

tion to a uniform experience with dogs in which morphinism suppresses the water exchange.

Conclusions: Morphinism in rats causes edema which tends to advance and decline at different rates in different tissues. Early and extensively affected is the skin. The water exchange becomes decidedly increased. Sudden withdrawal induces a fresh edema, especially of the brain, the skin passing first through a dry stage. The water exchange is first depressed, then greatly increased. Ingestion of food has not varied sufficiently in amount to account for any of the findings.

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Further Notes on the Relation of Nutrition to the Development of Cancer.

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In previous papers¹ we had shown that malignant tissue differs from the normal tissues of the body in that it contains no demonstrable or very little of the growth promoting fat soluble vitamins. We had also shown that many of the so-called cancer producing substances and forces, such as coal tar, other lipid solvents, x-rays, radium, other lights and heat act directly to dissolve or otherwise remove these fat soluble vitamins from the tissues. While these studies were interesting in that they indicated that cancer may be nothing more than the result of the removal of the fat soluble vitamins from a tissue, it seemed quite unlikely that a lipid solvent, no matter how often applied to a tissue, could remove sufficient of the vitamin to induce cancer. When a solvent is brought into contact with a medium it removes only a certain fraction of the dissolved substances from the medium.

That the local action of coal tar is not alone responsible for coal tar cancer has been indicated further by the fact that all animals painted with coal tar do not develop the disease while cancers have been known to develop in man years after a single injection of paraffin or a single dose of x-rays. There seems also to be little evidence to show that the appearance of cancer in man is related directly to the extent or severity of a previously existing local lesion. In fact, many patients carry definite precancerous lesions for years without

¹ Burrows, M. T., and Jorstad, L. H., *Am. J. Physiol.*, 1926, lxxvii, 24.

any evidence of malignant degeneration. All these facts indicate, therefore, that factors other than the local lesion must be responsible for the malignant changes. To throw light on the possible nature of these other factors it has become of interest to study more carefully the action of coal tar and x-rays on animals fed a normal dietary and animals fed varying quantities of both vitamin B and the fat soluble vitamins. These studies showed that the typical precancerous change can be induced more readily by a single application of coal tar or x-ray in a rat fed a diet either high in vitamin B or low in the fat soluble vitamin than by repeated applications in the well nourished rat. We also found that these applications of coal tar or other lipid solvents cause not only local changes in the tissue but a drop in the fat soluble vitamin content of the whole organism. The appearance of more cancers in animals after repeated applications of coal tar may be due, therefore, as much to the systemic effect of the solvent as to the local effect.²

In other experiments with growing cells *in vitro*, facts were gleaned to show that the source of the protoplasmic lipoids of body cells is probably the fat soluble vitamins of the food. We were unable to find any evidence to show that body cells can grow unless supplied with these vitamins. It is the excess of these vitamins in the tissue about the cells or in the yolk of the egg which inhibits the growth of the cells. It became evident, therefore, that any tissue stimulated to grow in a medium free from the fat soluble vitamins but containing ample of other nutrient materials might use up its excess of these vitamins and thus transform itself into a cancerous tissue. Berkefeld filtrates of the Jensen sarcoma of rats contain large quantities of growth stimulating substance but no demonstrable quantities of the fat soluble vitamins. Tests of these filtrates in feeding experiments and in the tissue culture have given no evidence that they contain other specific or toxic substances. It became of interest, therefore, to use these filtrates to stimulate the growth of the tissue. It seemed evident if we could find a normal tissue with the proper nutrient reserve it would become changed readily by them into a cancer.

The storage of food in tissues varies not only with the animal but also with the age of the animal. Fragments of the tissues of embryos of various ages and of adults were treated with Berkefeld filtrate of this sarcoma and then transplanted under the skin of young rats. A few malignant sarcomas developed in the fragments of 15 and 16 day rat embryos.³

² Jorstad, L. H., *J. Cancer Research*, 1926, x, 229.

³ Burrows, M. T., *Arch. Path. and Lab. Med.*, 1927, iv, 168.

