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CORRESPONDENCE

THE DANGERS OF PROTEOLYTIC ENZYMES TO WORKERS

SIR: In view of the world-wide concern (*New Yorker*, January 16, 1971) regarding the hazard to workers exposed to proteolytic enzymes used in the detergent industry, and the necessary time-lapse before comprehensive accounts of research can appear in scientific journals, it would be appreciated if space were available in your columns to summarize our investigations on this problem.

In November, 1968, asthma due to "Alcalase" was identified by us on clinical grounds, and proven on the basis of skin and inhalation tests. Further investigation was not encouraged at that time, although other cases had occurred in the experience of a local medical practitioner. In May, 1969, after the publication of a report by Flindt¹ of respiratory symptoms in a factory in the United Kingdom, an approach by the unions concerned led to a joint investigation by the Division of Occupational Health and ourselves. In association with relatively high environmental levels of enzyme, we found that 50% of 98 employees of one factory developed respiratory symptoms during "runs" when the enzymes were used, and approximately 65% showed skin sensitivity on testing with an appropriate extract. Amongst these current employees, tests of ventilatory capacity revealed no evidence of persisting functional abnormality (Mitchell and Gandevia²). In a second factory, where environmental levels were lower, and subjects with respiratory symptoms tended to be excluded, the sensitization rate was somewhat lower. Symptoms were present on enzyme exposure in subjects both with and without skin sensitivity; similar findings in Britain by Newhouse *et alii*³ were interpreted differently, in that the symptoms in individuals with negative skin tests were attributed to unrelated respiratory infections rather than to enzyme exposure. Our view on this important point was established in the course of a second study, in which 29 individuals, selected on certain defined criteria, were exposed to an aerosol of dilute "Alcalase" solution for one minute, using doses of the same order as the subjects had encountered, or might encounter, in a day's work under the conditions then existing. This investigation confirmed the development of asthma, as judged clinically and by serial ventilatory tests, in both sensitized and unsensitized subjects, the manifestations appearing, as with certain other occupational allergens (Gandevia;⁴ Gandevia and Milne⁵), either immediately, after four hours or so, in the night following challenge, or in various combinations of these separable reactions (Mitchell⁶). The reaction often lasted a day or so, but lasted a fortnight in one highly sensitive individual.

This study yielded further valuable information, in that it indicated the existence of a second acute respiratory syndrome attributable to enzyme exposure. This reaction was characterized by the appearance of fine rales in the chest in 11 of 29 subjects within a few hours of challenge, and persisting for hours or days. These signs were not necessarily associated with symptoms (except, of course, in those subjects also developing asthma), were not associated with change in serial ventilatory capacity estimations, and were not confined to sensitized subjects. On these grounds, together with the absence of evidence of alveolar or interstitial disorder as judged by clinical, functional and radiological studies, we ascribed this reaction to bronchiolitis, or to disease affecting small peripheral airways (Gandevia and Mitchell⁶). Subsequently, careful observation revealed that these easily overlooked reactions were identifiable in the course of ordinary industrial exposure, in spite of improved working conditions in Australia and in the United States.

By this time (mid 1970), the New South Wales Technical Committee on Enzyme Cleaning Products had been formed

under the chairmanship of Dr W. J. Hensley. Through its medical subcommittee, these findings were made known, and recommendations were made concerning the future medical surveillance of employees. Recommendations and standards were also adopted in regard to the control of enzyme levels in the environment and to handling procedures. Prompted by our demonstration of bronchiolar involvement and by the known effects of inhaled proteolytic enzymes on several species of animals (Gross *et alii*), we also recommended more elaborate studies of the mechanical properties of the lungs in subjects who had already been working with enzymes during the preceding two years; in our view there was some risk, the magnitude of which we could not assess, of the development of emphysema. In fact, serial observations of the mechanical properties of the lungs in three subjects had already indicated that this possibility was a real one, although for various reasons, notably the difficulty of excluding non-industrial disease in these highly selected subjects, the observations fell far short of proof.

This investigation has recently been completed by one of us (C.M.), and a report has been furnished to the Division of Occupational Health, to industry and to the unions. As the study was known to be in progress through public statements of the Technical Committee, the report was subsequently released to the Press, with the concurrence of the Chairman. A total of 36 men was studied, comprising 10 subjects previously classified as "relatively heavily exposed" (under previously existing working conditions), 14 classified as "moderately exposed" and 12 classified as "lightly exposed" on the basis of known places and types of work and the relevant environmental enzyme levels. Lung volumes were measured by the nitrogen washout method, and the mechanical properties of the lung were examined by the methods developed in this unit by Professor H. J. H. Colebatch and his colleagues Dr K. E. Finucane and Dr M. Smith (Finucane and Colebatch⁷).

