

THE EPIDEMIOLOGICAL APPROACH TO INVESTIGATING  
OCCUPATIONAL CANCER

Professor J.M. Harrington

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G.E. Burrows, ICI

Q. Professor Harrington emphasised the importance of the exposure data in a good epidemiological study and in the Company we are looking to computerised medical reports and environmental data and I am just wondering how much detail we should be going into. Its very easy on a continuous plant to get a pattern of exposure data but in a batch process for instance do you capture it morning and afternoon, once a day, once a week, how important is it over 20 years. Is it... I would just like your views on that point.

J.M. Harrington:

Ah I think its a good point. I know that ICI have been doing this and there is IBM I think have been doing it as well and I have been peripherally involved in Fisons attempts to do the same sort of thing. I would say that you still need to come down and say what do we consider to be the probable hazardous occupations and we will try and make sure that those are adequately monitored because we may well need to go back and look at that group of people. That in some ways avoids the question of saying "Ah but what we are looking for is the unknown" my thing is that maybe I am cynical about this, I am afraid that some sort of sod's law or whatever is going to apply, in that the one thing you wont have collected because you didn't know about it, is the one thing you need in 20 years" time so that the safer way, perhaps is to be to go "look we will list the number chemicals or processes we deal with and list the ones we think cause (a) the greatest exposure to the workers and (b) the chemicals and materials which we think either are known to be hazardous or suspected to be hazardous and those are the ones we will choose to follow but we wont follow everybody".

Dr. J.R. Glover, Burmah Oil

Q. With due respect to Professor Harrington I dont think he quite

answered the question. I think what was being asked was how many units do you go down to, is it days per week, or days or is it hours and I think we have got to write down the actual hours in each day if we are going to record it, the exposure, because we are talking about an 8 hour day and a five day working week, so I think the lowest limit we can go down is to one hour, I don't think we can go below that in actual recording the exposure. I think that's what he was asking.

J M Harrington:

Ans Well, with due respect to Dr. Glover I think I did answer it, but if he wants to be really specific about it I would agree that what I meant is that if you decide a particular job is hazardous then you have to go right the way down to whatever is a reasonable amount. You may in fact for some particular processes actually need to consider minutes, I don't know. I am trying to think. There may be things in the pharmaceutical industry for example which you have to handle for very relatively small periods of time but I would have thought an hour for most other occasions would be the minimum you would go for. Then you have to watch those workers as they go between departments as well.

Dr. F.J.C. Roe

You said, in some senses completely correctly, that occupational cancers are indistinguishable from the background cancers in terms of type. However, there is something else to be said here surely. Cancers like haemangiosarcoma of the liver in the V.C.M. workers and mesothelioma in the asbestos workers came to light because they are, as far as we know, rarely attributable to other causes. To some extent this is not really in keeping with the impression you gave.

J M Harrington:

Ans I would agree with that but I would say that they are relatively rare tumours and for a lot of the other tumours just in terms of numbers, you are in fact talking about tumours which are histopathologically

no different. The problem that bothers me about this and this is why I sometimes wonder whose got their figures right, if the only tumours we seem to be picking up are the relatively rare ones how much are we losing in the general lish-lash of lung cancer and stomach cancer or what-have-you, because the rare ones are the ones that are going to be most noticable, they are the ones that Creesh and Johnsons of this world discover. But I would accept that for some of those, and I think mesothelioma probably exemplifies it, there is virtually no serious contender other than asbestos.

Dr. F.J.C. Roe

Ethylene oxide has recently been found to increase the risk of mesothelioma in rats. This points to a danger. We should not assume that all mesotheliomas are due to exposure to asbestos.

J M Harrington:

Yes, I think if you look at some of the earlier studies which were done saying that mesothelioma is associated with asbestos exposure that the range of percentage of people who had mesothelioma and were supposed to have asbestos exposure ranged from something like 50 to 95% and this seems to depend on the zeal with which the investigators inquired about asbestos and when you think about it we all are exposed in some form or another, it may not be occupational but there has been exposure there and then there the danger is as Dr. Roe says to go overboard and say that is the only cause, there isn't anything else.

Dr. Munn, Monsanto

Q. In relation to the point that Dr. Roe made about mesothelioma being caused experimentally by substances other than asbestos I wonder if he could perhaps say a little about the experimental technique that was used. Asbestos causes pleural mesothelioma as a result of inhalation. We all know that there are experimental techniques involving

implantation of other materials into the plural cavity which result in mesothelioma from other materials but this is not a common procedure in workmen, is he referring<sup>to</sup> the experimental induction of mesothelioma as a result of inhalation of the new material by the animals?

Dr. F.J.C. Roe

I share Alex Munn's reservations about the interpretation of experiments in which mesothelioma is induced by the direct introduction of materials into the pleural cavity. Such experiments are uninterpretable in terms of humans exposed by the inhalation route. In the case of the rats exposed to ethylene oxide, exposure was by inhalation.

