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SMOKING AND HEALTH

An appreciation of the present  
position of research.

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1. PRODUCTION OF A 'SAFER' CIGARETTE

Since we last reviewed this subject there has been a steady development in our ideas and one result is that it is possible to describe a strategy of research which could be valuable as a basis for co-ordinating our joint efforts.

There are various methods of making a cigarette whose condensate shows a smaller mouse skin effect than that from normal flue cured tobacco. These will be discussed in detail under other items of the Agenda, but two issues remain outstanding, whether such cigarettes would be sufficiently attractive to establish a market in their own right, and further whether their claim to acceptance could be fortified by claims of greater safety. That such cigarettes would be more attractive than those currently on the market is rather unlikely and therefore to sell them we should need some incentive. On present thinking it would be impossible for the manufacturers to use the incentive of making health claims, the arguments against this are well known and this seems to leave an impasse.

A possible way out has been under discussion in recent weeks. This originated from a suggestion put forward by Sir John Richardson and Sir Charles Dodds. It is that the T.R.C. should set up and finance an entirely independent committee, on which it would not itself be represented, whose sole function would be to keep under review current animal bio-assay tests and to state their opinion of their relevance to the human situation. T.R.C. would invite some eminent scientist

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1. to be chairman but that is all they would do. This chairman would have a completely free hand to choose and to ask those who he wished to join him. The freedom from any influence by the tobacco industry would be beyond question and while Government and Medical Authorities might not be willing to go as far as to endorse the findings of the committee they could not help being aware of them. Thus the manufacturers, while making no health claims, could say that their products had been tested by the bio-assay methods considered relevant or valuable by the Committee. Furthermore, a great deal of the work at Harrogate and a fair amount of that carried out by the companies would now have a much more immediate objective, that of producing evidence which could be put before this committee. There would be two broad lines of advance. First to show that our test methods did in fact show up differences between cigarettes, since instinctively we assume that all smoking materials cannot be identical in their physiological effects and it would be a poor test that did not bring this to light. The next line would be to endeavour to understand what actual processes were happening in the empirical tests since any advance in our knowledge could be of immediate advantage in lending credibility to the test as a valid index.

2. BRIDGING THE GAP

While the setting up of this independent committee would give relevance to much of the Harrogate work and the work privately financed by the Companies, there would still remain the central problem of relating animal experiments to human experience.

Both Sir John Richardson and Sir Charles Dodds considered that it was unlikely that it would ever be possible to bridge the gap in a meaningful sense. Probably in their minds was

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2. the realisation that we cannot even at present predict from experiments on mice the effects of a material applied to say a rat. But their argument rests almost entirely on excessive reliance on the catch phrase .. "bridging the gap" which now seems to have outlived its usefulness. The basic concept still provides a valid objective of research and what we are really thinking of in this context is of parallel exploration of the metabolic pathways of chemically caused carcinogenesis in animals and in man. This may be difficult to do but no one can assert that it is not a feasible objective.

3. METABOLIC PATHWAYS OF CHEMICAL CARCINOGENESIS  
IN ANIMALS

Harrogate has started to work on the project of tracing how inhaled materials can arrive at the basal cells of an animal. The working hypothesis is that when smoke aerosol is taken into the lungs some of it "dissolves" in the mucous blanket. The vapour phase is in the molecular form and there may well be something approaching a physio-chemical equilibrium between the concentration in the air-space and the concentration of the separate materials in the mucus. The droplets of the particulate phase on the other hand will almost certainly tend to lose their identity once they are taken up in the mucus and their content of chemical substance will be held as separate materials spread throughout the mucus.

The investigation of this first stage in the pathway is straightforward although difficult. It involves extracting mucus from the lungs of animals that have been made to inhale smoke and then investigating what chemical materials are present in the mucus and in what state. In due course, when techniques have been fully established, it does not seem impossible to extract mucus from human smokers and investigate its content of smoke materials.

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3. The present position is that Harrogate is learning about the chemistry of mucus and the techniques of handling it. It would be convenient for them in the early stages to get mucus of smoking animals, such as pigs and sheep, from Huntingdon Research Station and they hope to establish that the material does not change significantly in the period required for transit.

While it would be logical to wait to know what materials are present in the mucus before endeavouring to find out how they can get to the basal cells this is not possible in view of the urgency of the problem. T.R.C. has therefore commissioned Huntingdon Research Centre to investigate the hypothesis that the pathway is via the cilia which are of course actively moving in the mucus. The hypothesis envisages that some of the chemical content of the mucus gets into the cytoplasm of the ciliated cell and spreads throughout the cell. At its lowest extremity the ciliated cell is in contact with basal cells and transport of material across the two touching cell membranes could lead to the entry of material into the basal cell.

