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ASBESTOS FIBRE DUST AND GASTRO-INTESTINAL MALIGNANCIES. REVIEW OF LITERATURE WITH REGARD TO A CAUSE/EFFECT RELATIONSHIP

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Abstract—Exposure to asbestos is associated with the subsequent development of gastro-intestinal malignancies. In the absence of an explanation to the contrary, this exposure must be regarded as causal. There appears to be a latent period before the effect is demonstrable. Thus on present evidence, only those causes that are identified as developing gastro-intestinal malignancies after a period of 20 yr or more from first exposure should be accepted. All anatomical sites of the gastro-intestinal tract appear to be affected. The degree of increased risk of gastro-intestinal cancer in asbestos workers 20 yr or more following first exposure approximates to 3-fold. There is no evidence that any other factor either contributes to our subtracts from the causal relationship between asbestos exposure and cancer of the gastro-intestinal tract.

INTRODUCTION

This review is based on a report prepared at the request of the Workman's Compensation Board of Ontario.

I have restricted my attention to population-based epidemiological or statistical studies that have produced data relevant to a consideration of the association between asbestos fibre dust exposure and the subsequent development of gastro-intestinal malignancies.

REVIEW OF THE LITERATURE

Of the references consulted, several were non-contributory in the sense discussed above, [1–10].

The second group of references [11–19] consists of those studies in which, although gastro-intestinal cancer was discussed, it was not further considered in relation to site. This, unfortunately comprises much of the literature available on the subject. Although in totality, this might seem to comprise a substantial amount of experience, in practice, this often consists of reports from the same group essentially describing the same series of individuals. Even if it were possible to obtain from the authors a breakdown by site and to attempt a consolidated analysis, it seems unlikely that this would contribute any more to a refinement of the association than those larger studies in which the numbers permitted a breakdown by site within the gastro-intestinal tract.

These literature sources will therefore not be discussed in detail, except to point out that in general their findings are consistent with the more detailed studies, but also to emphasize that without specification by diagnosis, it seems very likely that a substantial proportion of the cases reported may be due to peritoneal mesotheliomas, a problem of diagnosis eloquently discussed by Newhouse and Wagner [19]. Indeed, it seems very likely that this difficulty accounted for the earlier suspicion raised by the report of Keal [16] that asbestos was associated with ovarian cancer, as peritoneal mesotheliomas are probably difficult to distinguish from relatively undifferentiated tumours. This indeed seems to have been the opinion of subsequent reviewers [20].

It may be noted that although the studies of Enterline and his colleagues [11–15]

seem to ignore this issue, that of Mancuso and El-Attar [17], although they did not separate off different digestive organ sites, for example stomach, colon or rectum, did at least provide data that enables one to determine the numbers of deaths due to malignant neoplasms of the digestive organs if those of the peritoneum were excluded. This study is important because a number of the methodological problems of other studies were understood by these workers, and one of them particularly was tackled by using an internal control, that is, those workers in the same plants with minimal exposure, to develop their expectation for occurrence of disease in those workers with more severe exposure. Although this may not completely remove possible confounding by socio-economic status and other factors, and although it is not clear that they used an ascertainment of confirmation of death that would ensure that all peritoneal mesotheliomas had been excluded from the other group, it is relevant that their observed expected ratio calculated with the removal of those who died of malignant neoplasm of the peritoneum and/or of mesothelioma is fully consistent with the data from more completely analysed studies, particularly those of Selikoff and others [21–27].

Of the studies in which details of the site of diagnosis of gastro-intestinal malignancies by major organ are given, five provide relatively scant information, either because the cohort under observation was small and/or the data was not sufficiently analysed [28–32].

