Occupational asthma and rhinitis due to Western red cedar (*Thuja plicata*), with special reference to bronchial reactivity

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Gandevia, B., and Milne, J. (1970). *Brit. J. industr. Med.*, 27, 235-244. Occupational asthma and rhinitis due to Western red cedar (*Thuja plicata*), with special reference to bronchial reactivity. With the increasing use of Western, or Canadian, red cedar (*Thuja plicata*) in the timber industry, a distinctive respiratory syndrome of rhinitis and asthma has been observed with increasing frequency in clinical and industrial practice. Six cases of asthma and four of rhinitis are described in some detail; the onset of symptoms some hours after exposure, the nocturnal predominance of symptoms, especially of cough, and their persistence for days or weeks after cessation of exposure may conspire to make diagnosis difficult if the occupational hazard is not appreciated.

Both immediate and late skin reactions to extracts of Western red cedar were mild or absent, and serum precipitins were absent in the two cases in which they were sought. Positive bronchial reactions, reflected in serial estimations of ventilatory capacity, occurred in response to provocative inhalations of extracts of the cedar dust, commonly at four to six hours and at night, rarely within the first hour. In some instances, a single provocative exposure to the nebulized extract over 90 seconds was shown to produce exacerbations of asthma for two or three successive nights, with normal or reduced ventilatory capacity during the intervening days. Regularly recurring asthma after an isolated exposure has not previously been documented, and is perhaps of fundamental importance to the understanding of non-occupational asthma. Bronchial reactions were not observed to house dust extract, to which patients consistently showed dermal sensitivity. Symptoms subsided gradually when exposure was avoided, but there was considerable individual variation as to how much exposure could be tolerated without relapse; symptomatic therapy, with or without specific hypo-sensitization, did not adequately control the symptoms.

The use of Western, or Canadian, red cedar (*Thuja plicata*) for indoor and outdoor furnishings and fittings has increased considerably in Australia in the past decade, and this trend is likely to be maintained because of its advantages in durability, its good appearance in natural finish, the ease with which it takes paint, and its resistance to attack by white ants. Although the wood is occasionally referred to as irritant or as producing respiratory symptoms, and although Doig (1949) briefly described two

minor 'epidemics' of asthma attributed to it, there appears to be no comprehensive description of the syndrome in the literature. The clinical picture presents several interesting and unusual features, so that in our collective experience of 40 cases, encountered in a thoracic medical unit and in the practice of occupational hygiene, the occupational cause has often been either overlooked or recognized only after considerable delay.

This paper reports six cases of asthma which have

been studied in some detail from the allergic point of view, including bronchial provocation tests. A further four cases of rhinitis, apparently rarely troublesome enough to require medical advice, are briefly described. The findings indicate that the study of occupational asthma due to a single identifiable cause may contribute to the understanding of the more complex, multifactorial asthma encountered in general medical practice.

Case reports

Case 1

S.J., a non-smoker aged 28, had worked in joiners' shops since the age of 15 years. There was no past or family history of respiratory or allergic disorders. For the past four years he had been constructing and installing interior fittings made from Western red cedar. About 18 months before admission he developed sneezing and rhinorrhoea in the afternoons of working days, the symptoms persisting into the evening. Bouts of coughing leading to shortness of breath began about six months before admission; at first the episodes occurred about 3 pm but later occurred by lunch time. The cough persisted into the early evening and would then ease; he regularly noticed marked shortness of breath when walking up a hill on his way home. A partial remission of symptoms occurred during a period when his exposure to cedar dust was considerably reduced.

In the past three months his symptoms had worsened and they now persisted into the night; they began to improve only on Saturday afternoons after 24 hours away from work, and he was relatively well on Sundays. At his worst he coughed up about 50 ml of yellow sputum daily. He felt generally unwell and had lost a stone (6.35 kg.) in weight in nine months. When first seen in the outpatients' department he had frank expiratory wheezing and mild nasal obstruction. On admission to hospital, after two weeks away from work, he was asymptomatic and the respiratory system was clinically normal.

On admission the forced expiratory volume at one second ($FEV_{1.0}$) was 2.1 litres and the forced vital capacity (FVC) 5.0 litres, the corresponding figures after a sympathomimetic aerosol being 3.4 and 5.0 litres. The highest values for $FEV_{1.0}$ and FVC recorded in this patient were 4.05 and 5.40 litres. Allergy skin reactions are shown in the Table and the bronchial provocation tests, which were positive, are described in a later section.

