Cancer and Environment: Higginson Speaks Out

IARC director says his views on the role of the environment have been misinterpreted, life-style is more important than chemicals

John Higginson, founding director of the World Health Organization's International Agency for Research on Cancer (IARC), is the formulator of a rather complex idea which has led many Americans to believe that cancer-causing agents lurk in everything we eat, drink, and breathe. That perception is wrong, he says, and is a misinterpretation of the hypothesis he first expressed nearly 30 years ago. In a long conversation with *Science* recently, Higginson tried to explain how his ideas have become distorted and argued forcefully against the adoption of too simplistic a view of the cancer process. Higginson, 57, was born and educated in Ireland and has been director of IARC since 1966—THOMAS H. MAUGH II

In the 1950's, you compared the incidence of certain types of tumors among blacks in Africa and America and concluded that about two-thirds of all cancers had an environmental cause and were therefore theoretically preventable.

That is a reasonable summary. Once Oettlé and I obtained good statistics from African black populations, we were able to calculate a theoretical concept of what the low incidence of cancer could be, and any increased incidence could then be considered due to an environmental component. Actually, the idea that geographical differences in cancer incidence are due to the environment goes back many years before that. David Livingstone, I think, said cancer is a disease of civilization, and therefore the idea that the differences were environmental has a long history. My contribution, if I may say so, was limited merely to giving a more concrete estimate of the impact of environmental factors, and to show that most cancers were not due to genetic factors and thus that prevention was not impossible. I ought to make that clear because people are giving me credit where it is not due.

But when I used the term environment in those days, I was considering the *total* environment, cultural as well as chemical. By cultural, I meant mode of life. When we ran that study of blacks in 1952, we started looking at their diets, how they lived, the number of children they had, the age of menopause, the age of menarche—all that was included in the term environment. I've checked it in every dictionary and every dictionary gives the same: Environment is what surrounds people and impinges on them. The air you breathe, the culture you live in, the agricultural habits of your community, the social cultural habits, the social pressures, the physical chemicals with which you come in contact, the diet, and so on. A lot of confusion has arisen in later days because most people have not gone back to the early literature, but have used the word environment purely to mean chemicals.

So, in effect, your conclusions have been misinterpreted all along?

They have been misinterpreted, funnily enough, not among the majority of the scientists with whom I have contact, but by the chemical carcinogen people and especially by the occupational people.

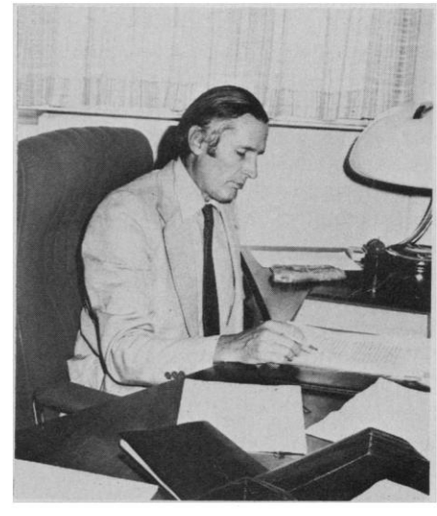
You've done a lot more research since the 1950's. Has something come up to change your original hypothesis?

I have found everything to buttress it, I have found nothing to disprove it. Nor do I know any other person who has produced data that are acceptable and published that contradicts it.

Then how do you explain the misinterpretation?

I think this has been due to a combination of reasons. One, many people have failed to distinguish between the environmental origin of cancers with clearly defined etiology—for example, smoking, alcohol, and occupation—and the large group of digestive and endocrine-dependent tumors whose environmental cause can be inferred only circumstantially. The idea of life-style was woolly and ill-defined and not expressable in biochemical terms with the technology available. Most scientists, myself included, don't like something woolly. Two, there was considerable interest in explaining human cancer in terms of virology, so that chemical carcinogenesis became unfashionable. The textbooks of the 1950's thus largely discussed occupational cancers which could be confirmed by nice, distinct, and easy animal models. Rachel Carson's book was a watershed, as suddenly we became aware of the vast quantities of new chemicals, pollutants, pesticides, fibers, and so forth in the environment. Naturally, such factors suggested themselves as an obvious explanation of many human cancers.