The question arose, therefore, may not the lesions produced by coal tar, x-rays, etc., be only precancerous lesions. The cancer may be the result of a later decrease in the normal nutrition of the animal. In proof for this belief we had already reported a case in 1927.⁴ The case was that of a young woman of my acquaintance who placed herself on a diet consisting of chopped meat and vegetables which she boiled twice, pouring the water off after each boiling. She ate little or nothing more than this diet for a period of 3 weeks. Eleven years previously she had received an injection of camphor in oil into the subcutaneous tissue of her right arm. During the time she took the abnormal diet the tumor on her arm became active, reaching the size of a walnut, only to recede again in 7 days on a normal diet rich in vitamins. We removed the tumor later, finding it to be a typical camphor oil tumor.

To throw further light on this problem it had become of interest to attempt to prepare solutions of homologous vitamin B obtained from sources other than tumor tissue, and to study carefully the history of cancer cases to see if a drop in nutrition preceded the development of the cancers. This latter study has been most interesting because it indicates not only that a drop in nutrition precedes the development of all the cases of cancer studied so far but it gives also for the first time some understanding of the age factor in cancer and how many infections, as well as hereditary and acquired defects, may affect nutrition. According to our interpretation of the above experiments it was not only the presence of the growth stimulus which led to the development of sarcomas in the embryonic tissue but to the presence of the proper amounts of other nutrient material in the tissue and the medium.

Forty-three cases of cancer have now been studied. These cases have varied between the ages of 23 and 75 years. All of them have had definite precancerous lesions of one form or the other. In eight of the breast cases the precancerous lesion developed with a recent or earlier existing cervicitis. In four breast cases the precancerous lesion dated back to inflammation acquired during the nursing of children. Four cases of cancers of the cervix could be traced to lacerations. Bruises localized 2 cancers of the face. In the other cases long standing chronic pyogenic infections, injuries from the use of tobacco, alcohol, or other cancer producing substances were evidently the localizing causes of the malignancy.

In none of these cases did the cancer appear, however, before

⁴ Burrows, M. T., and Jorstad, L. H., *J. Am. Med. Assn.*, 1927, lxxxviii, 1460.

there was definite evidence of a drop in the general nutrition of the patient. In 8 of the cases deliberate or starvation from poverty preceded the development of the cancers by 1 to 25 years. The cancer developed in 8 cases with the recurrence of an active tertiary syphilis. Starvation from worry associated with gastric disturbance lasting over 2 years preceded the development of the cancers in 2 cases. Poor dietary in the treatment of diabetes preceded the development of the cancer in another case. Chronic proctitis with arthritis and chronic tonsillitis with arthritis and a kidney lesion were present in 2 cases. In the other 22 cases abscessed teeth preceded the development of cancers.

A few of the earlier cases had suffered recurrence of their cancers after careful operations. Removal of the focal infections together with the cancers and a good dietary has been followed by no recurrences for a period of 10 months in 4 of these cases. Where the general condition of the patient could not be improved in 2 of the earlier cases the cancers recurred quickly after most careful operations and x-ray treatment.

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Duration of Sleep and the Insensible Perspiration.*

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Sanctorius¹ has an aphorism, No. XV in his Sect. IV on Sleep and Vigilance, which reads as follows: "If the night's rest be less than usual, there is a diminution in the exhalation of the concocted perspirable matter, but the perspiration of crudities is augmented." On the first point I have seen no actual data. Benedict and Root² state that the insensible loss is less with quiet sleeping and more with restlessness. A hot uncomfortable night increases the weight loss per hour. These authors give a good review of the literature on the subject of insensible perspiration. The papers like the work of

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¹ Sinclair, "Code of Health and Longevity," Edinburgh, 1807, vol. iii, p. 167.

² Benedict and Root, "Insensible perspiration: Its relation to human physiology and pathology," *Arch. Int. Med.*, 1926, xxxviii, 21; also Benedict and Joslin, "A Study of Metabolism in Severe Diabetes," Carnegie Inst. Pub. No. 176, Washington, 1912, p. 91.