Progress As the patient had a skilled and responsible post he was anxious to return to his usual job, but on the third day at work he became wheezy at 5 pm and developed frank asthma at 10 pm. He subsequently avoided the dust as far as possible and worked mainly on installations away from the mill. When seen six months later, he had had no upper or lower respiratory symptoms other than transient recurrences on isolated occasions when brief exposure to cedar dust had been unavoidable. Following a further severe recurrence associated with protracted exposure he changed his job and has since remained free of symptoms.

Case 2

M.R., a non-smoker aged 28, was first referred to the outpatients' department in 1956 with the diagnosis of 'bronchitis' of seven months' duration. There was no past or family history of respiratory disorder or allergy. A carpenter working in a joinery, he had had no respiratory symptoms until he began to use Western red cedar about eight months previously. He developed irritation of the throat over the first month, followed later by sudden episodes of cough, wheezing, and breathlessness characteristically developing whilst driving his car home from work, and lasting about three hours. Gradually these episodes were associated with or replaced by nocturnal wheezing occurring approximately once a week and relieved by bronchodilator drugs.

A period of complete freedom occurring over the Easter vacation was considered significant. No abnormal physical signs were observed during the three visits at this time, and ventilatory tests showed on each occasion an $FEV_{1.0}$ of approximately 3.3 litres and an FVC of 4.5 litres, with a negligible response to a bronchodilator aerosol. He was able to avoid the dust and remained well until a further exacerbation of upper and lower respiratory symptoms for one month caused his return to the clinic late in 1967.

On this occasion he had audible wheezing, his $FEV_{1.0}$ was 1.98 litres and FVC 3.63 litres, increasing to 2.25 litres and 5.44 litres after a sympathomimetic aerosol. The symptoms persisted in a mild degree over a month in spite of negligible exposure to cedar dust; wheezing had never previously persisted for more than three hours at a time. The results of allergy skin tests are set out in the Table and the bronchial provocation tests, which were positive, are described in a later section.

Progress During his stay in hospital, his best $FEV_{1.0}$ reached 3.65 litres and FVC 5.0 litres. He has since carefully avoided all cedar dust and remained free of all respiratory symptoms.

Case 3

Y.J., a non-smoker aged 36, was a graduate in engineering with a company making window fittings from Western red cedar; his work entailed frequent exposure to the dust in the factory. He gave no past or family history of respiratory disorder or allergy. At the beginning of his second year of employment he noticed the gradual onset of a predominantly unproductive cough, which would disappear dramatically if he could produce a small plug of mucus. A few weeks later he developed severe rhinorrhoea, worse in the morning, with minimal obstruction and no sneezing. Within three months of the onset of cough, he developed difficulty in breathing and wheezing, usually in the later afternoon.

In the past month he had begun to waken at about 3 am with cough and wheezing, sometimes of alarming severity, and only partially controlled by bronchodilator drugs. He noticed that symptoms were worse after unusually long exposures to cedar dust, but because of their insidious onset and persistent nature he did not regard the cedar dust as more than a possible aggravating factor; he did not mention his work until specifically asked.

On examination at this time there was mild expiratory

wheeze and some fine, short, peripheral rhonchi on inspiration at the bases. Tests of ventilatory capacity showed an FEV_{1.0} of 2.9 litres and FVC 4.2 litres, with no response to a sympathomimetic aerosol. No abnormality was present in the nose. Skin test results are shown in the Table, and bronchial provocation tests, described in detail below, were regarded as positive.

Progress During a period of three weeks away from work his symptoms improved and were in fact absent whilst he took six-hourly doses of orciprenaline and aminophylline. If these were omitted, he developed mild cough and wheeze in the evenings. He had one severe episode of asthma during this absence from work about seven hours after working with Western red cedar in his home. On returning to work, the symptoms recurred after about 10 days, in spite of prophylactic bronchodilator therapy and also an extended course of subcutaneous hyposensitization therapy. Within a month of resigning his position six months later, his symptoms had disappeared, except for evening episodes of mild wheezing and cough on two successive evenings twice weekly. It transpired that these always followed hyposensitizing injections of cedar extract, which he had continued. Since stopping them, he has been free of symptoms for over a year. His FEV_{1.0} after resignation was 3.63 litres and FVC 4.85 litres after a sympathomimetic aerosol; these are the highest values recorded for this patient.

Case 4

W.J., an athletic non-smoker aged 42, was a supervisor constantly exposed to cedar dust in the same factory as the preceding patient. Some 20 years previously he had had a successful nasal operation for recurring nasal obstruction; about this time he recalled occasional mild tightness in the chest whilst working on a farm, insufficient to cause him to see a doctor. Between 1955 and 1965 he developed acute but brief asthmatic symptoms on occupational exposures to levels of sulphur dioxide and acetic acid which did not upset other workers.

