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Preliminary Communications

Production of Calciphylactic Facial, Oesophageal, and Mediastinal Lesions by Combined Treatment with Dihydratichysterol and Thorium Dioxide

Calciphylaxis is a condition of hypersensitivity in which, during a "critical period" after sensitization by a systemic calcifying factor (for example, vitamin-D compounds, parathyroid hormone), treatment with certain challengers (for example, metallic salts) causes an acute local tissue-calcification followed by inflammation and sclerosis. The topical calciphylaxis thus induced by subcutaneous injection of challengers results in a cutaneous calcinosis reminiscent of calcareous scleroderma. However, in suitably sensitized (for example, dihydratichysterol-treated) rats, calciphylactic reactions can also be elicited rather selectively at pre-determined sites (for example, in the pancreas, thyroids, parathyroids, bile ducts, uterus, spleen, Kupffer cells, lungs, salivary glands, lacrimal glands) by the intravenous administration of challengers that have a particular affinity for any one organ (Selye, Cantin, and Jean, 1960; Selye, Jean, and Veilleux, 1960; Selye, Grasso, and Dieudonné, 1961).

Here we should like to report on a curious calciphylactic syndrome that can be elicited by a single intravenous injection of thorium dioxide in suitably sensitized rats.

MATERIALS AND TECHNIQUES

Forty female Holtzman rats, with a mean initial body weight of 97 g. (range, 95–102 g.), were subdivided into four equal groups and treated as follows:

Group 1, dihydratichysterol (D.H.T., or "calcamin"®, Wander Co.), 1 mg. in 0.5 ml. corn oil, by stomach-tube on first day. **Group 2**, "thorotrast"® (Testagar Co., a suspension containing 25 mg. of $\text{ThO}_2/\text{ml.}$), 1 ml., intravenously on second day. **Group 3**, D.H.T. (as Group 1) + thorotrast® (as Group 2). **Group 4**, D.H.T. (as Group 1) + thorotrast®, 0.6 ml., intravenously on second day.

The experiment was terminated on the sixth day by killing all survivors with chloroform. Specimens of

various tissues were fixed in alcohol-formol (8 parts absolute alcohol, 2 parts 10% formaldehyde) for the subsequent histochemical demonstration of calcium phosphate by von Kossa's silver-nitrate technique.

RESULTS

The rats treated with D.H.T. alone or thorotrast® alone showed no noteworthy changes and therefore need not be discussed in detail here. Suffice it to point out that the single dose of 1 mg. of D.H.T. produced little or no metastatic calcification even in the organs (cardio-vascular system, gastric mucosa, kidney) that are normally predisposed to the development of calcific

FIG. 1.—Typical aspect of the facial lesions induced by D.H.T. + thorotrast®. The fur was clipped and the left external ear removed in order to expose the swollen and calcified areas round the snout (which made it impossible for the animal to close its mouth) the eyelid, and the base of the external ear. In this instance the skin of the forepaws is also calcified, but this was rather unusual.

FIG. 2.—Macroscopic appearance of the pharyngeal and oesophageal lesions induced by D.H.T. + thorotrast®. A: Fresh specimens. B: After defatting and staining with AgNO_3 . The organs on the left of each picture are those of the rat treated with D.H.T. + thorotrast®; the other specimens come from a control rat given D.H.T. alone.

deposits under the influence of heavy overdosage with vitamin-D compounds. Conversely, all rats treated with D.H.T. plus 1 or 0.6 ml. of thorotrast® (Groups 3 and 4, respectively), though apparently quite normal during the first two days, began to become manifestly ill on the third day. They developed a peculiar stiffness, swelling, and whitish discoloration of the skin of the snout, the eyelids and their surroundings, as well as round the base of the ears. These lesions progressed rapidly during the following days, and towards the end of the experiment the rats could no longer close their mouths because of the stiffening of the lips. In addition, the rats of these two groups developed a gasping type of breathing and had obvious difficulties in their attempts to swallow the occasional crumbs of food that they were able to ingest despite the stiffness of their lips (Fig. 1).

