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12th April 1979

Dr. B.W. Stewart,
Senior Research Fellow,
Pathology Department,
Medical School,
University of New South Wales,
KENSINGTON, N.S.W. 2033.

Dear Bernard,

Thank you for allowing us to talk to you last Friday. Attached is a draft of what we think you told us. I should be grateful if you would check it and, in view of the current postal dispute, telephone any alterations to me.

Yours sincerely,

Brian Munday.

Encl.

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INTERVIEW WITH DR. B.W. STEWART (Senior Research Fellow ~~in Pathology~~ Cancer Council at the Medical School of the University of New South Wales, Kensington) on 6th April, 1979 at the University of New South Wales.

(Present: Dr. B.W. Stewart, Dr. B. Munday, Mr. F.B. Gill).

Dr. Stewart said that he agreed with Dr. McCullagh's description of how cancer may occur (see point 3 of the interview with Dr. S.F. McCullagh of 19th March, 1979).

The word "cancer" is not a technical, medical word - it can only be defined by reference to what society understands it to mean. It derives from the Latin word, "cancer", meaning "a crab", and imports the idea of the crab's claws reaching out through the body's tissues. The technical, medical term is "neoplasm" ("neoplasia" is the disease). Similarly, in medicine, a tumour is just a mass or lump (technically speaking, a boil is a tumour).

All mammalian tissue consists of cells. Each cell contains a full complemert of genetic information (but e.g. the normal cells in the liver use only that part of the information which tells them how to act as liver cells). DNA is the material in the nucleus of a cell which contains this total genetic information. It comprises chromatin (which becomes chromosomes immediately before a cell divides) together with its protein coat. The DNA has a highly organised structure like a coiled spring.

The present medical consensus is that a chemical carcinogen (a carcinogen is a cancer causing substance) somehow modifies the genetic material in the cell so that it expresses inappropriate properties (e.g. the synthesis of wrong hormones, or the production of proteins which should have been produced only at the foetal stage). (~~Asbestos is thought~~ not to be a ~~chemical~~ carcinogen). The worst type of inappropriate expression by a cell is for it to divide when it is meant to remain static. Carcinogenesis by asbestos is complex and may involve processes other than those thought to occur in simple chemical carcinogens.

Laboratory research shows that, in a group of dividing cells, the fastest dividers survive the best. Working against this inappropriate division is the body's defence system which somehow restrains the proliferation of abnormal cells. A neoplasm is the result of the body's defence mechanism losing the contest between it and the proliferation of abnormal cells. It may be that the aging of the body's tissues eventually reaches a stage where this defence mechanism is unable to keep the altered cells in check. A ceil can be modified by a carcinogen but can nonetheless be maintained in a stable state because of the body's immunological, hormonal or other defence system.

Cancerous cells divide faster than normal cells and, because the relevant part of the body tissue contains a constant number of cells at any one time, the abnormal cancerous cells replace the normal cells and so the tumour grows.

Sir McFarlane Burnett won a Nobel Prize for his theory that every human being has many abnormal cells but we never become aware of them because the body's defence mechanism keeps them under control. One cannot say that a person will never get cancer - what can be said of a person, who dies from a cause other than cancer, is that cancer never developed in his tissues i.e. his body's defence mechanism kept the abnormal cells under control.

Very broadly speaking, the development of cancers, in general, can be roughly divided into three stages:-

1. The first stage is the entry of the carcinogen into the body. With most cancers, the cancer does not become evident until there is some clinical manifestation of it in the form of a tumour.

There are a number of human tumours (but mesothelioma is not one of them) where it is possible to talk about developmental stages; although the question as to when one can say that there is a first (i.e. pre-malignant) stage with cancer is a problem of semantics because the pre-malignant status of the cells is neither normal nor invasive.

It is thought that, at this first stage, the single cell changes to a number of invasive cells. However, it is hard to generalise about tumour growth because there are exceptions to any rule in relation to cancer in general.

It is still being debated as to what the pre-malignant signs are - in some patients they can be seen to develop but, in other patients with the same tumour no development can be seen.

There are only one or two anatomical sites where it is possible to pick up pre-cancerous or pre-malignant signs. For example, cancer of the cervix can be picked up by Pap smears - a not very satisfactory analogy is rust on a car: at first it is merely a discolouration and can be rubbed off, but in time this ceases to be possible as the rust commences to eat into the metal.

On the other hand, with lung cancer (called bronchogenic carcinoma), one cannot say there is any damage until it actually appears and then, of course, it is too late. The same applies to mesothelioma. With mesothelioma, there are no known developmental circumstances, i.e. there are no definitive pre-existing signs which will indicate when a cancer will develop and ~~no~~ not always pre-existing injury is evident.

Asbestos induced mesothelioma is the classic text-book tumour for demonstrating the possible very long latent part of a cancer (ultra violet light induced skin cancers have a short latent period and cigarette induced lung cancer has an intermediate latent period). The other peculiarity of mesothelioma is its relationship with asbestos - the relationship is such that if a person develops mesothelioma, one always searches for his previous involvement with

asbestos. On the other hand, with bladder cancer, for example, it is known to be connected with working in the chemical industry but it is ~~also known to occur~~ where there is no connection with chemical manufacturing.

The degree of association between asbestos and mesothelioma is so incredibly high (compared with the association between other cancers and carcinogens) that it is almost impossible to say that asbestos was not the cause; however, not every case of mesothelioma has been able to be definitely attributed to asbestos.

It is not known how asbestos causes cancer because the current laboratory methods of measurement are tailored for measuring the situation where carcinogenic chemicals break down the DNA structure in a cell. The available evidence suggests that exposure to asbestos is sufficient to produce malignant changes but it is not known how or why asbestos has tumorigenic properties. It is suspected that physical, as opposed to chemical action, may be responsible for the tumorigenic action of asbestos. To the extent that the presence of asbestos fibres in tissues serves as an irritant to provoke multiplication of cells, the opportunity is increased for the establishment of an abnormal cell whose DNA (i.e. genetic information) has been changed by some other action, such as that of another carcinogen. Since the outstanding characteristic of malignant cells is successful competition with normal cells, asbestos and another carcinogen could make a formidable combination.

There do not seem to be any early signs which can be used to diagnose or predict most cancers. In a living human being, it is not possible to observe anything of clinical significance until the neoplasm has grown to about 100,000 abnormal cells. Of course, when conducting a microscopic autopsy on a laboratory rat, much smaller neoplasms can be picked up.

2. The second stage is manifested by what is often called a benign tumour. Here the cells are altered to the point where they are different in appearance, are proliferating slowly but still retain some of their original characteristics e.g. the abnormal liver cell at this stage will look a little like a normal liver cell.

3. The third stage is the malignant cancer. Benign tumours are localised and can be easily removed. Not every tumour goes through to a malignant stage e.g. DDT produces benign tumours in mice - its effect on humans is still unknown.

A malignant cancer has two bad characteristics:

a. Instead of growing by expansion (as is the case with the benign tumour), the cells invade the body like tree roots in soil, (hence the crab's claw analogy).

b. The abnormal invasive cells can grow elsewhere in the body because they migrate about the body and cause one or more secondary deposits (known as metastases).

Chemical and radiation treatment of cancers is aimed at killing cells which are dividing at the time of the application of the treatment. Cells are most vulnerable when they are dividing and cancers have a greater proportion of their cells dividing at any time (compared with normal cells). Therefore chemotherapy and radiation, which kills off all dividing cells, has a more devastating effect on the cancerous cells (than on the normal cells) because a greater proportion of them are dividing and consequently they suffer the greater loss.

F.B.G.
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