requires exposure to certain environmental factors before it is fully expressed.

With all of this understanding, however, we still can't answer the simple question, 'What causes asthma?'. But in a paper on page 426 of this issue, Van Eerdewegh and colleagues[1] describe how they exploited the heritability of asthma to get closer to the solution.

Van Eerdewegh *et al.* have succeeded in identifying a gene that is associated with susceptibility to asthma. The authors initially studied 460 Caucasian families in which there were at least two siblings who were diagnosed as asthmatic by a physician, and who were using medications for their condition. The authors screened the genomes of all the members of these families by using a set of highly variable DNA markers. With this approach — known as linkage analysis — they found that a specific DNA 'signature' on the short arm of chromosome 20 occurred about 1,000 times more often in pairs of affected siblings than would be expected by chance. When Van Eerdewegh *et al.* repeated the analysis using a more restricted definition of asthma (that noted above plus the presence of bronchial hyperresponsiveness), they increased the statistical significance by a factor of ten and narrowed the region of interest to one that contained 23 genes, as defined by the Human Genome Project.

To figure out which of these genes was responsible for the linkage signature, the group identified single nucleotides within the genes that varied from person to person. They then carried out two case–control association analyses, in which they investigated whether a particular sequence variant occurred more frequently in the asthma patients than in nationality-matched controls in US and UK populations. By assessing linkage disequilibrium (the non-random association of genes across the genome) and haplotypes (combinations of single nucleotide variations on one chromosome that tend to be inherited together), Van Eerdewegh *et al.* narrowed the region further and implicated one gene as most commonly associated with asthma. This is the *ADAM33* gene, which encodes a protein-processing enzyme known as a metalloprotease[2].

Finally, the authors wanted to be sure that the identification of *ADAM33* in the case–control studies was not confounded by different ethnic mixes between cases and controls. So they carried out another family-based study, called the transmission-disequilibrium test, in which the observed frequency of gene variants transmitted from healthy parents to children with asthma was compared to the frequency that would be observed if the gene distribution occurred purely by chance. The results again showed that variations in *ADAM33* are significantly associated with asthma.

Further support for the importance of this gene came from an earlier study[3] of the genetics of bronchial hyperresponsiveness in mice. This study pinpointed a region on mouse chromosome 2 that is close to the region containing a mouse counterpart of *ADAM33*. This striking body of data is strong evidence that *ADAM33* is indeed an asthma-associated gene. It is now up to the community of asthma investigators to determine whether the finding is broadly replicable, and to define the functional implications of this association.

What do we learn from the identification of *ADAM33* as an 'asthma gene'? First, this study would seem to confirm that these genetic techniques can be used to unlock the riddle of complex inherited traits. Second, the results suggest that although asthma and allergy are closely related conditions, they have at least some distinct genetic determinants. In Van Eerdewegh *et al.*'s analysis, linkage was not improved when high levels of the IgE antibody in blood serum — a defining feature of allergy — were included in the definition of asthma. Worldwide, the prevalence of allergy far exceeds that of asthma. So the newly discovered variations in *ADAM33* may be the first genetic clue to what turns the runny nose of a person with allergies into an asthma-related wheezy chest. Third, if the results are replicable, the haplotype defined could be used to identify uniform populations of asthma patients for clinical studies.

Fourth, the most tempting mechanistic interpretation of Van Eerdewegh *et al.*'s data is that the metalloprotease encoded by *ADAM33* has a regulatory role, perhaps in processing proteins that influence fibroblast cells and airway smooth-muscle cells — both of which are known to be activated in asthma. It also seems reasonable to speculate that *ADAM33* could be important in other airway-obstructing diseases, such as chronic obstructive pulmonary disease. But definitive insights await a full functional analysis of normal *ADAM33* and its genetic variants.

We still can't answer the question, 'What causes asthma?'. But we are closer to understanding this complex disease. The study by Van Eerdewegh *et al.*[1] teaches us that there are probably fundamental differences in the airway walls of unaffected people and asthma sufferers. The results broaden the horizons of asthma biologists and physicians beyond a purely immunological interpretation of the disease. This improved understanding is just one benefit derived from the Human Genome Project. ■

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1. Van Eerdewegh, P. *et al. Nature* **418,** 426–430 (2002); advance online publication, 10 July 2002 (doi:10.1038/nature00878).
2. Yoshinaka, T. *et al. Gene* **282,** 227–236 (2002).
3. De Sanctis, G. T. *et al. Nature Genet.* **11,** 150–154 (1995).

100 YEARS AGO

Alcohol as a motive power has formed an interesting set of experiments in France at the present time, the object being to produce a home-made substitute for petrol which all has to be imported. According to *Heilden's Magazine* for July the results obtained are of a satisfactory nature, both for the heavier and lighter types of cars, and it is stated that passenger cars driven by alcoholic traction have been proved to hold their own against those with petrol as a motive power. The price of alcohol at present is higher, but by the use of beetroot in its manufacture its market value has been greatly reduced. The experiments showed that the amount of alcohol consumed by the engines (which were designed to burn petrol) was 50 per cent. higher than that of petrol, but it is stated that with engines properly constructed to use the new motive power this difference would be greatly reduced… Attention is also directed to the ease with which it can be prepared from potatoes, and consequently, on account of its general utility for heating, lighting, &c., it would seem that an opportunity is open for Ireland to create a most important industry.
From *Nature* 24 July 1902.

50 YEARS AGO

Last season, following the reports that rearing under the bright emitter type of 'infra-red' lamp caused an increased incidence in chicks of a crooked-toe deformity, we reared several hundred chicks from our own stock on solid floors so that we could study the problem at first hand. Despite the fact that we did everything possible to induce the condition… we failed to produce a single case of crooked toe. Towards the end of the season… we were able to obtain some growing birds from an outside source, which had been reared under 'infra-red' and which showed the deformity… Chicks, apparently normal on hatching, from the crooked-toe parents have been reared along with some of our own chicks under the same 'infra-red' lamp, and whereas 100 per cent of the progeny from the crooked-toed parents have developed the deformity, our own chicks have remained quite normal. When second batches of chicks from both sources were reared together, neither the progeny from the crooked-toed parents nor our own stock developed the malformation. It would therefore appear that this particular type of crooked toe is of a hereditary nature.
From *Nature* 26 July 1952.