subjects, whether manifest in the fasting or in the stimulated state, is independent of coexisting obesity and glucose intolerance although both are often contributory factors. Which is chicken and which is egg is unresolved but experimental evidence favours a causal role for hyperinsulinæmia. Long-continued administration of insulin to animals in supra-optimal doses can give rise to histological and biochemical lesions resembling those of human atheroma[13] and insulin encourages the synthesis of cholesterol and other lipids by arterial-wall tissue[14,15] both in vivo and in vitro. Of the many factors known to cause exaggerated insulin secretion some, such as obesity and high sucrose consumption,[16] have been implicated, on epidemiological grounds, in the pathogenesis of atherosclerosis whilst others, such as increased consumption of sugary alcoholic drinks,[17] have so far not been. Conversely, certain types of vegetable fibre, the exclusion from the diet of which have been claimed to increase the risk of atheroma,[18] reduce the immediate and overall insulin secretory response to ingested carbohydrate[19] without adversely affecting glucose tolerance. The role of the insulinotropic gastrointestinal hormones in providing the link between composition of the diet and the hyperinsulinæmia of atherosclerosis is undetermined and awaits investigation by the newer methods of measuring them in blood.

## COSMETIC TALC POWDER

FROM time immemorial man, like his evolutionary predecessors, has been exposed to airborne dusts. Such exposure is a corollary of living and survival. Not unexpectedly, therefore, the lungs have efficient means of clearing themselves of inhaled particles and a functional reserve such that the accumulation of uncleared dust may be considerable before there is any obvious loss of work-capacity. However, it has long been recognised that heavy exposure to dusts, such as quartz and asbestos, may lead to loss of function and, in the case of asbestos, to cancer of the pleura and of the lung itself. The observation that even casual exposure to asbestos may be associated with increased risk of mesothelioma, now occurring at the rate of nearly 200 new cases a year in the United Kingdom,[1] has brought into question the safety of other common dusts such as cosmetic talc. There are two main concerns. Firstly, will inhalation of a dust cause loss of function through fibrosis or emphysema? And, secondly, will it predispose to cancer? Although talc can cause granulomas when introduced into the tissues or body cavities,[2] exposure to cosmetic talc has been widely assumed not to predispose to pulmonary fibrosis. However, the fact that no association has been seen between the use of talc and loss of lung function might simply reflect the lack of methods sensitive enough to detect losses of function that are small compared with those due, for example, to smoking and to heterogeneity in $\alpha_1$-antritypsin status. For similar reasons any effect of talc exposure on cancer incidence would probably escape notice unless deliberately sought. Until lately facilities for studying the long-term effects of inhalation of dusts in laboratory animals have been scarce, and even now the predictive value of animal models is questionable. Thus, even in the case of tobacco smoke, where the cancer hazard to man is indisputable, duplication of the effect, by the inhalation route, in laboratory animals has proved difficult or impossible,[3] although inhaled asbestos dust has given positive results in animals.[4]

The possibility that talc causes cancer dramatically hit the headlines of the daily Press when workers in Cardiff[5] reported finding talc particles in cancers of the ovary and uterine cervix. The report was greeted with scepticism because the particles were not positively identified as talc, because their presence did not prove causation, and because they might have found their way onto the sections as a result of contamination of tissues *after* removal from the body. Subsequent mineral analysis failed to confirm that the particles were talc[6] and the passage of six years without publication of confirmatory evidence suggests that the early scepticism was well-founded. A meeting of talc-powder manufacturers and independent scientists took place at Cardiff during May, 1976, under the chairmanship of Dr J. C. Gilson, director of the Medical Research Council Pneumoconiosis Unit. At that meeting the toxicology of talc was reviewed and the need for further information discussed. Assessment of toxicity necessarily starts with a consideration of the physical and chemical specifications of the test material, and this, unfortunately, is also where much of the assessment ends in the case of cosmetic talc because most of the published reports—epidemiological, clinical, and experimental—concern exposure either to industrial talcs that are variously contaminated with minerals known to be hazardous or to talc of undefined physical and chemical characteristics.