Elmes and Simpson [28] identified 170 men who made up the total population of insulation workers in Belfast in 1940. These men were traced up to 1966, 5 men were untraced and the mortality experience of the remainder was compared with that of other men in Northern Ireland during the same time period. Seventeen deaths due to non-respiratory malignant disease were observed, compared to 5.16 expected using rates from Northern Ireland males. Of the 17, 15 were classified as gastro-intestinal, though 3 of these were mesothelioma and another 1 classified as gastric and 1 classified as rectal carcinoma could have been mesotheliomas. If these are excluded together with the one observed carcinoma of the pancreas and one lymphosarcoma of the small intestine, there still remain three deaths due to carcinoma of the stomach, 4 to carcinoma of the colon and 1 from rectal cancer, to compare with an expectation of the 5.16 from all non-respiratory malignant disease considered together. This is obviously consistent with at least a 2-fold excess of gastro-intestinal cancer excluding mesotheliomas, though further refinement is not possible because of the small numbers. It may be noted that the authors attempted to adjust the excess mortality by factors correcting for social class, domicile and smoking. The adjustment factor for all cancers is 1.22, which if applied to the basic prediction for all cancers in this cohort of 6.84, produces an adjusted prediction of 8.35. As a considerable amount of this adjustment is for factors more relevant to respiratory cancer, it still seems unlikely, if adjustment had been possible for the small numbers of observed compared to expected gastro-intestinal cancers, that the excess would have been eliminated.

Kleinfeld, Messite and Kooyman [29] studied 152 asbestos workers who had 15 yr or more of asbestos exposure by 1945, or achieved 15 yr of exposure to asbestos dust between 1945–1965. The expected mortality was calculated by a proportional mortality analysis using as base yr the mortality from U.S. white males in 1948 as this was the median yr of death among the 46 deaths observed. This comprises 7 observed deaths of which 2 were cancers of the stomach, 1 of the colon, 1 a lymphosarcoma of the small intestine, and 3 peritoneal tumours.

This particular report is almost impossible to interpret. Apart from the potential bias of proportional mortality analyses of this type [33], there is an additional bias in that it is not certain that the mortality experience in the cohort was correctly ascertained for comparing with the expectation to avoid the bias noted recently in studies of cohorts exposed to vinyl chloride [34–36]. Thus, although the observed proportion is likely to be greater than the expectation if the mesotheliomas and other diagnoses could be excluded, and thus this report would again be compatible with others, no particular reliance could be placed on such a finding.

Knox and others [30] described the mortality experience of 794 men and 220 women, who had been exposed to asbestos fibre dust for a period of 10 yr or more in an asbestos textile factory in England. The men were considered in four groups, the majority had exposure to asbestos fibre for 10–19 yr and no exposure prior to 1933, the remainder had had an exposure for 20 yr or more, and were sub-divided according to whether their exposure prior to 1933 was 10 yr or more, less than 10 yr or none. In 1933 ventilation systems were introduced, and thus presumably the 57 workers exposed for 10 yr or more prior to 1933 had had the greatest dust exposure. They only, however, comprise 918 person-years at risk of death. These were designated group 1 in their report. Expected numbers of deaths were computed from national figures, though dividing up the groups according to intensity of exposure enable an internal comparison to be made. Data of observed numbers compared to the expectation were supplied for all neoplasms with cancer of the lung or pleura separately identified. Excluding the latter group, for the total cohort 14 deaths were observed compared to an expectation of 18.39. In those men exposed for 20 yr or more, who had worked at least for some period prior to 1933, the observed numbers were 8 compared to an expectation of 4.99. Details were provided of the cause of death. Of these, 5 occurred in Group 1, one was a cancer of the stomach, 2 colon cancers, 1 gallbladder, and 1 prostate. This total of 5 compared to an expectation of 2.61. It is obvious the expectation of this subcohort, and possibly the period of observation of the other cohorts was insufficient to confirm or refute the findings of others, particularly that of Selikoff and his group [21–27] though it may be noted that the findings in this study were confirmatory for lung cancer.