The reason for these difficulties in respiration and deglutition became immediately obvious at necropsy. Though the degree of the lesions was subject to slight individual variation, every animal in Groups 3 and 4 showed intense calcification in the musculature surrounding the fauces (soft palate, palatine arches, and

There was surprisingly little calcification in any of the other organs, although occasionally some calcium incrustation occurred in the pulmonary septa and the spleen. Although heavy deposits of thorium dioxide were microscopically visible in the Kupffer cells and splenic phagocytes, calcium deposition never occurred in the liver and only occasionally in the periphery of the splenic Malpighian follicles. The cutaneous, pharyngeal, oesophageal, and mediastinal lesions all stained black with von Kóssa's procedure. The mineral deposits were associated with active connective-tissue proliferation and inflammatory infiltration, particularly by eosinophils and pseudo-eosinophils, the presence of which is especially characteristic of calciphylactic responses in general.

These lesions were accompanied by an intense acute osteitis fibrosa characterized by pronounced bone absorption with an abundance of osteoclasts, and fibrosis in the bone-marrow. The bones of the rats treated with D.H.T. alone showed no comparable lesions. It may be assumed that here—as in many other forms of calciphylaxis elicited by different challengers—the bone lesions result from an acute transposition of calcium from the skeleton into the affected soft tissues.

DISCUSSION

It would be premature to speculate upon the factors responsible for the singular distribution of the calciphylactic lesions that result when thorium dioxide is used as a challenger in the D.H.T.-sensitized rat. The cutaneous calcinosis induced by topical application of challengers (for example, metallic salts, mechanical trauma) to the skin of rats sensitized either by D.H.T. or by parathyroid hormone resembles the calcareous form of scleroderma (the so-called "sclérodémie calcaire" of French dermatologists). This similarity was pointed out long ago (Selye, 1932; Selye, Cantin, and Jean, 1960; Selye, Jean, and Veilleux, 1960). Now we learn that symmetrically arranged cutaneous lesions of this type can be induced in the skin of the face—even without any topical damage—by the intravenous injection of a thorium-dioxide preparation following sensitization by orally administered D.H.T. These experimental skin lesions are associated with similar connective-tissue responses in the oesophagus and mediastinum. This fact could also be taken to suggest the possibility of a connexion with systemic scleroderma, since the latter is known to exhibit a predilection for these same sites and there are few, if any, other systemic pathogens in either experimental or clinical pathology that exhibit a rather selective affinity for the skin, the oesophagus, and the mediastinal connective-tissue. Yet our data are far from proving the existence of any fundamental pathogenic relationship between the experimental syndrome that we produced and the spontaneous disease of man that it superficially resembles.

SUMMARY

Rats were sensitized by a single oral dose of dihydro-tachysterol and, 24 hours later, challenged by a single intravenous injection of a thorium-dioxide suspension ("thorotrast"®). This treatment induced multiple morbid foci characterized by calcification, connective-tissue proliferation, and infiltration with inflammatory cells, among which eosinophils and pseudo-eosinophils predominate. The lesions tended to be selectively

FIG. 3.—Histological appearance of the oesophagus after treatment with D.H.T. + thorotrast®. A: Cross-section through the wall of the oesophagus shows continuous layer of calcium deposition in the wall (von Kóssa. $\times 35$); B: Higher magnification of the oesophagus (corresponding to adjacent portion of picture above). Note strict limitation of calcification to connective tissue between epithelium and outer fascial layer (von Kóssa. $\times 120$.)

base of the tongue), as well as in the oesophagus between pharynx and cardia (Fig. 2). Histologically, the calcium deposition at the root of the tongue was predominantly in the connective tissue and striated musculature, while in the oesophagus it occupied the entire thickness of the wall between the epithelium and the surrounding fascial layer (Fig. 3). In addition, particularly heavy masses of precipitated calcium salts were visible in the loose connective tissue surrounding the pulmonary hilus.

