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An Agent, Transmissible to Mice, Obtained during a Study of *Pemphigus vulgaris.*

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The frequent symmetrical distribution of the cutaneous manifestations of *Pemphigus vulgaris* and their resemblance to trophic lesions as well as the limitation of the pathologic changes to the skin and nervous system have suggested a neurotropic etiologic agent of the disease. Carol[1] has summarized the work of earlier investigators in this field and has recorded his own results following intracerebral inoculation of pemphigus material into rabbits, guinea pigs, monkeys, and mice. He concluded that a specific virus of pemphigus could not be demonstrated by the methods hitherto employed. We, however, felt that there was more likelihood of the transmission of an etiologic agent of pemphigus to animals if the resistance of the animals was previously lowered by irradiation. The results obtained by the inoculation of blister fluid and spinal fluid from 3 cases of *Pemphigus vulgaris* into the brains of irradiated mice are recorded here.

Case I, D. R., an adult female, had been sick for 6 months when bacteriologically sterile blister fluid was obtained 23 days before death. Five mice which received a generalized x-ray dose of 400 r. were inoculated intracerebrally with 0.03 cc. of fluid. Three weeks later all were sick. One was killed on the 22nd day, another died on the 94th day, and the remainder recovered. A 40% bacteriologically sterile emulsion in physiologic saline of the brain of the killed animal was used for passage. All of the animals which received the brain emulsion became sick in the second week after inoculation and died by the 27th day. The active agent has since been transmitted for 46 passages and at present 0.03 cc. of a 5% emulsion of bacteriologically sterile infectious brain material kills 90 to 100% of the mice in 7 days. The animals usually show signs of illness 2 to 4 days after inoculation. The coat becomes rough, the back humped, and they appear to walk on the toes. Loss of weight and pallor often become apparent at this time. Later the humping of the

[1] Carol, W. L. L., Prakken, J. R., Ruiter, M., Snidjers, E. P., and Wielenga, D. K., *Arch. f. Dermat. u. Syph.*, 1937, **175**, 265.

back increases markedly, ataxia may develop, and wasting and apathy progress until the animal dies. Hyperirritability frequently occurs and is sometimes so pronounced that the slightest tactile stimulus causes the animal to leap high in the air. Occasionally a hyperirritable animal shows rapid, apparently uncontrollable, head movements.

Histologic examination has as yet been confined to the brain and meninges which show necrotic areas filled with polymorphonuclear leucocytes, perivascular collections of mononuclear cells and occasional plasma cells. All of the brains examined histologically in this study were bacteriologically sterile on aerobic and anaerobic culture.

It has also been found possible to infect non-irradiated mice by intracerebral inoculation of bacteriologically sterile infectious brain material from irradiated mice and vice versa. The active agent was transmitted from non-irradiated to non-irradiated mice for two passages. No more than 2 such passages were made as it was felt that the active agent could not be maintained as well thus as in irradiated animals. The mortality rate in these 2 passages was very similar to that observed when non-irradiated mice were inoculated with infectious irradiated brain, namely, 50-60%.

The clinical and histologic pictures in the infected non-irradiated animals were identical with those observed in the infected irradiated mice.

Case II, W. H., an adult male, had been sick for one year when bacteriologically sterile spinal fluid was obtained in December, 1936. He was alive in July, 1937. The fluid was inoculated intracerebrally into 5 irradiated mice. Passage was made from a sick animal killed on the 34th day, using a 40% emulsion of bacteriologically sterile infectious brain material. Although the active agent increased in virulence with successive passage so that, later, a 20% bacteriologically sterile emulsion could be employed it could not be transmitted for more than 7 passages. Clinical and histologic pictures of the infected animals were identical with those found in Case I.

Case III, P. R., an adult male, was ambulatory and had been sick for 3 weeks when bacteriologically sterile blister fluid was obtained. He was not seen again. The fluid was inoculated intracerebrally into 7 irradiated mice. Six showed definite signs of illness in 10 days and one died on the 3rd day, a second was killed on the 14th day, and another died on the 30th day. An unsuccessful attempt at passage was made with the brain of the animal which died 3 days after inoculation. Histologic examination of the brain of the animal

which was killed 14 days after inoculation showed perivascular collections of mononuclear cells in the meninges.

Guinea pigs were not susceptible to the strain obtained from Case I inoculated either intracerebrally or subcutaneously.

The activity of infectious brain material could be preserved for at least 5 days in the ice box at 8°C.

Control animals were of 3 groups. Both control and test animals were irradiated at the same time. One group remained uninoculated and was observed for the effects of irradiation. A second group was inoculated intracerebrally with 0.03 cc. of bacteriologically sterile blister fluid obtained from a normal human subject by the application of cantharides plaster. The third group was inoculated intracerebrally with 0.03 cc. of a 40% emulsion of bacteriologically sterile irradiated normal mouse brain. Passages were made of the brains of the control mice of the latter 2 groups at the same time interval and in the same concentration as the infected animals. Forty to 50% of the control animals of each group died. Control mice died usually without any apparent period of illness, and histologic examinations of their brains did not show the inflammatory changes observed in the infected animals.

Summary. Definite clinical and pathologic changes were produced in irradiated mice inoculated intracerebrally with bacteriologically sterile blister fluid from 2 cases and spinal fluid from one case of *Pemphigus vulgaris.* In 2 of these cases serial transmission of the active agent was carried out with bacteriologically sterile material. Identical changes were produced in a smaller proportion of non-irradiated mice using infectious irradiated brain material as the primary inoculum. Control animals did not show the clinical and pathologic changes of the infected animals. Further study is necessary to determine the nature and properties of the active agent and its relation to *Pemphigus vulgaris.*