During the 1930's, 1940's, and 1950's, industry had shown a great deal of insensitivity to potential dangers in the workshop, and its unwillingness to attack cancer hazards, associated with the changing political climate among scientists and politicians and environmental pressure groups, made it easy to place



the responsibility for all environmental cancers on industry. The environment thus became identified only with industrial chemicals. Even tobacco was neglected. This interaction of scientific and social hypotheses prevented wider recognition of the fact that many cancers could not be explained so simply.

There's one other thing I should say that has led to the association of the term environment with chemical carcinogens. The ecological movement, I suspect, found the extreme view convenient because of the fear of cancer. If they could possibly make people believe that cancer

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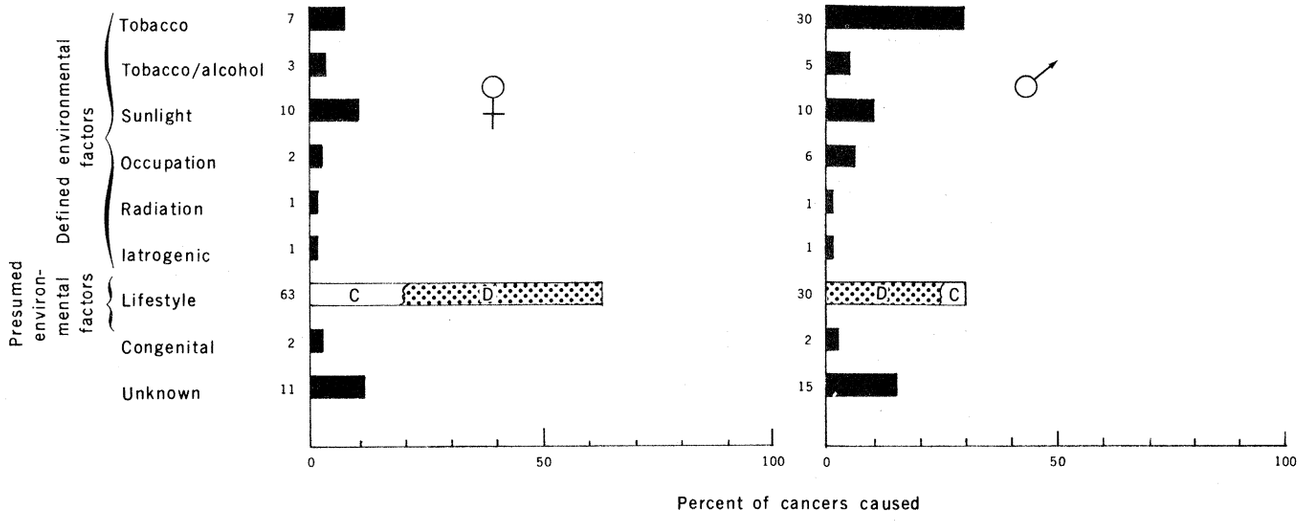

Fig. 1. John Higginson's best estimates for the proportion of cancers attributable to various causes. The relative importance of diet (*D*) and behavioral or cultural patterns (*C*) in life-style are only very rough estimates.

was going to result from pollution, this would enable them to facilitate the clean-up of water, of the air, or whatever it was. Now I'm all for cleaning up the air, and all for cleaning up trout streams, and all for preventing Love Canals, but I don't think we should use the wrong argument for doing it. To make cancer the whipping boy for every environmental evil may prevent effective action when it does matter, as with cigarettes. I think that many people had a gut feeling that pollution ought to cause cancer. You asked me, were people dishonest? I don't think that some people were intentionally dishonest, but rather that they found it hard to accept that general air pollution, smoking factory chimneys, and the like are not the major causes of cancer. I mean, people would love to be able to prove that cancer is due to pollution or the general environment. It would be so easy to be able to say "let us regulate everything to zero exposure and we have no more cancer." The concept is so beautiful that it will overwhelm a mass of facts to the contrary.

You mean there is no relationship whatever between pollution and cancer?

No. The dangers of point-source pollution are well recognized. But you cannot explain much of existing cancer patterns only in terms of simple general pollution by industrial chemicals in low doses. You can't explain why Geneva, a non-industrial city, has more cancer than Birmingham in the polluted central valleys of England. In the United States, reports are coming out that there are few differences in cancer patterns between the so-called dirty and clean cities. In fact, the only thing you can say is that air pollution may, and I emphasize MAY, increase lung cancer in cigarette smokers. These and other epidemiological discrepancies simply cannot be explained by variations in general pollution. Some can, however, be explained by differences in life-style. In other words, I believe that overemphasis on chemical carcinogens has distorted our approach to the environmental theory for many cancers.

