PHYSIOLOGICAL NOTES ON THE CANCER PROBLEMS.

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PHYSIOLOGY dealing with normal conditions and functions, and pathology with functions divergent from normal, it can never be otherwise than helpful to keep a close eye upon the former science when studying the latter.

Some four years ago it seemed to me that in regard to cancer this fact had not been adequately kept in mind, and I am attempting to supply the deficiency. Cancer problems seem to resolve themselves into two classes.

1. What happens? For example, in the case of an organ, say, the mamma, we have at one pole the normal and at the other the cancerous organ. What has happened in the interval?

This problem seems, thanks to the labours of the Cancer Research Fund Committee and other equally able and energetic inquirers, to be approaching solution.

2. Why does it happen? Not only has no satisfactory solution been found, though not a few have been proposed, but Dr. Bashford, the eminent Superintendent and Director of the above-named fund, deprecates as premature any attempt to solve it, thinking, as I understand him, that a complete solution of the first will probably bring in its train that of the second.

Whilst accepting this position, it seems to me that there are certain physiological considerations that will have to be reckoned with, and that it is not premature to examine them now. An examination will at least reveal any lacunae existing in our knowledge and so perhaps induce competent persons to endeavour to fill them up.

Every machine, whether made by man or by Nature, consists of various parts. The integrity of these and their harmonious co-operation are essential to effect the object for which the machine was designed. Any departure either from the integrity or the co-operation must affect this result. The integrity may be impaired by causes either intrinsic or extrinsic. For example, a watch may be affected by an intrinsic cause—for example, rupture of the mainspring or loosening of a screw—or by an extrinsic one—for example, accumulation of dust. Further, the part apparently chiefly affected may be not that in which the primary default occurs—for example, the hands are seen to be moving round at a greatly accelerated pace. Their misbehaviour is flagrant, but the primary cause is not in the hands but in a broken mainspring.

From all this we see that a machine may suffer either from something added to it or from something taken away from it. Secreting glands such as the submaxillary or mammary are machines with a definite purpose, and, like all other machines, they may be interfered with either extrinsically or intrinsically—that is, by something added or by something taken away. As in other machines, the part which exhibits the most obvious derangement may not be that in which is the root of the derangement.

Theoretically, then, the damage which leads to cancer may be due to something taken away, not from something added. It may not be in the cells, the changes in which are so conspicuous, but in something behind the cells. Have these distinctions received due consideration from those who have attempted to solve the problems of cancer?

The submaxillary, being easily accessible, was the first gland to be submitted to experimental examination. Upon such experiments and subsequent similar ones was founded our knowledge of the physiology of secretion. These glands are formed in the embryo before any differentiation of material into nervous tissue. They are therefore presumably endowed with their own intrinsic powers of growth, and are self-contained entities. Nevertheless, in their maturity they come to be absolutely dominated by nerves, without the active intervention of which no secretion is produced.

The chorda tympani having been exposed and divided, electrical stimulation of its distal end causes saliva to flow. It has therefore been called the motor-nerve of the gland. Continued stimulation causes continued secretion. But only for a limited time. Why does it cease? It ceases because the nerve has been converting into saliva material

previously stored up in the secreting cells. If the cells ready to be called into action be compared with those from which secretion has been going on, it will be seen that the latter are comparatively empty. Before secretion can be again produced this material has to be replaced. Here we come upon a great lacuna in our experimental knowledge. Is this replacement due to an inherent endowment of the cells? Is it, like the secretion, dependent upon nervous stimulation? No direct experimental answer has been given to this question. Indeed, I do not know that it has ever before been asked.

There is, indeed, one experiment recorded which seems to bear upon it. In a young animal the chorda tympani on one side was divided and the external wound allowed to heal. Both glands were removed some time after, and it was found that the one, the nerve of which had been divided, was much smaller—that is, it had grown less than its fellow. This has been held to show that the general nutrition of these glands depends upon the motor nerve. It has been overlooked that the chorda tympani besides being the motor nerve is, or contains fibres which are, the vaso-dilator of the gland. The vaso-dilator, then, of the gland is destroyed, while the vaso-constrictor (sympathetic) is left intact. How can the blood supply be otherwise than interfered with? The two glands being unequally supplied with blood, how could they maintain an equal growth? The argument is strengthened if the sympathetic is really the trophic nerve.

