

HISTORICAL PERSPECTIVES IN OCCUPATIONAL MEDICINE

Biological Miracles and Misadventures: Identification of Sensitization and Asthma in Enzyme Detergent Workers

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The discovery that the enzymes used in biological washing powders were asthma-causing sensitizers derived initially from the concern of an industrial physician as to the possibility of pulmonary damage due to the proteolytic nature of the material. This caused a search for possible cases of enzyme-related illness. Careful history-taking led to a hypothesis concerning sensitization and allergic illness which was supported experimentally by skin prick tests and inhalation challenge tests, and later by radioallergosorbent tests (RAST).

It seems that the consequences of handling this potentially allergenic material as a fine powder had not been anticipated; and failure to analyze cases of sickness, to identify asthma, and to consider its workplace source had prevented its recognition elsewhere. Contributing to this failure was the pattern of development and manifestations of allergic illness, which seldom occurred in the workplace and was not confined to enzyme workers or atopics. In some cases the incidence of illness had been suppressed, or investigation prevented.

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INTRODUCTION

In 1969 I published my discovery that, apart from their potential to cause direct proteolytic damage on inhalation, the enzymes used in biological washing powders were sensitizers and were causing allergic asthma [Flindt, 1969]. I have been asked to describe how I came to identify a problem that had apparently been neither anticipated nor recognized elsewhere.

This is not an account of a tidy academic research

project conducted from an ivory tower, but of something that evolved in a dynamic industrial situation, alongside the routine work of a busy industrial medical department.

BACKGROUND FACTORS

Personal

I trained at St. Thomas's Hospital, London, and after resident posts in internal medicine, chest medicine, surgery, anesthetics, and casualty, spent 3 years in Borneo, mainly as a surgeon, but for much of the time sole doctor to a 100-bed general hospital. Back in England, a period in general practice was followed by one as assistant editor of a medical journal. I was then, in 1955, one of 96 applicants for a post as an industrial physician within the Occupational Health Service for the Unilever factories on Merseyside.

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I was offered the appointment because of, or in spite of, my making it clear that my primary concern would be the health of the employees.

The Company

Unilever detergent manufacture on Merseyside was at the Lever Brothers factory at Port Sunlight, the original soap factory built by William Lever at the end of the last century. From the earliest days, William Lever was ahead of his time as a paternalistic employer, building a model village for his workforce, and establishing enlightened conditions of employment, which included joint consultation and generous sick pay and pension schemes. Prior to the National Health Service, the company had its own hospital, and, at the time I joined its comprehensive occupational health service, some of the nursing staff were still employed to visit sick employees in their homes.

Industrial relations were good at the factory and this, coupled with the ethos of the firm, made it possible for me to enjoy a remarkably satisfying relationship with management and employees. My experience within the industry up to the time of enzyme introduction had always had a large clinical component. However, a silicosis problem in connection with the manufacture of domestic scouring products had caused a special interest in the behavior and control of fine dusts as well as in chest diseases.

INTRODUCTION OF ENZYMES

Preliminary development work on enzymes had started in July 1966, but they were first introduced into a production department, initially on a development scale, in November 1966, while I was away in London on a 3-month industrial medicine course at the School of Hygiene and Tropical Medicine. During this course I attended a lecture at the Brompton Hospital by Professor Jack Pepys on immunological aspects of pulmonary disease. At the time, this had seemed of purely academic interest.

Initial Misgivings

I returned to work at the factory in December 1966, and first learned of development work on methods of incorporating enzyme powder into existing detergent products. Although I had to assume that the research establishments of the enzyme and detergent manufacturers had done their homework, I was uneasy about the material from the start. I found it hard to believe that a substance that was proteolytic in the presence of water was harmless to the lungs. It was a skin irritant at moist chafing sites, and there were rumors of epistaxis and hemoptysis in the early days of its handling on the continent, probably accounting for the recommendation that, when handling enzyme concentrate,

masks should be worn, and exhaust ventilation used at tipping-in points. The material was said to be safe once mixed, at about 1% strength, with other ingredients to form the end-product.

Commercial Aspects

My concern as to possible health hazards came at a commercially inconvenient time for my employers. The industry is highly competitive and they were a step behind their main competitors in introducing a biological washing powder onto the UK market. There was great urgency to evolve from pilot plant, through development plant, to full production.

EVOLUTION OF INVESTIGATION

Dust Control

Being unhappy about potential inhalation risks, I campaigned for improved dust control. I did not think it likely that the initial exhaust-ventilation systems would trap all the fine dust, or that simple filter-type oro-nasal face masks, even if worn, would be adequate protection. I was also anxious to improve standards of enclosure of the plant between the enzyme tipping-in point and the exhaust-ventilated packing machines.

A difficulty in the later stages, when I was being pressed for "proof," was that the more successful I was in improving dust control, the less likely I was to pick up and investigate new cases of illness. Most of the cases on which I built my hypothesis were discovered retrospectively.