Mancuso and Coulter [31] reported on a cohort from an asbestos company identified through the use of Bureau of Old Age and Survivors Insurance Data. The cohort comprised individuals employed at any time during the period 1938–39. These were followed through the BOASI source to mid 1960. Person-years at risk were computed and compared for selected underlying causes of death on the basis of death rates from the state of OH from 1950 to 1960. Ohio data was used as corresponding data for the state in which the plant was located was not available and the period 1950–1960 was used instead of 1940–1960 because of the unavailability of earlier data. It was believed that OH death rates reflected the expectation from the corresponding state though it was noted that any excess in observed deaths over expected deaths due to specific causes of mortality would be underestimated for causes of death with rising mortality trends and somewhat over-estimated for causes with declining mortality trends because of the use of mortality rates from the second part of the observed 20 yr period. This would have been important if an excess of deaths from carcinoma of the stomach had been claimed. In practice this was not so, although a detailed tabulation showed that the observed numbers (with the expected in brackets) for digestive organ and peritoneum were 18 (8.07), while by major organ the breakdown was esophagus 1 (0.53), stomach 2 (1.87), large intestine except rectum 3 (2.29), and rectum 2 (1.15). This report, however, only permits a maximum 20 yr follow-up and no data was supplied to permit analysis by duration of employment or intensity of exposure. Furthermore, the study was restricted to ages 25–64 and the authors themselves felt that the order of excess noted for lung cancer 19 (5.61) and peritoneal cancer 3 (0.08) were conservative estimates. Nevertheless, this must be regarded, as far as it goes, as a largely negative study.

Meurman, Kiviluoto *et al.* [32] studied 1092 asbestos workers first employed at two anthophyllite asbestos mines between 1936–1967. Follow-up was to June 1969, 95% of the workers being traced, 248 of whom had died. A unique feature of this study was that not only were the deaths observed compared to an expectation for national mortality data (the year 1958 was used as the mid year of deaths in the cohort), they also selected a matched control cohort of individuals residing in a town 60 km northwest of the mining community during the period 1936–1967, using a local population registry. Seven digestive organ cancers were observed in the asbestos workers, 9 in the control cohort compared to an expectation of 14.9 from national rates. There was no excess

in any age group, for example, at ages 65–74 the corresponding numbers were 4, 4, and 4.2. In a subgroup of employees, exposed for 10 yr or more, 2 deaths from digestive system cancer were observed compared to 2.1 expected. It may be noted that in a comparable analysis for lung cancer there were 8 cases observed compared to 2.4 expected. Thus, it would seem that this study has failed to shown any evidence of an excess of digestive organ cancer even though the cohort superficially seems reasonable in size. However, this may be a spurious assessment because those who most recently entered the cohort can have only had a 2 yr period of observation while the numbers of workers who had a 20 yr period of follow-up is likely to have been very small. As reviewed below, it is only this group which showed the excess in the studies of Selikoff *et al.* [27]. Furthermore, it is possible that using a single year for deriving expected rates may have over-estimated the expectation, especially for stomach cancer, which has been declining in mortality during the time period considered. Thus, although this must be regarded as a negative study, it is still possible that further follow-up of the cohort might reveal findings similar to those of other workers.

There remain studies by 2 groups of workers [21–27] and [37, 38] which seem to be more contributory to the subject under consideration.

McDonald and his colleagues have produced two reports on mortality experience of workers in the Chrysotile Asbestos Mines and Mills of Quebec [37, 38]. The cohort identified for the study comprised 11,788 persons born between 1891–1920, who had been employed for 1 calender month or more. These were then traced by various mechanisms in order to establish live or dead status as of Nov. 1, 1966. Information was obtained concerning 10,421 (88.4%) of the cohort. Of those traced, 2457 (23.6%) were dead. For the majority of these copies of death certificates were obtained and for those suspected as dying from gastro-intestinal cancer. Of the total cohort, 1203 had worked 30 yr or more, while 3738 had worked for less than 1 yr and an additional 1080 had worked for more than 1 yr, but had had low dust exposure. A "dust index" for exposure was determined and the analysis was performed by calculating what was described as equivalent average death rates per 1000 men for different categories of malignant neoplasms according to the dust index. These rates were age standardized. Table 4 of the 1971 report [37] indicates an increasing trend of mortality for intestinal or rectal cancer by dust index, the ratio between the highest and the lowest categories being 3.5, but an inconstant trend for esophagus and stomach cancer considered together mainly because the lowest category of dust index had almost as high a mortality rate as the highest, the ratio being 1.3 even though those with a dust index towards the middle of the scale had a substantially lower mortality than either of the two extremes of the distribution. A comparison with Quebec mortality rates was carried out for all causes of death and for lung cancer, but if performed for gastro-intestinal cancer, was not reported. For all causes of mortality, the expected numbers of deaths were 1824 in men compared to 1674 observed, while for lung cancer, the numbers were 91 and 94 respectively. In the discussion of results in the 1971 paper, the authors indicate that they feel that an excess of lung cancer in most heavily exposed categories of workers might be of the order 3 to 5-fold, possibly substantially less than that reported by Selikoff and his colleagues. They did not attempt to further interpret the findings for gastro-intestinal cancer.