A year after starting his present job three years pre-

viously, he noticed the insidious onset of 'a heavy cold' with persisting nasal obstruction. After three months this became associated with wheezing occurring towards evening. After a further six months he developed persistent cough with mucoid and occasionally mildly purulent sputum, together with asthma which would wake him at about 1 am. There was little variation from day to day and he had no significant relief at weekends. The nocturnal asthmatic episodes would cease after a week or so away from work, but some wheezing and limitation of exercise tolerance would persist. Exacerbation of symptoms developed usually about a week after he returned to work. On examination minimal wheezing was noted on full expiration, and the nasal mucosa was moderately swollen and reddened. Skin test results are shown in the Table, and bronchial provocation tests, regarded as positive, are described below.

Progress This patient remained under observation for 12 months but continued at his job. His symptoms were not controlled by bronchodilator drugs, although the nocturnal episodes responded partially to an orciprenaline aerosol. He felt that his symptoms became a little less severe than formerly, possibly as a result of subcutaneous hyposensitization therapy with extracts of cedar wood and other allergens to which he showed dermal sensitivity, but his opinion was not confirmed by serial estimations of ventilatory capacity, which showed no major change (usual levels of FEV_{1.0} ranged from 1.0 to 2.2 litres, with FVC up to 3.3 litres).

Eventually he took other employment and over about six weeks gradually lost all his symptoms, except for occasional mild 'tightness' in the chest in the mornings, which resolved spontaneously over an hour or so. His FEV_{1.0} and FVC were 2.9 and 4.2 litres respectively, with no change after a bronchodilator aerosol. The increase in FVC and the residual evidence of mild airways obstruction are of some interest, although allowing no conclusive inferences.

The next two cases were found in the course of a

TABLE
RESULTS OF INTRADERMAL SKIN TESTS

Case	30 minutes						24 hours					
	1	2	3	4	5	6	1	2	3	4	5	6
House dust	+++	++	-	+++	++	+++	-	+	-	-	-	-
Penicillium	+	-	-	-	-	-	-	-	-	-	-	-
Aspergillus	+	-	-	-	-	-	-	-	-	-	-	-
Western red cedar (a)												
B strength	-	-	-	-	-	-	-	-	-	-	-	-
D strength	+	+	-/-	+/-	-	-	-	+	-/-	+/-	-	-
Western red cedar (b)												
B strength	-	-	-/-	+/-	-	-	-	-	-	-	-	-
D strength	+	+	-/-	+/-	-	++	+	+	-/-	+/-	-	-
Maple D strength	+	+	-/-	+/-	-	-	-	-	-/-	+/-	-	-
Pine D strength	+	+	-/-	+/-	-	-	-	+	+/-	+/-	-	-
Control (Coca's)	-	-	-/-	+/-	-	-	-	-	-/-	-/-	-	-

Note: Where two results are shown separated by an oblique stroke, the patients were tested on two occasions separated by several months during which hyposensitization with cedar extract was attempted.

survey of 91 employees in the factory in which cases 3 and 4 worked. Although studied less thoroughly, they are of interest as they illustrate milder forms of the syndrome. Case 5 attended his doctor once in the early stages, before he recognized the relationship to his work, and gained little relief from symptomatic treatment. Case 6 had never visited a doctor.

Case 5

M.B., a non-smoker aged 40, admitted to some daily cough and sputum over years. He had also had seasonal vasomotor rhinitis for many years but had worked in dusty timber mills all his life without any other respiratory symptoms. He had been in his present job for nearly eight years without any change in his 'hay fever' or bronchitis until 18 months before the survey, when he noticed wheezing after about two hours of heavy exposure to the dust of a sanding machine. Asthmatic reactions recurred after all such heavy exposures for some months until he was transferred to a less dusty area, when the episodes ceased.

There were no abnormal chest signs on examination, other than a loose cough. The results of limited skin tests done in the factory are shown in the Table. His $FEV_{1.0}$ on Friday morning before work was 2.28 litres (FVC 3.69 litres) and after work 2.00 litres; on the following Tuesday before work it was 2.45 litres and after work 2.26 litres (FVC 3.36 litres). There is thus a consistent fall of about 0.2 litre in $FEV_{1.0}$ on both working days, and an apparent recovery over the long weekend of 0.45 litre; the average (statistically significant) decrease in $FEV_{1.0}$ over the working day for men similarly exposed was 0.1 litre whilst over the weekend there was no significant change (Gandevia, 1970). He denied any symptoms and regarded his dust exposures on these days as mild. Small 'sub-clinical' variations of $FEV_{1.0}$ in one case are, of course, not conclusive in themselves but they are consistent with the subject's history and with what is known of the time relationships of exposure, bronchial reaction and recovery in less severe cases.

