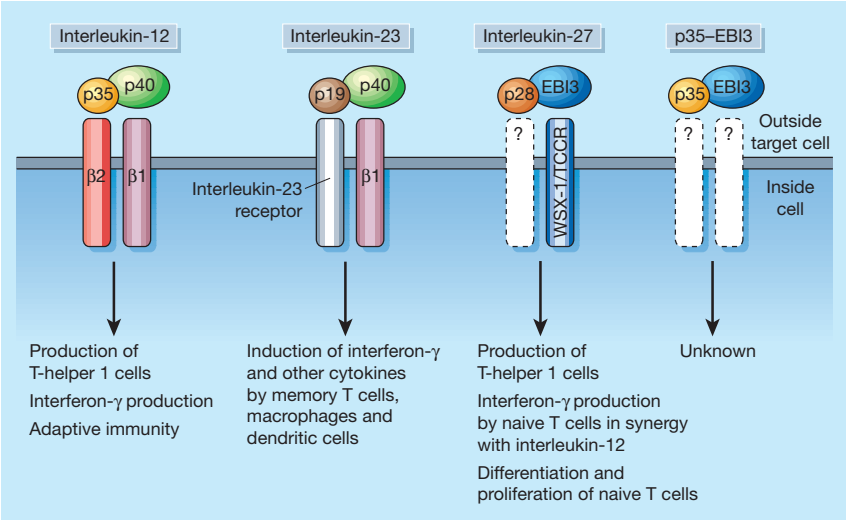

Figure 1 **The interleukin-12 family. These cytokine proteins are released from macrophages and dendritic cells in response to pathogens, and bind to receptors on target cells, activating a variety of functions. In each cytokine a protein akin to p35 (such as p19 or p28) pairs with a soluble protein related to p40 (such as EBI3). p40 is a component of interleukins 12 and 23; their receptors both include the interleukin-12 receptor β1 subunit. Interleukin-27 comprises the p35 relative p28, and the p40 relative EBI3. It binds to the receptor subunit WSX-1/TCCR, and probably another, unknown, receptor subunit. EBI3 can also associate with p35, but the significance of this is unclear. Cua *et al.*[1] show that, because of subunit sharing between these proteins, interleukin-12 has been wrongly assumed to be a major contributor to autoimmune disease. Instead, interleukin-23 is the main culprit, at least in a brain autoimmune disease in mice.**

immune encephalomyelitis (EAE), in p19-deficient and p35-deficient mice. The results show that although p19-deficient mice generate T-helper 1 cells and interferon-γ, they do not develop EAE, but that administering interleukin-23 to these animals is enough to provoke the disease. In contrast, in p35-deficient mice the production of T-helper 1 cells is blocked (as expected, because these mice lack interleukin-12), but the animals are highly susceptible to EAE.

So interleukin-23 can trigger this autoimmune disease, but the role of interleukin-12 is more complicated. The authors find that adding interleukin-23 is not enough to induce EAE in p40-knockout mice (which lack both interleukins). But administration of interleukin-12 followed by interleukin-23 does cause disease. All of this suggests that interleukin-12 contributes to EAE, but that it also has a protective role in this particular model. Although this may seem strange, it is consistent with the finding that interferon-γ also protects against EAE in an 'adjuvant' model[9]. Yet interferon-γ often has a protective effect in adjuvant models, for reasons that are not clear. By contrast, the administration of interferon-γ to people with multiple sclerosis exacerbates the disease[9]. Will the protective effects of interleukin-12 in mice be reflected in humans? The jury is still out.

Are there any other suspects to consider? Interleukin-12-related cytokines that share cytokine or receptor subunits continue to be identified, the newest member of the family being interleukin-27. Composed of the EBI3 protein, which is related to p40, and a p28 protein, akin to p35, interleukin-27 promotes interferon-γ production and drives the development of T-helper 1 cells. EBI3 may also be able to form dimers with other proteins, such as p35 itself. This might add another layer of complexity to interferon-γ regulation. Moreover, cytokine receptors are notoriously promiscuous — exactly which receptors bind which cytokines needs to be sorted out. In short, there is still considerable work to be done to pin down the functions of cytokines in immunity and autoimmunity[10].

What are the implications for treating patients? Antibodies that block interleukin-12 have been widely used in mouse models of autoimmune disease and are being tested in humans. It now seems that interleukin-23 should also be considered a target, although the antibodies against interleukin-12 might serendipitously block this cytokine, too. Treatments aimed at blocking protein subunits that are shared by interleukin-12 relatives (or their receptors) will also be of interest, as it is possible, given their common role in promoting interferon-γ production, that many members of this family contribute to autoimmune disease. Certainly, there is far more complexity here than initially envisioned. But this gives ample opportunity for intervention. ■

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100 YEARS AGO

In the essay to which he refers in his letter in NATURE of January 29, Dr. Wallace attaches less importance to the rearing of a few men of exceptional qualities than to the weeding out of the worst and raising the average; but surely, without giving undue and exclusive credit for advance to the pioneers and prophets, we may take it that men like Darwin and Wallace himself, to mention only one type, will, under natural selection, render the later more conscious steps of man's evolution easier. Dr. Wallace, in the letter referred to, speaks of the "fittest" not surviving under existing civilisation, meaning that many of the specialised types, which form important elements in our polymorphic communities, are not fittest to survive, and continue to reproduce their kind in more primitive or ideal communities. But this, of course, accords well with the principle of the "survival" of those types "fittest" to the actual environment. (Survival, of course, does not postulate direct reproduction any more than it postulates long life; the "worker" bees "survive.") Further, Dr. Wallace's hopeful attitude shows that he really trusts "natural selection" to steer the best races of man to a point whence their further, more self-conscious, progress (still, as always, under natural selection) will be more and more in accord with Nature's will, and so less wasteful and pain-fraught.

From *Nature* 12 February 1903.

50 YEARS AGO

***Chinese Science Revisited (2).* By Dr. Joseph Needham. Another emphasis which must be mentioned is that on popular education. There is a touching and genuine thirst for scientific knowledge among the Chinese people. Shops which sell anatomical models and geological charts have a crowd around the windows all day. If the visitor from the West wanders into one of the modern bookshops on a Sunday, he will almost have to step over rows of children and boys and girls of various ages sitting on the floor and against the bookcases reading popular science, and not paying the slightest attention to him. The assistants never insist on readers buying books, though they usually do, as they are relatively extremely cheap …Will it not make some difference to the world that five hundred million people are awakening to the significance of natural science and all that that implies?**

From *Nature* 14 February 1953.