In a subsequent paper [38], no additional data was presented, however, they did state "the primary method of analysis used in our report on deaths up to 1966 had two main weaknesses. The first was that length of the exposure might well have been related to length of survival and thus might tend to obscure differences in mortality between exposure groups—the second lay in the fact that deaths accumulated over many years were used in a single calculation of mortality." Thus the authors have admitted that their analysis had many of the potential pitfalls of such analyses [34–36]. Nevertheless, it is difficult to see how a significant trend for colo-rectal cancer within the different exposure categories could have been introduced by the errors admitted. Rather the comparison with Quebec mortality will have underestimated the magnitude

of the increased mortality due to asbestos exposure. Clarification of the present position (G. W. Gibbs, Personal Communication, 1976) elicited the information that deaths up-to the end of 1974 had been ascertained and are currently in the process of analysis. It may be noted that in their 1974 report, the authors indicate that the analysis they propose will be based on man-years of exposure to minimize those errors noted. It is unfortunate the data is not available from this cohort in the detail and format that would be required for proper interpretation as this is probably the largest experience likely to become available in the forseeable future.

The second group of workers that have reported extensively, but generally speaking, repetitively on the same cohorts, is that of Selikoff *et al.* [21–27]. The publications of these workers have been frequent and, in addition, particularly in recent years, earlier papers have been updated in a number of ways including presentations at meetings. Unfortunately, presentations at meetings often do not permit adequate description of details of ascertainment of studied individuals and their subsequent follow-up and the analysis of their experience. This has caused some difficulty in interpretation and at times has lead to the suspicion that the data may not be as firm as the published claims or the claims made in presentations may have indicated.

Three differing, but in one respect overlapping cohorts have been identified and studied by these investigators. The first is a cohort of 632 asbestos insulation workers, who were members of the NY and NJ locals of the asbestos workers union, that is locals 12 and 32 of the International Association of Heat and Frost Insulators and Asbestos Workers. These men had all entered employment prior to Dec. 31, 1942 and were alive on that date and in the initial publications were followed through to Dec. 31, 1962 [21, 22]. Coincidentally, as this cohort of 632 workers was identified another 890 workers, who entered the relevant union locals between Jan. 1, 1943 and Dec. 31, 1962 were also identified, but these have never been the subject of an independent report except to the extent they contribute to the reports on the third cohort to be described. Subsequently, a subsegment of the cohort of 632 workers comprising 370 who were alive and examined and followed from Jan. 1, 1963 were described as being of particular interest with regard to the interaction between smoking and asbestos exposure and lung cancer [23, 24]. This particular subsegment, however, though having their experience in relation to gastro-intestinal cancer described, is not of particular value with regards to the question of prime interest in this report and they will not be referred to further.

The second cohort comprised 933 Amosite factory workers, who started work in a single factory some time between June 1941, when the factory began production and Dec. 1945. The plant continued production until Nov. 1954, when it closed its doors and in the first publication, the population was followed through to June 30, 1971 [25].

The third cohort comprised the entire membership of the International Association of Heat and Frost Insulators and Asbestos workers of the U.S.A. and Canada on Jan. 1, 1967, comprising 17,800 workers who also included those members of cohort one that were still alive on the date of ascertainment. This cohort has never been described in an independant publication, but was referred to in two reports which served also to update the experience of the other two cohorts [26, 27].