Spores

The enzyme concentrate was heavily contaminated with viable spores of *Bacillus subtilis*, the source organism. This organism was not considered pathogenic, and I was able to take advantage of its presence. Wanting to monitor the plant atmosphere, I had been told that at that time there was not a suitable micro-method of enzyme assay. So, to get a rough indication of the position, I used a bacteriological slit-sampler. With this, air from selected sites impinged on segments of culture plates, which were then incubated and the colonies counted. By this means, and by culturing dust from girders and ledges, I was able to confirm atmospheric contamination.

A Plant Inspection

During pilot plant and development stages, I had constantly urged improved dust control. To reduce my frequent interventions, it was then agreed that I would wait until the full production plant had been completed and then do a

comprehensive inspection at the time of the first test run. As I knew it would not be feasible to expect operatives to wear masks throughout a shift, and as I had recommended complete enclosure, I did not wear respiratory protection for this prolonged inspection, on December 15, 1967. Contrary to later reports, which have persisted [Editorial, 1969; Pepys, 1992], at no time during production at this factory were the workers "heavily exposed to concentrated clouds of enzyme dust." The general atmosphere on this occasion, as at other times, was visually clear.

The feature that disturbed me was that, in spite of measures of enclosure far more stringent than was customary for other detergent plants, there were still a small number of places, such as ill-fitting inspection hatches, where tiny puffs of dust could be seen escaping. The inspection was completed late on a Friday afternoon, after the senior management had gone home. I decided to raise the matter first thing on the Monday morning.

A Troublesome Cough

The next morning I had to make a long journey to a family funeral. On the journey I developed an unusual chest ache, and my wife noticed that I kept clutching my chest. I made light of it and said that it was probably muscular. A slight feeling of malaise followed and a cough. The cough was mostly unproductive, except that on the first day I produced a small goblet of pink-tinged translucent sputum and, sporadically over the 3 months while the cough lasted, small, less than pea sized, amounts of pink, or blood-flecked sputum. The cough was uncontrollable, the impulse coming from within the chest, and worse in cold air. I particularly remember my embarrassment at having to walk away from the graveside to get out of earshot of the other mourners. There was also a feeling that I could not take a completely full inspiration, the end point being "spongy" rather than final.

These symptoms, coupled with my findings at the plant inspection, caused me to telephone a director at his home address, to tell him that production must not restart until all hatch covers had been modified and enclosure of any doubtful areas made good.

During the symptomatic period, I went on holiday to a ski resort in Switzerland, at an altitude of 6,000 feet. I felt unwell on the flight out, and, next morning while shopping, felt so faint I had to return to my hotel, crawling up the stairs to my bedroom, where I rolled on to the bed. I then developed Cheyne-Stokes respiration for several minutes. It was a strange experience to have one's breathing outside one's control and to observe the phenomenon of switching cyclically between hyperventilation and apnea.

Feeling better the next day, I took a cable car to 10,000 feet, but became so faint by the time the top was reached

that I got straight into the downward car and sat on the floor, slowly improving as we descended.

I believed that these alpine events could have been due to impaired gas exchange. Cheyne-Stokes breathing has been described in mountaineers, but at appreciably higher altitudes, and I considered that alveolar impairment had lowered my threshold of tolerance to reduced oxygen pressure, and even the feeling of faintness during the flight could have derived from the fact that cabin pressures are lower than at ground level, roughly equivalent to an altitude of some 6,000 feet.

I thought that the cough, hemoptyses, and altitude experiences could all have derived from enzyme dust inhalation during my prolonged plant inspection, and that I had sustained some sort of alveolitis due to the proteolytic nature of the material. Being a non-smoker, it was likely that it had been able to penetrate deeply into my lungs.

Other Case Histories

Because of my fears about pulmonary effects, I had not waited for patients to come to me. While continuing to press for increasingly stringent standards of dust control, I asked the nurses to let me know of workers sent home, and started to review earlier and recent sickness absences. I took meticulous histories from individuals who had been off work with such labels as bronchitis, influenza, and bronchial spasm. These histories were time-consuming as they might relate to events that had occurred some time previously, and then had to be correlated with management records of materials handled at the relevant times. Because of the pressures of my routine work, it proved best to take the histories while workers were on the night shift, and for some time I was leaving the factory after midnight.

The firm continued to be cooperative over my inconvenient demands for more rigorous dust control, but they were puzzled as to why I should feel that we should take greater precautions than had been found necessary elsewhere. Accordingly, it was arranged for me to visit a continental manufacturer of the raw enzyme material, as well as a user detergent factory.

A Trip to the Continent

On January 17, 1968, during the period in which I was still having symptoms, I visited a continental factory which was said to be handling the material safely, and to have done so for some time prior to its introduction to the United Kingdom. In the early days there had been primary irritant effects on skin and nose, and a few workers had had to be moved to other work on account of unspecified chest symptoms. It was implied that they must have been unduly sensitive to the material. The factory doctor also said that employees tended to attribute symptoms to new ingredients. It

was believed that respiratory protection at the tipping-in point of raw enzyme, and generally improved dust control, had eliminated any problems. Additionally, they were using a stickier, less dusty, formulation.