The long thin fibrous shape of asbestos particles enables them to be carried more deeply into the lungs than spherical particles of similar mass. The fact that the normally effective clearance mechanisms have difficulty in coping with large, long thin particles deposited deeply in the lungs is an important determinant of the hazards from asbestos dust. Geologically, talc (which is nominally a hydrated magnesium silicate) and certain amphiboles—tremolite, actinolite, and anthophyllite—may occur in juxtaposition and consequently talc may be contaminated with these minerals. Apart

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from this, talc may contain chlorite, quartz, carbonates (such as calcite, dolomite, and magnesite), and occasionally other minerals in lesser amounts. During the past few years, major cosmetic manufacturers in the United Kingdom and the United States of America, as represented by the Toilet Preparations Federation and the Cosmetic, Toiletry and Fragrance Association, have drawn up specifications for cosmetic talc which ensure the virtual absence of fibrous amphiboles.[7-10] At present there is no direct statutory control of the quality of cosmetic talc in any country and it is questionable whether such control is necessary to bring minor manufacturers into line with the standards now adopted by the major firms. The presence of fibrous particles in talc reduces its free flow and lubricity, thereby rendering it less cosmetically desirable. Such contamination is thus self-limited. More important, however, is the fact that the fibrous materials most likely to contaminate talcs which do not comply with the specifications—namely, tremolite, anthophyllite, and actinolite—are not those most clearly associated with carcinogenic hazard (crocidolite, amosite, and chrysotile). Furthermore, it would be sensible to consider what controls, if any, are necessary for talc as used in medicines, before introducing legislation specifically in relation to cosmetic talc.

If the inhalation of particles of amphibole and silica contaminated talc dust were found to be harmless, one might reasonably assume that talc free from these materials is safe. Kleinfeld and his colleagues have studied the incidence of cancer and respiratory diseases in talc miners and millers in New York State. The talc concerned, which is heavily contaminated with both amphiboles and free silica, was initially reported to be associated with an increased mortality from mesothelioma and cor pulmonale.[11] Later the same workers reported that men employed in the mine after dust levels had been reduced had death-rates from malignant diseases that were similar to those for White males in the U.S.A. generally.[12] Also in the U.S.A., Fine and his colleagues[13] have reported a higher prevalence of productive cough and chronic obstructive lung disease among rubber workers exposed to a non-fibrous industrial-grade talc than among control workers. From their data they calculated that a safe exposure level would be provided by a threshold limit value of 0·25 mg/m$^3$ mass-respirable particulate talc. In Italy, Rubino and his colleagues[14] compared the spectra of causes of death among talc miners, talc millers, and agricultural workers. The talc miners were exposed to dusts containing 5% silica at levels far in excess of threshold limit value. Significantly more of them than of the controls died from respiratory disease, but death-rates from all forms of cancer, including lung cancer, were significantly lower among the miners than among the controls. By contrast, among the talc millers, exposed to dusts containing 0·05% silica, but no detectable asbestos, at concentrations of 20 million particles per cubic foot (27 litres), there was no excess of deaths from pulmonary disease or cancer of any site compared with the control group. The deficit of lung cancer among the talc miners is plausible in so far as a similar deficit of lung cancer among coal miners seems to be real.[15] A continuing study of over 3200 persons, mainly women, at a factory in Britain where cosmetic talc has been made and packed for over fifty years, has so far revealed no evidence of health hazard,[16] but follow-up would need to be extended for at least a further decade before one could be confident of a negative result. Other less informative epidemiological studies are reviewed by Hildick-Smith.[6]

In most of the work in animals the quality of the talc has not been specified. An exception is a report by Wehner and others[17] who studied the effects in hamsters of repeated exposure to aerosols of cosmetic talc up to total doses of respirable particles equal to nearly 2000 times those received by humans using cosmetic talc during baby care. Exposure had no adverse effect on bodyweight, survival, incidence of pathological changes in the respiratory tract, or incidence of neoplasia at any site. Another exception is the report by Wagner and his colleagues,[18] who saw no mesotheliomas in 48 rats after intrapleural administration of cosmetic talc whereas 18 out of 48 rats similarly exposed to chrysotile asbestos acquired such tumours. The same workers exposed rats to cosmetic talc by the inhalation route on five days a week for up to a year. At the highest level of exposure —about three times that studied by Wehner and his colleagues[17]—there was slightly more pulmonary fibrosis than in controls, but no substantial excess of pulmonary neoplasms. A number of less relevant animal studies, all of which gave negative results for carcinogenicity, are reviewed by Hildick-Smith.[6] In summary, there is no reason to believe that normal consumer exposure to cosmetic talc has in the past led either to cancer at any site or to measurable loss of lung function. It seems unlikely that future exposure to cosmetic talc of the specifications now agreed to by major manufacturers will present a health hazard.

