Up to the present time no evidence has been advanced to show that the organisms multiply in sewage, so that in the present state of our knowledge alternative (a) is more probably correct.

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RECENT EXPERIMENTAL WORK ON THE AETIOLOGY OF HODGKIN'S DISEASE*

BY

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Recent work on the aetiology of Hodgkin's disease has served to bring fresh interest to bear on the nature of this condition.

In 1930 L'Esperance reported having isolated the avian tubercle bacillus from cases of Hodgkin's disease and claimed to have reproduced the condition in chickens. These claims have been investigated by Davidson (1933), the workers of the Rose Research on Lymphadenoma (1932), van Rooyen (1933), and others, all of whom failed to reproduce the disease in birds or to isolate the avian tubercle bacillus from human lesions in the disease. In 1930 Twort found that the subcutaneous inoculation of a guinea-pig with a suspension of Hodgkin lymphatic tissue produced after three to four days a swollen inflammatory nodule, in which no bacteria could be demonstrated by the application of ordinary methods. The workers of the Rose Research on Lymphadenoma (1932) next published an extensive series of observations on the pathology of the condition, showing that neither spirochaetes, yeasts, diphtheroids, nor acid-fast organisms were responsible for the causation of the disease.

THE ENCEPHALITIC SYNDROME IN RABBITS

Among the many findings of the last-named workers those of M. H. Gordon were perhaps of the greatest significance. He found that the intracerebral inoculation of rabbits with suitable suspensions of lymphadenomatous tissue was followed in three to four days by highly characteristic changes affecting the central nervous system of the animal. The sequence of events was: initially, slight impairment of locomotion, this being followed by progressive ataxia, muscular incoordination with spasm, spastic paralysis of the hind limbs, and frequently accompanied by incontinence of urine and faeces. The severity of these lesions produced in the rabbit were to some extent dependent on the acuteness of the case from which material was derived. Thus tissue from an acute case of Hodgkin's disease produced, in addition to the foregoing changes, violent convulsive movements, head retraction, opisthotonos, and grinding of the teeth. Animals affected to such an extent inevitably died, but in the less severe type of lesion several recovered completely, and a few passed into a chronic state in which severe muscular atrophy and wasting were much in evidence.

This "encephalitic" syndrome, as described by Gordon (1932), was found to be highly specific in character, and

could not be elicited by the intracerebral inoculation of rabbits with material derived from cases other than those of Hodgkin's disease. This fact has been utilized by the writer (1933), who attempted to use this finding to form the basis of a biological test for the more accurate diagnosis of Hodgkin's disease.

The test has proved of value as an aid to the clinical and post-mortem diagnosis of this disease, particularly when the appearances presented are not entirely typical of the condition. In view of the satisfactory results obtained from the Gordon biological test, it has been proposed that material removed at biopsy and necropsy from suspected cases of Hodgkin's disease should be subjected not only to histological examination, but also to this animal inoculation test. It must be emphasized, however, that a rabbit which exhibits the encephalitic syndrome reveals no cultivable bacterium in either its brain or meninges. Hence, prior to the acceptance of a positive result in any animal, the possibility of bacterial infection being responsible for the effects manifested should first be excluded by appropriate methods of bacteriological examination.

ITS AETIOLOGY

From the theoretical standpoint one or other of the following causes might be responsible for the production of the condition.

- (a) Trauma following damage by mechanical irritation.
- (b) A specific neurotoxin present *in vivo* in lesions of Hodgkin's disease, or produced *in vitro* by changes in the tissue of the lesion after removal from the body.
- (c) The action of a virus specifically associated with the disease and producing an effect on the nervous system of the rabbit.

The complexity of this problem, combined with the incomplete state of our knowledge regarding diseases produced by ultra-microscopic viruses in general, render it extremely difficult to express a dogmatic view regarding the nature of the pathogenic agent under discussion. I propose, therefore, merely to discuss the arguments relative to the above-mentioned hypotheses, guided by the experimental evidence so far advanced.

HISTOLOGICAL CHANGES IN THE RABBIT'S BRAIN

Below is a discussion on trauma and the histological changes produced experimentally following intracerebral inoculation with Hodgkin tissue and with a variety of other substances.

The chosen site of inoculation lies in the occipital lobe of the rabbit, and is situated well behind the motor area of its brain. Histo-pathological changes following the inoculation of Hodgkin tissue into this area were relatively slight in character. They revealed the occurrence of some localized haemorrhage occupying the path of the needle, and surrounded by a zone of lymphocytic infiltration. Occasionally similar infiltration of the meninges overlying the point of inoculation was also noticed, but this finding was too inconstant to be regarded as a regular feature. It may be stated that the slight histo-pathological changes produced in the experimental animal were not sufficient to account for the progressive degree of disability produced in the living animal. On the contrary, it could be shown that very severe damage could be inflicted to the brain tissue of the occipital lobe without in any way reproducing Gordon's encephalitic syndrome.