localized in the facial skin, soft palate, palatine arches, base of the tongue, oesophagus, and mediastinal connective-tissue. The cutaneous changes thus produced resemble the calcareous form of scleroderma. It is emphasized, however, that neither this resemblance nor the singular localization of the associated lesions in internal organs proves any fundamental relationship between the pathogenic mechanisms responsible for the development of these experimental lesions and systemic scleroderma as it occurs in man.

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Medical Memoranda

A Case of Extensive Interstitial Calcinosis

As cases of widespread calcinosis affecting skin and subcutaneous tissues are rare the following case is worth reporting.

CASE REPORT

The patient, a man aged 38, was first admitted to hospital in June, 1957. In January, 1956, he developed pyrexia—103–103.5° F. (39.4–39.6° C.)—and painful swelling of the joints of the hands, wrists, ankles, elbows, and knees. These persisted for one month and then gradually subsided, but some stiffness of the hands and some painful limitation of movements of the elbows and knees still persisted. One year later he again developed pyrexia—103–103.5° F. (39.4–39.6° C.)—and painful swelling of the same joints persisted for five months until admission, while for the last 40 days his general condition greatly deteriorated, and an erythematous rash appeared on his face. Ten days before admission steroid treatment was started.

On admission his temperature was 103.5° F. (39.6° C.). He was an ill-looking, wasted man with diffuse slightly desquamating erythema on the face. There were marked painful swelling and limitation of movements of all metacarpophalangeal and proximal interphalangeal joints, wrists, elbows, ankles, and knees. His hands were bluish and cold, with some atrophy of the interossei muscles.

On investigation the haemoglobin was 11.2 g./100 ml.; W.B.C., 5,200 (normal differential); E.S.R. 110 mm./1st hour (Westergren). No L.E. cells were found after numerous examinations. Serum proteins, electrolytes, urea, sugar, liver-function tests, and E.C.G. were normal. Urine showed scanty erythrocytes. X-ray pictures of chest, hands, skull, pelvis, and thighs were normal.

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The high pyrexia, the joint involvement, and the rash rendered the diagnosis of disseminated lupus erythematosus (D.L.E.) highly tenable. The absence of L.E. cells could perhaps be attributed to the steroid treatment prior to admission. After intensive steroid treatment in hospital his general state improved considerably; the pyrexia subsided completely, and the joint changes greatly improved. He was discharged in September, 1957.

Second Admission.—He was readmitted in January, 1959. He had been relatively well since his discharge, receiving a maintenance dose of 20 mg. of prednisolone daily. For the three months prior to this admission he had felt weak and tired. On examination his general condition was fairly good, diffuse erythema over the whole face; moderate

FIG. 1.—Calcium deposits in the wall of the pelvis and the abdomen.

FIG. 2.—Calcium deposits in the soft tissue of the forearm.

swelling and limitation of movement of the fore-mentioned joints. His hands were bluish and cold. On palpation the skin, subcutaneous tissue, and muscles were of normal structure, but large calcium deposits were felt about the elbows and knees. Radiographs showed calcifications of the soft tissues at these areas. He was discharged in March, 1959.

Third Admission (August, 1960).—He had felt moderately well on a maintenance dose of 15 mg. of prednisolone daily. Five days before admission he had a mild pyrexia—100.5–101.5° F. (38–38.6° C.)—and a painful redness at the lower third of the right arm. On examination he was a fairly healthy-looking man; temperature 100.2° F. (37.9° C.). Diffuse erythema was present over the whole face. His hands were bluish red, and there were marked atrophy of the interossei muscles. Massive calcium deposits were present on the arms, the upper third of the forearms, the buttocks, the posterior and lateral aspects of the thighs, the