

**Research & Development**

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28th February, 1966

**S. J. G.**

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Dear Jim,

BIOLOGICAL TESTING COMMITTEE

I have been giving some thought to the matters raised by this Committee, particularly the difficult questions of the candidates for the initial series of tests.

First of all I should like to say how much I agree with the context of the letter by Leo Laporte and to yourself on January 27, because I find myself in the same position. I do not know the full details of the work to be carried out by T.R.C. and B.A.T. We have snippets of information via letters and visits made by colleagues and myself but we have no coherent picture of what is going on.

If the "country members" (i.e. Leo Laporte, Bob Griffith and myself) are to make any real contribution, I feel it is essential that some way be found to bring us fully up to date with the present position and, keeping us up to date with future developments. The assembly of this information will be an onerous and time consuming job for someone. It may be that the labour involved in this will not be commensurate with the contribution Leo, Bob and I can make at a distance. In this case it might be better not to attempt to have the "country members" on the Committee but only keep us briefed of progress.

In deciding the samples for the first series of tests, it is perhaps necessary to go back in history a little and review how we got to our present position, which tests we have available, and what limitations these tests impose on us in terms of the type of information they can yield.

As I see it, the position has evolved as follows:

- (1) It was originally postulated that smoke acted as a direct carcinogen on lung tissue by virtue of the polycyclic hydrocarbons contained therein.

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- (2) Later work suggested that (1) might be too simple a model and Berenblum's two stage hypothesis became popular. Essentially this suggested that smoke induced carcinoma of the bronchi by the combined effect of initiators (polycyclic hydrocarbons, polonium, etc) and promoters (phenols and other compounds).
- (3) During the past two years the "irritation" aspect of smoke has become popular. In this area attention is being given to the general biological effect of smoke on lung tissue e.g. inhibition of ciliary activity, effect on mucous flow, enzyme balance of cells, etc.

We have now reached the position that both the 'carcinogenic' and the 'irritant' effects of smoke are under examination. The relative importance of the two factors depends to a large extent on the views of individual workers. Present views range from the one extreme, for example Passey who puts the major emphasis on 'irritation' almost to the exclusion of the carcinogenic effect to the other extreme that the carcinogens in the smoke are by far the most important substances to be studied. Other workers pay attention to both aspects and their views lie between these two extremes.

Ideally we should like a test that measured the combined effects of the "carcinogens" and "irritants" in the tissue under discussion. If we had a test available in which we could inject freshly formed smoke into an animal's lung and measure the development of neoplasms in the bronchi, we could quite readily draw up a programme of samples, e.g. types of tobacco, effect of filters, etc. Unfortunately we are not in this happy position. In the case of irritants, we have a range of tests from Paramecium through clam gill to intact animal lung. To measure carcinogenic action we are reduced to painting mouse skin. In this latter case most of the volatile and semi-volatile material of the smoke is rapidly lost so that even if there were an inherent difference between "instant" and "aged" smoke we could not demonstrate it by this technique.

It seems to me therefore that we have two mutually exclusive biological tests:

- (1) Those designed to record the irritant or general biological activity of smoke.
- (2) Skin painting techniques which measure the 'irritant' effect of the smoke plus an unknown quantity of the promoter effect,

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depending on the method of preparation of the smoke and the rate of loss of components from the painted skin.

We have learned a great deal about smoke since the early days of mouse painting and I would like to suggest two lines of investigation at some future date:

- (1) Application of 'instant' smoke to the skin of an animal (mouse skin or rabbit's ear). Immediately after application of the 'instant' smoke the area would be covered by a dark plastic cover to keep in volatiles and reduce oxidation and breakdown of constituents.
- (2) The application of 'instant' smoke to the bronchi of animals under anaesthesia. As far as I remember, the work of Blackburn and others involved the use of 'old' tar. 'Instant' tar containing a fair concentration of irritants might yield a more significant result.

We can now turn to the samples to be investigated. There were some good ideas advanced at the Biological Testing Committee meeting held in Millbank on February 3rd and it was clear that although there were conflicting opinions, these were sincerely held by their advocates. I do not want to add to the detail and will therefore only advance a few points:

- (1) I agree that there should be a control cigarette. I would suggest a flue cured cigarette, largely on the basis that present evidence suggests that this type is the most hazardous, both by mouse painting and by ciliastatic tests. I appreciate our U.S.A. friends would like a blended cigarette and I sympathise with their point of view. However from the biological point of view a blended cigarette is a 'half way house' in terms of tobacco type and is further complicated by the addition of casing and flavours.
- (2) I agree a known carcinogen should be used.
- (3) A cigarette of a blend of air-cured tobaccos. I note that Dr. Fordyce suggests a Polish cigarette. I have no objection to this, but suggest that the French Gauloise might be considered. This is a cigarette composed largely of 'fermented air-cured tobaccos, smoked on a large scale by a European population. The advantages of this over the Polish would seem to be:
  - (a) The French Regie has research and development facilities of its own and B.A.T. has several contacts with it through its scientific members.
  - (b) The Regie has compiled quite a bit of information on the chemical and biological properties of its products. Additionally they have carried out a fair amount of statistical work.

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It would seem to be worth considering a cigarette on which we might be able to obtain reliable information. I am less certain that such information would be available from Polish sources. I am, of course, not aware of what information we have on Polish cigarettes.

Because of the interest aroused by Beffinger's views around the world, I feel it is most important that a 'fermented' cigarette be examined. This is probably the thinking behind the note by Dr. Fordyce to Dr. Green WBF/FA/46-D2, 2/2/66.

If the decision was taken to use Polish cigarettes I would not disagree. I just advance the above points in favour of French cigarettes.

- (4) An American blended cigarette should be included, partly because as a commercial brand it is of considerable importance to B.A.T. and partly because it may be construed as a "half way House" biologically between a flue cured blend and a fermented air-cured blend.

At this stage there is not enough evidence to suggest that tobaccos from San Paolo, Airferm or ammonia treatment processes are worth examining at this time, as to date I have seen no evidence that Airferm or ammonia treated tobaccos are less ciliastatic than air cured tobaccos although they may be worth examining at a later date if they achieve commercial recognition. In the aetiology of bronchial carcinoma the effect of puff parameters and carbon filters may prove to be of considerable importance, but my worry here is that mouse painting may not be the technique for their examination. Carbon filters, and, to a degree, modification of puff parameters have a marked effect on the particulate/vapour phase ratio. If the effect of smoke on lung tissue is the combined effect of "carcinogenic activity" and "irritation", carbon filters and puff parameters should prove extremely important in controlling the biological activity of smoke. However, the tests envisaged will use mouse painting which can only measure part of the biological activity of the particulate phase. Consequently the differences between these samples may not be very striking in terms of the carcinogens measured by mouse painting, whereas one might find large differences using ciliastatic tests or the Leuchtenberger exposure technique on mice.

I might perhaps add that the Smoking & Health question has been coming to the boil in Australia in recent weeks and I will brief you on this separately. Some of Beffinger's ideas are

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becoming popular with some sections of the medical profession, largely with those individuals who like a simple answer to complex problems.

At this stage there is no real evidence to show whether Beffinger is right or wrong and it will probably need a great deal of work to find the answer. The Beffinger theory in its various forms is something we shall have to continue to take seriously even though there is quite a body of evidence to suggest that his theory is fallacious.

With kind regards,  
Yours sincerely,



W. W. Reid

cc. Dr. Fordyce

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