Case 6

A.P., a non-smoker aged 51 years, with no past or family history suggestive of respiratory disorder or allergy, started work at the factory seven years previously, working at first with various timbers with no symptoms. During the fourth year, approximately a year after beginning to work with Western red cedar, he developed rhinorrhoea and sneezing every morning at work, progressing to nasal obstruction later in the day. After some months he noticed wheezing at night at about 8 pm which lasted for an hour or so and was relieved by the production of sputum; he denied cough and sputum during the day. Symptoms were never present on Sundays. A year before the survey he was transferred at his own request from a dusty area of the factory next to a sanding machine to a different job with minimal dust exposure. His symptoms disappeared immediately and have not recurred since he has avoided the heavier exposures.

No abnormal physical signs were present in the chest on the day of examination and a deliberate cough on

request was unproductive. The results of a limited series of skin tests are shown in the Table. At the time of the survey his $FEV_{1.0}$ was 3.0 litres and FVC 4.2 litres on a Friday morning after starting work; the figures after two days' absence from work over a long weekend were 2.9 litres and 4.2 litres, indicating no significant effect on ventilatory capacity over the working week in his current non-dusty job. This patient's history was convincing, and his case is recorded to support the observation, noted in other instances, that mild forms of the syndrome can apparently be controlled by reducing exposure without necessarily eliminating it.

Cases of rhinitis

The factory survey also extended our understanding of the clinical syndrome by revealing four subjects (including a father and son) with rhinitis attributable to working with Western red cedar. Nasal symptoms apparently rarely led to medical consultation, perhaps because they were relatively mild, the cause was usually obvious or alleviation was readily obtained by reduction in exposure. Nevertheless, it was suggested to us that a number of men had left their jobs because of them.

All four sufferers had worked with other timbers for years without nasal symptoms, but after varying periods from a few weeks to two years with Western red cedar they complained of rhinorrhoea and nasal obstruction on weekdays only. The symptoms tended to be worse in the afternoon and evening, especially nasal obstruction; in two subjects, rhinorrhoea and sneezing sometimes developed acutely within half an hour of exposure, changing during the day to persistent nasal blockage. In two cases, the severity of symptoms was influenced by the severity of exposure. Two of the four patients were smokers, admitting to chronic cough and sputum; one thought that these were mildly aggravated during the working day but the other denied any effect, and both denied wheezing or shortness of breath. Three of these men had skin tests; all three showed mildly positive (one-plus) reactions to the cedar extract at 30 minutes, with negative reactions at 24 hours. Two showed immediate reactions of similar size to house dust, to which the third subject showed a strong immediate response (three-plus). Ventilatory capacity during two working days was studied in three of these men, each of whom showed no change (less than 0.1 litre) in $FEV_{1.0}$ over one day, whilst on the other day decreases of 0.2, 0.3, and 0.7 litre were observed. The significance of these findings is doubtful.

Special investigations

Chest radiographs were normal in all six asthmatic subjects, except for some hyperinflation and thickening of the bronchial walls consistent with asthma in

cases 3 and 4. Except for *Haemophilus influenzae* in one culture in case 3, repeated sputum cultures in all cases yielded no pathogens. Sputum microscopy in cases 1 to 4 inclusive during symptomatic phases showed that eosinophils predominated over neutrophils, even in apparently mucopurulent specimens, the eosinophils usually forming 60 to 90% of the cells present. Blood eosinophilia was inconstant and mild but occasionally reached 10% of a total white cell count within the normal range. Erythrocyte sedimentation rates were normal.

Skin sensitivity

Five of the six asthmatic patients showed negative prick tests to potent commercial extracts of a variety of grass pollens and, in the four tested, to tree pollens and other common inhalants; the fourth patient (case 1) showed several very weakly positive reactions of doubtful significance at 30 minutes. There were no delayed reactions. The results of intradermal tests are set out in the Table. All but case 3 showed definite immediate reactions to two commercial house dust extracts, and in case 2 the reaction was still apparent at 24 hours. In case 1, mildly positive reactions to two moulds were observed, but there was a reaction of comparable size to one of two control solutions; a bronchial provocation test with penicillium gave a negative result. Extracts of maple, pine and Western red cedar dusts, all from one factory, were specially prepared (see Appendix, p. 243), and a second cedar extract was prepared from dust from another factory. D strength was diluted successively 1 : 10 to give strengths, C, B, and A; only the results for strengths D and B are shown as representative. Case 1 showed mildly positive immediate reactions to each of the four D strength materials but not to the B strengths; case 2 reacted similarly, except for a negative result to maple; case 3 showed uniformly negative results, and case 4 uniformly 'weak positive' reactions, including a slight reaction to the control, and excluding a negative reaction to one of the B strength cedar extracts. Case 5, tested only with one D strength of cedar extract, showed a negative reaction. Case 6, also tested only with D strength cedar, was the only patient to show an unequivocally positive reaction of immediate type.