H.R.C. have undertaken a three months study to verify some preliminary experiments which showed that low levels of smoke could cause ultra-structural changes in the cilia of epithelial cells suggesting that they might be acting as channels to the inside of the cell. They also propose to carry out autoradiography studies using labelled benzpyrene suspended in mammalian mucus and to trace the penetration of the benzpyrene into the epithelial cells. If this is successful a three years study will be commissioned.

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4. METABOLIC PATHWAY IN MAN OF CHEMICALLY CAUSED LUNG CANCER

Despite the virulence of the attack by the medical profession on smoking there is little interest on their part into the mechanism of how the inhalation of smoke could cause the disease. They seem satisfied with the epidemiological results that there is an association between the number of cigarettes smoked and the number of cases of lung cancer.

It is certain that if the Industry is ever going to know how the disease is caused then they will themselves have to stimulate and to some extent direct the work since even if they make ample money available it would still be almost useless just to exhort medical research centres to work on the problem. The only feasible method is to think up some investigations, plan them out ourselves and then pay some trained medical research man to carry them out. We must face the situation quite frankly that as amateurs we may not propose very clever investigations but once we start and have hired staff we can rely on them to point this out and the project will be improved. The crux is simply that unless we make a start nothing will ever happen.

A study of the literature suggests the following five lines as possible starters for such researches.

- (a) The state of coverage of the lung by cilia disclosed at autopsy of accident cases. *Ausbert?*
- (b) The investigation of macrophages from healthy smokers to find out if they contain significant amounts of smoke material.
- (c) The exact location of lung cancers as disclosed at autopsy.
- (d) The smoking habits of people suspected of having lung cancer.

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4. (e) The relevance of recent advances in molecular biology to chemically caused carcinogenesis.

(A) There is considerable controversy whether the inhalation of smoke leads to permanent damage to the cilia. If there are large bare patches on the lung surface of a confirmed smoker then, as Kotin has pointed out, these could provide a direct path of contact for the smoke aerosol with the basal cells. If, on the other hand, repair of the cilia \* continues until late in life then the pathway to the basal cells is possibly something more like what has been suggested, that is solution in the mucus and transport through the ciliated and intermediate cells. The relevance of the answer to this question is obvious. A straightforward way of getting some information would be for a medical research man to take every opportunity of participating in autopsy of accident cases, and to inspect the lungs, and at the same time endeavour to obtain as dependable information as possible of the victim's smoking habits.

(B) The role of the macrophage in the lungs of a smoker seems obscure. If they do in fact engulf smoke particulate matter they might be unable to digest it in the same way as they do other organic debris. It has been therefore suggested that macrophages containing smoke material are the carriers of this to the basic cells. No one has as yet committed themselves to a clearly expressed hypothesis, but a useful preliminary experimental step would be to collect macrophages from healthy smokers and investigate whether they contain significant amounts of smoke material.

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\* CARSON et alia Am.N.Y.Acad.Sc. 1966 130 (3) 935.

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4. (C) There is some medical opinion which asserts that squamous lung cancer is predominantly found in the main bronchi, usually near to the primary or secondary bifurcations, and a different type of cancer, adenoma, is found in the alveoli. If these suggestions were examined in detail and the result, whatever it may be, were put on a firm basis this would be of great importance for our studies. The task is not easy since by the time a cancer can be diagnosed and located it has grown and may have metastasised from its original site, but undoubtedly the standard of information at present available could be improved on. The immediate interpretation of such information would start off from the epidemiological result, which is apparently generally accepted, that squamous cancers are associated with smoking but adenomas are not.
- (D) The fourth line of research is currently being considered by T.R.C. This is to obtain the consent of doctors to investigate the smoking habits of such of their patients as they suspect may have lung cancer. This would involve not only finding out how much they smoked but the manner of their smoking, frequency of puffing, how deeply they inhaled, indeed measuring the whole gamut of parameters that are open to measurement. In the first place T.R.C. has remitted this suggestion to the Puffing and Inhaling Working Party to report on what facilities would be required and then it is proposed to ask our medical adviser, Sir John Richardson, on how we should approach hospital authorities.