I then visited one of the two main manufacturers of the enzyme itself. I was well received and, after visiting the manufacturing plant, we had a discussion at which all my questions were answered candidly. Apparently it had been possible to sensitize guinea pigs, which are notoriously easy to sensitize. As to the enzyme workers, a few with chest symptoms had been removed to other work in the early days, but the combination of greatly improved dust control, and perhaps the fact that the workforce was now a selected population, without the susceptibles, seemed to have eliminated health problems. In theory, a factory manufacturing the neat raw enzyme material might have been expected to have a more hazardous environment, but here the material as initially manufactured was in liquid form, and only at the last stage of the process was a dry material conveyed to the bagging-off point under well-controlled conditions. My user factory, on the other hand, received the neat material as a dry powder and, in the early days, it passed through the plant and was packed in this form, although diluted.

I did not return from either of these visits totally reassured. I would have liked to take careful case histories from potentially affected employees. I could not obtain the detail I sought, not because it was wilfully withheld, but because it was not available and it would not have been tactful or helpful to have pressed for it.

An Abortive Enquiry

I tried another line of enquiry. For some time prior to the incorporation of proteolytic enzymes with other detergent powders, there had been marketed, both on the continent and in the United Kingdom, pre-soak preparations, in which enzymes were the active ingredient. Surely, if there was a problem, this should have come to light in their manufacture, which had involved longer use of a more concentrated material. I asked the medical officer to one of these firms if there had been any chest problems among the workforce. He said there had been none, although he did say there had been some skin problems. This news puzzled me, because he was a competent doctor, and would have been unlikely to miss what should have been a more conspicuous problem than mine.

Absence of Proof

My firm was being long-suffering with me, because it was still the established view that there was no problem. For me to continue to press for improvements would soon require further proof than my opinion, based on my clinical judgement.

I made a long car journey, during a rail strike, to take documentary evidence to a senior research scientist who had cleared the material for safety. He said he could tell me that my evidence was worthless without looking at it. However, on hearing of our differences, a main board director invited me to London to present my case at a specially convened meeting.

Some people, including medical colleagues, probably thought I had developed an obsession about enzymes, and found it hard to understand why I stayed late at the factory night after night.

Increasing Concern

The more histories I took, the more concerned I became. I had visited some of the patients in their homes, and was impressed by the severity of breathlessness described by some of them. Robust and normally phlegmatic individuals, who had never had a day's sickness absence hitherto, said that they had clutched the ledges of their open windows, fighting for breath, and thought they might die. A woman packer became severely breathless on going home after work, and took nearly an hour to cover the quarter mile journey. She crawled up her garden path, just managed to open her front door, and collapsed in the hallway. She was taken to hospital where it was assumed that a pre-existing heart condition was responsible.

On 24th January, I wrote a memorandum to the directors spelling out my fears, and specifically those concerning the possibility of sensitization. I said that I did not think it likely that engineering methods alone would produce safe working conditions. For the safety of operatives, I recommended urgent development of a method of receiving and handling the enzyme preparations "in liquid form, or in large enough aggregates, possibly blended or encapsulated, to eliminate dust formation. In whatever form it would have to be stable enough to resist attrition during mixing and packing."

A Breakthrough

This came when I was in bed on Saturday morning, January 27, 1968. I was reading medical journals, but also thinking about my findings. There were some puzzling features that I had been unable to explain. One was that, in spite of steadily improving dust control, there seemed to have been more, rather than fewer, cases of potentially enzyme-caused illness, and individuals who had been more heavily exposed in the past without symptoms were now getting them.

Another feature was that only a few of the illnesses happened at work, although some had started while patients were on their way home. Some individuals had had a constitutional illness, without predominant chest symptoms, but

I considered that others, although seldom diagnosed as such by their own doctors, had experienced asthma. I had seen one patient with an asthmatic attack, which had started at work, and which responded to ephedrine.

I felt like Archimedes as I leapt out of bed, scantily clad, and went straight to the telephone. Not only did I think I had the answer, but, of equal significance, I thought of a possible way in which I might support my hypothesis.

It seemed that all the loose ends could be tied up if, in addition to being able to cause direct proteolytic effects, the material was acting as a pulmonary sensitizer, capable of causing allergic asthma, and possibly alveolitis, in those sensitized. Although we now know that late reactions can also be IgE mediated, and the role of IgG antibodies is not straightforward [Pepys, 1992], at the time my hypothesis included the possibility that some of the delayed illnesses might be IgG precipitin-mediated reactions. Confirmation of allergy might be obtained by skin prick tests, and possibly by precipitin tests. The possible significance of the lecture I had attended over a year earlier became clear.

Hence my telephone call to Professor Pepys at his home [Pepys, 1992]. I said "I believe I have a problem in the organic pulmonary sensitizer field. Can you help me?" I asked him in what form and quantity he would like blood for precipitin tests, and we arranged a meeting on 31st January at the Brompton Hospital in London, at which I would provide materials with which to prepare solutions for skin prick testing.

A Final Memorandum

Evidence continued to accumulate that, in spite of rigorous dust control, potentially enzyme-induced illness was occurring at all stages of the production process, including the packing of end-product. This, coupled with my increasing conviction concerning sensitization, associated with unease as to the possibility of insidious development of extrinsic allergic alveolitis, caused me, on 29th January, before the London meeting, to send another memorandum. This further detailed the hazards from inhalation of organic dusts and concluded, "Whatever the outcome of further investigations, I consider that the evidence so far accumulated, and still being added to, about the clinical effects on employees indicates that it is too dangerous to handle any formulation which can liberate respirable dust under existing conditions in this factory. Additionally, serious consideration will have to be given to the possible risk to consumers in marketing a preparation which can liberate respirable enzyme dust when agitated, especially if there is a liability to elutriation within the packet."