Reactions at 24 hours were observed only to D strengths; they were small red lumps about 5 mm in diameter, unlike the well-defined delayed reactions sometimes observed to house dust and aspergillus extracts in susceptible subjects. Such positive reactions to the cedar extracts were observed in cases 1, 2, and 4. In case 4, reactions of similar size were also observed to maple and pine, the latter also causing reactions in cases 2 and 3. In cases 3 and 4, all the tests were repeated after a course of hypo-sensitization therapy with negative results. Patch

tests, using alcoholic extracts of cedar, maple, and pine, were negative in cases 1 to 4 at 48 hours.

As mentioned previously, but not shown in the Table, three men with rhinitis but not asthma showed one-plus immediate reactions to D strength cedar and no reaction at 24 hours. All three showed positive immediate reactions to house dust.

By comparison with the typical immediate or delayed reactions found in many allergic patients, the results of skin tests to cedar extract are most unimpressive, and in fact one of 20 control subjects, with no known exposure to Western red cedar, showed a similar immediate reaction. None of the controls showed a positive delayed reaction. Indefinite reactions of this kind are not likely to be helpful in clinical practice in confirming the diagnosis.

Serum precipitins

In cases 3 and 4, agar gel double diffusion tests, using varying concentrations of the patients' serum and of cedar extract, failed to reveal precipitin lines after eight days (for details of methods, see Appendix).

Bronchial provocation tests

Inhalation tests were performed with C and D strength extracts of Western red cedar (see Appendix) according to a similar routine in use in this unit for other inhalants. Following initial estimations of FEV_{1.0} a control solution, coloured to resemble the cedar extract, is inhaled from a Wright nebulizer for 90 seconds, and the estimations are repeated over 15 minutes, usually without change. Occasionally a rapid fall in FEV_{1.0} of brief duration is noted, in which case FEV_{1.0} estimations are continued until they rise and become stable at the initial level, usually after about 15 minutes. The allergen is then inhaled similarly, the inhalation being stopped if wheezing develops. FEV_{1.0} measurements are made over a period of 45 minutes, during which time immediate type sensitivity reactions become manifest. If no reaction to C strength develops after an hour, a second inhalation, of D strength, is sometimes given. If a reaction develops, it is either observed until recovery occurs or modified by giving a bronchodilator aerosol. It is preferable that tests should be done when the patient's ventilatory function is at its best, largely to avoid the risk of false positive or unduly distressing reactions.

In routine practice, it is difficult to follow reactions into the evenings with objective tests, and reliance must sometimes be placed on overnight symptoms. Interpretation then depends preferably upon the performance of tests in a symptom-free interval using both test and control solutions on separate occasions. Whenever possible, objective tests were performed on the present subjects during

the night. The results invariably supported the validity and accuracy of the patient's own observations, and the simplified schemata (Figs 1 to 4) are therefore based on a combination of symptoms and measurements. To simplify the notes which follow, the step involving observation after the control solution is omitted. No immediate or delayed bronchial reactions to a house dust aerosol were found in any of the four cases; this test is shown in the Figures only if done in the period plotted. All initial tests were performed between 9 and 11 am unless otherwise stated.

Case 1 (Fig. 1) The provocation tests were done when the patient had been asymptomatic and not exposed to cedar dust for over a week, the initial values for $FEV_{1.0}$ and FVC being 3.9 and 5.1 litres respectively. An aerosol of red cedar extract (RC) produced no immediate reaction but wheezing developed 8 hours later and worsened during the night. Recovery occurred after about 22 hours, at 8 am on the next day. Repetition of the inhalation on this day produced an immediate reaction, such that the inhalation was stopped after 45 seconds; the $FEV_{1.0}$ fell to 2.7 litres. Severe asthma continued for up to 6 hours ($FEV_{1.0}$ 1.0 litre, increasing to 2.1 litres after an orciprenaline aerosol). Next morning he had not completely recovered ($FEV_{1.0}$ 3.1 litres) but he remained well throughout the day in spite of the administration of a control aerosol. During the night the $FEV_{1.0}$ fell to a minimum of 1.1 litres, and minimal wheezing persisted throughout the next day with a mild exacerbation during the night. By the morning of the next day he was well and remained so for two days. A control aerosol produced no immediate or late reactions. A further inhalation of cedar extract produced a negligible immediate reaction but frank asthma within 6 hours ($FEV_{1.0}$ 1.8 litres), persisting during the night ($FEV_{1.0}$ 1.0 litres) with complete recovery by the following morning. Asthma recurred on each of the following three nights but was of decreasing severity. He was well for the next two days and nights but developed severe nocturnal asthma on the following afternoon, his first day back at work.

