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Influence of Cortisone on Leptomeningeal Reaction Induced by Talc.* (20511)

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Ragan and co-workers(1) have demonstrated a marked retardation in the wound healing of rabbits treated with large doses of cortisone. This observation has been extended to the inflammatory and reparative processes of other mesodermal structures. Blunt(2) has studied delayed healing in experimental fractures of rabbits. Ducommun(3) and Scheinberg and Saltzstein(4) showed that ACTH and cortisone prevented the formation of intra-abdominal adhesions following the intraperitoneal instillation of talc, while Scheinberg, Saltzstein and Johnson(5) observed similar results in the prevention of pleural and pericardial adhesions.

Because cortisone diminished the inflammatory response of other serous surfaces, a study of its action on the meningeal reaction to the intrathecal administration of a sterile irritant was undertaken. Of several substances tried talc was the most effective in eliciting a meningeal reaction.

It was also felt that control of the meningeal reaction might be of value in the treatment of tuberculous meningitis as well as other granulomatous affections of the meninges. In such instances it seemed possible that the reduction of exudation and inflammatory response would make the offending organism more accessible to the action of the chemotherapeutic agent. Furthermore, the use of cortisone in the prevention of post-traumatic adhesions also suggested itself.

Materials and method. Eighteen white male rabbits weighing from 3.0 to 4.8 kg received a cisternal injection of 1 cc of a saline suspension of talc after a similar quantity of cerebrospinal fluid had been withdrawn. The talc suspension was sterilized by autoclaving. Ten animals were treated with cortisone, while 8 served as controls. In the cortisone-treated group 4 animals received a cisternal injection of 1 cc of a 1:9 suspension of talc, while 6

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received a 1:4 suspension. In the control series 2 animals were injected with a 1:9 suspension, whereas a 1:4 suspension was employed in the remaining 6.

The 10 treated rabbits received daily intramuscular injections of a saline suspension of cortisone acetate (Merck) for 15 days after the intrathecal administration of talc. Eight of these rabbits received cortisone for 2 days prior to the cisternal injection, while 2 received no such pretreatment. Nine rabbits received 10 mg cortisone per kilogram and one 5 mg/kg intramuscularly.

All cisternal injections were carried out under nembutal anesthesia. The talc suspension was administered slowly (15-20 seconds) to avoid respiratory arrest resulting from acute pulmonary edema(6).

All animals were sacrificed 15 days after injection. The brain and meninges were fixed in 10% formalin. Sections were stained with hematoxylin and eosin.

Results. Following cisternal injection, transient tonic and clonic convulsions were observed in several rabbits shortly after the talc administration. No permanent neurological lesions were seen. In no instance was evidence of meningeal infection found.

The average weight loss of the cortisone-treated rabbits was 625 g, whereas that of the control rabbits was 314 g. Although the difference in the mean weight loss appears significant, it must be pointed out that certain control rabbits lost more weight than some of the cortisone-treated animals. However, all the cortisone-treated animals appeared markedly lethargic and emaciated after 2 weeks.

In this series of experiments 2 animals died while receiving cortisone. One, treated with 10 mg/kg, died on the 7th day after intrathecal injection, and the other, on 5 mg/kg, died on the 11th day. The exact cause of death could not be determined in either instance.

In the control group there was diffuse thickening and opacity of the meninges, especially in the area of the brain stem, whereas in the treated animals the translucency of the normal meninges was better preserved. The differences observed grossly were not as striking as those seen histologically.

Microscopic sections from the control group revealed primarily a phagocytic, histiocytic response with some fibroblastic and minimal angioblastic proliferation. Foreign-body giant cells appeared to engulf individual talc crystals, and dense adhesions were present in certain locations between pia and arachnoid membranes. The talc particles were easily visualized under polarized light because of the doubly refractile quality of the crystals (Fig. 1).