I arranged a meeting with the production director at which I handed him the memorandum. Following our discussion he met the other board members, and I was later summoned to meet them. In view of the magnitude of what

I was asking them to do, it was an understandably tough meeting, but I did not feel able to modify anything I had said, or to await the results of the London meeting or further immunological tests. So, production with the end-product containing unmodified enzyme powder ceased. Thereafter, the process involved "encapsulation" or aggregation of the enzyme at the start of the process, with an alternative of receiving it, already "prilled" from the manufacturers.

Detailed Investigations

Investigations moved steadily forward following the meeting with Professor Pepys and his colleagues on 31st January. While the team at the Brompton Hospital prepared enzyme and spore culture solutions for skin and precipitin tests, and subsequently did skin prick tests on control asthmatic patients, I continued to take histories from potentially affected individuals and to do a range of hematological, sputum, radiological, lung function and other tests, as well as taking blood for precipitin tests. On 29th February I visited the London School of Hygiene, and saw Dr. A. M. Thomson, pulmonary physiologist, and then had an extremely helpful discussion with mycologist Dr. Ian Murray.

Opposition

A manager complained about my interviewing employees from his department. He told me not to mention the name of the enzyme-containing product to them, that I was creating alarm and despondency, and that he would contact his boss about me. He considered that my objective was to justify my closure of the plant; alternatively, that I was looking for kudos in the event of making a discovery. I tried to disabuse him of his misconceptions, but I was doubtful that the message had gone home. I told him that I was deadly serious, and that any alarm and despondency were caused by the situation and not by my efforts at clarification. Another manager was not happy about my arranging photographs to demonstrate methods of dust control and personal protection.

Stresses

There were times, in the middle of the night, when my morale was at a low ebb. What if I was wrong? But the worst alternative was to be right, and not be able to prove it. I kept trying to think of ways to convince the skeptics. I had not realized that no amount of effort on my part would overcome the comprehension block, and I wasted emotional effort over this. At one point, never previously having had cardiac symptoms, I was having about 12 extrasystoles a minute.

Confirmation

Skin prick tests

In mid April, Professor Pepys telephoned to say that he had skin prick tested 81 patients attending his asthma clinic at the Brompton Hospital, and had not obtained any significant reactions to either enzyme or bacterial culture solutions, so he would send me the solutions to test on my patients.

On 19th April I prick tested my wife and myself, with negative results. My dermatographic wheals were equally as strong at the diluent and dry prick control sites as at the enzyme and spore culture sites. This confirmed that my earlier alveolitis was almost certainly due to direct proteolytic effects rather than sensitization.

On 22nd April I sent for three employees, choosing those whose histories had been most suggestive of extrinsic allergic asthma or alveolitis. I had tempted Providence and asked a photographer to stand by, telling him I hoped I would not be wasting his time.

The first patient was an office worker within the enzyme plant, a known pollen asthma sufferer who had started to get asthma attacks in the winter. I pricked through solutions of Alcalase and Maxatase, enzyme products from the two main manufacturers, and of spore culture extracts from each product. The carbol saline diluent was the control.

It is believed that hypnosis can affect prick test results, so to avoid any element of suggestion, I walked away and looked out of the window, trying to think of nothing in particular. Then passed the longest 5 min I can remember, before I inspected the arm. The results, at 10 min, can be seen in the photograph (Fig. 1). There was no reaction at the control site; strong wheal and flare reactions at both enzyme sites; and lesser similar reactions at the two bacterial culture sites. The reactions to the bacterial cultures almost certainly derived from the enzyme too, the bacterium being the source organism.

The other two patients gave similar results. In all, I tested 28 people. Twenty out of 25 symptomatic patients gave positive reactions to enzyme solutions at strengths of 1 or 10 mg/ml. The other 3, who had not experienced symptoms, were negative. I had been able to confirm sensitization, associated with chest symptoms, in individuals who had worked at all stages of the process, including packers of the diluted end-product working at the enclosed exhaust-ventilated packing machines.

These were exciting results but we had to be cautious. The likely response of skeptics might be that this represented an interesting immunological phenomenon, perhaps an index of exposure, but not necessarily associated with asthma.

