EXPERIMENTAL STUDIES ON THE ETIOLOGY OF TYPHUS FEVER.

VI. SKIN LESIONS IN EXPERIMENTAL TYPHUS FEVER OF GUINEA PIGS.

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In a previous article mention was made of specific vascular and nodular lesions in the corium of the skin in experimental typhus fever of guinea pigs. With a few exceptions, among whom are Löwy and Wolbach, other workers in this field, notably Otto and Winkler, Otto and Dietrich, and Neill, have failed to find the lesions in the experimental disease. Hence no agreement on their presence in infected guinea pigs has been reached. Their recognition would be less difficult if the skin lesions could be intensified and consequently be made to appear in the form of an exanthem. This procedure, furthermore, would furnish another means for the precise definition of experimental typhus in the guinea pig. A further advantage would be the ease with which examinations for histopathology could be performed by merely excising the exanthematous areas. In this way, also, the possible incitant of the lesions might be studied. A number of tests could then be made at different periods of the fever without killing the animal. Finally, a cutaneous rash would be an additional indication of the identity of the experimental disease with typhus fever in man.

In this paper the exanthematous reaction which the typhus virus produces in guinea pigs will be demonstrated by a method suggested by the experiments of Rivers and Tillett in transmitting the chicken-pox virus from man to rabbits.

Methods.

The method consisted, in brief, of irritating a limited area of the skin of a guinea pig before the onset of the febrile or active stage of the disease, thus localizing the effects to the particular area. We sought for a mild irritant such as would not produce a dermatitis that would be confusing. After experimenting with a number of irritants, as ether, chloroform, adhesive plaster, mustard paste, and tar, applied to the shaved skin, and with depilation by means of calcium sulfide, we adopted finally simple shaving as the most satisfactory procedure.

The method employed for the demonstration of the exanthem was to select a white animal or one with an abdomen free from pigment and to clip the hair of the entire anterior abdominal wall with a No. 00 clipper. After lathering freely with ordinary white, alkaline, hand or toilet soap, we shaved this portion closely. In most instances the shaving was repeated on alternate days to clear the area of rapidly growing hair. The abdominal wall was prepared in this way on the 9th or 10th day after the inoculation with the typhus virus, or about 1 day before the onset of fever. A normal, uninoculated guinea pig was similarly treated in each experiment as a control.

Thus the normal appearance of the skin can be preserved so that an exanthem or other changes may be noted. However, by a more active or destructive irritation, a dermatitis is induced usually in the form of a hyperkeratosis. The inflammation then obscures any exanthem, but the histopathological lesions in the deeper layers of the skin become thereby more pronounced and numerous. A satisfactory procedure to effect this more severe dermal reaction consists of rubbing the skin briskly for a few seconds with ether or chloroform immediately after shaving, and once each day thereafter.

The typhus virus, in the form of defibrinated blood, or of saline solution suspensions of cerebral or of splenic tissue, was inoculated intraperitoneally, under chloroform anesthesia, in more than 40 guinea pigs, of which all showed the histological or exanthematous lesions to be described. The virus was originally derived from the blood of a typhus fever patient and was in at least its 100th animal passage when the following observations were made.

Effects on the Skin.

On the 1st day of the experimental fever in guinea pigs, the skin shows a peculiar hyperemic redness which spreads over the entire

shaved area. This darkening of the natural tint persists for about 3 days; thereafter the normal color is restored. On the 2nd, but more often on the 3rd day of the fever, a distinct exanthem is noted, usually along the lateral areas and groin of the prepared portion of the skin. The eruption appears first as faint, hyperemic rose spots from pinpoint size to 1.5 mm in diameter. These are few in number, scattered, and fade on pressure. Within a few hours, they become macular and distinctly petechial; the color changes to copper-red. They do not completely disappear on pressure at this stage, as the center always remains visible. The number of these faint macules increases so that on the 4th day of fever about 25 or 35 distinct lesions may be seen in an area 7 by 6 cm. They persist throughout the febrile stage, fading however, as the defervescence is reached. In some animals a faded exanthem is evident on the 1st or 2nd day of convalescence. In one instance, in addition to the rash, there was noted a purplish diffuse hemorrhagic area measuring 1 by 0.5 cm.

With guinea pigs when the more intensive method of irritation is employed, the resultant hyperkeratosis obscures the exanthem. In these animals, however, the histopathological lesions in the deeper layers of the skin are more pronounced and numerous than those which occur in the corium of infected guinea pigs whose epidermis has either not been treated or but mildly irritated.

The histopathology of the lesions in the corium has already been described as consisting of nodular areas similar to those present in the brain, testicle, heart, and other organs. These nodules are composed mainly of endothelial leucocytes, or monocytes, together with a few leucocytes of the mononuclear and polymorphonuclear types. They are always to be found in proximity to the capillaries and arterioles. The endothelium of the vessels in certain areas is swollen and necrotic and the vascular lumina may contain thrombi. Surrounding the vessels, a collar of one or more layers of monocytes is seen. In addition, there are small and localized hemorrhages.

Microscopically the macular spots consist of an exudation of serum with formation of small vesicles beneath the cornified layer and a proliferation of monocytes in the stratified epithelium. Hemorrhages into the epidermal layers and necrosis of the epithelial cells are also manifest. In instances in which more intensive methods of irritation
are employed, these lesions, under a much thickened cornified layer, are more marked and extensive.

CONCLUSIONS.

The skin of guinea pigs in which the virus of typhus fever is propagated, when mildly irritated in advance of the febrile reaction, shows a characteristic exanthem during the height of the experimental disease. More drastic methods of irritation, however, cause a dermatitis which obscures the rash but produce in the corium more marked specific histopathological changes. The exanthem may aid the study of the specific incitant of typhus fever in the lesions.