coprotein[6], although it has not yet been studied specifically in SLE. It seems more likely that the pentraxin protein abnormality, which is potentially related to pathogenesis of anti-nuclear autoimmunity in human SLE, is the well-recognized failure of SLE patients to mount substantial acute phase responses of C-reactive protein to non-infective autologous tissue damage[2,7].

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Mechanisms of thalidomide teratogenicity

To the editor—In response to the May issue article by Parman *et al.* proposing oxidative damage as a mechanism of thalidomide teratogenicity[1]: It seems that few, if any, of the proposed mechanisms of thalidomide embryopathy take into account the fact that thalidomide's effects on the skeleton are restricted to enchondral bone formation (that is, bones that are formed through a cartilage intermediate.)

Most of the structural elements of the skull (including the teeth) are spared in thalidomide embryopathy, since they are not generated through enchondral intermediates. The os petrosum, on the other hand, is, and malformations of the os petrosum are common in thalidomide victims, resulting in damage to the inner ear and deafness. It is difficult to explain these profound differences in terms of general mechanism such as oxidative DNA damage.

Further progress in this field may result from the recent identification of the molecular defect responsible for Holt-Oram syndrome. The malformations associated with this syndrome closely resemble those caused by thalidomide with respect to upper limb and cardiac development. Holt-Oram syndrome is caused by mutations in *TBX5*, a member of the brachyury gene family[2,3], and it is possible that interference with the normal expression or function of *TBX* gene products may be involved in thalidomide embryopathy. *TBX5* is expressed around the time that developing embryo is most sensitive to thalidomide[2].

Thalidomide victims still deserve our public and scientific attention. As they grow older, their medical problems increase. And there are many new cases related to the use of thalidomide to treat erythema nodosum leprosum (recently approved by the US Food and Drug Administration) and similar conditions.

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Biomedical research—from numerators to denominators

To the editor—In your May issue, John Bell highlights the demise of traditional clinical research in recent decades and the move from bedside, clinical research to benchside molecular biological research[1]. He describes the extent to which the limitations of traditional clinical research—"the measurement of complex variables in crudely defined disease states"—has driven the move to molecular biology that seeks insights into disease causation. Surprisingly, he seems not to have noticed an equally dramatic shift from bedside, clinical research to population-based epidemiological research.

The main limitation of traditional clinical research in addressing the causes of disease was not the lack of molecular biology but the focus on cases (numerators), without reference to the population (denominators) from which cases are derived. To elucidate the causes of disease we focus more and more on epidemiological methods. We must measure and compare disease incidence rates in defined populations among persons exposed and not exposed to putative causal factors (including gene markers). Perusal of the major peer-reviewed clinical research journals over the last two decades confirms the extent to which traditional bedside research has been displaced by epidemiological research on causation. Molecular biology, in contrast, is crucial in the elucidation of disease mechanisms (but contributes to our understanding of causation by refining case definitions in heterogeneous syndromes, facilitating work on gene-environment interaction and enhancing the precision of exposure measurements).

Bell reminds us that all disease depends on an interaction between genetic and environmental causal factors. We need to move, therefore, from simplistic, hierarchical concepts of causation that ascribe a more fundamental role to genes than environment in the development of disease[2]. The mysteries of human disease clearly will not yield to laboratory based investigation of cells and molecules alone. The clinical researcher of the future (or the researcher concerned with clinical questions) will need to combine biological, clinical and epidemiological approaches to study the full spectrum of disease in defined populations. It would also be helpful to discard naïve concepts of what constitutes 'basic' and 'applied' research. We should instead think in terms of 'laboratory', 'clinical' and 'population-based' research, each of which may be basic or applied, depending on the nature of the problem addressed. Clinical research might then benefit from the best of three worlds.

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