the results of the successful inoculation of the chorio-allantois with fungi.

During the year of March, 1938, to 1939, work was started at Barnard Hospital to determine the possible virus etiology of a number of skin diseases, the causes of which are obscure. We have been equipped with the apparatus to carry on the technique of chick egg inoculation as practised in Goodpasture's laboratory and as elaborated by Goodpasture and Buddingh.[3] Dr. Floyd S. Markham, who has been carrying on the virus work, assisted in the inoculation of the chick membranes with fungi.

A wide variety of pathogenic fungi have been used, representing the causative agents of diseases which affect: (1) the superficial layer of the skin; (2) mucous membranes; (3) dermis and subcutaneous layers; (4) internal viscera. These organisms are known to produce pityriasis, superficial desquamations, localized granulomata, deep-seated ulcerative lesions, mucous membrane plaques; lymph stream invasion with dermic and subsequent epidermic involvement and visceral or generalized diseases. These microbes produce the following diseases: seborrheic dermatitis, tinea versicolor, endomycosis, geotrichosis, moniliasis, blastomycosis, coccidioidal granuloma, sporotrichosis, maduromycosis, trichophytosis, epidermophytosis, microsporosis, favus, cryptococcosis, paracoccidioidal granuloma, chromomycosis and actinomycosis.

The fertilized eggs used were 12 to 14 days old. Inoculations from cultures of the fungi were made directly on the chorio-allantoic membrane. The embryo lived from 4 to 11 days after inoculation, depending on the type of organism used. Macroscopically the diseases manifested themselves as thickened or thin, white, grayish or grayish-brown, confluent or discrete plaques on the membrane, depending again on the variety of fungus.

The infected membranes were fixed in Zenker's, embedded in paraffin, sectioned and studied. Histopathologically, the reaction of the tissue manifested itself in the form of nodules, ulcers, superficial growths and hyperplastic lesions, which were comparable in most instances to those seen in human infections. Further microscopic examination showed an increased activity in the membranes, as was evidenced by the intense infiltration, particularly with the invasive type of organism, of ectodermal cells, blood cells, fibroblasts, monocytes, accompanied in most cases by inflammatory changes in the mesoderm and marked edema at the sites of fungus growth. The thickening of the membrane in some cases was due to the cellular infiltrate, in others where the organism is known to produce granulomatous lesions, to the mat of mycelial elements of the fungus, but in most cases to the combination of both. Those membranes parasitized by *Monilia albicans,* in addition to the marked proliferation and hypertrophy of the ectoderm, showed, in the mesoderm, pearls of growth which correspond in human tissue to an increased hyperkeratinization. A degree of tissue specificity was also demonstrated in that fungi affecting mucous membranes and the superficial layer of the skin particularly involved the ectoderm, whereas those found affecting the dermis, subcutaneous layers and internal viscera seemed to affect in addition the entoderm and mesoderm. Intra-amniotic, intra-cerebral and body injections will be carried on to determine absolute specificity of tissues in the chick embryo to the various fungi.

The fungi stain very easily in section with methylene blue and eosine. In most cases the organisms revert to the forms seen in human lesions—their parasitic role. This reversion in morphology is complete with the yeast-like organisms in approximately 6 days, whereas with some filamentous forms it begins on the fifth day and is complete on the tenth or eleventh day.

In summary, it can be said, therefore, that the chorio-allantoic membrane of the developing chick can be successfully inoculated with pathogenic fungi. The organisms produce fatal mycoses with most microbes which in tissue response simulate closely human lesions, showing a degree of specificity as found in infection in man. This method, as contrasted with the use of standard laboratory animals, is much less expensive and, more significant than that, reduces the time elements from weeks or months to days. The inability to find suitable experimental animals or human volunteers enhances the value of the use of the chorio-allantois for fungous inoculations.

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[3] E. W. Goodpasture and G. J. Buddingh, *Am. Jour. Hyg.*, 21: 319, 1935.

THE TRANSMISSION OF LYMPHOCYTIC CHORIOMENINGITIS BY MOSQUITOES

ONE year ago a highly virulent spontaneous infection occurred among rhesus monkeys that were being used in this laboratory for the study of experimental malaria. The severity of the infection was such that eleven monkeys died in a week. The infection was characterized by dependent edema, serosanguineous nasal discharge, marked prostration and extremely rapid course. At death the outstanding gross abnormalities were partial consolidation of the lungs and an abundant collection of straw-colored fluid in the serous cavities. The causative agent of the epizootic was identified by Dr. Thomas Francis, Jr., as being the virus of lymphocytic choriomeningitis. Under normal conditions the mode of transmission of this disease, either in man or animals, is unknown, but since the

virus was found to be present in high concentration in the circulating blood of some experimental animals, the possibility of an insect vector was considered. Experiments completed have demonstrated the ability of *Aedes aegypti* mosquitoes to transmit the disease to guinea pigs by bite.

In the initial experiment a guinea pig was inoculated subcutaneously with 1.0 cc of a 1–10 dilution of frozen and desiccated blood from one of the monkeys which had died 6 months previously. On the seventh day following inoculation, when the guinea pig was obviously ill, a lot of normal *Aedes aegypti* was allowed to feed upon it. Five days later seven of these mosquitoes were first allowed to bite a normal guinea pig, then were ground finely in a mortar with normal saline and injected into another normal guinea pig. The guinea pig which received the injection of killed mosquitoes died on the seventh day, and the one which was bitten by the same insects died on the eighth day. Before death another lot of normal *Aedes aegypti* was allowed to feed upon the latter animal. These mosquitoes also produced a fatal infection when six days later fifteen of the insects were permitted to bite a normal guinea pig, thus establishing two serial consecutive guinea pig-mosquito-guinea pig passages.

Other experiments have shown that the mosquitoes are capable of transmitting the virus as early as the fourth day and at least as late as the fifteenth day after feeding on an infected animal. Death has occurred between the eighth and eighteenth day following the bite of infected mosquitoes, while duplicate guinea pigs which were inoculated with an emulsion of the same mosquitoes usually died twenty-four to forty-eight hours earlier. In one experiment the bite of sixteen mosquitoes caused death on the eleventh day, while the bite of four mosquitoes from the same lot produced no obvious signs of illness. However, the surviving animal was later shown to be immune when inoculated with a large dose of known living virus. The study is being extended to include other hosts and vectors.

The virus of lymphocytic choriomeningitis in guinea pigs dying following the bite of infected mosquitoes was identified by means of a specific immunity test. The virus was neutralized by known immune guinea pig and immune monkey serum. The latter was from a monkey which survived the epizootic mentioned above and was found by Dr. J. E. Smadel, of the Rockefeller Institute, to contain both complement-fixing and neutralizing antibodies against a known strain of lymphocytic choriomeningitis virus.

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INCREASED GLYCURONATE EXCRETION FOLLOWING ADMINISTRATION OF SULFAPYRIDINE[1]

IN the course of the isolation of urinary excretion products of sulfapyridine,[2] a urine concentrate containing a diazotizable substance in concentrations considerably above the solubility of sulfapyridine or its acetyl derivative was obtained. This suggested, among other things, that the drug might be excreted in part as a sulfate or a glycuronate. Concurrent with isolation studies, we have followed the glycuronate[3] excretion in two normal males on a carefully controlled diet after the administration of a single dose of five (5) grams of sulfapyridine. A pneumonia patient was similarly studied. In each case, the glycuronate output was markedly increased during the first twenty-four hours and fell to normal within two to four days. The glycuronate concentrations paralleled the urine levels of sulfapyridine.

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