## HÆMOPHILUS ENDOCARDITIS

*Hæmophilus* endocarditis is rare. Until lately the published reports were small-scale and conflicting; now three substantial and independent investigations have been reported from the United States.[1-3]


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FJCR/SR

14th June, 1977

Dr. Gavin Hildick-Smith,
Director, Medical Affairs,
Johnson and Johnson,
New Brunswick,
N.J. 08903,
USA.

Dear Gavin,

Herewith a copy of what I have sent to the Lancet. I felt I had to shorten it. I will let you know the reaction of the Journal. Sincere thanks for your help.

With best wishes,

Yours sincerely,

Francis J.C. Roe

Enc.

P.S. Thank you for your letter of 9th June. I have taken into account your two points on the original p. 8 (now p. 6) in a slightly different way from that proposed by yourself - But I think I have met your two points.

# COSMETIC TALC POWDER

From time immemorial man, like his evolutionary predecessors, has been exposed to airborne dusts. Such exposure is a corollary of living and survival. Not unexpectedly, therefore, the lungs have efficient means of clearing themselves of inhaled particles and a functional reserve such that the accumulation of uncleared dust may be considerable before there is any obvious loss of work-capacity. However, it has long been recognized that heavy exposure to dusts, such as quartz and asbestos, may lead to loss of function and in the case of asbestos, to cancer of the pleura and of the lung itself. The realization that even casual exposure to asbestos may be associated with increased risk of mesothelioma, presently occurring at the rate of nearly 200 new cases a year in the United Kingdom[1], has brought into question the safety of other common dusts such as cosmetic talc.

There are two main concerns: firstly that the inhalation of a dust will cause loss of function through fibrosis or emphysema and secondly that it will predispose to cancer. Although known to be capable of giving rise to granulomata when introduced into the tissues or body cavities[2], it has hitherto been widely assumed that exposure to cosmetic talc does not predispose to pulmonary fibrosis. However, the fact that no association has been seen between the use of talc and loss of lung function might theoretically be simply a reflection of the lack of methods sensitive enough to detect losses of function that are small compared with those due to smoking and other factors and to heterogeneity in $\alpha_1$-antritypsin status. For similar reasons any effect of talc exposure on cancer incidence is unlikely to have been noticed without deliberate study. Until recent years facilities for studying the long term effects of inhalation of dusts in laboratory animals have been in short supply and even now the predictive value of animal models is questionable. Thus even in the

case of tobacco smoke, where the hazard to humans is indisputable, it has proved difficult or impossible to duplicate the effect in laboratory animals by the inhalation route [3], although, in the case of inhaled asbestos dust, positive results have been reported in animals [4].

Historically, the possibility that talc causes cancer dramatically, if unfortunately, hit the headlines of the daily press when workers in Cardiff [5] reported finding talc particles in cancers of the ovary and uterine cervix. The report was greeted with scepticism particularly because the particles were not positively identified as talc, their presence did not prove causation and it was very possible that they had found their way on th sections as a result of contamination of tissues after removal from the body. Subsequent mineral analysis failed to confirm that the particles were talc [6] and the passage of six years without the publication of confirmatory evidence suggests the early scepticism was well founded.

A meeting of talc powder manufacturers and independent scientists took place at Cardiff during May 1976 under the chairmanship of Dr. J.C. Gilson, Director of the Medical Research Council's Pneumoconiosis Research Unit. At that meeting the toxicology of talc was reviewed and the need for further information discussed. The review was facilitated by a survey of the available literature provided by Dr. G.Y. Hildick-Smith [6]. Assessment of toxicity necessarily starts with a consideration of the physical and chemical specifications of the test material, and this, unfortunately, is also where much of the assessment ends in the case of cosmetic talc because most of the published literature - epidemiological, clinical and experimental - concerns exposure either to industrial talcs that are variously contaminated with minerals known to be hazardous or to talc of undefined physical and chemical characteristics.