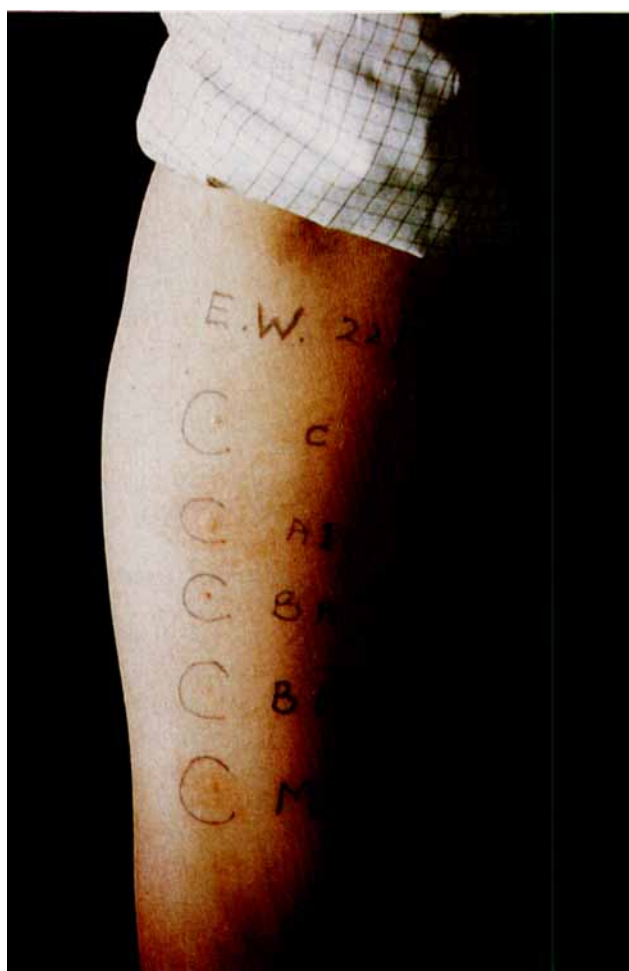


FIGURE 1. Wheal and flare prick test reactions at 10 min to the enzymes Alcalase (A) and Maxatase (M) and lesser similar reactions to derived bacterial culture solutions (BA & BM). The appearance at the control site (C) is not a wheal, but a glistening drop of the carbol saline diluent.

Inhalation challenge tests

It was decided that with a new problem it was justified to do inhalation challenge tests in hospital, with known doses of material, this being considered less dangerous than to continue to expose people to unmeasured dosage in the factory. In May 1968, three volunteers were intensively investigated at the Brompton Hospital, where inhalation challenge tests were conducted by Dr. Freddie Hargreave. Finally, Professor Pepys telephoned me to say that all three patients had given dual responses, with marked falls in FEV₁, initially, and after 4–5 hr, to enzyme solutions appreciably more dilute than had given no responses in a volunteer control individual.

The skin prick tests and the inhalation challenge tests had thus corroborated the indications from the case histories

that the enzyme material was a pulmonary sensitizer capable of causing asthmatic reactions in those sensitized.

Later, the value of prick tests in identifying specific IgE-mediated reactions in such patients was corroborated by radioallergosorbent tests (RAST) on sera.

A CHANGE OF JOB

During the enzyme investigation, I had turned down offers of better jobs, the first within Unilever, the second as chief UK medical officer with a large international company, because I did not feel ready to abandon the work.

However, shortly after the enzyme issue had clarified, I accepted an appointment as a lecturer in the Department of Occupational Health at the University of Manchester, starting work there in October 1968. It involved a drop in salary, but my investigation had revealed an unexpected aptitude for research and I had always enjoyed teaching. I had no ambition to climb the academic ladder, but I was attracted by the opportunity to pursue research free from the routine work of a busy occupational health center, and without commercial constraints.

My initial effort over the enzyme problem had been devoted to identifying whether there was a disease entity, and if so, its nature; but, although the main scientific loose ends had now been tied up, further epidemiology would have been desirable. I assumed initially that it would be possible to do this from my new post. I would be taking a ready-made research project to the university, without having to dream up a new one. I told the firm I would be happy to continue the work if they wished, but that, in any event, I would always be available to advise. However, by the time I left, the climate did not seem right, and I was not asked to assist further.

I became immersed in my new life at the university, my main initial responsibility being organizing and lecturing on postgraduate courses for British and overseas doctors. I kept a low profile on the subject of enzymes.

PUBLICATION

My investigation had not been conducted with a view to publication, let alone in the expectation of making a significant discovery. On an earlier occasion when I had made a discovery, its publication had been vetoed on commercial grounds. I thought that this would be the case if I sought permission to publish, but in any event I did not think I had completed the work to a point where it would be suitable for publication. I assumed that, armed with the information that I had given them, the company would get together with their competitors and, ideally, would withdraw the material from the market altogether, or at least switch to safer formulations and handling methods.

It was important that something should be done, be-

cause, in addition to the health of workers, I was still worried about the consumer. The fact that I had been told that the consumer was not my business did not assuage this concern. I knew that, not only packers, but the women who had fixed plastic daffodils to the outside of sealed packets as part of a sales promotion, had been affected.

My company had already changed to a less dusty product, with the enzyme incorporated in aggregated form, but I felt that if others continued to market a dustier product, there was the potential for a world wide epidemic of asthma.

I remained uneasy, also, because I remembered a previous occasion when my company had altered a product on safety grounds, but a competitor had refused to do likewise and gained a commercial advantage.

About 6 months after I left the firm, I read in a newspaper that: "A soap and detergent company which claimed that its new product removed dirt and stains found that it also removed 10 workers, suffering from a mysterious chest illness."

