with the writer's kind regards

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AN EXPERIMENTAL INVESTIGATION INTO THE CAUSATION OF CANCER.

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I BROUGHT before you, gentlemen, in a former paper[1] certain positive results obtained in the course of an experimental study of the causation of cancer. I propose now to give you a short account of the continuation of a series of experiments upon the same subject. A double purpose will thereby be served, for it will show that, so far as I am concerned, the experimental side of the cancer question is limited, whilst the time of other investigators will be saved by stating the directions in which my work has failed. In the present series of experiments I assumed that a protozoon was present in cancer, and I have endeavoured to trace it from the tissue forwards into the soil, and thence onwards into the animal. I endeavoured to prepare each animal as far as possible for the reception of the germ by the methods which clinical experience has taught us to be the most favourable for its production or for its development. With this object in view, very old or very young animals were selected, and of varieties as far as possible removed from the wild type, for it is well known that fancy breeds are more delicate and are more prone to new growths than their wild fellows.

Mr. Haviland has come to definite conclusions in regard to the frequency with which cancer occurs in different localities. His results were arrived at entirely by statistical methods, and it therefore appeared to be worth while to ascertain whether they could be checked by experiment. In his book on *The Geographical Distribution of Disease in Great Britain*[2] Mr. Haviland says: "In the counties having a high mortality from cancer we find that the tributaries of the large rivers rise from soft, marly, or otherwise easily disintegrated rocks, and then fall into sheltered valleys, through which the main rivers flow. These rivers invariably flood their adjacent districts during the rainy season, and have generally their water coloured by the suspension of alluvial matter. The Thames counties characterised by their tertiary soil and frequently flooded river, form, as it were, a typical cancer field."

Dr. Fiessinger, who practises at Oyannax, a small town in the Department of the Ain, situated on the banks of the

[1] BRITISH MEDICAL JOURNAL, ii, 1893, p. 830.
[2] Lond., 1892 edit., p. 37.

Ange and the Sarsouille, in a similar manner has traced out a series of cases of cancer occurring almost in the form of small epidemics. He points out[3] that these outbreaks are particularly liable to occur on the banks of streams and at the edges of woods, though he does not, like Haviland, attribute them to the soil, but thinks that they are associated with the insects which abound in such situations. Lastly, those who had the good fortune to hear Mr. Shattock's recent Morton Lecture will not have forgotten Mr. Law Webb's most interesting case, where his patients seem to have suffered from the infective nature of cancer possibly transmitted through the agency of water.

Acting upon these hints, I obtained soil from the valley of the Warwickshire Avon about ten miles below Stratford, from the Thames at Oxford, from the Ouse at Bedford, and from the Kennet at Malton, in Yorkshire—all places of evil reputation, according to the statistics of Mr. Haviland, on account of the frequency with which cancer occurs in their neighbourhood. In each instance soil was taken from a low-lying district near the river after a heavy rainfall, when the floods had recently subsided, and from land situated below the town so that the soil might be saturated with as many impurities as possible.

The soil of the Avon was taken from that part of its course which is marked in Mr. Haviland's first series of maps in the deepest blue—that is to say, where the mortality from cancer is more than 7 for every 10,000 females living. The soil had been under cultivation for many hundred years; it was subject to seasonal floods, the flood water being usually discoloured by alluvium. The surrounding country is flat, so that the floods do not easily run off.

The soil from the Thames was taken from a point just opposite the mouth of the Cherwell, in one of the wettest Februaries of late years, when the rainfall in Oxford had been 0.72 inch above the average.[4] The mortality of this part of the Thames valley is given by Mr. Haviland's amended statistics as 4.5 annually for every 10,000 females living between 1851 and 1860; the district is therefore marked in his map a lighter blue.

The soil from the Ouse was taken in that part of its course where the mortality from cancer was about the same as that of the Oxford district.

The soil from Malton was sent to me by my friend Dr. Colby, who believes that cancer is increasing in the district for which he is the medical officer of health. Dr. Colby took the soil from a field which is liable to be flooded by the Yorkshire Derwent. Mr. Haviland showed in 1875 that the Pickering district, which immediately adjoins Malton, and is served by the same river, had a cancer mortality of more than 7 per 10,000 females living in it, and it is shaded in the deepest blue in his maps.

