The iceberg analogy of autoimmunity*

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IMPORTANT contributions to the understanding of autoimmune processes have come from studies on populations (Serafini, Torrigiani & Masala, 1964; Jacobs *et al.*, 1969; Whittingham *et al.*, 1969a; Couchman, Wigley & Prior, 1970; Hooper *et al.*, 1971) which have shown a substantial proportion of subjects, usually elderly, with serological stigmata of autoimmunity. *The iceberg analogy of autoimmunity* is applicable in this context in that what is seen above the surface of the sea is only a small part of the total mass of the iceberg, corresponding to that relatively small number of patients with symptomatic autoimmune disease in the entire population.

In the figure the *iceberg* represents the total population. The *man in the boat* is the clinician who sees as the top of the iceberg those patients with symptomatic autoimmune disease (clin AID) to which he ascribes a clinical diagnosis. The *snorkel-diver* is the histopathologist who, by viewing the iceberg from the surface or by making a shallow dive below the surface sees the same diseases as the clinician and, in addition, histologically evident but clinically insignificant autoimmune lesions (subclin AID). These are the mild non-destructive, focal in-

flammatory changes of gastritis, thyroiditis and sialadenitis seen in random histological surveys of tissues available by biopsy (Edwards & Coghill, 1966) or at necropsy (Waterhouse & Doniach, 1966; Bastenie *et al.*, 1967). The *aqualung* diver is the serologist who by diving deeper below the surface sees serological evidence of autoimmunity (serolog AID) in an even larger proportion of the population with and without symptomatic autoimmune disease; the results of the population surveys indicate that this is a substantial portion of the iceberg. The 'unseen', the lowest portion of the iceberg, represents that remaining segment of the population, mostly young and mostly healthy, in whom stigmata of autoimmunity have not as yet appeared or will never appear.

The *sun* beating down on the exposed top of the iceberg causes it to melt, and this in our analogy represents the various *environmental agents* which

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FIG. 1. The iceberg analogy of autoimmunity. For explanation of representations see text.

act synergistically with autoimmunization to augment its deleterious effects. For example, it is considered that environmental agents, particularly trauma, infection and drugs, can initiate autoimmune processes which culminate in immunopathological events manifested by self-perpetuating disease or exaggerated and damaging host responses. Solar trauma can initiate or exacerbate systemic lupus erythematosus (SLE) and mechanical trauma is said to exacerbate rheumatoid arthritis. Streptococcal infection is implicated in rheumatic carditis (Kaplan, 1969), and viral hepatitis may be a precursor of lupoid hepatitis (Mackay & Whittingham, 1967; Sherlock, 1969). Alpha-methyldopa (Worledge, Carstairs & Dacie, 1966) and procaine amide (Dubois, 1969) are the best known and the most interesting of the drugs known to initiate autoimmune processes, these being autoimmune haemolytic anaemia and SLE.

To continue the analogy, the iceberg melts from the top. This represents the increased mortality and morbidity experienced certainly by sufferers from frank symptomatic autoimmune disease, but seemingly also by individuals with asymptomatic stigmata of autoimmunity (Whittingham *et al.*, 1969b). Moreover, as the top of the iceberg melts the deeper portions move nearer the surface, representing the probable recruitment of asymptomatic subjects into the group with symptomatic autoimmune disease, and possibly the recruitment of non-autoimmune subjects into the autoimmune group, as the population ages.

The iceberg analogy of autoimmunity can be further applied to co-existences of autoimmune diseases in one individual and associations of different autoimmune diseases in families. This is particularly exemplified by the familial occurrence of clinical or serological features of Hashimoto's thyroiditis, pernicious anaemia and other diseases in the 'thyrogastric cluster' (Mackay, 1971). Various pressures tend to develop within icebergs, causing the mass of ice to break and disintegrate into smaller portions so, in our analogy, these smaller icebergs could represent the *single autoimmune disease* populations, for each of which there is a 'clinical' component above the surface and a 'subclinical' serological component below the surface. Certain specialist clinicians, in their own particular boats, might see only these isolated smaller icebergs in the form of the single disease in which they may be interested. However, the divers more easily recognize the origin of the smaller icebergs from the larger parent iceberg (or cluster of autoimmune diseases) because, beneath the surface of the smaller iceberg (single autoimmune diseases), there may be 'tell-tale' histological and serological features of other autoimmune diseases.

The bird is included so as to mention a new

natural model of human autoimmune disease, i.e. thyroiditis in obese chickens (Witebsky *et al.*, 1969), complementing the natural models of 'lupus-type' autoimmune diseases in NZ mice (Helyer & Howie, 1963). These avian and murine models illustrate the failure of immunological homeostasis characteristic of autoimmune disease, but have not as yet helped to explain the basic defect. Allison, Denman & Barnes (1971) proposed that T (thymus-processed) lymphocytes normally have the 'homeostatic' function of preventing autoimmunity, through two effects. (1) T lymphocytes are unresponsive to self-antigens, and so neither react with host antigens nor co-operate with B (bone-marrow-processed) lymphocytes, to facilitate production of autoantibody; (2) T lymphocytes exert a specific feed-back control over autoantibody formation. The extent to which T and B lymphocytes are concerned in avian and murine models of autoimmune disease is uncertain. Thus, spontaneous thyroiditis in obese chickens is prevented by bursectomy (removal of B lymphocytes) and by antiserum to B lymphocytes, but not by thymectomy or by antiserum to T cells (Wick *et al.*, 1970; Wick, Kite & Witebsky, 1970; Wick, Kite & Cole, 1971), whereas experimental autoimmune thyroiditis in chickens produced by immunization with thyroid tissue in adjuvants is prevented by thymectomy (Jankovic *et al.*, 1965). The autoimmune syndromes of NZ mice were stated to be retarded by early thymectomy (Holmes & Burnet, 1966) but other authors find the disease accelerated by neonatal thymectomy (Howie & Helyer, 1966; East *et al.*, 1967; Steinberg, Law & Talal, 1970). More detailed study of these chicken and murine models of autoimmune disease should determine which cell system, T or B, is predominantly involved.

The iceberg analogy of autoimmunity is presented to illustrate in human populations the totality of autoimmune disorders, that which is clinically overt and that which is clinically silent with only histological stigmata. The clinician, on seeing multiple features of autoimmunity in a particular patient or on eliciting a family history of an autoimmune disorder, may recall the iceberg analogy, and so may be encouraged not only to explore the surface but also to plumb the depths of this remarkable complex of diseases.

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