The mean values for forced expiratory volume at one second (FEV₁) and vital capacity (VC) were comparable in all three groups, but the ratio FEV₁:VC was significantly reduced in the heavily exposed (HE) group by comparison with the lightly exposed (LE) group (HE 0.65 ± 0.08 [mean ± S.D.]; LE 0.76 ± 0.06; $P < 0.05$). Total lung capacity (TLC) was significantly greater in the HE group by comparison with the LE group (HE 7.08 ± 1.06 l.; LE 6.64 ± 0.97 l.; $P < 0.02$). Residual volume and functional residual capacity were similarly greater in the HE group. Deflation pulmonary compliance at functional residual capacity was greater in the HE group (HE 0.57 ± 0.32 l./cm H₂O; LE 0.37 ± 0.10 l./cm H₂O; $0.1 > P > 0.05$). The volumes of gas retained in lung at 10 and 6 cm H₂O (V₁₀ and V₆) were greater in the HE group than in the LE group (V₁₀: HE 6.72 ± 1.09 l.; LE 5.26 ± 0.89 l.; $P < 0.01$. V₆: HE 5.42 ± 1.02 l.; LE 4.19 ± 0.86 l.; $P < 0.01$). Pulmonary conductance measured during tidal breathing (HE 0.73 ± 0.45 l./sec/cm H₂O; LE 0.62 ± 0.30 l./sec/cm H₂O) and during deflation from TLC (HE 0.42 ± 0.20 l./sec/cm H₂O; LE 0.46 ± 0.18 l./sec/cm H₂O) was similar, indicating that large airway size and distensibility were comparable. The results in the moderately exposed group were intermediate between those of the other two groups.

These results (of which the above is a necessarily brief review) indicate loss of elastic recoil in the HE group. The airways obstruction indicated by the reduced FEV₁:VC ratio in the HE group is probably secondary to the loss of elastic recoil.

Age, height and smoking habits in the three groups were comparable. Neither these, nor, in our view, any of the factors conceivably influencing the selection and classification of the subjects, can be considered as responsible for the observed differences. We therefore conclude that the observed loss of elastic recoil is attributable to occupational exposure to the proteolytic enzymes, and we believe it is likely to be permanent.

¹ *J. occup. Med.*, 1964, 6: 481.

² *J. appl. Physiol.*, 1969, 26: 330.

¹ *Lancet*, 1969, 1: 1177.

² *Amer. Rev. resp. Dis.*, in the press.

³ *Lancet*, 1970, 1: 689.

⁴ *Med. J. Aust.*, 1970, 2: 332, 372.

⁵ *Brit. J. industr. Med.*, 1970, 27: 235.

⁶ *Aust. Ann. Med.*, 1970, 19: 408.

In the absence of severe, long-standing and chronic airways obstruction in the present cases, the only known and generally accepted cause of loss of elastic recoil is emphysema. However, we have specifically avoided the use of this term, first, because we have no proof of the appropriate structural changes, secondly, because the label would be applied at the comparatively unfamiliar level of subclinical functional disorder (in none of these subjects would a clinical diagnosis be possible on conventional criteria), and thirdly, because there is no evidence to indicate the prognosis and whether it conforms to that obtaining in "clinical" emphysema. Answers to these problems clearly require studies of these men over years. In the interim, whilst we must emphasize that our evidence of permanent ill effects relates only to workers exposed to levels unacceptable by current standards, we are not prepared to give an assurance that it is safe to be exposed even to the current low levels over periods of perhaps years or decades. From the prognostic and perhaps the compensation viewpoint, we may point out that theoretically even subclinical loss of elastic recoil impairs such defence mechanisms as cough, and renders the airways more susceptible to any bronchoconstrictor influence.

We should stress that the latter findings are not relevant to ordinary users (preferred to the marketplace jargon "consumers", a term perhaps more appropriate to enzymes than to housewives). Lest there be any misunderstanding of our views in relation to users, we should perhaps state that there is no doubt that acute respiratory symptoms may be provoked in some susceptible "allergic" individuals (in spite of statements to the contrary emanating from industry and at least one of its sales representatives), and that they may develop skin sensitivity (personal observations). Any risk of more persistent symptoms must be remote. We should also make it clear that we do not advocate the use of inhalation challenge, which is certainly contraindicated in users.

Finally, we should like to record our appreciation of the cooperation of industry and its medical officers, unions and employees, as well as the opportunity to collaborate with the Division of Occupational Health. Without this cooperation, an understanding of the problems, if not the ultimate solutions, could not have been achieved in so short a time. In principle, collaboration of this kind on the part of management and unions could achieve speedier resolution of other similar problems which inevitably accompany increasing technological and industrial development.

Division of Thoracic Medicine, BRYAN GANDEVIA.
University of New South Wales CHARLES MITCHELL.
School of Medicine,
Prince Henry Hospital, Little Bay, N.S.W. 2036.

NEWER CONCEPTS IN REGARD TO THE AETIOLOGY OF ALLERGIC RESPIRATORY DISEASES

SIR: I was most interested to read the article on "Newer Concepts in Regard to the Aetiology of Allergic Respiratory Diseases", by Dr R. Munro Ford (Journal, April 17, 1971), but amazed and disappointed that food allergy still gets no mention. The concept of food allergy is not new, of course, but is simply ignored, even by a lot of allergists.