The ascertainment and follow-up of all three cohorts essentially followed an identical pattern and may be summarized as the identification of a total group of occupationally exposed workers within defined limits, who are established as being alive on a date subsequent or immediately following the last date of the period of time used to establish the cohort. It is important to note that this procedure removes nearly all the potential biases that have been described by others [34–36]. All were subsequently followed by periodically confirming that the men were alive and for those who were dead eliciting copies of death certificates, tracing hospital records wherever possible and collecting histological material for the large majority where it seemed likely that a cause of death of interest had in fact occurred. Considerable care was taken in this review of the cause of death to confirm that certified. Indeed, where it was not possible to obtain

detailed information, preferably histological, though it seemed likely that an individual had died of malignant disease, then the case was categorized as dying from other cancer and included in the tabulations under the heading "All other cancer". (I. Selikoff, Personal Communication, 1976.) This certainly explains the reason why there is an excess of observed and expected deaths under this category, but also they may serve to underestimate the difference between observed and expected in other categories to the extent that individuals who in fact died of, e.g. stomach or colo-rectal cancer were incorrectly tabulated under all other cancer. Thus the reported observed/expected ratios are conservative. The calculation of expected deaths was based on age specific mortality data derived from U.S.A. National Centre for Health Statistics. To the extent that these reflect a different expectation than the cohort then the results of the analysis will be in error. For example, it might be anticipated that a group of NY, NJ workers might not necessarily have the mortality experience identical to that of national rates while it is not clear the extent to which U.S.A. national rates are similar to Canadian rates for the expectation of deaths for that relatively small portion of the third cohort which was established and living in Canada. The effect of an error from this source, however, is likely to be very small. A possibly more basic criticism is the fact that all comparisons are based on expected rates derived from national data and no control from another source was established for any of these cohorts. For some of the data, internal controls are, however, available, especially when analysis is performed according to duration of employment. Duration of employment has in fact been used by these investigators as the closest approach to determining a dose response relationship. This is because most of the workers studied performed a number of different jobs, the nature of which could not be clearly specified in terms of intensity of dust exposure.

The latest published results [27] can be summarized as follows. In cohort one, the 632 workers, of whom 623 have been exposed for 20 yr or more from first employment, 18 cases of carcinoma of the stomach were observed with an expectation of 5.1, and for carcinoma of the colon and rectum 22 with an expectation of 7.5.

In cohort two, the 933 Amosite workers, 10 cases of carcinoma of the stomach were observed with 4.89 expected and 16 of carcinoma of the colon and rectum, 7.65 expected. It may be noted that in Table 4 of [27], the ratio of observed to expected tabulated for cases before 1953 for carcinoma of the stomach is printed as 7.78, but this is an error. It should be 1.78. It may also be noted that the observed to expected ratio increases the longer the period since the establishment of the cohort. Table 8 of the same publication considers occurrences according to duration of employment for carcinoma of the stomach. A clear trend is observed of increasing ratios of observed to expected with increasing duration of employment, though these are based on small numbers. For carcinoma of the colon and rectum, all the ratios show an excess of observed compared to expected, though in this instance a trend is not seen.

In cohort 3 (the 17,800 workers) the numbers permit a breakdown according to observation periods for less than 20 yr from onset of work and more than 20 yr from onset of work. Unfortunately the latest published results (Table 5 of [27]) are only up to the end of 1972 and consider all gastro-intestinal cancers (excluding peritoneal mesotheliomas) together. Nevertheless, there is no indication that a risk is demonstrable less than 20 yr from onset of exposure, the numbers observed being five with an expectation of 4.6, while for 20 yr or more from onset of exposure the figures are observed 56, expected 33.2. Subsequent analyses up to the end of 1974 have confirmed this distribution, and demonstrated that it holds for the major sites at risk, esophagus, stomach and colo-rectum (I. Selikoff, Personal Communication, 1976).

DISCUSSION

There is no doubt that an association has been demonstrated between exposure to asbestos and the subsequent development of cancers of the gastro-intestinal tract, particularly that of the esophagus, stomach, colon and rectum. The important question is the extent to which this association can be interpreted as being causal.