The soil thus obtained seemed to fulfil all the conditions required by Haviland for the successful propagation of cancer. I did not, of course, for an instant expect to find any cancer germ in this soil, nor did I look for it. I merely assumed that it might be, or might be made to become, the habitat of a hypothetical cancer organism. After assuming, for the sake of experiment, that such a germ existed, and

[3] *Rév. de Méd.*, 1893, p. 13.

[4] The *Times* March 28th, 1893, "London Water in February."

that a part of its life was passed in earth, the next step was to provide the organism. Carcinomata of various kinds were therefore taken directly from the operating theatre; they were freed as far as possible from healthy tissues, were ground up in a mincing machine, and were afterwards braised in a mortar with normal saline solution. The pulp was then placed in the glass receptacle of a steam spray producer, and the soil was subjected to the action of the spray for about ten minutes at a time, though it was often difficult to obtain a continuous spray for so long, as the nozzle got clogged. The rest of the cancerous pulp was afterwards thoroughly incorporated with the soil, which was then spread in tin trays to a depth of two inches, and the soil thus prepared was repeatedly moistened with sufficient water to keep it damp without making mud of it. Cages of open wirework were put upon the soil, and white rats were placed in the cages, so that their feet and tails remained in constant contact with the earth.

Each animal was fed daily with bread moistened with half a drachm of tincture of belladonna to prevent as far as possible any secretion of sweat. I hoped by this means to put the rats into the most favourable conditions for the absorption of cancer germs should they exist. Wasmuth, however, has shown[5] that the healthy uninjured skin of man and animals is permeable to microbes, which enter between the sheath and shaft of the hairs, but not through the orifices of the sweat and sebaceous glands, and as this may be assumed to be true for the hypothetical parasite, the precaution of administering belladonna was futile. The rats from time to time were sprayed with cancer pulp, and throughout the experiment care was taken to keep the mucous membrane of their vaginæ in a state of slight but chronic irritation by the daily application of lin. iodi, so as to provide, if requisite, a *locus minoris resistentiæ*. I hoped by these means to provide a suitable soil and a suitable receptive medium.

It will be sufficient to give details of the rat living upon the soil from Bedford, for what was done to one was done at different times to all. It was treated with scirrhous glands on January 9th, with scirrhous breasts on January 14th, 30th, and 31st, and on February 4th, with a colloid on February 21st, and with rabbits' livers containing coccidia on June 8th, 1893. Five other rats underwent the same treatment. They lived upon the soil for about eleven months each; four were killed, and two died, one from cold, and the other at the *post-mortem* examination was found to have a large tapeworm lying free in its peritoneal cavity. A careful necropsy was made in each case, but in no instance could a trace of cancer be detected in any of the organs or tissues either by the naked eye or microscopically. The lungs of two of the rats which had been subjected to the spray were found to be shrunken, and their edges were studded with dense white nodules. The centre of each nodule was softer than the outside, and consisted microscopically of round cells of the type of ordinary granulation tissue, whilst the external portion was formed of the pulmonary alveoli blocked with cells apparently derived from the epithelial lining. There was a considerable quantity of extravasated blood in the vesicles, and the red corpuscles were in many cases undergoing disintegration. Numerous spheroidal and granular cells, such as are common in irritated

[5] *Centralbl. f. Bakt.*, December 20th and 28th, 1892.

epithelium, and exactly resembling those found in the segmentation cavity of an incubated hen's egg, lay in the blocked vesicles. They were in all probability eosinophile leucocytes. The deeper portions of the cortex of the nodule consisted of newly-formed fibrous tissue. The explanation of these appearances in the lungs seems to be that as a result of the irritating action of the spray, or of substances introduced by the spray, there was congestion leading to an extravasation of blood into the alveoli; farther irritation led to multiplication of the epithelial cells lining the pulmonary alveoli; finally there was a fibrillation and contraction of the newly-formed inflammatory products. In other words, there were set up all the changes leading to the condition known as "pseudo-tuberculosis," the results of a defensive or phagocytic inflammation.