It never ceases to amaze me how many patients one sees in general practice who have had asthma for years, who are on the usual therapy, but have never had any allergy investigations. The reason is clear: most doctors and patients have been disappointed by the results, and they feel the allergy investigations, at least for perennial symptoms, are not worth while. Being sent to an allergist has been synonymous with having skin tests and then being condemned to a long course of injections. Unfortunately, it sometimes takes months or years before it is clear to the patient that he is not deriving any benefit, and they are given up in disgust. Happily, this state of affairs is changing, and allergists should have a fair idea in advance what the chances of desensitization will be.

Seasonal asthma that is mostly from pollen sensitivity has always had better treatment results, with or without desensitization.

Chronic asthma, or attacks recurring regularly every few weeks, worse in winter, are usually due to food allergy. Some American authorities^{1,2} claim that food allergy is a major factor of up to 50% of cases of perennial asthma. No wonder our results are bad if this is right, and I am beginning to think it is, since I have had patients

¹ Rowe, A. H., and Rowe, A., jr (1963), "Bronchial Asthma, its Diagnosis and Treatment", Thomas, Springfield, Illinois.

² Donaldson, B. F., "Strong Medicine", Cassell, London.

on food elimination diets on the recommendation of our local allergist.

It seems that by excluding food allergy one can lower the total allergen load to such an extent that the common house dust allergy can be minimized by general measures, without, in most cases, having to desensitize. Food allergy is, of course, most important in children, and most infantile eczemas, children with recurrent "sniffles", colic, diarrhoea, bronchitis, can be rendered asymptomatic by food elimination, mostly cow's milk.

In conclusion, Sir, I hope you will excuse a mere general practitioner for advising such an eminent allergist as Dr Munro Ford, but I suggest that if he uses strict elimination diets as part of his investigations, he will find very few cases of "intrinsic" asthma remain.

19 Gerrale Street,
Cronulla, N.S.W. 2230.

P. W. KENT.

DIAGNOSTIC TRAPS

SIR: In the last 18 months I have had to deal with two pregnant women who have been told that a rash in early pregnancy was "only an allergy", when, in fact, the correct diagnosis was rubella.

The first young mother specifically asked a general practitioner in a neighbouring town whether she had German measles. She had only just become pregnant. She was reassured. I met her when her pregnancy was well advanced and delivered an infant which perished one week later with multiple stigmata of congenital rubella. The virus was isolated from the foetus.

Today I have been dealing with another young primigravida, who was told by a hospital resident that she did not have German measles when seven weeks pregnant. Fortunately, I saw her shortly afterwards and was able to send sera to Sydney for rubella antibody titres. This young mother has a rising antibody titre to rubella, and there is still time to terminate her pregnancy.

The diagnosis of rubella is too difficult for any doctor, no matter how experienced, to venture an opinion in pregnancy without the support of serial antibody titres. No doctor need hesitate to admit that he is not sure of the diagnosis, and we should all insist that any pregnant patients with a rash or suspected rubella have urgent diagnostic titres performed in order to avoid quite unnecessary tragedies.

B.M.I. Building,
Alinga Street,
Canberra City, A.C.T. 2601.

MARGARET COSTIN.

METHAQUALONE: EFFICACY AS A HYPNOTIC AND SIDE EFFECTS

SIR: I should like to comment on the paper entitled "Methaqualone: Efficacy as a Hypnotic and Side Effects", by Kessell *et alii*, which was published in the Journal of March 6, 1971.

Dr Kessell and his co-workers decided "to undertake a double-blind comparison of the effects of methaqualone, alone and in combination with diphenhydramine hydrochloride". One of the stated purposes of this investigation was to study side effects of these drugs. All of the 76 patients were taking a psychotropic drug in addition to the hypnotic under investigation. The investigators therefore did not do what they set out to do. The study was not of methaqualone alone, nor of methaqualone in combination with diphenhydramine hydrochloride, but of a combination of one of these drugs with a variety of psychotropic agents. Interaction between drugs is now rightly receiving increasing attention, and this may well account for the type of side effects which Kessell *et alii* have noted, and which, significantly, have not been found by any other investigators who have published trials of "Mandrax"¹⁻³.

¹ Burke, J., and Mahadevan, M. (1966), *Clin. Trials J.*, 3: 417.

² Macdonald, J. M. (1966), *Practitioner*, 197: 671.

³ Norris, W., and Nisbet, H. I. A. (1966), *Brit. J. Anaesth.*, 38: 886.

⁴ O'Connor, C. A., and Brodwin, P. (1967), *Brit. J. clin. Pract.*, 21: 287.

⁵ Harris, P. G. (1967), *Practitioner*, 199: 351.

⁶ Derbez, R., and Grauer, H. (1967), *Canad. med. Ass. J.*, 97: 1359.

⁷ Douglas, G., and Thompson, M. (1968), *Brit. J. clin. Pract.*, 22: 19.

⁸ Halder, I. (1968), *Brit. J. Psychiat.*, 114: 465.