The long thin fibrous shape of asbestos particles enables them to be carried more deeply into the lungs than spherical particles of similar mass. The fact that the normally effective clearance mechanisms have difficulty in coping with relatively large, long thin particles deposited deeply in the lungs is an important determinant of the hazards from asbestos dust. Geologically, talc (which is nominally a hydrated magnesium silicate) and certain amphiboles - tremolite, actinolite and anthophyllite - may occur in juxtaposition and consequently talc may be contaminated with these minerals. Apart from this, talc may contain chlorite, quartz, carbonates, such as calcite, dolomite and magnesite, and occasionally other minerals in lesser amounts. During the last few years, major cosmetic manufacturers in the United Kingdom and the United States of America, as represented by the Toilet Preparations Federation and the Cosmetic, Toiletry and Fragrance Association, respectively, have evolved specifications for cosmetic talc which ensure the virtual absence of fibrous amphiboles [7, 8, 9 and 10]. At present there is no direct statutory control of the quality of cosmetic talc in any country and it is debatable whether such control is necessary to bring minor manufacturers into line with the standards now adopted by the major firms. The presence of fibrous particles in talc reduces its free flow and lubricity, thereby rendering it less cosmetically desirable. Such contamination is thus self-limited. More importantly, however, is the fact that the fibrous

materials most likely to contaminate talc which fail to comply with the specifications referred to above, namely, tremolite, anthophyllite and actinolite, are not those most clearly associated with carcinogenic hazard (i.e. crocidolite, amosite and chrysotile). Furthermore, it would be sensible to consider what controls, if any, are necessary for talc as used in foods and medicines, before introducing legislation specifically in relation to cosmetic talc.

It is arguable that, if the inhalation of particles of amphibole and silica-contaminated talc dust were found to be harmless, it could reasonably be assumed that talc free from these materials is safe. Kleinfeld and his colleagues have studied the incidence of cancer and respiratory diseases in talc miners and millers in New York State. The talc concerned which is heavily contaminated with both amphiboles and free silica was initially reported to be associated with an increased mortality from mesothelioma and cor pulmonale[11]. Later the same workers reported that men employed in the mine after dust levels had been reduced, had death rates from malignant diseases that were similar to those for white males in the U.S.A. generally[12]. Also in the U.S.A., Fine and his colleagues[13] have reported a higher prevalence of productive cough and chronic obstructive lung disease among rubber workers exposed to a non-fibrous industrial grade talc ~~at~~

than among control workers. From their data they calculated that a safe exposure level would have been 0.24 mg/m$^3$ mass respirable particulate talc as a time weighted average. In Italy, Rubino and his colleagues [14] compared the spectra of causes of death among talc miners, talc millers and agricultural workers. The talc miners were exposed to dusts containing 5% silica at levels far in excess of threshhold limit value. Significantly more of them than of the controls died from respiratory disease, but death rates from all forms of cancer, including lung cancer, were significantly lower among the miners than among the controls. By contrast, among the talc millers, exposed to dusts containing 0.05% silica, but no detectable asbestos, at concentrations of 20 million particles per cubic foot, there was no excess of deaths from pulmonary disease or cancer of any site compared with the control group. The deficit of lung cancer among the talc miners is plausible in so far as a similar deficit of lung cancer among coal miners seems to be real [15]. An on-going study of over 3200 persons, mainly women, at a factory in Britain where cosmetic talc has been made and packed for over 50 years, has so far revealed no evidence of health hazard [16], but follow-up would need to continue for at least a further decade before one could be confident of a negative result. Other less informative epidemiological studies are reviewed by Hildick-Smith [6].

Most studies in animals suffer the deficiency that the quality of the talc used was not specified. An exception is a recent report by Wehner and others[17] who studied the effects in hamsters of repeated exposure to aerosols of cosmetic talc up to total doses of respirable particles equal to nearly 2000 times those received by humans using cosmetic talc during baby care. Exposure had no adverse effect on body weight, survival, incidence of pathological changes in the respiratory tract or incidence of neoplasia at any site. Another exception is the report by Wagner and his colleagues[18] who saw no mesotheliomas in 48 rats after the intrapleural administration of cosmetic talc, whereas 18 out of 48 rats similarly exposed to chrysotile asbestos developed such tumours. The same workers exposed rats to cosmetic talc by the inhalation route on five days a week for up to 1 year. At the highest level of exposure - about three times that studied by Wehner and his colleagues[17] - there was slightly more pulmonary fibrosis than in controls, but no meaningful excess of pulmonary neoplasms. A number of less relevant animal studies, all of which give negative results for carcinogenicity, are reviewed by Hildick-Smith[6].

In summary, there are at present no grounds for believing that normal consumer exposure to cosmetic talc has in the past led either to cancer at any site or to measurable loss of lung function. A fortiori, it seems unlikely that future exposure to cosmetic talc of the specifications now agreed to by major manufacturers will present a health hazard.

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