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Cold Hypersensitivity

Even if the doom-laden forecasts[1] of a return to ice-age conditions do not come true many people in countries with a temperate climate will continue to suffer from the effects of cold. Physiologically man is a tropical creature better suited to losing heat than retaining it. When naked and at rest his neutral environmental temperature is 28°C (82°F): with a drop of only 8°C his metabolic rate must double or he will suffer a lowering of body temperature.[2] In comparison the Arctic fox can maintain a steady thermal state in a temperature of −40°C and by doubling its metabolic rate could cope with a temperature of −120°C. As the lowest temperature recorded on earth is about −70°C it has nothing to fear from its environment.

Man's main response to cold, putting on clothes, is no reflex adaptation but requires a conscious decision. Where the ability to make or carry out that decision is impaired there is a risk of cold-induced damage. Frostbite—localized tissue necrosis resulting from freezing—is largely a problem of abnormal exposure to cold,[3] but accidental hypothermia is an ever present threat to the elderly.[4] In neither condition is there a defect in the body's response to cold, but there are people who react abnormally, either because of an isolated idiosyncracy or as an additional twist from the dagger of a pre-existing disease.

Chilblains spoil the winter games of many inadequately clad children, yet others seem resistant. The familial tendency may reflect genetic predisposition[5] or just the sharing of similar unsatisfactory apparel. In colder climates where adequate clothing is a necessity of life chilblains are less frequent. Elderly people are less likely to develop them than the young, but when they do the lesions may be more chronic, in some cases because of coexisting arterial disease. Most chilblains clear within one or two weeks, though repeated attacks are the rule. Their course remains uninfluenced by the innumerable homespun remedies which may be applied. They are sometimes seen in association with discoid lupus erythematosus and are nearly always present in patients with angiokeratomata of the extremities.

The combination of cooling and water loss makes the horny layer of the skin brittle so that it tends to break rather than flex, causing chapping. Here again the elderly fare badly since the same conditions worsen asteatotic eczema, and even where no skin changes are visible winter itch (prurigo hiemalis) may be a torment.

When the hand is cooled in water at 0°C the skin temperature rapidly drops to near that of its surroundings, but if immersion continues reflex vasodilation occurs raising the temperature 5 to 8°C. The vasodilatation is short lived but is repeated at intervals of five to twenty minutes. This so-called "hunting phenomenon" is assumed[6] to be beneficial, delaying the onset of tissue damage, though this view has been disputed.[7] In Raynaud's phenomenon this reaction is lost, and even trivial exposure to cold produces prolonged vasospasm leading to incapacity through loss of sensation, stiffness, swelling, and in severe cases painful gangrene. In the absence of an occupational cause such as exposure to vinyl chloride or the use of vibrating tools organic disease should be sought. Systemic sclerosis and other connective tissue diseases, partial arterial occlusion, and shoulder girdle compression are prominent amongst the possibilities. Cold agglutinins may be found in the presence of otherwise benign Raynaud's phenomenon, but the detection of cryoglobulins raises the question of underlying multiple myeloma or a lymphoma.

Resistance to cold is greatly lowered by immersion in water. The maximum survival time has been estimated as one hour in water at 0°C and six hours at 15°C, which is the highest sea temperature around the British coast.[8] Many of the deaths in those lost at sea are due to hypothermia not drowning, but this cannot explain the occasional fatality which occurs within a few minutes of entry into cold water. Here an abnormal factor is likely, and one of the possibilities is anaphylaxis caused by previously unsuspected cold urticaria.[9] Such severe reactions are rare, but in milder cases the symptoms may be so slight that medical advice is not sought. The commonest form, acquired essential cold urticaria, starts in adult life, often suddenly, and causes weals at the site of local cooling. Cold drinks may produce lesions in the mouth and on the lips. The passive transfer (Prausnitz Küstner) test is often positive, and symptoms can usually be reproduced by applying an ice-cube to the forearm for 2-15 minutes. In some cases the Donath-Landsteiner test for paroxysmal haemoglobinuria is positive, and an association with cryoglobulinaemia due to chronic lymphatic leukaemia has been reported.[10] The condition may be a result of abnormal release of kinins.[11] Burch and Giles[12] studied digital tonometry in four patients but were unable to elicit a consistent pattern of increased tension, after exposure to cold. In one patient, however, the blood flow changes closely resembled those seen after injections of bradykinin. Treatment is generally unsatisfactory, but large intramuscular doses of penicillin,[13] cyproheptadine,[14] and desensitization by controlled exposure to cold[9] all have their advocates. Sufferers must be warned against swimming even in heated pools.

Much rarer is familial cold urticaria, an autosomal dominant condition in which there is a lifelong tendency for generalized cooling to precipitate urticaria or macular erythema associated with general malaise, aching joints, and shivering.[15] A leucocytosis is usual, but the Prausnitz Küstner is negative, and symptoms cannot be produced by local application of cold. Anaphylaxis has not been reported. Most patients learn by experience how to abort or deal with their attacks.