This decided me. I knew what the mysterious chest illness was, and felt that for a doctor to know the nature, cause, and prevention of a still-occurring disease and not divulge it was immoral, outweighing any other considerations. Accordingly I visited Dr. Douglas-Wilson, the editor of *The Lancet*, to see if he thought there was a case for a Preliminary Communication to alert people. He felt strongly that not only should something be published, but that, incomplete though I felt it to be, I had done enough work to warrant a proper paper. He promised to expedite publication as soon as I could get a text to him. Professor Pepys agreed to produce a paper for the same issue concerning the work done in his department, and in particular the inhalation challenge tests.

Fortunately, because I had initially hoped to continue the work at the university, I had retained copies of the data left with the company, and my working notebooks. These were retrieved from a tea chest in my garage, and I wrote up the story.

The Lancet published our papers remarkably quickly, together with an editorial about them [Flindt, 1969; Pepys et al., 1969; Editorial, 1969]. There was nothing essential in the paper that I had not already told the firm, and I sent them a copy before publication. I had titled it in such a way that I thought it might escape the attention of the media. This did not happen.

Consequences of Publication

The impact was immediate and considerable. Although some companies continued to deny the problem, academic and government bodies and trade unions became actively involved throughout the world, in some cases leading to bans on detergent enzyme use. In the United Kingdom, there were questions in the House of Lords, and the rival

companies set up a committee under the auspices of their trade association. In the United States, Professor Selikoff rapidly organized an international symposium at the New York Academy of Sciences, which I attended. I was also invited to address learned societies in England and, on the initiative of Dr. Manuel Adrianza, in Venezuela, where factory handling of enzymes had been exported.

I parried questions from the media, referring inquirers to the published work.

My findings were confirmed in several countries, and housewives as well as factory workers had been affected. Why had the problem been neither anticipated nor discovered earlier?

FAILURE TO ANTICIPATE

It seems that the risk of proteolytic effects was underestimated and the risk, and the occurrence, of sensitization and asthma not identified. I think several factors were responsible, and that some of the factors causing lack of anticipation contributed to the failure of recognition.

Factors Relating to the Material

Nature

On commonsense grounds it might be thought that, unless human tissues were inherently resistant, a substance that was proteolytic in the presence of moisture might be harmful to the lungs. Although there was no literature on this concerning *B. subtilis protease*, published work about the use of papain to cause emphysema in experimental animals [Gross et al., 1965] might have given pause for thought, and perhaps led to animal experiments, such as were done independently [Goldring et al., 1970].

As to sensitization, although the manufacturers had sensitized guinea pigs, extrapolation from other organic pulmonary sensitizers was presumably not made. Apart from the enzyme itself, the existence of conditions like farmer's lung and mushroom grower's lung, let alone pollen asthma, might have led to consideration of whether the contaminating spores, albeit of a relatively harmless organism but handled in bulk, might present a hazard.

In respect of the enzyme, it should now be accepted that large molecular-weight organic substances, such as proteins, are potential sensitizers. Enzymes are proteins, and, as I confirmed later in respect of α -amylase [Flindt, 1979], they do not have to be proteolytic to sensitize and cause asthma. However, until specific causes are identified and published in accessible journals, extrapolations are seldom made. This emerged at a prosecution following a death from papain dust [Flindt, 1978a].

In an attempt to reduce this problem, as well as a specific paper on papain [Flindt 1978a], and a preliminary note

about α -amylase [Flindt, 1979], I wrote a general article on health and safety aspects of handling enzymes for a non-medical journal read by chemists and chemical engineers [Flindt, 1978b]. I was also given the opportunity to give papers at the Vth ILO International Conference on Pneumoconiosis on pulmonary disease due to proteolytic enzymes, identification of illness due to allergenic dusts, and prevention of illness due to allergenic dusts [Flindt, 1978c,d,e]. Later I reviewed the general topic of enzyme inhalation at the Vth International Symposium on Inhaled Particles, organized by the British Occupational Hygiene Society [Flindt, 1982].

Form

At the time the cases occurred, the material was a fine powder. Particle size analysis would have shown a potential to become airborne on agitation, and of being respirable. I remember the anger of a senior executive because I told him I could not tell if a proposed alternative formulation would be safe by looking at it. Before I left the industry I had encouraged the development of a method of assessing the dust-liberating potential of an enzyme powder, and this was done [Soap and Detergent Industry Association, 1971].

Method of handling

It appeared that there was a lack of understanding of the realities of factory conditions and the behavior of fine dusts by those who cleared the material for safety, as well as in the factories. People found it difficult to accept that invisible and hazardous dust may derive from a production method which had proved safe for less noxious materials. In explaining the capacity of such dusts to cause illness, I found the analogy of pollen asthma helpful.

Safety of end-product

The alleged safety of the end-product may largely have been a matter of faith, based on the believed lack of hazard to the consumer. I did not share this faith and was able to identify sensitization and illness in packers of the end-product. Again, a method of testing for potential liberation of enzyme dust on agitation would have anticipated this.

FAILURE TO RECOGNIZE

Industrial enzyme-caused illness must have been widespread, and, in theory, more readily identified than in the general population. Why was it missed by management, and by doctors within and outside the industry?

