BRITISH MEDICAL JOURNAL

LONDON

SATURDAY MARCH 27 1943

MAMMARY CANCER IN MICE

The rapid advances now being made in our knowledge of the aetiology of breast cancer in mice are exciting widespread interest, which is quite understandable if only because these tumours have been regarded as most typical examples of malignant neoplasms: they are carcinomas arising in glandular epithelium; they are not filterable, though they are transmissible from host to host indefinitely by means of cell grafts, a crucial test of malignancy; and they occur in mammals. The advances have become possible because special strains of mice have now been maintained so long by strict brother-by-sister mating—about 7 years is the necessary minimum—that practically all heterologous genes have been lost and closely related members of a strain are now almost as closely alike as identical twins. In some strains the incidence of cancer of the breast is uniformly high, in others uniformly low; and by such operations as cross-breeding and cross-fostering three major factors have been demonstrated co-operating in the production of these tumours. One factor is an inherited susceptibility; another is some specific element which ordinarily passes from mother to young in the milk; and another is the action of oestrogenic hormones on the mammary gland. Outstanding facts that have to be explained are conveniently illustrated in statements published by Bittner. He observed that in the high-cancer inbred mouse strain A the incidence of cancer of the breast is 96% in females which are allowed to breed freely, but is only 5% in those which are not allowed to breed at all. He observed also that, whilst in breeding females of strain A the incidence is, as just mentioned, 96% in those which have been suckled by their own strain A mothers, it is only 5% in those which have been suckled only on females of the low-cancer strain C 57 black; and, conversely, that in strain C 57 females which have been suckled only by their own strain C 57 mothers the incidence is only 0.5%, whereas it is up to 11% if suckling has been on strain A mothers. With other strains of mice the corresponding figures may be very different, but it would appear that in general the three-factor explanation holds good as a first approximation provided it be recognized that the different factors may vary very greatly in relative importance from strain to strain of mice. Much of the more recent work has been done in America, particularly by Bittner, Andervont, Little, and W. S. Murray, and a detailed knowledge of the present situation may be gathered from the many papers published in *Cancer Research* and in the *Journal of the National Cancer Institute*, both American publications. A comprehensive general review with an extensive bibliography has been published recently by Bittner.[1] All that can be usefully attempted here is a stocktaking statement of what appears to be the more important facts accumulated by workers of established reputation.

Existing special inbred strains of mice fall naturally into two main groups—high-cancer with characteristic incidences near 100%, and low-cancer with characteristic incidences around 2%. Low-cancer strains are of two types: those which, like strain C 57, are low because the individuals are so lacking in sensitivity that tumours develop only under exceptional circumstances, and those which, like strain C, are low simply because in them milk factor is wanting. Bittner has produced a substrain of this latter type, his Ax, by starting from a sensitive strain A female which had become non-cancerous because suckled on a low-cancer C 57 female. Mice of either of these two strains, Ax and C, can form the starting-point of permanent high-cancer lines provided they have been suckled on high-cancer females and so have acquired milk factor. How far significant hormonal features should be regarded as being ultimately only manifestations of genetically controlled hereditary strain characters is an open question. Hereditary susceptibility is a strain characteristic and is transmissible alike by both male and female parents. In Bittner's experiments with strains A and C 57 the mode of transmission was found indistinguishable from that of transmission by a single dominant Mendelian gene; but other workers, using other strains of mice, have found greater complexity. Andervont, for instance, found evidence that multiple genetic loci are involved when he showed that the degree of susceptibility varies with the strain of mouse: hybrids obtained by crossing high-cancer females of C3H strain with low-cancer males of strains I or C 57 or Y had incidences of 100%, 95%, and 71% respectively. Little found that in his mice susceptibility is influenced by several of the known genes. Hardly anything is known of how genetic constitution becomes manifest as susceptibility; whether it is through determination of the chromosomal constituents of mammary cells or by some less direct means.