A number of authors have described the criteria which should be applied before deciding that the most likely interpretation of an association is causation. Perhaps one of the clearest of these expositions is that of Bradford Hill [39] and I shall discuss this issue according to the headings he uses.

Strength. There can be little doubt that the demonstrated association between gastro-intestinal cancer and asbestos exposure is weak. The risk ratios quoted, i.e. the ratio between the observed and the expected deaths, rarely seem to exceed three and in many instances are around two. The worry over weak associations is the possibility that they may be explicable on the basis of other factors whose relevance was not considered either in the study design or in the subsequent analysis. The most obvious example is socio-economic status and, indeed, as most of the comparisons that have been conducted are between the observed mortality in an identified cohort and an expectation based on national mortality rates, this might be expected to confound the issue. Nevertheless, it may not be correct to anticipate that this would necessarily operate in the direction of causing a spurious association to appear. Thus, asbestos insulation workers are not necessarily unskilled, falling more under the category of skilled workers such as might be categorized under the British Registrar General's category of 3 rather than 4 or 5. This might indicate an expectation of mortality very similar to the national average. In addition, although it might be expected that in a low socio-economic group, stomach cancer might be higher than the national expectation, the reverse would be anticipated for colon and rectal cancer, yet both appear to be increased in most studies to almost the same extent. It seems difficult, therefore, to believe that socio-economic status should be a cause of a spurious association when different directions of effect in these two cancer sites would be anticipated. Furthermore, in those studies where either internal controls have been utilized or control has been attempted for socio-economic status, the analyses indicate that socio-economic status does not explain the differences observed.

In many respects use of national mortality data to derive expectation may underestimate the magnitude of the difference and thus the strength of the association. It has been frequently observed that occupational groups have lower all-causes mortality (other than those possibly associated with the occupation) than would have been expected from the general population. This has been almost universally the experience of cohorts studied for disease experience subsequent to asbestos exposure when causes other than those suspected or established as due to this exposure, were considered. Nevertheless, it has not so far been established how a correction for this "healthy worker effect" could be applied.

In his discussion of this criterion, Bradford Hill points out "We must not be too ready to dismiss a cause and effect hypothesis merely on the grounds that the observed association appears to be slight." Although this seems to have been the grounds an advisory committee on asbestos cancers convened by the International Agency for Research on Cancer [20] failed to conclude that a causal relation existed, they did not discuss all the criteria that should be applied and indeed met at a time when some of the more recent evidence was not available.

Consistency. As already discussed, a number of the studies reported, which failed to show the association, seemed either to be too small or possibly to be observing a cohort for too short a period since exposure to expect that an association might be demonstrated. For those studies which do not seem to have such limitations, even those which do not specify gastro-intestinal cancer by organ of origin, the criterion of consistency seems to be met. Although most of the studies were analysed using a similar approach, a number of different cohorts are involved, some exposed to different types of asbestos and in different countries and for this reason the consistency criterion is important.

Specificity. This characteristic, essentially demanding an almost one to one relationship between a suspected causal agent and the ensuing disease, is obviously not met. Thus asbestos is accepted as an etiologically relevant agent for one type of pulmonary fibrosis

and in malignancies for lung cancer and for the very different pleural and peritoneal mesotheliomas. With regard to gastro-intestinal cancer, the association exists for esophageal, stomach, and colorectal cancer, though with regard to the latter, it is not particularly clear as to whether or not the association has been demonstrated for rectal as distinct from colonic carcinoma. Few studies enable the data to be distinguished on this point, though it seems certain that the association is present for colonic carcinoma.

However, as Bradford Hill points out, "one to one relationships are not frequent. Indeed, multicausation is generally more likely for a disease than single causation" so that the lack of specificity does not necessarily rule against causation.

Temporality. This fourth criterion is designed to distinguish between those associations which arise because of or after a disease has occurred or which clearly preceded the disease in a reasonable causal chain of events. As all the studies reviewed have been essentially the same type, namely cohort or prospective, even if some of the cohorts were established in retrospect, the temporality of the association has been clearly demonstrated.