In contrast to the controls, the meningeal response of the treated animals was consid-

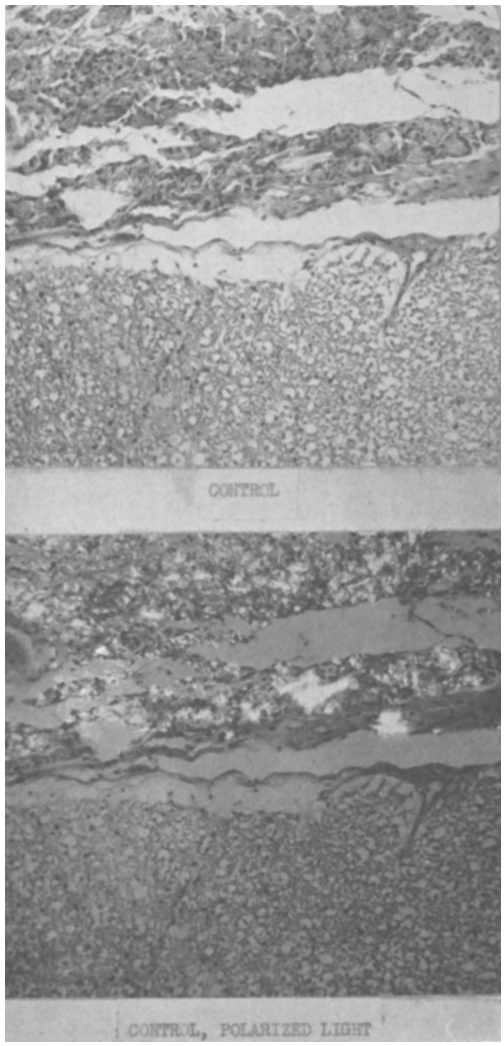

FIG. 1. Photomicrograph of leptomeningeal reaction in an untreated rabbit 15 days after cisternal injection of sterile talc. Note fibroblastic and phagocytic response. When viewed under polarized light, talc crystals may be seen. × 105.

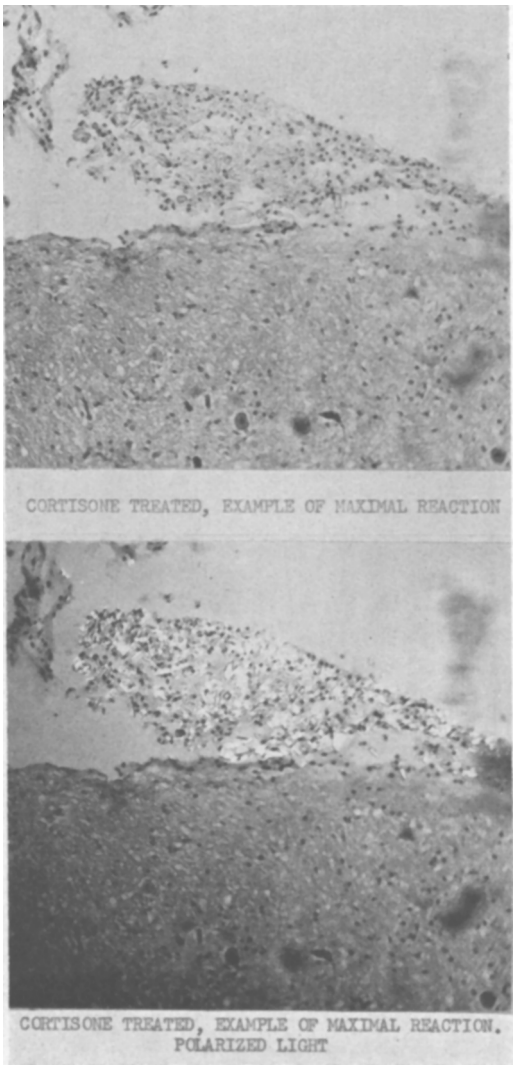

FIG. 2. Maximal reaction to talc seen in a rabbit treated 2 days before and 15 days after cisternal injection of talc with 10 mg cortisone/kg. There is minimal meningeal reaction. Talc crystals may be seen under polarized light. × 105.

erably diminished, although the degree of reaction varied from animal to animal. The extent of this variation is indicated in Fig. 2 by examples of maximal and, in Fig. 3, by the minimal meningeal response in cortisone-treated animals. Often loose collections of talc crystals could be seen lying free in the subarachnoid space without evident reaction (Fig. 3). Even when the presence of talc elicited a histiocytic response, individual crystals were generally not engulfed by phagocytes. No adhesions between pia and arachnoid were established.

Evaluation of the degree of meningeal reactivity was entirely subjective, and no attempt to quantitate the cellular response was made.

