Contact allergy from Frullania and respiratory allergy from Thuja

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Summary: Occupational allergic contact dermatitis in 52 forest-workers was caused by sesquiterpene lactones from liverworts *(Frullania)* and by usnic acid from lichens which grow on various trees including cedar *(Thuja)*. Occupational asthma and rhinitis in 35 wood-workers was caused by wood dust of western red cedar *(Thuja plicata)*. Characteristically, the respiratory symptoms occurred in the evening and at night and not during working hours; inhalation challenge with plicatic acid from the wood provoked immediate, late or dual (combined immediate and late) asthmatic reactions. Another class of compounds, tropolones, derived from *Thuja plicata* wood, was responsible for dermatitis in a wood-worker. These distinct industrial hazards in two groups of workers at the tree-felling and wood-working levels in the forest-products industry can be identified by clinical history and examination supplemented by specific cutaneous or respiratory clinical investigation.

Résumé: *Allergie de contact provoquée par le* Frullania *et allergie respiratoire provoquée par le* Thuja

On a identifié chez 52 forestiers une dermatite de contact (allergie professionnelle) causée par des sesquiterpènolides présents dans des "hépatiques" *(Frullania)* et par l'acide usnique extrait des lichens qui poussent sur divers arbres, notamment sur les cèdres *(Thuja)*. Une rhinite et un asthme d'origine professionnelle constatée chez 35 travailleurs du bois étaient provoqués par la poussière du bois de cèdre rouge occidental *(Thuja plicata)*. Fait typique, les symptômes respiratoires apparaissaient dans la soirée et durant la nuit et jamais durant les heures de travail. L'inhalation expérimentale d'acide plicatique extrait du bois a provoqué une crise asthmatique immédiate ou tardive ou une réaction mixte (à la fois immédiate et tardive). Une autre classe de substances, les tropolones, provenant du bois de *Thuja plicata* était l'allergène impliqué dans une dermatite chez un forestier. Ces maladies professionnelles particulières, décelées chez deux groupes de travailleurs préposés à l'abattage des arbres et au travail du bois dans l'industrie forestière peuvent être identifiées par l'anamnèse et par l'examen clinique, complétés au besoin par diverses épreuves spécifiques, cutiréactions et examens cliniques des voies respiratoires notamment.

Cedar-poisoning is an ill-defined term commonly applied to skin and respiratory disorders occurring in workers in the forest-products industry in British Columbia. As a result of our investigations we are able to define the disorders rather precisely and, perhaps of equal importance, we are now able to state with assurance what is not cedar-poisoning.

An informal poll conducted on 100 general medical patients in British Columbia revealed that one half had heard of cedar-poisoning, one quarter knew somebody who had it, and five individuals asserted that they themselves had had it. On investigation, the opinion of these five turned out to be incorrect. Actually cedar-poisoning is rare — we have been able to find only about 87 cases. Since, on the present evidence, the skin is more often affected than the respiratory tract, we will consider the skin effects first.

Slivers of western red cedar *(Thuja plicata)* and of other woods can mechanically injure the skin of wood-workers; the usual complications of such minor injury, such as infection, can ensue. We have no evidence that drinking of, or bathing in lake water in which cedar logs are lying has any injurious effect. It is possible to burn one's hands when taking cedar wood out of a drying kiln or to suffer maceration of the skin from handling wet wood as in any wet-work occupation. Foreign bodies which enter the conjunctival sac are multitudinous and, as might be expected, sawdust can be included in the list. We know of no significant effect upon the eye other than mechanical injury or irritation from sawdust and contaminants of sawdust. Of course, all sorts of additives, preservatives, stains, etc. employed in the preparation of wood products may be injurious for skin and eye; there is nothing specific about cedar in this respect.

All sorts of skin diseases may be called cedar-poisoning until a thorough dermatological examination reveals some other cause such as scabies, psoriasis, lichen planus and so on. We

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know of a case of gonorrhea acquired upon a partially decomposed cedar tree-trunk.

Lichens and liverworts *(Frullania)* are interesting and beautiful plants which grow on trees and also on the ground. We have observed 12 forest-workers contact-sensitive to lichens* and 52 contact-sensitive to liverworts.† The chemical compounds responsible for such eczematous allergy have been precisely defined and the immunologically specific side-groups on the molecules identified.