Bittner has recently shown that by means of a high-speed centrifuge the milk factor can be spun down from extracts of lactating mammary gland, and he has reached the conclusion that very probably the milk factor is a colloid of high molecular weight and may be a virus. The milk factor certainly exhibits some of those qualities of living things which one usually associates with the presence of a virus. The milk may be frozen or dried without loss of potency. The factor is present in the milk of all high-cancer mice, and the fact that the milk remains unchanged in quality and potency from generation to generation indefinitely is taken as evidence that the milk factor must increase in amount, possibly by self-multiplication. The milk acts quantitatively over a certain range of dosage, maximum effect in high-cancer strain A, for example, being reached only when suckling has extended to some 24 hours or when some 2 c.cm. of milk has been given by mouth. Milk may differ in potency from one high-cancer strain to another, but the factor itself is not necessarily strictly strain-specific, since, for example, the milk factors obtained from foster mothers of the two strains C3H and A will both notably increase the incidence of breast cancer in strain C 57 mice. Milk factors, too, from different sources seem much alike in another respect, for none has been noticed producing its own histologically characteristic varieties of breast cancer. The factor is present in the milk of high-cancer strains during the whole lactation period, and mice are known to be susceptible to its influence up to the age of 4 to 5 weeks at least. A number of facts indicate that the milk factor can lie dormant for long periods and may even multiply without ever being associated with frankly cancerous tissue. In high-cancer strains, for instance, the earlier litters are born and receive potent milk long before their mothers reach the minimum cancer age, which is at about 5 months, and there is no indication that such transmission from first litter to first litter, generation to generation, cannot continue indefinitely. The few females of high-cancer strains which remain free from breast cancer to the end of their natural lives commonly transmit milk factor to their suckling young as effectively as other females of their strains. Also, in males

[1] *Trans. Stud. Coll. Phys. Philadelphia*, 1941, 9, 129.

of sensitive strains the milk factor commonly lies latent throughout life unless provoked to tumour-forming activity by prolonged administration of oestrone or similar substance. Practically nothing is known of what is happening to the milk factor during these long periods of apparent latency. There is evidence that the milk factor is recoverable from circulating blood and from spleen of high-cancer mice of pre-cancer age. When young females of high-cancer strain are compared with their own litter-mates which have been fostered on low-cancer females, and have therefore received no milk factor, it is found that the mammary gland shows a richer terminal arborization pattern. There is no evidence that milk factor leaves the body in significant quantity except in the milk. No decided infectious or contagious tendency has been observed in groups of mice living together, and when crosses are made between low-cancer females and high-cancer males continuous presence of the male parent makes no difference to the incidence; he cannot in any way transmit the milk factor he absorbed as a suckling.

If the ovaries are removed whilst the mice are still very young, liability to develop cancer of the breast in later life is reduced. This suggests oestrogenic hormonal factors. The involvement of oestradiol, a natural ovarian hormone, is shown, for example, in the observation that if male mice of sensitive strain—which never develop breast cancers spontaneously—be treated with oestradiol or kindred substances over prolonged periods the incidence of mammary cancers becomes high, attaining in some strains the level of that found in the breeding females. Other constituents of the complex hormonal system of the body are also known to be involved, and there are associated changes in the pituitary gland and in the adrenals. The significant changes which take place in the mammary gland are in some way specific; the fully active lactating mammary gland is not one of the intermediate stages leading to cancer. Little describes how prolonged administration of oestrone produces a gradual hypertrophic change in the mammary gland and how this change progresses steadily until the fully cancerous condition is reached. In advanced stages the changes are patchy in distribution, for in some areas of the gland they proceed more rapidly than in others: in the early period of the frankly malignant condition a cancer may spread more by conversion of neighbouring cells than by multiplication of cells already malignant. Little's findings are remarkably like those described by Sir Robert Muir in his studies of cancer of the breast in women. In mice the milk factor is present in tumour tissue in considerable amounts, as can be shown by feeding tests. Testosterone has an action antagonistic to that of oestradiol, and will reduce the incidence of cancer of the breast if administration is started sufficiently early, but neither oestradiol nor testosterone will affect the growth of an established cancer.