Primary Irritation

Usually, primary irritant effects from an industrial material come to light quickly, and the source is readily apparent. This was true of the early use of the material in industry, and led to the initial precautionary recommendations for handling enzyme concentrates. However, unlike frank hemoptysis or epistaxis, the source, let alone the insidious development of potential lung damage from smaller concentrations, could easily go unrecognized.

Sensitization

Diagnosis of asthma

Even nowadays there is a widespread failure to diagnose asthma. Among 25 of my symptomatic patients only 2 had been labelled as asthma by outside doctors. Many of them were diagnosed as bronchitis and treated with antibiotics.

Diagnosis of allergy

Even if asthma is diagnosed, the possibility of extrinsic allergy is not always considered. This can lead unnecessarily to potentially harmful treatments as by corticosteroids. One of my patients had been referred by a specialist chest physician to our factory physiotherapy department for breathing exercises for his asthma. After attending for treatment, he would return each time to the environment which was causing it. Another patient, an atopic liable to pollen asthma in summer, developed asthma attacks in winter. These were treated symptomatically, without the recognition that another allergen had emerged.

Another finding of my investigation, which could have confused, was that sensitization occupational asthma is not confined to atopics.

Skin prick tests

The investigation demonstrated the efficacy and simplicity of skin prick tests in the identification of IgE-mediated sensitization; and I was able to use the method in confirming papain and α -amylase as asthma-causing sensitizers. I also found it helpful, to my surprise, in the case of the small-molecule hapten chloramine-T [Bourne et al., 1979].

In all these cases subsequent RAST tests on sera were positive.

Spotting the Association

Pattern of sensitization illness

Although enabling me to identify it, the pattern of sensitization illness also tended to prevent both patients and

their doctors from recognizing the causal link. Some patients would indignantly deny a likely association, saying that they had been exposed to far greater amounts of dust in the early development stages of production, without symptoms.

Delayed attacks

Another deceptive feature was that attacks of asthma in the sensitized did not always occur immediately after exposure. For example, some of the patients were woken in the night by breathlessness after working on a day shift. Such patients were treated as having suffered a respiratory tract infection.

Non-enzyme workers

Enzyme-caused illness was not confined to enzyme workers. The first patient on whom I obtained a positive skin prick test was not an enzyme worker, but his office was close to the exhaust-ventilated tipping-in point of enzyme concentrate. He was the atopic pollen asthma sufferer who began to have asthma attacks in winter, starting shortly after he got home from work in the evening. As an office worker with no official link with enzyme work, a casual enquiry from his doctor might not have elicited the clue. At that time, asthma was not an acknowledged consequence of enzyme inhalation, and in any event the exhaust-ventilation system and enclosure methods were providing a false sense of security.

The first patient I identified as sensitized and liable to asthma from another enzyme, papain, was not a papain handler and worked in an adjacent room, and at another factory, the 35-year-old man who died from asthma, after a fellow worker had tipped 1.25 kg of papain powder some 10 meters from him, had never handled papain [Flindt, 1978a].

Survivor populations

Often in industry the need for improved environmental control manifests itself in skin or chest symptoms in exposed workers. This leads to improved conditions, but occasionally some of the more sensitive workers have to be moved to other work. Especially in the case of relatively innocuous primary irritants, or substances of low-sensitizing potential, these measures usually suffice, and a state of equilibrium ensues, with "hardened" or resistant staff continuing to work in the improved conditions. This was what seemed to have happened initially at the enzyme-manufacturing plant.

Uninvestigated cases

At some detergent factories there had been little analysis of the nature of the illness in workers transferred to other work.

Unrecorded cases

Not all symptomatic workers were transferred within their factories. Others were dismissed, or left of their own volition when they or their wives thought that something at work was affecting their health. The reason for the departure of this last group in particular may not always have come to the attention of management.

Blocked investigation

In one country, a chest physician was refused access to a factory from which he was seeing unexplained cases of asthma. After a report of my article appeared in a local newspaper, the enzyme workers came out on strike, and the management then asked the physician if he would do an urgent investigation to reassure the workers. He found that several cases of asthma gave positive skin prick tests to the enzyme. Even after this, the parent company continued to deny publicly the existence of the problem.

Concealment of information

I mentioned earlier my puzzlement at the denial by a factory doctor of chest illness in the manufacture of presoak products. I had been particularly depressed by this information because at the time I was very much alone in my beliefs, and was probably thought of as an obsessional alarmist. A few years later, shortly before he died, this same doctor, who now worked for another firm, came to me and apologized. There had been chest problems at his factory, but his employers had told him not to tell anyone.

As a counter to these depressing experiences, I should record that it was the managing director of Powell and Scholefield, the firm which invited me to investigate possible hazards to papain and α -amylase workers, who persuaded me to write the paper which warned the chemical industry of the hazards [Flindt, 1978b].

Inaccurate information

Misinformation probably also impeded identification, and was not always deliberate, because information available to senior management is not always accurate. For example, a senior manager who had been to another enzyme handling factory told me that he had been assured that there had been no problems there. However, when I spoke to a junior technician, who had been on the same visit and had talked informally with more humble members of the factory, a different story emerged.