I'm not saying one shouldn't clean up the environment; of course you should, people shouldn't be exposed unnecessarily. [But the simplistic approach] has prevented possible acceptance of the idea that there may be doses of carcinogens which, for practical purposes, are unimportant. If you consider smoking plus asbestos or smoking plus uranium, those combinations lead to more lung cancer as everybody knows. But the corollary, then, that small bits of 20 different carcinogens add up to produce a cancer—there are simply no experimental or human data that this is the case. Certainly I used to believe this myself, and I spent many years in the laboratory looking for suitable experimental models to study combinations of chemicals—with little success. Most work has been carried out at relatively high doses and models are more often additive rather than multiplicative. Furthermore, some carcinogens even inhibit the action of others. The existence of noneffect doses of carcinogens has been very poorly investigated, and there is practically no research on this subject apart from experiments on two-stage carcinogenesis, which is a very different story. And, as Berenblum has pointed out, we are probably being exposed to so many carcinogens all the time that what happens is mostly incomplete at the target-cell level; the cells die and nothing ever happens. Because you and I walk across the street, we are exposed to sunlight, which is a well-recognized carcinogen, but we may only develop one skin cancer in a lifetime, or even none . . . , despite the thousands or millions or billions of cells that have been exposed to sunlight. Only a very rare cell goes on to a cancer. So it may be that zero exposure is out. From an epidemiological viewpoint, I believe that attempts to prevent most tumors through control only of mutagens and carcinogens will prove to be a disappointing approach, as will concentration only on the initiation phase of carcinogenesis. Research should be directed to other possible factors. That's the message which I feel is the adequate summary of the data of the last 30 years.

Beyond smoking and tobacco, what do you consider the most important components of life-style?

Two, diet and behavior.

What types of behavior?

Can I just explain what I mean by behavior in a simple sense. Brian McMahon and other people showed, for example, that if a woman had her first child at an early age, she protected herself against breast cancer; if she had the child at a later age, there was a much greater chance of cancer. Now we know that pregnancy leads to changes in the body . . . , but we don't know what those are, and hence the biochemical expression of the behavioral pattern is incomplete. On the other hand, the term behavior, as "when I am going to have my first baby," is a technically accurately expressed term which largely depends on the culture in which you live. Another example is the fact that sexual activity from an early age leads to a lot more cancer of the cervix. Why, we don't yet

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know. Is it the transfer of a virus, the fact that frequent sexual intercourse modifies an individual's hormonal reactions, a stimulation of the vaginal epithelium? We don't know, but again it's a behavioral pattern. And if you take these two factors, you're dealing with a good lump of female cancers, breast and cervix, which in the United States and most countries account for 50 percent of female cancers.

That sounds fine and simple, but running parallel with that is the fact that we've had changes in dietary patterns. . . . The age of menarche in the American female, for example, has dropped extensively. We are having children beginning to have their menarche as early as 10 or 11 in portions of the world, compared to Africa where it is often as late as 16. That difference is probably related to dietary factors. For years we have talked about an improving diet, taller people, better people, but this automatically leads to modifications, for example, of the pituitary axis. These changes themselves, associated with behavior patterns, may tie in together to modify the susceptibility of an individual. Diet is under environmental control, the behavioral pattern is under environmental control, so this is what I mean by environment. But as you see, it's a highly complex system, dealing with humans, and therefore we don't have good models.

Are there any kinds of analogous behaviors in men?

The men are funny, you see. . . . The group of cancers you would attribute to life-style for males [neglecting alcohol and tobacco] is much smaller. The major sources are stomach, large intestine, and prostate. Now people have gone around trying to prove that sexual activity is related to prostatic cancer—frustrated sexual relationships, and so forth. But, to date, nobody has come up with a reasonable solution. Now let's take prostate cancer in three groups of males, Japanese, U.S. whites, and U.S. blacks. We'll call the Japanese prostatic cancer incidence one. The incidence in U.S. whites would be about 30 and in U.S. blacks, 60. You look at that and there's no way you can possibly explain that on exposure to air pollution, diffuse dietary pollution, or anything like that. It is just ridiculous to try to do so.