In the absence of direct, is there available any indirect, evidence? The motor nerve of the gland is called into action in several ways: (1) By contact of the afferent nerves with various substances, alimentary and others (fine sand, Pawlow); (2) by sight or smell of food; (3) by thinking of food; this includes appetite or desire for food. The first is the usual mode of excitement. It is known that for the first three months or so of extrauterine life no saliva is secreted. But during all that time the sensory mouth nerves are being continually excited by the contact of milk. It is possible that this excitation is necessary to establish central paths of communication between the afferent and efferent nerves. But it may also be that the communication already exists, and that it takes three months of motor-nerve excitement to develop the gland up to a state of secreting potency.

That this is the true explanation seems probable from the case of the mammary glands. These are at birth in a very imperfect—or, as we might say, unfinished—state, the cells being very few. During the interval between birth and puberty there is some, but only slight, development. At the latter epoch this advances; but it is not till the approach of term that any secretion occurs. Lactation finished, the glands again dwindle, and many cells disappear.

Let us now turn to the male mammary glands. These do not actually remain in the inchoate state of the female glands at birth, but their development makes very little progress. They remain permanently in about the same state as the female glands up to the advent of puberty. Nevertheless, it is well known that the male glands are capable of lactation. The history of such cases shows that they acquire this property only after a rather lengthy stimulation of the sensory nerves in the nipple, and also by the psychical excitation of the motor nerve. In the case of the salivary glands, we speak of “mouth-watering” as a result of such psychical excitation. Women commonly speak of the “draught” of milk, which means the sensation caused by that increased blood flow which attends secretion, and which in this case is determined by seeing the infant or hearing its cry. Gould and Pyle quote the “instance of an old Chippewa who, on losing his wife in childbirth, put his infant to his own breast and earnestly prayed that milk might flow; he was fortunate enough to eventually produce enough milk to rear the child.” In this case there is reason to think that the psychical influence may have begun to operate at a very early date. The experiments of Pawlow have greatly enhanced our estimate of the potency of psychic influence in stimulating secretion.

In the above instances the forces which undoubtedly cause ripe cells to secrete have been in operation at a time when the cells were not ripe. This certainly lends force to the supposition that the growth of the cells up to a state of ripeness is due to the action of the motor nerves.

The question now arises, What is the relation of the motor nerves during periods of long quiescence? For example, during the interval between two lactations, or after the menopause. Is it possible that the nerve has also some inhibitory influence, and that while it does not drive the cells in one direction it prevents them from developing in another. Prevents them, for example, from exercising that inherent and intrinsic power of growth the possession of which seems to be indicated by their mode of origin. If this is so, abolition of the nerve (for example, its withering) at the menopause might leave the cells at liberty to exercise this faculty of growth, unless it also was abolished at the same time. What results such an unfettered mode of growth would give we have not the least idea. But it might lead to the formation of gametoid cells, or of cells which could not resist the entrance of leucocytes (according to the views of Dr. Forbes-Ross). Such symbiosis resulting in the formation of a new entity, with new endowments, something after the fashion of the formation of a lichen from the combination of a fungus with an alga.

There are other ways in which a new mode of life might conceivably be imparted to cells. Suppose these failed to develop in a certain way, either from their own degradation or from partial failure of nerve stimulation, the motor nerve might be able to make them grow, but not in a shape which would enable them to secrete. In case it be held that the sympathetic and not the chorda tympani is the trophic nerve of the submaxillary gland, my arguments would not be affected, but we should only have to substitute its name for that of the chorda tympani.

The continual and unrestricted growth of inoculated cancer cells indicates that these bodies possess, as Dr. Bashford points out, properties hitherto unknown in the higher animal kingdom. But the cancer cell, though a living entity, is not, strictly speaking, a viable one *per se*. The inoculated cancer mass when it lives and grows is not a mass of cancer cells only. But of these *plus* a new growth of connective tissue furnished by the host.