FIG. 1. Case 1. Schematic representation of ventilatory capacity changes on exposure to various inhalants. HD = house dust; RC = Western red cedar; C = control; W = return to work.

This case demonstrates that a single provocative exposure can cause symptoms, not only after several hours but also on two or three successive nights, with relative or complete freedom during the daytime periods. It also illustrates that recent experience of the inhalant may modify the pattern of reaction to a further exposure, and that a control solution may falsely appear to cause a nocturnal reaction when given a day or so after a dose of the active material.

Case 2 (Fig. 2) This patient was asymptomatic after being away from cedar dust for four weeks ($FEV_{1.0}$ 3.5 litres, FVC 4.7 litres). An inhalation of cedar extract caused minimal reduction of $FEV_{1.0}$ to 3.3 litres after half an hour, but severe asthma, requiring orciprenaline and theophylline, occurred during the night. Ventilatory capacity was normal during the next day and night. On the following day cedar extract produced an immediate reduction in $FEV_{1.0}$ to about 2.8 litres during the first half hour or so, followed by a severe asthmatic attack during the night. This persisted into the next day and became worse during the following night. By mid-morning he had recovered.

FIG. 2. Case 2. Schematic representation of ventilatory capacity changes on exposure to various inhalants. RC = Western red cedar.

This patient illustrates a predominantly nocturnal pattern of reaction, again possibly slightly modified by recent previous experience. This and the previous case illustrate a feasible testing situation when the patient can avoid the dust, has only intermittent contact with it, or develops symptoms only on heavier exposures.

Case 3 (Fig. 3) Contrary to instructions, this patient had continued contact with cedar at work until two days before admission; his asthma had persisted and he had mild wheezing, with an $FEV_{1.0}$ of 2.6 litres and FVC 3.5 litres. By the second day his $FEV_{1.0}$ had risen to 3.3 litres (FVC 4.1 litres) but moderate nocturnal asthma continued, with a decrease of $FEV_{1.0}$ to about 2.4 litres each night. There was no immediate reaction to a cedar extract but the $FEV_{1.0}$ fell from 3.6 to 3.1 litres after 7 hours, to 2.6 at 10 hours and at 2 am (17 hours) he awoke with severe asthma ($FEV_{1.0}$ 1.2 litres). Twenty-six hours after the provocative aerosol the $FEV_{1.0}$ was 3.6 litres and he was free of symptoms. This patient was tested again after a two weeks' holiday in which there had been gradual but marked improvement; only mild evening wheezing persisted. Exacerbation of the latter was obviously produced by administration of cedar extract. When finally tested after two months away from work, and without symptoms, nocturnal asthma was again produced by the cedar extract.

In this subject, study during a symptom-free interval proved difficult and initially reliance had to be placed on the regular exacerbation of nocturnal asthma by administration of the provocative aerosol. It is of interest that, after months away from work, nocturnal asthma was regularly precipitated by hyposensitizing injections, which had been dutifully continued twice weekly.

FIG. 3. Case 3. Schematic representation of ventilatory capacity changes showing spontaneous variations and response to control and Western red cedar extracts. C = control; RC = Western red cedar.

Case 4 (Fig. 4) This patient had virtually chronic asthma which had not completely remitted during the two weeks' holiday before study; mild wheezing in the evenings and early mornings persisted, with the $FEV_{1.0}$ ranging between 3.2 and 2.1 litres. Inhalation of cedar extract led to the development of slight wheezing after 5 hours ($FEV_{1.0}$ 2.0 litres) and very severe asthma during the night ($FEV_{1.0}$ 1.1 litres). In spite of orciprenaline by aerosol, full recovery did not occur during the next day, and the patient described the episode as his worst attack for some months. Five months later, after attempted hyposensitization by the subcutaneous route, a further test was done with similar results. Six months later the patient was given a Wright peak flow meter which he used several times in each 24 hours for several days of a dusty period at work, during a fortnight's holiday, and on return to work. The findings confirmed the patient's history of gradual improvement during the second holiday week, and of deterioration after return to work. The lowest recording, at night before his holiday, was 140 litres/minute. After two weeks off work, the readings became reasonably stable between 300 and 450 litres/minute, when his $FEV_{1.0}$ was 1.6 litres. At this stage, cedar extract was again administered by aerosol; 12 hours later the peak flow had fallen to 180 litres/minute. He was awake most of the night with asthma, more severe than for a fortnight, and lasting for a longer period. The peak expiratory flow was 220 litres/minute after an orciprenaline inhalation.