[1] Calder, N., *The Weather Machine and the Threat of Ice*. London, B.B.C. Publications, 1974.
[2] Burton, A. C., and Edholm, O. G., *Man in a Cold Environment*. London, Hafner Publishing, 1969.
[3] Ward, M., *British Medical Journal*, 1974, **1**, 67.
[4] Exton-Smith, A. N., *British Medical Journal*, 1973, **4**, 727.
[5] Winner, Albertine L., and Cooper-Willis, E. S., *Lancet*, 1946, **2**, 663.
[6] Lewis, T., *Heart*, 1930, **15**, 177.
[7] Keatinge, W. R., *Survival in Cold Water*. Oxford, Blackwell Scientific Publications, 1969.
[8] Molnar, G. W., *Journal of the American Medical Association*, 1946, **131**, 1046.
[9] Horton, B. T., Brown, G. E., and Roth, G. M., *Journal of the American Medical Association*, 1936, **107**, 1263.
[10] Rawnsley, H. M., and Shelley, W. B., *Archives of Dermatology*, 1968, **98**, 12.
[11] DeLaus, F. V., and Winkelmann, R. K., *Archives of Dermatology*, 1968, **98**, 67.
[12] Burch, G. E., and Giles, T. D., *Archives of Internal Medicine*, 1974, **134**, 663.
[13] Illig, L., *Current Problems in Dermatology*, 1973, **5**, 79.
[14] Wanderer, A. A., and Ellis, E. F., *Journal of Allergy and Clinical Immunology*, 1971, **48**, 366.
[15] Tindall, J. P., Beeker, S. K., and Rosse, W. F., *Archives of Internal Medicine*, 1969 **124**, 129.

Current Status of Antilymphocyte Globulin

A decade has passed since antilymphocyte globulin (A.L.G.) was first shown to have immunosuppressive properties. Fortunately these revelations coincided with a burst of new information about the physiological role of different lymphocyte populations in the initiation of immune reactions, so that the relatively selective effects of A.L.G. could be reasonably well interpreted.[1 2] In animals it is remarkably effective in abrogating immune reactions mediated by small lymphocytes which traverse the peripheral blood. These include the first steps in homograft rejection, the ability to mount the skin reactions of delayed hypersensitivity, and primary antibody responses requiring the participation of T-lymphocytes. In addition, memory for some immunological events—reactivity to an antigen which has previously been encountered—can be ablated by A.L.G. However, A.L.G. does not suppress antibody responses which do not require the participation of T-lymphocytes nor those fully established at the time it is first administered. Early investigations of these immunosuppressive effects also showed that there was a high degree of synergism between A.L.G. and steroids and cytotoxic drugs,[3] and a non-specific effect on a variety of inflammatory reactions.[4]

Early on the most promising clinical application of A.L.G. seemed to be its potential for abolition of homograft rejection—even when a tissue such as skin, which provokes a vigorous response, was grafted across strong histocompatibility barriers. Furthermore its possible value in controlling aberrant immune responses—autoimmune disease—did not escape attention.[5] Such processes could be suppressed in animals with spontaneous or experimentally induced autoimmune disease provided that A.L.G. was administered during the stage of disease induction; but established disease proved almost totally refractory to treatment. The stage seemed set for a concerted study of the value of A.L.G. in the clinical applications of immunosuppression.

To what extent A.L.G. has fulfilled its early expectations was the subject of a recent symposium held at the Royal College of Physicians, London.[6] The meeting was organized by the Hoechst-Behringwerke Pharmaceutical Company, which has now produced a purified, standardized horse antihuman lymphocyte globulin (Pressimmune). Many of the papers concerned clinical trials of A.L.G., predominantly in recipients of renal transplants but also in patients with autoimmune disease. Unfortunately, the difficulties which persistently confuse the evaluation of such trials remain unresolved. Methods of raising antisera to human lymphocyte antigens are extremely variable, and there are still no simple in vitro tests for assessing the immunosuppressive potency of each batch which command general agreement. Moreover, the A.L.G. now used in such trials, though highly refined in terms of globulin reactive with lymphocytes, does not really discriminate between different circulating populations of such cells and should not be regarded as an agent which reacts specifically with T-lymphocytes. It is also expensive. On the other hand, the more refined varieties of A.L.G. now available rarely provoke the immediate toxicity so common in earlier days, such as thrombocytopenia and severe serum sickness. Nor have fears yet been borne out that so powerful an immunosuppressant might provoke a rash of lymphoreticular tumours; the undoubtedly increased incidence of such neoplasms in transplant recipients[7] is almost certain to have a more complicated pathogenesis than immunosuppression alone.

Surprisingly, A.L.G. has not proved of indisputable benefit in renal transplantation, though this was one area of clinical practice in which its value should theoretically have been most easily proved. A number of controlled trials in Scandinavia and in Britain reported at the conference showed that while A.L.G. may help in overcoming oliguric rejection crises it otherwise adds little to conventional immunosuppressive regimens. Typifying the difficulty in reaching objective conclusions without controlled trials was Professor C. W. Putnam's assertion that he would not undertake liver transplants without A.L.G. and Professor R. Y. Calne's riposte that he never used it for this purpose.

The place of A.L.G. in the management of autoimmune diseases has not been studied so extensively, and the available evidence is more fragmentary. Nevertheless, A.L.G., either alone or in combination with steroids and cytotoxic drugs, has been given to patients with disorders characterized by circulating immune complexes without precipitating serum sickness or glomerulonephritis of unacceptable severity. Thus its use in such conditions can at least be attempted. Furthermore such combinations have the powerful immunosuppressive effects which experimental work has predicted, as was shown by Dr. S. C. Knight. The studies so far undertaken give a hint, but no more, that A.L.G. may benefit patients with these disorders. There is, in particular, a strong suggestion from the work of Professor R. Storb and his colleagues in Seattle that a regimen of cyclophosphamide, procarbizine, and A.L.G. effectively controls graft-versus-host disease in patients with aplastic anaemia who have received bone marrow grafts. Such treatment is effective even in those recipients who have been sensitized by previous blood transfusions from prospective donors, indicating that A.L.G. may obliterate some forms of immunological memory in man as well as in animals.

The other disease in which the possible advantages of massive immunosuppression have received particular attention