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4. (E) The last line of possible advance is difficult to describe shortly because of the complexity of current molecular biology. It appears that after several years the central dogma is being successfully queried and Temins views are being confirmed. Apparently an oncogenic virus can invade a cell and its RNA can cause the creation of an RNA-DNA hybrid the DNA built up in the cell coding with the RNA of the virus. This hybrid, inside the cell unwinds in the classical manner and the DNA strand leads to creation of a duplicate strand and forms a new double helix. This DNA duplex is now stable and can divide in the usual manner replicating its DNA. Thus the subsequent daughter cells no longer carry their own hereditary DNA but that one embodying the code of the virus RNA. Obviously there is speculation that this may be the mechanism of virus induced carcinogenesis.

The importance of this is that it supports what has gradually become believed that cancer may originate in a disturbance of the basic generative principle, that is in a change in the coding of the replicating DNA in a cell. There is also now widespread speculation how this concept might apply to chemically caused carcinogenesis.<sup>1</sup> A number of authors have expressed the idea that the step of "initiation" might be correlated with an action on the synthesis of RNA from DNA.<sup>2</sup> More specifically Gelboin<sup>3</sup> proposed in 1965 that the chemical can fix on the DNA molecule thereby preventing duplication of the portion of DNA to which it is attached. Thus the hereditary message passed on will be altered by deletion of part of the instructions. Alternatively a foreign

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1. HENNING & BOUTWELL Cancer Research 29 510-514 1969  
DIETER PAUL Cancer Research 29 1218-1225 1969
  2. ALEXANDROV et alia Cancer Research 30 1192 1970
  3. GELBOIN Proc.Nat.Acad.Sc.U.S. 53 1353 1965

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4. (E) molecule might with a little distortion, replace one of the purine or pyrimidine bases and if it has a strong hydrogen cross-bond the helix may never be able to unzip past this point. Again there would be a permanent loss of a portion of the genetic instructions, and since it would affect both strands the recognized repair mechanism would be ineffective. In support of this Falor <sup>4</sup> believes there is some evidence that in human beings chromosomal aberration precedes histologic change as the initial sign of malignant transformation.

The change in our thinking from a couple of years ago is striking and most encouraging. Admittedly this is hypothesis but all experience goes to show that once a framework of thought about a problem is created progress is possible. What happens is that as experimental facts accumulate the details of the framework are amended and adjusted to accommodate these facts and gradually the whole picture clears. We see that today the first hypothetical framework exists, that framework which traces a possible pathway from the inhalation of smoke in the lungs to the start of a cancer in the basement cells. It proposes that some definite chemical constituent reaches the basement cells by one or other of two pathways which are experimentally identifiable. The invading molecule "initiates" the carcinogenic action by deleting some of the genetic information of the cell, a portion of the instruction book is torn out! If this portion contains some important feed back instructions which are essential to the cells orderly

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4. FALOR Cancer 24(1) 148 1969

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4. (E) behaviour then it is scarcely surprising that, to quote Allison,

"A well regulated member of a multicellular community is transformed into the malignant maverick that characterizes a cancer cell."

The hypothesis tells us something about the molecular species which does this, either it is capable of combining strongly with the nucleic acid backbone, or it can with a squeeze substitute for one of the purine or pyrimidine bases but with a stronger hydrogen cross-bond.

It will be noted that on this hypothesis virus-induced cancer is different from chemically induced cancer, and this latter has a clearly defined stage of initiation. The cell with the mutilated DNA instructions could presumably go on replicating, just waiting for the additional facilities of promotion to join in forming a growth colony.

This field of research is of such great interest to us that it would seem only prudent to commission some molecular biologists to investigate these ideas.

5. CONCLUSION

These considerations show that there is a line of action which is within our ability to follow if only we have the will. It offers reasonable chances for the Industry to emerge with a safer cigarette which will be recognized as being just that --- a safer cigarette. However, no one is going to do this for us, we must ourselves accept this as an objective and develop a series of steps to attain it. This

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5. note has sketched out a set of such steps, there are probably better ones, but the important point is there must be some planned set of steps. We cannot go on supporting or ourselves carrying out individually good pieces of research in the hope that in due course everything will fall into place.

The key steps proposed are firstly supporting the setting up of the independent committee and secondly embarking on a serious exploration of how human beings get lung cancer from smoking. This would involve a number of investigations on human beings, investigation of the chemical interaction of inhaled smoke and mucus, and investigation of the molecular biology of chemical carcinogenesis.

No reference has been made to either irritative effects or to cardiovascular effects simply because of priorities. We are already carrying out work in these fields which is promising but work on lung cancer should come first.

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