This patient again illustrates the difficulty of definitive diagnosis in the more severe and persistent forms of the syndrome. Reliance must be placed on exacerbation, rather than on precipitation or provocation of symptoms, and on serial ventilatory measurements during holidays.

FIG. 4. Case 4. Schematic representation of ventilatory capacity changes occurring spontaneously and in response to control and Western red cedar extracts. C = control; RC = Western red cedar.

Discussion

Clinical features

The clinical picture of Western red cedar asthma is reasonably characteristic (Milne and Gandevia, 1969), and a clinical diagnosis may sometimes be made in the absence of a history in which exposure to the material is volunteered. The patient, who may have worked with a variety of timbers for many years without respiratory symptoms, usually complains at first of eye and nasal irritation, rhinorrhoea or nasal obstruction. After some weeks he may develop an irritating cough, usually worse at the end of the day or at night, later followed by episodes of nocturnal cough and wheezing, often with the production of mucoid, tenacious or apparently mucopurulent sputum; he may also notice diminution of exercise tolerance, either constantly or in the latter part of the day. Partial or complete relief may occur over weekends or in the intervals separating periods of intermittent exposure, but in more severe cases the symptoms, especially the nocturnal episodes, persist for days or weeks after cessation of exposure. Symptoms may recur on the first day, or evening, after return to work, but sometimes they do not reappear for a few days. It seems possible, as illustrated experimentally in our case 1, that recent experience of exposure may modify the pattern of response such that repeated exposure may produce a more rapid bronchial reaction, suggesting in turn some interdependence of the immediate and late sensitivity mechanisms.

When the episodes, whether of rhinitis, asthma or both, are isolated and the patient recognizes their relationship to intermittent exposures to *Thuja plicata*, the diagnosis is easy. However, sometimes the employee does not realize the significance of an occasional change in the timber on the production line (perhaps not affecting his own work), or he is reluctant to associate nocturnal symptoms with his day's work. In these cases, the diagnosis depends on the doctor's awareness of a specific hazard and his perseverance in investigating the occupational background.

The situation is more difficult in severely affected subjects who are continuously exposed, in whom the clinical picture does not necessarily differ greatly from that of many cases of non-occupational asthma. There may be no change in symptoms over a weekend, and only partial recovery during absences from work of two to four weeks; deterioration after return to work is also sometimes delayed for a week or so. There is some similarity to the syndrome associated with exposure to toluene di-isocyanate vapour (Gandevia, 1964), with which it also shares three features of value in the differential diagnosis from non-occupational disorders, namely (1) the complaint of cough often exceeds that of wheeze (so

that the diagnosis of 'bronchitis' is preferred to 'asthma'), (2) the regularity of the nocturnal symptoms, and (3) the absence in many cases of any previous history of respiratory symptoms or of allergy.

Diagnosis

Diagnosis in our experience has not been materially assisted by dermal sensitivity tests, which had in fact misled the medical advisers of some of our patients. Both immediate and delayed reactions to cedar extract were small and inconstant, whilst five of the six cases (or eight out of nine, if the patients with rhinitis are included) showed immediate sensitivity to house dust. Whatever basic significance this finding may have, it is demonstrably irrelevant clinically in at least eight of the subjects, and probably all nine, and no bronchial sensitivity to house dust was demonstrated in the four patients tested. We have also failed to identify serum precipitins in two severely affected patients. In this, and in the unimpressive skin reactions, our findings are at variance with those reported by Komatsu (1964) in workers with *Thuja standishei*. However, as their extract produced skin reactions averaging 12 mm in controls (20 mm in the timber workers) whereas ours produced none, it is possible that this difference is relative. Sosman and his colleagues (Sosman, Schlueter, Fink, and Barboriak, 1969) recorded negative skin tests, positive delayed bronchial reaction, and the presence of serum precipitins to an unspecified form of cedar in one patient. When the diagnosis could not be established from the history, delayed reactions, occurring after four to six hours and also at night, to bronchial provocation tests provided an effective diagnostic aid in our series. A strong immediate reaction to provocative inhalation and skin tests (Mitchell, 1970) is comparatively uncommon, although clinical histories sometimes suggest such a response. If applied to patients with episodic asthma in an interval free of symptoms and of dust exposure, even a qualitative approach, preferably in duplicate, without objective ventilatory estimations, would probably suffice to establish the diagnosis, provided that no reaction occurs to control solutions. As the most likely diagnostic error is house dust sensitivity, negative results to aerosol house dust should also be required if dermal sensitivity is present. When the test cannot be given in a symptom-free interval, serial estimations of ventilatory capacity must be carried out to establish that any reactions produced exceed the naturally occurring fluctuations; duplicate tests and control studies are essential. Especially in the latter cases, these tests are tedious and time-consuming, and they require tolerance and cooperation on the part of the patient.