Preliminary experiments with intrathecal hydrocortisone. To avoid the systemic toxicity of parenterally administered cortisone, the use of intrathecal hydrocortisone suggested itself. Accordingly, using sterile precautions,

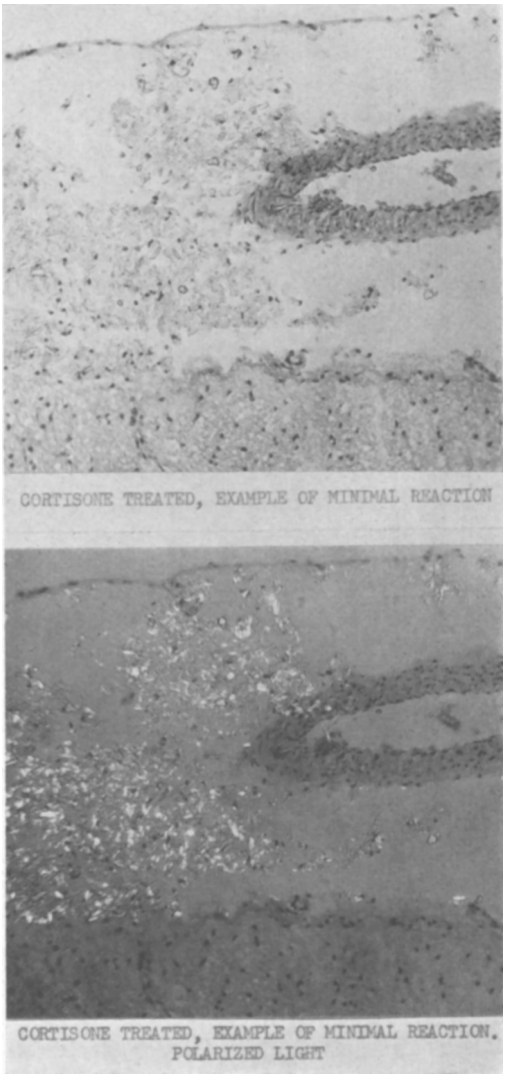

FIG. 3. Minimal reaction to talc seen in a rabbit treated similarly to that shown in Fig. 2. There is almost complete absence of meningeal reaction. Talc crystals may be seen under polarized light. × 105.

3 animals received 10 mg (0.4 cc) of a saline suspension of hydrocortisone acetate (Merck) as well as 1.0 cc of a 1:4 sterile saline suspension of talc in a single intrathecal injection. On the 7th day another dose of 10 mg hydrocortisone was administered by the same route. In order to assess the effect of the hydrocortisone suspension on the meninges, 3 animals received 10 mg of hydrocortisone plus 1.0 cc saline, followed on the 7th day by another equal dose of hydrocortisone. Following the intrathecal administration of hydrocortisone both with and without talc, the animals showed striking convulsive behavior, extensor rigidity, and marked tachypnea for approximately 1 hour following the injection. There was complete recovery in every animal, and no residual neurological abnormalities were noted. No attempt was made to determine whether the hydrocortisone or the vehicle, including 0.9% benzyl alcohol, was responsible for the immediate clinical reaction. One of the animals injected with talc and hydrocortisone died on the 12th day; the cause of death was not ascertained.

The microscopic appearance of the meninges of the 2 surviving animals injected with talc and hydrocortisone showed some diminution of the meningeal reaction, although this effect was not as striking as with cortisone. The animals, however, did not show the emaciation and lethargy characterizing those treated with cortisone, and the weight loss averaged 240 g as compared to a mean weight loss of 625 g in the cortisone group. The gross and microscopic appeance of the meninges of those animals injected only with hydrocortisone was not abnormal.

Summary. Eighteen rabbits received intrathecal injections of 1.0 cc of talc suspension and were sacrificed 15 days later. Eight rabbits were untreated, serving as controls. These developed a meningeal reaction consisting of the appearance of histiocytes, macrophages, and giant cells. Ten animals treated with daily injections of 5 and 10 mg cortisone/kg showed a marked diminution of the meningeal response. Preliminary experiments with the use of hydrocortisone, injected intrathecally (10 mg) on the 1st and 7th days, also suggest diminution of the meningeal response to talc, though not as striking as with the use of intramuscular cortisone.

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Effects of Pressor and Depressor Agents on Pulmonary and Systemic Pressures of Normotensives and Hypertensives.* (20512)

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Hypertrophy of the right ventricle does not occur in uncomplicated essential hypertension (1). This well established observation indicates that pulmonary artery pressure is normal in hypertensive patients. Cournand (2) found normal right ventricular pressures in 5 hypertensives and used this as evidence that the pulmonary arterial system lacked vasomotor function comparable to that of the systemic arterioles. Normal pulmonary arterial pressures have been observed in a few hypertensives by others (3-6).