Since we announced a systematic research program for cedar-poisoning of the skin seven years ago, we have found one wood-worker contact-sensitive to the heartwood of western red cedar. He lives in Holland. Probably more will turn up now we have defined the clinical picture — recurrent eczema of the hands, notably affecting the finger webs — and the chemical compound responsible.‡ This is the solitary established case of allergic contact dermatitis from cedar wood *(Thuja)* presently known. Maybe we have missed a few cases, but the vigilance and the cooperation of those physicians who have referred cases for investigation lead us to believe that true cedar *(Thuja)* sensitivity is most uncommon.

As regards lichen and liverwort contact sensitivity, we can almost diagnose the disorder by the history alone. Patch testing is now supplementary although at the start of the investigation such testing was essential and led directly to the unravelling of the whole complex problem. (It is a sorry state of affairs that prepaid insurance plans take the view in such situations where contact sensitivity can destroy the earning power of a bread-winner by intractable eczema, that the patient should pay for the numerous patch tests required).

The afflicted forest-worker has contact dermatitis of the hands, wrists, forearms, face and neck. There are many subtle variations on this theme. In wet weather, when his pants are wet, the lower limbs are affected. If he works with an open shirt, fragments of lichen and liverwort may lodge at the waistline and the primary site of involvement may be the skin of the abdomen — an odd and incongruous distribution until one is aware of it. Occasionally the eruption becomes disseminated or generalized and one is confronted with an *homme rouge*, a red man, with all the differential diagnosis which that distribution entails. In a sensitized individual the eruption begins within two or three days after the start of work in the forest, gradually spreads and causes very severe itching; the eruption may be frankly eczematous with vesiculation and weeping, or may become chronic and lichenified and so resemble, and in fact be misdiagnosed as, so-called neurodermatitis. The disorder is worse in wet weather, is more severe in some geographic areas than in others (reflecting, we feel sure, the ecological features of the plants responsible) and, most important of all, the dermatitis resolves within two to four weeks of leaving work in a forest area. Secondary infection and boils occasionally prolong the course but the dermatitis *per se* resolves. So, the dermatitis largely affects exposed skin surfaces and results from the handling of wet vegetation. Whether the lichens and liverworts which are responsible are growing on cedar trees or any other type of trees which they frequent is quite irrelevant.

We have observed contact sensitivity to fir *(Abies)*, pine *(Pinus)* and hemlock *(Tsuga)*, but these species are not related to cedar *(Thuja)*. Cedar is also a common name for several other botanical species; for instance cedar-wood pencils made of the wood of *Libocedrus* can cause contact sensitivity. *Libocedrus* is not indigenous to our forests. Just recently, sensitivity to liverworts has been established as the cause of so-called pine poisoning in Oregon and a case or two have now turned up in Seattle. It can confidently be predicted that more cases will be found now that it has become known what to look for and test with. Overall the total number of cases is small — only 52 liverwort sensitizations have been found in British Columbia. This number may be low, however, because some affected forest-workers have had the problem for 20 or more years and having consulted numerous physicians on many occasions in the search for relief, live with their problem as best they can or quit work.

A forest-worker may be exposed to liverworts for a period varying from one month to 15 years before he becomes sensitized to the plants. It is not known why allergic contact dermatitis should have such a varied or prolonged incubation period before sensitization occurs. Atopic individuals are not more susceptible to liverwort contact sensitivity than are non-atopic individuals. The only long-term remedy for a sensitized worker is avoidance of exposure to the offending plants. An individual with a low level of sensitivity may be able to carry on in forest-work in a changed job category; a highly sensitized individual will probably have to quit forest-work and will require retraining.**

Unlike skin manifestations, which affect forest-workers, respiratory symptoms are due to allergy to the dust itself of western red cedar wood and they occur therefore among wood-workers rather than among forest-workers. Among 35 proved cases of occupational asthma and rhinitis due to western red cedar diagnosed during the past 2½ years, there were 18 sawmill workers, 12 carpenters and cabinet makers, four construction workers and one wood carver. There were no loggers or other forest-workers. The main and possibly the only culprit-allergen which causes the symptoms from inhalation has been defined. Plicatic acid, the major non-volatile fraction present in extractives of western red cedar, has been identified by inhalation challenge as the responsible allergen. The respiratory symptoms are not due to chemicals responsible for the characteristic odour of the wood.[3,4]

The incidence of respiratory symptoms among wood-workers exposed to western red cedar is unknown and could only be established by thorough surveys of the population at risk. Such a survey has been conducted in Japan in a furniture factory where red cedar is used and 3.4% of workers were found to suffer from asthma and close to 10% from rhinitis and conjunctivitis due to red cedar dust.[5]

The usual history obtained from these patients is as follows: The symp-

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*Lichens are plants composed of a fungus and algae; the sensitizing compounds are usnic acid and atranorine which are produced by the fungus component.