Although it serves only to confirm the clinical

histories given by some patients, the most interesting finding in the present study is the occurrence of asthma, following a single provocative exposure, on two or more successive nights, with daytime intervals when ventilatory capacity tests are normal. We know of no previous objective demonstration of this phenomenon; beyond invoking circadian variation in bronchial sensitivity, perhaps in the presence of a continuing antigen-antibody reaction, we are unable to offer any hypothesis as to the mechanisms involved.¹ Nonetheless, as it may well be of fundamental importance in the understanding of asthma in general, further study is obviously indicated. Equally, it would be valuable to know why symptoms may persist for days or weeks following cessation of occupational exposure. Investigation of these problems is feasible only in cases in which the asthma is known to have a single, identifiable cause, a situation rarely encountered outside occupational medical practice.

Management

The effective treatment of asthma due to Western red cedar is elimination of exposure. In milder cases, mere reduction in the amount of exposure, or the use of an efficient respirator, appears to suffice, an observation suggesting that dust control at source may be more effective than expected in a condition which is presumably allergic. However, serial estimations of ventilatory capacity in one such case, with no clinical symptoms after avoiding major exposure, still showed an asymptomatic reduction in FEV_{1.0} during the night of about 30% (Mitchell, 1970).

Hyposensitization injections had no demonstrable effect in case 3; indeed, the fact that they were regularly nocturnal exacerbations became apparent only after occupational exposure ceased. In case 4, there is perhaps some evidence of a beneficial effect in that reactions to standard aerosol dosages tended to be less dramatic after hyposensitization, and naturally occurring fluctuations in the patient's asthmatic state were subjectively less marked. However, his 'everyday' level of ventilatory capacity was no better, and possibly worse.

Bronchodilator therapy, although helpful at night, does not fully control symptoms and does not return ventilatory capacity to normal. Steroids have been symptomatically effective (we have no objective data in our own patients) but cannot be regarded as desirable.

The role of pre-employment selection in reducing

the prevalence of the disorder is uncertain, although it seems wise to exclude those with any evidence of respiratory allergy or obstructive airways disease. None of the present asthmatic subjects had a previous or family history of asthma or allergy; by contrast, three exposed subjects with non-occupational asthma known to us have suffered no ill-effects from working with *Thuja plicata*. Komatsu (1964), on the other hand, found that a family history of asthma was disproportionately common among affected employees. There is evidence, from a factory survey, of a greater reduction in ventilatory capacity during a day's moderate exposure in smokers with a productive cough than in those not so afflicted (Gandevia, 1970), but this is probably a non-specific phenomenon; some subjects with non-occupational asthma or chronic bronchitis were not affected by working in the dust.

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Appendix

Technical procedures and methods

Wood extracts were prepared by mixing 10g of fine wood dust in 100 ml Coca's solution and allowing this to stand for two weeks; the supernatant fluid was removed, Seitz-filtered, and tested for sterility before use. This solution is described as D strength, 1 : 10 falling dilutions being used to prepare C, B, and A strengths. For the double diffusion tests, concentrations of 20 ml of D

¹Similar patterns of bronchial reaction (immediate, delayed or late and nocturnal) have since been observed in workers with proteolytic enzymes used in the detergent industry (Mitchell and Gandevia, in preparation).

strength to 5 ml were achieved by suspending the extract in dialysis tubing immersed in a 50% solution of Carbowax; the patient's serum was concentrated two-fold in a similar manner. For patch tests, the test material was soaked in 70% alcohol and applied to the skin with plastic adhesive tape; the tests were read at 48 hours. Coca's solution was used as a control in the skin and inhalation tests, although in the latter water coloured faintly with coffee was also used on occasion. Antigen

antibody precipitation tests were carried out on 1% ion agar using a double diffusion technique, the materials being prepared as above and tested against one another in varying strengths. Duplicate tests were set up, one being refrigerated at 4°C and the other incubated at 28°C; both were studied for eight days. Sera from five control subjects showed no precipitation lines.

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