Assuming that cancer is produced by an organism, it is clear that the organism must gain access to the body unless it be held that the host was born with the germ—an untenable hypothesis. It is probable that such a germ would only grow and multiply in those bodies whose tissues afford it a proper food supply. The only ways in which such a parasite could effect an entrance into the body is by the respiratory or digestive tracts, direct inoculation of a wound, or by implantation into the skin or mucous membranes. Messrs. Ballance and Shattock have shown that cancer cannot be produced by feeding experiments; my own results prove that it cannot be introduced through the mucous membranes. Many experimenters (Hanau, Langenbeek, Follin, and Lebert) have demonstrated the extreme difficulty with which cancer can be inoculated from without, and even the positive results which they have attained do not appear to be absolutely free from fallacy. It seemed, therefore, that cancer might possibly enter the body through the respiratory passages, and might then travel to the tissues most suitable for their growth and development, as is the case with many infective organisms. The rats were therefore sprayed in the manner I have described, and their mucous surfaces were kept in a state of chronic irritation, for cancer occurs where epithelial cells, or rather tissues, are undergoing degenerative changes.

Another question which arises out of a consideration of the etiology of cancer is, How is the disease distributed? The conclusions arrived at by Surgeon Hehir and by the great Italian school of scientific medicine in regard to malaria appear to have a certain bearing upon this question. Ague certainly, and cancer possibly, are produced by specific organisms of the nature of protozoa, which gain access to the body from without.

The disease cannot be inoculated in either case, or, in other words, in neither disease does the organism when once it has been introduced into the body leave it again in a condition fitted to reproduce the disease. Malaria however differs from cancer in its termination. In malaria there is no tendency on the part of the parasite to kill its host; in cancer the disease usually progresses steadily towards a fatal issue. This at once marks a difference between the two organisms, and it may lead to a better knowledge of the distribution of these diseases. In a very able paper, which appeared in the *St. Thomas's Hospital Reports*, for 1892,[6] entitled Specific Diseases Considered with Reference to the Laws of Parasitism, Dr.

[6] N. S., vol. 20, pp. 59-106.

Payne points out (p. 86) that if death is a usual or frequent consequence of any parasitic disease, it raises the presumption that the vitality of the infecting organism is not destroyed, or even that the continuance of the species may be favoured by this event. Many difficulties at once offer themselves in regard to the parasitic theory of the origin of cancer if it be considered from this standpoint. The disease is too exclusively human for any wide distribution to be effected by the disintegration of the host's body such as takes place in anthrax, the plague, or typhus. It is possible to assume that the hypothetical protozoon causing cancer is only one stage in the development of a higher organism, that is to say, it is one stage in the alternation of generations which is so frequent in the lower forms of animal and vegetable life, and it is this point which I have endeavoured to elucidate, but so far without success. It is of course possible, too, to assume that the cancer germ is exclusively human in its proclivities, as appears to be suggested by the ease with which Hahn and von Bergmann are reported to have transferred cancer from one part to another of a cancerous patient's body, though here again their experiments are open obviously to another interpretation.

The "cancer organism," which was described by Dr. Ruffer in his earlier papers, appears to be exclusively human in this sense, for after grafting cancer upon the irritated mucous membranes of animals I have succeeded[7] in obtaining appearances which resemble these bodies, and which I have not yet found as a result of the simple irritation of tissues, or after the grafting upon them of such normal epithelial cells as those on the anterior surface of the cornea. In the rabbit the structures resembling Ruffer's "cancer" bodies are intracellular, and are also found between the cells, but they entirely disappear within a week of the introduction of the cancerous tissue, and I have not yet ascertained what becomes of them. They are, perhaps, destroyed by the cells which they have invaded. If this be so, and assuming that such bodies are the cause of cancer—an assumption which is still gratuitous, for it has to be proved—we have an explanation of our inability to produce the disease artificially in animals. It may be that the "cancer bodies" are merely phases in the degeneration of cells, and that, as the changes become more marked, these striking appearances disappear.

The result of my experiments is negative as regards the propagation of cancer, but interesting preparations have been obtained showing the various forms of cell degenerations. Many of these degenerated cells have been described by different writers as parasites. They are met with, as I shall show next week at the Oxford meeting of the British Association,[8] in normal epithelium which has been slightly irritated, and I am therefore bound to confess myself an unbeliever in any of the "cancer bodies" which have yet been discovered. No evidence has been adduced to show that they are other than the results of cell degenerations, modified, it may be, by the conditions under which they occur, but not differing essentially from the changes which take place in cells as a result of chronic irritation. The cause of cancer has still to be discovered, but we are one step nearer to it if by a process of exclusion we are able to say that it is not due to any one appearance or group of appearances met with in carcinomatous cells.

[7] British Medical Journal, 1893, ii, p. 830.
[8] *Journal of Pathology and Bacteriology*, vol. iii, 1894.