Chairman. You will remember of course Dr. Munn that the villages in Turkey that have, 50% of whom die of mesothelioma, without any exposure to asbestos, I think the blocks there are called zeolite, which is perhaps similar physical structure but is a different material. Dr. Goulding to you want to say something? No.

## CARCINOGENS - PAST, PRESENT AND FUTURE

Dr. R. Murray

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R Hurd/

H.G. Parkes, British Rubber Manufacturers' Association

Q. Something he just happened to mention attracted my attention and thought he might be able to solve a mystery for me. He referred to an I.L.O. Report of 1921 Bladder carcinogens and it just happens that I have had occasion myself during the past ten days or so to re-read that extremely interesting and comprehensive Report in detail and he mentioned that

chiefly in that Report as being the principle carcinogens responsible for the bladder cancer experience but reading and re-reading, as indeed I did that Report, I was unable to discover how it was that the authors of that Report came to that particular conclusion because the Report in fact deals with a very wide range of aromatic amines and it doesn't seem to show why those two are specially selected. Can he tell us why?

R Murray:

A. I wish I could. I think it was just probably the hunch of Carotzi. Carotzi was a great man because he had worked in the Clinic Adela Voro in Milan from early 1900's and in fact he was the first secretary of the Permanent Commission of International Association on Occupational Health and he was the first head of the I.L.O.'s Industrial Hygiene Division so he came to the I.L.O. in 1919 with a great deal of background of knowledge, I don't think anyone before that time had ever incriminated those substances specifically but I believe that it was probably Carotzi's hunch as a result of his observations rather than anything which he had heard from anybody else. But its fascinating that as early as that the substances responsible for the condition had been recognised.

Dr. J.R. Glover, Burmah Oil

Q. Could not a possible answer to that be (I can't give you names and dates) but it had been described in the Analyne Dye Industry hadn't it

and if Carotzi was working there he would know that they were the basic dyes and so the hunch might just have been going back to the basic aromatic amines because bladder cancer had been described in the Analyne Dye Industry in the 1880's I think. I think he was probably working backwards to the basic materials.

R Murray:

An One of the interesting things about this is that the first description although it may have been recognised, the first description was in 1895, and at that time Rehn thought it was due to analyne and this error still appears in the literature. People still talk about analyne cancer and analyne is not a carcinogen and the reason for this was revealed by my late colleague Michael Williams and his colleague Walpole, who were able to demonstrate that the analyne as manufactured at the time of Rehn's discovery contained as an impurity foraminodiphenile so it was probable that it was the foraminodiphenile which Carotzi did not recognise which was responsible for the so-called analyne cancer.

Dr. A. Munn, Monsanto Europe S.A.

Q. In relation to Dr. Glover's comments I really must point out that neither they are as carcinogens and however many tragic cases of occupational bladder cancer they may have caused, they were not really major raw materials in the dye stuffs industry, they were relatively minor. The major raw material was in fact analyne, as has been suggested by Dr. Murray, it was not in fact until the publication of the work which Case carried out sponsored by the Dye Stuffs Manufacturing Industry it was possible to exonerate analyne from responsibility in the bladder cancer associated with dye stuffs manufacture. I wonder if I might take Dr. Murray up on a relatively minor point which, its a minor technical point but one which I think has or could have fairly profound commercial repercussions. It was his reference to aromatic amines being responsible for bladder cancer in the rubber industry in the past. It was not an aromatic amine that was responsible it was a product called Nonex S. It was not an aromatic amine

which was a condensation product of betanaphthalamine itself an aromatic amine with Paralderhide and the reason why I say its commercially important that this should be clearly understood and recorded is that many aromatic amines are currently in use in the rubber industry many of them have been extensively tested, animal studies for carcinogenicity and have been cleared, and there is one country in Europe Italy, which introduced regulations about aromatic amines two or three years ago singularly stringent regulations which will be very relevant in respect of betanaphthalamine or benzadine or non excess for that matter but which are totally irrelevant to the very important anti-oxidents which are currently in use today and which are complex aromatic amines, so I am anxious that this myth of aromatic amines having caused bladder cancer in rubber workers should be dismissed and that it should be so recorded in the proceedings at least of this meeting.

*R Murray*  
*An* I bow to Dr. Munn's knowledge of this subject. I had always believed that the bladder cancers in the rubber workers were due to the betanaphthalamine impurity in nonoxes, I accept his point that there are many aromatic amines which are not carcinogens. They tend to come under suspicion and the most recent one is menthalinebisoxychloraniline and I am not sure about the carcinogenicity of mocca but I take his point that you cannot make regulations about aromatic amines in general as though they were all carcinogens. I think that this point ought to be stressed.

Dr. F.J.C. Roe, Consultant

Q. Would Dr. Murray tell us, please, the present position in the jute industry, I imagine it is <sup>now</sup> more or less a dead industry, but during the 1960's my colleagues and I looked at an oil that was <sup>then</sup> currently being used for jute-batching in Dundee and we found it to be highly carcinogenic in our mouse skin studies - indeed it was one of the most carcinogenic oils I had ever seen. There was evidence in the literature that keratoses and skin cancers had been

occurring in the women doing this work during the 1950's and early 60's. I wonder what the present position is. As far as we know we launched our paper and nothing ever happened. Did anything happen? Is there still a problem, or is the jute industry dead, or has it gone back to Pakistan?

