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STERILE CUTANEOUS PUSTULAR REACTION*

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This paper reports an experimental animal model for the production of one type of intraepidermal pustule. A number of dermatologic disorders of unknown etiology contain intraepidermal pustules.

In addition to the naturally occurring pustular diseases, pustules can be induced on the skin of man by the local application of substances which are known to produce a "pustular patch test" (1). The most common patch test substances producing pustules are fluoride, iodide, nickel, and arsenates.

Recently, it has been shown that systemic or local iodides will increase the inflammatory response at sites of induced inflammation (2). It has also been shown that a 5% nickel sulfate patch test over a prepared site will consistently produce a pustular patch test in man (3). The site is prepared by the injection of dead bacteria.

In unpublished work, Stone and Willis succeeded in producing pustular patch tests over sites of induced inflammation in experimental animal models. During the study, it was noted that the lower abdomen of the rabbit developed pustules to 2.5% or 5.0% nickel sulfate patch tests in a linear pattern in sites of trauma. In the presence of nickel sulfate, a scratch would become a continuous double row of intraepidermal pustules (Fig. 1).

METHODS AND RESULTS

All projects were carried out on adult white male rabbits (7–10 pounds). Occasional animals showed marked generalized pustules over nickel sulfate sites if tested on the same day that they were clipped. The studies were done with animals clipped in advance. A 1% nickel sulfate solution patch tests will usually produce pustules along the scratch. A 5% solution was used because it always produces pustules. When 5% nickel sulfate is applied to nontraumatized sites, pustules do not occur.

Part 1: Six rabbits were scratched with a needle on both sides of the upper abdomen. The scratch was into the upper dermis but it did not cause bleeding. Five per cent nickel sulfate was applied to one side and tap water to the other (1 cc each) on gauze and then occluded separately under plastic. At 24 hours, there were no pustules in the water control sites. The sites covered by nickel sulfate had developed into a continuous double row of pustules with one row on each side of the scratch. Six pustular areas were opened and cultured on blood agar and thioglycollate medium. All were sterile by this method. Erythema surrounded these rows of pustules which were about 2 mm in diameter. Characteristic lesions were biopsied at 24 hours and showed a marked destructive reaction. As mentioned before, these lesions at 24 hours were too destructive to permit detailed interpretation. Histologically, the area of the pustule showed an intraepidermal accumulation of polymorphonuclear cells and an intact stratum corneum (Fig. 2). Considerable cellular debris was present in the pustule. At the edges of the lesion, the basal cell layer was still intact, but there was a defect in the center which was immediately over a massive subepidermal infiltrate of polymorphonuclear cells, fibrin, and cellular debris (Fig. 3). There was some similar reaction deep into the dermis which contained hair follicles. Biopsies of control sites revealed some areas of upper dermal edema, a mild infiltrate of mononuclear cells and very few polymorphonuclear leukocytes. The epidermis was not invaded by cells.

Part 2: Six animals were injected at four sites on each side of the upper abdomen with normal, pyrogen-free, saline, and the exact site of the needle insertion was marked. Occlusion with nickel sulfate was as described in Part 1. At 24 hours, there was a pustule, not at the site of needle penetration, but at the center of the wheal that was produced by

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FIG 1. Pustules form in a double row on each side of a scratch. One part of "S" was stroked twice and developed two double rows. From lower abdomen on day of clipping, so a few spontaneous pustules are present. Area covered with 5% nickel sulfate for 24 hours.