If, however, we look for what we call latent carcinoma, we find that, in the United States, about 10 percent of all men of 75 have a latent cancer sitting in their prostates. And it's almost the same, 10 percent, in Japan and Germany. So we have the first part of the cancer here, initiated, but quite obviously the factor that is making it invade and kill the individual is operating much more powerfully in the U.S. black, less powerfully in the U.S. white, and not at all in the Japanese. Now again, I can't think of any behavioral patterns that would explain this, so one tends to think of dietary factors. [This is supported by studies of Japanese who have moved to the United States.]

Now when you look at diet, the classical thing is to think of diet in terms of carcinogens. We have a vast body of evidence that goes back to 1940, and which we studied extensively in the Bantu, for example, showing that diet has nonspecific factors—the amount of fats, the amount of fiber, and so on. We say lack of fiber is a risk factor for colon cancer, well how in the world can you say lack of fiber is a carcinogen? It's a ridiculous expression. So one would prefer to use the term carcinogenic risk factor. It is about the only dietary thing there is that has stood up for 30 years. But fats, protein, carbohydrate, vegetable inhibitors may also be important—a lot of research is going to be in this area. But the problem is, we are being asked to give an answer now, "How should we deal with diet?" and we just don't have the answers. The only thing I can say is reduce calories and fat, and possibly add some fiber, but without making any promises as to what will happen.

We simply don't know enough at the present time in many areas to advise legislation or marked changes of life-style. If you take Copenhagan, for example, we have found that colon cancer is four times more common in Copenhagen than in Finland. Yet both populations drive cars and live exceedingly well. But there are significant dietary differences. So you might say, let's tell the Danes to eat the Finnish type of diet. But then you find that the Finns have the highest rate of heart disease in Europe, and probably in the world, so what they're gaining on the swings they're losing on the roundabouts. One has to be terribly cautious, in my opinion, of making advocation. Now you take urban and rural Denmark. People have said that breast and colon cancer are related to fat intake. Well, when we compare urban Copenhagan and rural Denmark, we find that the incidence of cancer of the breast is higher in the urban area . . . , but they eat much more fat in the rural area, 50 percent more. It's quite contrary to the hypothesis. There is obviously something in the way they live in the rural area compared to the town that hasn't been solved yet, so let's not rush into a simplistic statement "Let's cut down on your fats" unless we know why.

Considering past failures in getting people to change their smoking and drinking habits, isn't your view of cancer rather pessimistic?

I'm sorry, I didn't mean to imply that at all. In fact, I think it actually offers a much more optimistic view in practice. It would appear to me almost impossible to reduce to zero the thousands of potential carcinogens to which one is or will be exposed. Nor should such action necessarily be justified in view of the intense commitments required in terms of national resources, without better supportive data. On the other hand, if cancers of the digestive system or endocrine-dependent systems are eventually related to life-style, it should not automatically be assumed that control of them will be impossible.

Quite obviously, Congress can't legislate an early first pregnancy to protect against breast cancer, but there is a good possibility that we may be able to mimic it with a pill when we know about the biochemical effects. Already there is evidence that contraceptives may reduce precancerous lesions in the breast. There are also two reports indicating that contraceptives protect against ovarian cancer by inhibiting ovulation. I am optimistic that once we have a better understanding of the mechanisms involved and the relation to behavior and nutritional patterns, not only may it be possible to intervene with some success but also to identify individuals at high risk. Intervention of this type is already being considered and is called chemoprevention, a comparatively new approach to cancer control.

However, the real reason I am optimistic is that in a wider intellectual climate some scientists are no longer thinking in terms of simple carcinogens, mutagens, and initiation, but are developing a new sophisticated approach to study all complex mechanisms involved in multistage carcinogenesis. This is largely thanks to the work of Berenblum, even if in many circles this approach remains unfashionable. Lastly, we do know that there are populations with low frequencies of these cancers; thus, the Japanese have a very low frequency of breast cancer and the Finns have only a quarter of the colon cancer incidence in the United States. Once we can explain these differences at a more fundamental level, I am confident that we will be able to take active measures to reduce this large group of cancers due to life-style in countries of high incidence.