Obviously the story is still incomplete. We cannot yet see clearly the significance which known facts have in relation to the aetiology of mouse tumours in general, or even whether they have significance in relation to all breast tumours of mice. Bittner thinks he has evidence of a second and much rarer type of breast cancer: one which is not generally distinguished from the common type, and which indeed is only peculiar, so far as is known, in the fact that its occurrence is not markedly correlated with capacity to transmit milk factor and produce cancer in the offspring. In considering possible indications for medical procedures in human beings it must be remembered that mankind is a very mixed stock and that the chances that a mother who is producing milk factor—if any ever do—should have a susceptible female child is more remote than among these special inbred strains of mice.

EXPERIMENTAL NEUROSES

No one who has observed the types of war neuroses that may follow exposure to stimuli that threaten danger can fail to be impressed by the similarity that exists, on the surface at least, between some of them and the phenomena of experimental neuroses in animals.[1] In both cases there is a stimulus which has a subsequent effect in producing a state of uneasiness. The human being exposed to air bombing, for example, becomes like the animal in the Pavlovian type of experiment—restless in the presence of anything that reminds him of the original stimulus, with insomnia, irritability, over-sensitiveness to stimuli (including jumping at noises, for example), altered social reactions (such as shyness), apprehensiveness, and visceral disturbances. The same tendencies to improve with a rest away from the scene of action or from the experimental laboratory, as the case may be, and to relapse on return to the old environment, are evident in both instances. The effect of rest, the greater susceptibility of certain individuals, and the relative inefficiency of sedative drugs are all similar. The possible importance of such observations, assuming—and it is still a large assumption—that the similarity is more than an apparent one, is this: that whereas it is necessary to postulate a motive or a wish to escape to account for the existence of symptoms depending on mental conflict, it becomes possible to conceive some symptomatic "neuroses" in fundamentally physical terms—i.e., as the expression of an uninhibitable excitation throughout the central nervous system. This is in accord with (*a*) the occurrence of neuroses after a certain period of time in people of sound morale, this being presumably a fatigue effect, since the first effect of fatigue is probably to loosen inhibition; (*b*) their greater tendency to occur in people of a certain temperament; (*c*) their occurrence in people in whom there is reason to suspect that their inhibitory processes are weak (e.g., certain obsessionals); (*d*) the failure of psychotherapy to do much for this type; (*e*) their specificity—e.g., a man may fly courageously but become extremely unhappy on the threat of air bombardment while on the ground.

There are risks in drawing parallels between dogs and men. It is well known that similar syndromes may have a very different pathology. There is little apparent resemblance between the differentiation of closely similar stimuli, which is the normal experimental condition in animal neuroses, and the frightening situations in which the fighting man finds himself; but, according to Gantt,[2] neuroses exactly similar to those set up by a difficult differentiation can be produced in dogs by exposure to fright. Man does not require to be frightened to develop the phenomena of fear. The "representative-imaginative" function of consciousness becomes the conditioned stimulus instead of the actual situation, so that in war neuroses considered even in this way there is already a psychological factor. It is already a psychoneurosis and not a pure neurosis—i.e., it is not simply a matter of a physical situation resulting in disturbance. But, after all, the same can be said of the experimental animal, in which waiting can also become a conditioned stimulus, as Liddell and Anderson have shown. A psychoneurosis in the strict sense of the term only exists when the individual makes use of the symptoms of physiological disturbance in a social way, either to disguise from himself that he is afraid or to escape from the dangerous situation.

[1] Anderson, A. D., and Parmenter, Richard · "A Long-term Study of the Experimental Neuroses in the Sheep and Dog," *Psychosomatic Medical Monographs*, Vol. II, Nos. III and IV, 1941.

[2] *Amer. J. Psychiat.*, 1942, **98**, 475.