†Liverworts are a lowly order of plant life allied to mosses. Since their leaves (the word leaf is actually botanically incorrect) resemble the liver, the plants were often prescribed for liver diseases according to the old Doctrine of Signatures which alleged that a plant which looked like a body organ was beneficial for disorders of that organ. This theory is not now generally accepted but we are left with the relic of the name, liverwort, to point out that most therapy is not efficacious and often absurd. The sensitizing compounds of liverworts, for the skin, are named sesquiterpene lactones.[1]

‡The contact sensitizers of *Thuja* heartwood are tropolones and related compounds. These compounds have fungistatic properties and are responsible for the endurance to adverse weather enjoyed by owners of homes roofed with cedar shakes.

**It happens that the lowly liverwort produces chemical compounds which are closely related to those produced by the family of plants which includes the *Chrysanthemum* genus *(Compositae)*. This situation came to light when a forest-worker was obliged to quit work in the woods on account of liverwort sensitivity and took up the hobby of growing chrysanthemums. He was found to be allergic to these flowering plants and to many of the 200 sesquiterpene lactones derived from them. These same lactones we have found to be responsible for ragweed *(Ambrosia)* contact dermatitis in the midwest provinces and states, for feverfew *(Parthenium)* dermatitis in India, for bushmen's dermatitis in Australia due to the wild artichoke *(Olearia)*, for contact sensitivity to the insecticide pyrethrum (derived from East African *Chrysanthemum* species), to the garden plant *Gaillardia* and to the garden weed tansy *(Tanacetum)*, and probably for bitterweed *(Helenium)* dermatitis in Arkansas as well as contact sensitivity to sage-brush *(Artemisia)* which is widespread, to artichokes and to chicory, handled by some housewives in the kitchen, and to several dozen other plants which will not be listed here. All the above plants are members of the *Compositae* family.[2]

toms first appear after a period of a few months to two years of steady exposure to the dust. These patients usually do not have a history of atopy. At first the symptoms are mild and rhinitis is often the first manifestation. This is followed by cough and later by wheezing. Characteristically, these symptoms occur in the evening and at night and not during working hours. They tend to become progressively more severe and prolonged and then may also occur during working hours. There are a few cases in which the clinical picture is different, with asthma or rhinitis occurring immediately on exposure to the dust at the onset of illness.

In the early stages the symptoms clear during holidays; later they may persist for weeks or months after cessation of exposure. In some patients it may take as long as six to eight months after leaving the job for nocturnal symptoms to disappear. It is unknown at present whether permanent lung damage can ever occur.

The majority of the patients when first seen have eosinophilia and some degree of airway obstruction. Chest radiographs are normal apart from some degree of overinflation. As yet there are no suitable extracts available for skin and serological tests. The diagnosis can only be firmly established by inhalation provocation tests with an extract of red cedar or with plicatic acid. These tests should be performed in hospital. The majority of these patients develop a late asthmatic reaction three to six hours after provocation. The reaction may last for 24 to 72 hours. A few develop only an immediate asthmatic reaction within 20 minutes of inhalation, lasting for one to two hours. The remainder show a "dual" asthmatic reaction (both immediate and late) after provocation. These reactions can be detected clinically and by appropriate physiological measurements. The timing of the reaction usually correlates well with the history given by the patients.

The most important step in diagnosis is to suspect this occupational hazard. The fact that in red cedar asthma, as well as in other occupational asthma, the symptoms occur after and not during work often renders difficult the recognition of the causal relationship.

The only sure way of curing the condition is for the patient to change his job. Where this is not feasible he should wear a dust mask at work; the use of disodium cromoglycate prophylactically is helpful. When acute symptoms are present they are treated on lines similar to those used in asthma due to any cause.

Our knowledge of the pathogenesis of this condition is scanty and therefore preventive measures are of uncertain efficacy, but lowering the level of the dust concentration would seem desirable. There is as yet no way of predicting which of the workers are liable to develop symptoms. Further research in the field of occupational lung disease in wood-workers is obviously needed.

Dr. George M. Barton, Western Forest Products Laboratory, Government of Canada, Vancouver, isolated chemical compounds for testing patients.

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