have a marked retarding effect on the rate of absorption of the hormone. Apparently, with the passage of time, the absorption rate is progressively diminished by the growing thickness of the capsule around the pellet. After a period of approximately 3 months, absorption is either completely stopped or so reduced as to have no demonstrable physiologic or therapeutic effect. It seems, therefore, that for purposes of implantation, pellets of a-estradiol and a-estradiol benzoate are not as efficient as crystals of the same chemical constitution.

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Portals of Entry of Poliomyelitis Virus in the Chimpanzee.*

HOWARD A. HOWE AND DAVID BODIAN. (Introduced by Carl Hartman.)

From the Department of Anatomy, Johns Hopkins University.

The lack of any direct evidence concerning the portal of entry of poliomyelitis virus in man has led to many animal experiments. The use of the resistant rhesus monkey and of "monkey strains" of virus in this problem, however, is open to the objection that the experimental conditions at the outset are widely divergent from those under which the disease takes place in human beings. A closer approxima-

* Supported by a grant from the Commonwealth Fund.