Such experimental damage may be deliberately produced by the intracerebral introduction into this area of chemical and mechanical irritants, such as turpentine, aleuronat, sodium nucleinate, quinine-urethane, or powdered glass. Likewise, the use of milk, dead bacteria—for example, *B. pyocyaneus*, *B. typhosus*, and *B.*

* Read in the Section of Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Dublin, 1933.

anthracis—carbon particles, or human lymphoid tissue affected with a variety of different pathological conditions, could similarly be injected intracerebrally without in any way reproducing the syndrome under discussion. Histologically, however, the brain of an animal injected with any of the irritant substances mentioned above reveals extensive damage, changes such as severe haemorrhage, necrosis, degeneration, and cellular infiltration being evident microscopically in the brain of a rabbit which was apparently in good health prior to necropsy.

It is thus clear that the encephalitic syndrome cannot be regarded as the outcome of gross changes produced in a rabbit following the introduction of non-specific irritant substances into the brain of that animal.

TOXIN OR VIRUS?

The only unequivocal proof of the existence of a living virus is by means of its demonstration *in vivo* and *in vitro*, the former by serial propagation in the living animal and the latter as evidenced by its multiplication in artificial culture.

Neither condition has been fulfilled in the case of this pathogenic agent. The weight of experimental evidence so far advanced is equally capable of indicating the cause of the encephalitic syndrome to be the outcome of specific toxic activity or to its being that of a living virus. Thus the ability of this substance to withstand desiccation, to resist 73° C. for half an hour, to be annulled by the action of weak antiseptics, and occasionally to give rise to immunity phenomena (Gordon, 1932-3) is a common property of both a virus and a toxin. This agent has been

further stated by Gordon to be non-filterable, but the writer has latterly been able to demonstrate in a series of preliminary experiments that filtration could be effected under certain conditions. He also observed that tissue suspensions appeared to be most active when suspended in broth ranging from pH 6.2 to pH 7.2. This aspect of the subject is under course of investigation and will be dealt with later.

CONCLUSION

It can be stated that the encephalitic syndrome produced in the rabbit is specific for Hodgkin lymphoid tissue, and may consequently be utilized as a biological test for the diagnosis of the condition. The precise nature of the syndrome produced in the rabbit is not the outcome of a simple traumatic and inflammatory change produced in the brain of the animal, but is probably due to the action of either a specific toxin or a filterable virus, derived from the human subject suffering from Hodgkin's disease. The present available data regarding the nature of this pathogenic agent neither confirm the possibility of these effects being the results of a specific toxic activity nor exclude them from being due to the action of a filterable virus.

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THE MANIPULATIVE TREATMENT OF PAINFUL FEET *

BY

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There are many causes of painful feet, but, if serious injury and disease are excluded, they nearly all fall within the following classification: (1) chronic foot strain; (2) minor deformities, corns, etc.; (3) chronic arthritis.

Chronic foot strain is a term used to describe those cases in which there are painful feet without radiographic or other evidence of disease. The patient complains of pain, which in the early stages is localized and perhaps only occurs after unusual exertion; later, the pain becomes nearly constant and radiates widely, tending to spread up the leg as far as the knee. On examination, when the feet are passively put through their full range of movements, pain is produced at the extremes of one or more of the movements. A superficial oedema of the feet and ankles is not infrequently present; it gets worse towards the end of the day and disappears during the night. The pain is due to failure of the muscles controlling the joints of the feet, allowing strain to fall either on normal ligaments or on "adhesions." The pathology of adhesion formation is similar to that of any other scar tissue. Some trauma or strain ruptures a few fibres of a ligament, joint capsule, muscle, or perhaps only a few capillaries, and a small haemorrhage into the surrounding tissues occurs. The usual process of repair ensues and ends in the formation of a scar, which at this site is called an "adhesion." Pain is caused whenever such scars or adhesions are placed under tension, and there are only two ways of relieving it. The first is palliative and prevents the adhesions from being stretched. The second is curative; it ruptures the ad-

hesions and prevents them from being re-formed. The customary method of treating chronic foot strain has been the former; arch supports are fitted which aim at stopping any strain falling on the adhesions. The relief given by supports, however, is only temporary, because they fix the feet in such a position that the adhesions can contract yet further until, eventually, even the small amount of movement permitted by the supports will cause pain. The rational treatment is curative. The adhesions should once and for all be ruptured, and should then be prevented from re-forming by massage and exercises.

Minor deformities and chronic foot strain are not infrequently found to be associated. For example, a painful hammer-toe may cause the weight to be thrown on the wrong part of the foot and thus give rise to a chronic strain. If the strain only is treated it will continue to recur until the primary trouble is remedied. In the opposite way a chronic strain may result in a painful callosity forming on the ball of the foot, but, however often the callosity is cut, it will continue to re-form until the chronic strain is cured and ceases to cause misuse of the foot. Each case of painful feet requires most careful consideration of the factors involved, so that all the causes of pain may be removed and recurrence avoided.

Chronic arthritis of the feet is common in patients over 45 years of age. It is often of the "rheumatoid" type and may be part of a generalized condition, or it may be localized to the feet. X-ray photographs seldom show more than some bony rarefaction, and the outstanding feature is stiffness due to infiltration and contraction of the periarticular tissues. Manipulative treatment should be used with caution, but in selected cases it may give great benefit. By a careful combination of manipulation, physiotherapy, and suitable footwear it should be possible to make every patient at least tolerably comfortable, while a number can be freed of all symptoms for many years.

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