Mental blocks

Although there were examples of dishonesty and misrepresentation, I have come to believe that self-deception

may have accounted for the apparent rationalizations of some industry scientists and medical advisers. They may not solely have been acting defensively to protect their firms or themselves, or for fear of litigation or of alarming consumers.

In the period after my paper was published, some firms continued to deny the problem, and, during his careful investigation, Paul Brodeur found that he got different answers to the same questions from industry-employed scientists than from independent ones. He also quoted the doctor whose defense of the material included the statement that "in any case, nobody ever dies of asthma" [Brodeur, 1971]. I was present when this remark was made.

The actions of lay management depend on the advice of their scientists and doctors. If this advice is tempered by what it is thought the management want to hear, or what the advisers have come to convince themselves is true, then the executive management cannot solely be blamed for their actions.

An Unanswered Question

In 1980 I was invited to give a paper at the American Medical Association Air Pollution Research Conference in New Orleans. As usual, I kept strictly to my first-hand experience with factory workers. The first questioner after my talk asked if I could say something about the possible consumer risk. Before I could answer, the session chairman said he would not take that question, but instead called on a physician in the audience who proceeded to give a mini lecture, complete with slides, about his work which downplayed the risk. My hosts were embarrassed. They told me that the objective was to give the press the impression that there was scientific controversy over the work.

Alarmist?

My published warning referred to the fine-powder material originally handled. I do not know if there were any deaths in the early years, particularly as the cause would not have been recognized. However, as described earlier, some of my patients had very severe asthma attacks, and an unrecognized extrinsic allergic source of asthma is particularly dangerous. This was demonstrated in my papain example [Flindt, 1978a].

I had little doubt of the magnitude of the potential problem among consumers had the fine-powder material continued to be marketed world wide.

Risk to Consumers

I would personally have been happier to see the use of enzymes in domestic detergents discontinued. Earlier products were capable of sensitizing and causing asthma in con-

sumers [Belin et al., 1970], and the initial attempts at "encapsulation" were not wholly successful. Even if they had been, this would not have overcome the problem. While I was at the university, a patient from a detergent factory was admitted to hospital with severe asthma. Unusually, skin prick tests to *B. subtilis* allergen were negative, but inhalation challenge was positive. He was removed from enzyme exposure, steroids were discontinued, and the asthma ceased. There were two recurrences. The first, when he wore clothes which, unknown to him, had been washed in biological detergent; and the second, after the floor of his otherwise enzyme-free workplace had been washed, without his knowledge, with a biological detergent solution [Flindt, 1995].

Thus, a domestic hazard still exists for sensitized people. It may be too early to know the true incidence of sensitization among consumers, for it is likely to take longer to appear than in industrial populations. However, we cannot afford to be complacent. Apart from the possibility of some powder escaping from imperfectly encapsulated material, the consumer will still be at risk from aero mists from liquid preparations or powders in solution, and the allergen will persist in enzyme-laundered garments, bed clothes, and carpets, with perhaps a build up in the domestic environment with time. Because sensitization capacity is not confined to enzymes that are proteolytic [Flindt, 1979, 1982], this potential hazard will also attach to the newer biological detergents, which may contain enzymes such as lipases, cellulases, or amylases.

Relations With the Industry

After publication, it became clear that my discovery was unwelcome to the detergent industry. It seemed almost as if the discoverer had caused the problem. I had to learn to be philosophical about misrepresentation of my motives and actions, and attempts to belittle the significance of my findings.

A senior industry executive, quoted by Brodeur, queried the bona fides and motivation of anyone who had ventured to suggest that there might be a hazard associated with detergent enzymes. Among those subject to censure were "independent medical researchers hoping to make a big health discovery and get famous" [Brodeur, 1971].

Slowly, the climate changed. I received apologies from two of the industry medical advisers who had done their best to denigrate my work in the period after publication, and in recent years I have collaborated on other topics with research scientists of my former employer.

In my teaching hospital out-patient clinic, after I left the industry, I had been seeing sensitized, and sometimes symptomatic, employees from another company which had been bitterly opposed to me and my findings initially, but which had had to install an expensive new enzyme-handling

plant after my paper was published. It later became less embarrassing seeing their patients after the parent company had advised their medical officer to "consult an expert, such as Dr. Flindt." When I retired from the university, this subsidiary of a formerly hostile firm contributed to my leaving present.

Postscript

I was finally persuaded to describe these events for the benefit of others. At first I had been reluctant to do this, and in particular to mention some of the more unfortunate experiences. However, to gloss over the problems would defeat the objective. I hope I have not underplayed the positive side: the advantages of working within an organization with such good industrial relations; the willing cooperation of the patients and most other company staff, and of others acknowledged in my published paper.

In writing this account, in order to avoid the distortions of hindsight, I referred to my original working notebooks, the entries covering some 250 foolscap pages. I was surprised to find how much had gone on, and over how long a period, before the approach to Professor Pepys and ultimate publication.

I have simplified the story, which has made the answers seem obvious. However, the unusual clinical manifestations had meant that a wider range of possibilities had to be considered in the early stages, including direct or adjuvant effects from the detergent and other constituents of the powders, as well as possible effects from the associated bacterial spores, including infection or endotoxin production. These are discussed more fully in the original paper.

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