R. Murray

I remember when this problem was first raised and my colleague Rogers, a dermatologist in Dundee, described cases not only of skin cancer but of keratosis in jute-batchers. There was a suggestion at the time that the batching oil should be replaced by technical white oil or solvent refined oil. I think this was probably only one of the wider reasons why the jute industry disappeared from Dundee. It was a crazy industry to have in Dundee anyway because you can't possibly grow jute anywhere else than in East Pakistan and I think the jute work is all done there and far as I know there are no longer any jute factories operating in Dundee. I don't know what the situation in Pakistan is.

J.M. Gilks, Shell International

Q. If I may just ask a question. My understanding is that the traditional or the well recognised aromatic amine carcinogens are in fact double ring compounds. There are some, and I am not aware of anyone that is truly recognised as a single ring compound, but there are indeed now some toxicological reports in animals, mice and one or two rats I think, that single ring compounds have also been reported to cause bladder cancer. I would be interested to get the opinion if I may of the Chair and your self, what view they would take of these reports that some of the single ring compounds in animals are carcinogenic when so far as I am aware its generally been accepted that the human carcinogens are all double ring compounds.

R Murray:  
A I think this is one of the things I am hoping to learn myself over the next couple of days.

Dr. Munn: The major aromatic amines which has been found to be



carcinogenic in the mouse I think, I am not certain about the rat, is arthatalodine. I say major in terms of volume of production and use and its general industrial and technological importance. There has never been any study, so far as I am aware, any good epidemiological study of workers exposed to arthatalodine. What I am very clear about however is that in the case study, the study by Bob Case of the British Dye Stuffs Industry, the Report of which was published in 1953, and in which analyne was exonerated, all of the arthatalodine being manufactured in Britain at that time was being made in analyne plants. The process was very similar analyne is manufactured by the reduction of microbenzine the nitro-group and nitrobenzine to analyne, arthatalodine is made by the reduction of the nitro-group in arthonitrotauludine to arthatalodine so that the tauludine workers were included in that study. Those engaged in the manufacture of the tauludine. I was familiar with working conditions in the plants of these, it was quite soon after I joined the industry and working conditions really were pretty appalling. I know that Dr. Murray was familiar with them as well. I find it difficult to believe that if, in fact arthatalodine had been causing bladder cancer in workers it would not have been revealed in that population studied by Professor Case. The analyne studied by Professor Case. Of course there was the lotion and one cannot be certain. There is no absolute certainty that arthatalodine has not caused cancer in man.

Dr. R. Goulding, Ministry of Agriculture

Q. Can I depart Mr. Chairman with your permission, with this preoccupation of aromatic amines and go to a rather more general if philosophical view, Dr. Murray quoted from the classics, there is another Shakespearean character who talked of books in the running, brookes sermons in stones, good in everything, I think its common parlance nowadays perhaps more from the other side of the Atlantic than here that there are carcinogens everywhere. I have been partaking a very sceptical view of this and wanted some pretty convincing proof, I think what Dr. Murray has done for me this morning has thrown away some of that scepticism because throughout his account he has given us incidences of

slight suspicions, rejected, not seriously considered, and only after a passage of many years has convincing evidence been substantiated and I am wondering Sir, and I am really looking to you as an epidemiologist should we not take all these alarms we have presented to us now, a lot more seriously and follow them up a lot more energetically so that we may or may not recapitulate this story that Dr. Murray has shown us over the last 100 years.

R Murray:

~~Dr~~ I agree very much with what Dr. Goulding says. I think we must listen to the alarms but without getting alarmed. I think the most important thing is that knowledge drives out fear. If you look at the epidemiology of exposures as I know is being done at the present time by our Chairman and by Donald Aitchison in respect of styrene and formaldehyde. The evidence ought to be there and we ought to listen very seriously and do such human epidemiology as is possible. How much we can do as a result of experimental animals or of bacterial or other tests how much we, reliance we ought to place on those, is something which I am hoping we will be hearing more about in the next couple of days.

Chairman: My answer is almost identical with Dr. Murray's. The only thing I would add to it is that to re-emphasise what I said at the beginning that we are not in the midst of a developing cancer epidemic which is what is so widely believed and I would therefore back up very strongly his statement about not being alarmed, but at the same time taking seriously in an objective scientific spirit the hints that materials may be carcinogenic to see when we do have human exposure whether there is in fact any evidence of this and I would like to add that as far as this country is concerned the evidence is that with the exception of one or two tumours, particularly melanoma, that the incidence of cancer at any specific age and particularly in the young age groups where you are likely to see the first effects of new materials, the incidence of cancer is if anything going down. This is of course dramatically true in the case of lung cancer for obvious reasons but is true over a wide range of cancers which cannot easily be attributed to artefact as a result

of improved treatment reducing mortality but is probably reflecting actually reducing incidence rates.