Biological Gradient. This criterion is most clearly expressed in terms of a dose/response relationship. As already indicated, there are few studies which enable this to be determined. The one that most clearly tackles this issue is that of McDonald and his colleagues [37, 38], though the authors of these reports accept that their analysis may have been faulty. However, the errors in the analysis are of a type which it seems likely will have underestimated the strength of the association or resulted in failing to demonstrate a dose/response relationship. It is difficult to visualize that the errors in the analysis would have created a dose/response relationship for colorectal cancer and this must be regarded as a strong point in favour of regarding this particular association as causal. Furthermore, other approaches to attempting to obtain dose/response relationships such as duration of exposure or period since initiation of employment contribute to the suspicion that a dose/response relationship does in fact exist.

Historically, the suspicion that asbestos exposure was causally related to lung cancer was delayed in its confirmation because insufficient time was allowed both to ensure that those individuals in the studied cohorts had acquired sufficient exposure and that they had been observed for long enough to exceed the "latent period" between initiation of exposure and development of disease. The studies of several workers, particularly those of Selikoff and his colleagues, appear to confirm the presence of a latent period which is probably 20 yr or more [27]. For this reason, it seems possible that the largest cohort under observation by Selikoff (cohort 3, the 17,800 workers) has yet to experience its greatest mortality from gastro-intestional cancer. Indeed, in many respects, this is a far younger cohort than the other two studied by these investigators and McDonald and his colleagues.

Even so, the various observed/expected ratios reported by Selikoff do not indicate any consistent trend to increasing ratios with further follow-up of the early cohorts established by this group. Nevertheless, this may not necessarily be expected in studies in which essentially the same small group of workers are repetitively reanalysed.

It may, however, be noted that in more recently established cohorts, the expectation for death from gastro-intestinal malignancies, or indeed any other asbestos related condition, may fall if there is a threshold effect for induction of these diseases and if measures taken almost universally in asbestos related industries to reduce exposure to asbestos dust have reduced the exposure of the majority of workers below the threshold. This indicates that it is highly desirable to study not only existing cohorts already under observation, but to attempt to establish more recently exposed cohorts so that if the risk is reduced to the extent that no further excess is demonstrated after suitably prolonged periods of observation, such absence of risk can be documented. Indeed, one of the important aspects yet to be established in relation to asbestos and cancer that has been clearly demonstrated in relation to smoking in the absence of asbestos exposure and lung cancer is the fact that the risk of disease is substantially reduced in individuals in whom exposure has ceased. Nevertheless, as asbestos appears to persist in the tissues

and possibly to act in this regard either as solely an initiating agent or as both an initiating and a promoting agent, whereas smoking clearly acts as a promoting agent alone, then expectation of a reduction of risk in individuals once exposed may be unrealistic.

Plausibility. In Bradford Hill's words, "It will be helpful if the causation we suspect is biologically plausible, but this is a feature I am convinced we cannot demand. What is biologically plausible depends on the biological knowledge of the day."

Data on this criterion cannot be obtained through epidemiological studies. Even though asbestos is generally inhaled, it may be anticipated that those who are exposed to inhalation would tend to trap many asbestos particles in the sputum and then these would then expose the gastro-intestinal tract when the sputum was swallowed. Indeed, unless all peritoneal mesotheliomas develop through penetration of fibres through the diaphragm, it is difficult to see how they could arise, except through penetration through the gastro-intestinal tract. Thus it would seem to be plausible to anticipate, even in the absence of demonstrated fibres in tumours, that swallowed asbestos fibres are carcinogenic, by whatever biological mechanism in fact operates, in all parts of the gastro-intestinal tract.

Coherence. In Bradford Hill's words, "On the other hand, the cause and effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease." Coherence in this sense is difficult to establish in the absence of information on the etiology of most cancers of the gastro-intestinal tract other than suspicions of the effect of highly spiced or irritant foods in producing gastric cancer or high fat or animal protein diet in producing colorectal cancer. Whether or not asbestos is acting in association with such factors cannot be determined on present knowledge. Thus, although it is obvious that asbestos exposure is not necessary for the development of gastro-intestinal cancer, we cannot determine whether alone it is sufficient or whether it acts in collaboration with other etiological agents. By analogy with lung cancer and cigarette smoking, it seems possible that asbestos may require to act in association with another agent though knowledge is just not available on this point.