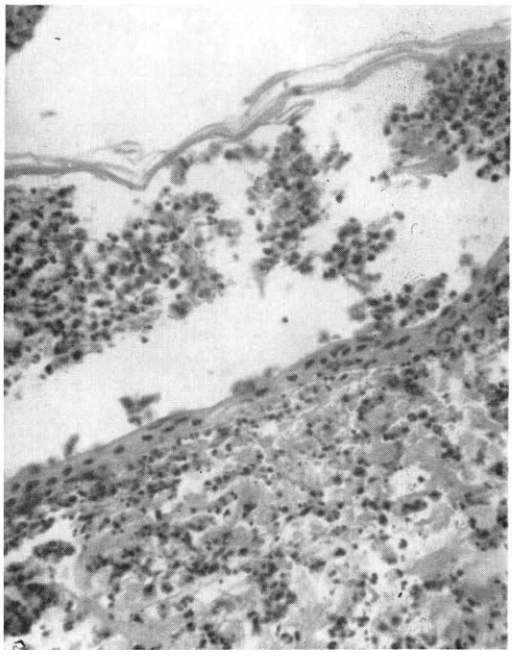

FIG 2. Lateral aspect of intraepidermal pustule with basal layer intact. (24 hours)

the saline. Control sites were all negative. Cultures and biopsies were the same as in Part 1.

Part 3: Solutions of nickel sulfate at concentrations of 1/100, 1/1,000, and 1/10,000 in pyrogen-free saline were injected directly into the upper dermis of the rabbit's abdomen. In all six animals there was no reaction from 1/1,000 or 1/10,000. At the site of injection of 1/100 there developed a slight erythematous reaction (4 mm) but no pustule. No pustules or progression occurred over a 72-hour period.

Part 4: Ten rabbits were marked with two lines (1 cm each) on each side of the abdomen. Each of the lines or one side of the abdomen was infiltrated slowly and as superficial as possible with 1 cc of hyaluronidase* containing 150 units. The control side was not injected. After 15 minutes, each site was scratched with a needle to the depth of the upper dermis. Each site was then covered with a solution of

* Wydase—bovine testicular hyaluronidase (Wyeth).

FIG 3. Upper dermis at 24 hours

5% nickel sulfate in an occlusive patch test utilizing plastic and porous tape.* At 24 hours, the sites were uncovered. There were no pustules at the sites infiltrated with hyaluronidase. All the control sites had a continuous row of pustules on both sides of the scratch. The pustules were cultured on blood agar and no growth occurred. Biopsy of the pustular lesions revealed the same histopathology as previously reported in Part 1.

Injection of 1 cc of normal saline under sites before scratching and nickel patches produced pustules over the entire area infiltrated.

DISCUSSION

Application of 5% nickel sulfate to the abdomen of a rabbit converts a simple scratch into a double row of intraepidermal pustules. When normal saline is injected into a site covered by nickel sulfate, the exact site of trauma of the needle penetration does not produce a pustule, but the site of edema produced by the wheal becomes a pustule. Sites infiltrated with hyaluronidase before scratching did not develop the pustular reaction when occluded with 5% nickel sulfate. It appears that injury severe enough to produce edema of the upper dermis is a major event in inducing the pustular response. As we stated previously (2), we feel that we may be interfering with the enzymes of inflammation.

Pinkus and Mehregan (4) have reviewed the ideas of Civatte (5) on the development of Munroes' abscess in psoriasis and seborrheic dermatitis. Their theory, based on histologic examination of clinical disease, essentially states that the papilla becomes edematous and its capillary becomes engorged. The capillary allows serum and leukocytes to escape into the suprapapillary epidermis, thereby damaging the keratinocytes in this region. The leukocytes then move upward with the epidermal cells. In their discussion they made it clear that they felt this is a mechanism involved in many skin diseases. The availability of a test model for studying intraepidermal pustules may increase our understanding.

We feel the best name for the phenomenon is the "sterile cutaneous pustular reaction." We use the word "sterile" only to imply that it is not a bacterially-induced lesion as it occurs in this experiment.

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SUMMARY

1. The application of a 5% nickel sulfate patch test to a scratch on the rabbit's abdomen results in a double row of intraepidermal pustules.

2. Injection of hyaluronidase prior to scratching the site and application of the nickel sulfate patch inhibits pustule formation.

3. The induced pustules are very similar to the pustules that occur with the pustular patch test.

4. There are many dermatologic disorders of unknown etiology which contain intraepidermal pustules. An experimental model is now available to study at least one type of intraepidermal pustule.

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