We can scarcely do otherwise than suppose that when, as in a certain percentage of cases, the inoculation fails, it does so because the new host refuses to supply the new connective tissue.

If we suppose a failure of physiological condition to be the cause of cancer, we are at once led to turn our attention to the law of senility. The term is synonymous with "old age," but, as commonly used, it connotes those bodily changes which occur in old age. Scanty or decolorised cranial hair, irretentive brain, loss of teeth, piping voice, impairment of hearing and vision, tremulous handwriting, stooping figure, tottering gait, shrivelled and inelastic skin, and so on, are all indications of diminished functional activity and corresponding impairment of structure. For example, who can suppose that the irretentive brain of old age is structurally identical with the retentive brain of youth? Such a proposition is unthinkable.

So far, then, from it being improbable that some cells and nerves of a gland may undergo senile deprivation, it is almost certain that some of them will. Worth notice is the fact that in spite of the general impoverishment of the hair, in not a few cases the eyebrows and the hair about the ears present a redundant growth. Senile changes are progressive, but not continuously so nor uniformly so in all parts of the body, nor is it common for all the signs to be present together in one person.

The fact of cancer being a disease of senility, which is itself a period of degradation of tissue, tallies with the supposition that cancer may be primarily due to a degradation of the tissue in which it arises. It is to be noted that no other explanation of the "law of senility" in cancer has as yet been offered. But besides general senility there is that form which affects only individual parts, such as the thymus at an early age and the female reproductive organs at or about the menopause.

The frequency of cancer in these latter organs at this period seems to me to enforce still more powerfully the idea that the disease has its prime origin in some structural or vital default, either in the cells in which it is first manifested or in the nerves which dominate these cells, possibly in both these combined. It seems to me quite certain that underlying the first visible evidence of cancer development, whether this be the gametoid cells of Messrs. Farmer, Moore, and Walker, or the secreting cells invaded

by leucocytes of Dr. Forbes-Ross, there must be some invisible antecedent influence leading to these changes.

The first-named authorities say: "We feel that the evidence justifies us in deliberately correlating the appearance of these neoplasms" (the gametoid cells) "with the result of a stimulus which has changed the normal somatic course of cell development into that characteristic of reproductive tissue. We look, then, upon this transformation as representing the immediate cause of the development of the malignant growth, but the remote cause must be sought for amongst those various stimuli, some of which—for example, continuous irritation—are known to favour their development." We here have a frank suggestion that something has to be added to the part to produce cancer, and this idea is, I fancy, pretty generally entertained.

"Irritation" is always sooner or later followed by exhaustion, so that events which appear to, and really do, follow irritation may be due to it only indirectly and directly to the subsequent exhaustion—that is, to the "something" taken away.

I submit that there is good reason to suspect that the origin of cancer may be intimately connected with senile changes in the nerve endings or in the cells, or perhaps with both these combined.

NOTE ON THE TRANSMISSIBILITY OF SYPHILIS TO APES.

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ALTHOUGH this note contains only a preliminary step in further investigations, we think it of some slight interest, since we have not seen that any confirmation of the work of Metchnikoff, Neisser, and others regarding the susceptibility of anthropoids to syphilis has yet appeared in

this country, to place the following observation on record.

A male chimpanzee was inoculated on the eyebrow by rubbing into it a portion of a chancre freshly excised. Signs of infection, indicated by some duskeness of the skin and a small nodule, appeared on the sixteenth day. For some days later these signs seemed to regress, but then general swelling and induration of the eyebrow with duskeness of skin became very evident. Later still exfoliation of the skin, leaving a surface yielding a serous or seropurulent secretion, has

Fig. 1.—Head of chimpanzee showing chancre on right eyebrow.

occurred. The cervical glands on the same side are enlarged. The general health of the animal seems unaffected, and there is no rise of temperature.

Although sought for, the *Spirochaeta pallida* was not found until the thirty-seventh day after inoculation.

Fig. 2.—Three spirochaetes from lesion, showing pointed ends $\times 1,300$.

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