Experiment. This criterion is used by Bradford Hill not in the sense that animal experimental data may help, he presumably relates this to biological knowledge; (in passing, it may be noted that animal experimental data on causation of gastro-intestinal cancers through asbestos exposure is still controversial), but in regard to the possible effect of an experiment in the human situation. Thus the strongest evidence might come if it were possible to remove exposure to an etiologic agent. The difficulties over this in relation to asbestos have already been alluded to, at least in terms of already exposed individuals. Furthermore, it seems unlikely in view of the ubiquity of exposure to asbestos that any occupational group that uses it could in fact be completely prevented from exposure of their lungs or gastro-intestinal tract. Thus, apart from the difficulty of long term observation that would be required, expectation of establishment of causation on this criterion may be somewhat academic.

Analogy. The final criterion used by Bradford Hill is the reasonableness of ascribing causation, if in fact a similar mechanism has been shown to operate for another condition. In practice, asbestosis is so unique that it seems unlikely that one would be able to demonstrate a similar chain of events in relation to gastro-intestinal cancer. The nearest one could come to analogy is that of the occurrence of lung cancer and pleural and peritoneal mesotheliomas.

Two further points require comment. Firstly, one of the difficulties of the literature is the absence of data relating to exact anatomical sites of cancers. Although it would be nice to be in a position to identify cancers of particular sites within the stomach or other parts of the gastro-intestinal tract or even more so a particular histological variety that would facilitate identification of clearly asbestos related cancers, data is just not available on this point and it is unrealistic to expect that it will become available from existing methods of epidemiological study. So far it has not been possible using

anatomical or histological criteria to clearly identify those cancers of the gastro-intestinal tract that are due to exposure to asbestos (I. Selikoff, Personal Communication, 1976). Nevertheless, in view of the nature of the agent, it may be unrealistic to separate off gastro-intestinal cancers even by organ. If one is dealing with a statistically rare event, and if the nature of the agent is such as to cause fairly uniform exposure to the gastro-intestinal tract, then maybe all we should expect is a general increase in the incidence of those cancers which normally occur. That the esophagus is not preferentially at risk compared to the stomach and the stomach compared to the colon seems to be established on the data that is available. Furthermore, the marked excess of peritoneal mesotheliomas in all series seems to suggest that in many, if not most instances, asbestos exerts its neoplastic potential when it comes to rest in the peritoneum and that possibly the rule is that either it is excreted or that it passes through the epithelium lining the gastro-intestinal tract and only rarely lodges for a sufficient period of time to induce neoplasia. If this is so, then what may be anticipated is an increase to a certain degree in the incidence of cancers that normally occur and in general all studies are supportive of this.

Secondly, it should be noted that the type of methodology normally utilized in occupational studies is such as to facilitate identification of strong associations (such as has lead to the demonstration of a causal association of asbestos and lung cancer, especially in the presence of smoking), but which does not facilitate the refinement of the nature of the relationship, especially if the association is relatively weak, as in the present case. Although further data can be anticipated in the years to come from continued observation from the cohorts studied by Selikoff and his colleagues and McDonald and his colleagues, the type of information that will be obtained is already known. Therefore, it seems likely that the data currently available is as good as may become available in the future unless extremely detailed studies of large cohorts carefully categorized by intensity of exposure, preferably with control through other occupational or general population groups, prove possible in the near future. It may be noted that no such studies are being conducted as far as I am aware and that even the study in Finland [32], which has some of the features of an ideal design, and from which further confirmatory evidence may become available after another decade of follow-up, appears to lack detailed information on extent of exposure.

A decision, therefore, has to be taken on the basis of available evidence and on the basis of weighing the data that is available in spite of the acknowledged deficiencies already discussed in this report.

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