Relevance of high and low penetrance

Sir—In their viewpoint item on misconceptions about the use of genetic tests in populations, Paolo Vineis and colleagues (March 3, p 709)[1] present a timely refresher in genetic epidemiology. This report will probably, however, be wrongly seen as a demonstration that the potential for causality and strong prediction arising from multifactorial genetic factors in common cancer is quite limited.

The statement that "the proportion of diseases attributable to low penetrant genetic traits is clearly difficult to establish and is probably much lower than the burden of disease attributable to certain environmental agents" suggests that necessary factors (smoking) can be compared numerically with sufficient factors (eg, genetic factors in combination with smoking).

Smoking causes lung cancer and explains most of the difference in incidence between smokers and non-smokers. Yet it is unclear why 10% of smokers develop lung cancer and others do not. There may be many sets of variant alleles of different genes that, in combination, strongly predict disease. Weatherall[2] described lessons to be learned from single gene diseases. The most common diseases caused by a single gene (monogenic diseases) in human beings are genetic disorders of haemoglobin, and these were the first to be explored at the molecular level. In, for example, thalassaemia, patients with the same genotype have different clinical manifestations because, even in monogenic disorders, other genes are also involved and environmental circumstances affect the clinical manifestations. In addition, genetic polymorphisms in carcinogen metabolism were purported to modify the age of onset and tumour location in individuals with inherited highly penetrant deficiency of DNA mismatch repair.[3]

Presently, how many genetic factors must cooperate with which environmental factors to cause which complex disease is unknown. However, that a limited set of common low penetrant genes in different combinations explains high risk to develop lung cancer better than smoking alone is not unfeasible.

Although the prospect of genetic tests that contribute to better prevention is still far away, the number of people to be examined to prevent one cancer death could easily become lower for genetic tests offered to the whole population in combination with conventional screening for breast and colon cancer of those with increased genetic risk. Genetic tests in which 50 or more factors are analysed are feasible with modern technology. Only when we have discovered the many pathways leading to common cancers, will we be able to conclude whether genetic testing can make a meaningful contribution to cancer prevention.

Vineis and colleagues show convincingly that single-gene tests will probably have a limited contribution to cancer prevention. The conceivable complexity of the mechanisms does not imply that strong prediction of the phenotype is not possible from the genetic and environmental background. We agree that simplistic extrapolation from monogenic disease due to a high penetrant gene to multifactorial disease partially due to low penetrant genes is unwarranted. We are still far away from explanations that address the complexities of for example, carcinogenesis, but we do not think that the search for strong causality has ended already.

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Authors' reply

Sir—We think that Gerard te Meerman and Elisabeth de Vries' points require some clarification. In particular, their question is whether necessary factors (smoking) can be compared numerically with sufficient factors (eg, genetic factors in combination with smoking). This question addresses the possibility of correctly apportioning the relative contribution of genes and the environment. However: smoking is not a necessary cause of lung cancer, nor is it the only known risk factor (others are asbestos, ionising radiation, BCME, arsenic, and other occupationl exposures), and non-smokers clearly have a finite, although small, risk of lung cancer; the statement that single gene-environment interactions represent sufficient causal complexes is probably true, but it is a hypothesis that requires much additional research.

The issue of interactions is relatively complex. The fact that one factor, such as smoking, explains 90% of the incidence of a cancer does not mean that the other factors cause the remaining 10%. The sum of single-factor attributable risks typically exceeds 100%, and the excess over 100% is due to interactions. This conclusion may seem counterintuitive, but an example can help. In the general population there are smokers, workers exposed to asbestos, and individuals with genetic susceptibility, with hypothetical attributable risks in the order of 90% (smoking), 5% (asbestos in some populations), and 12% (hypothetical estimate for *GSTM1*, based on a relative risk of 1·3 and a frequency of 50% of the null genotype).

These are reasonable estimates, whose sum exceeds 100%; the excess will increase if we add other types of genetic susceptibility, other environmental risk factors, or both. However, subgroups in the population share more than one environmental or genetic risk factor; in fact, we expect that the simultaneous presence of both envrironmental and genetic factors is the basis for "sufficient" causal complexes. The attributable risk in excess of 100% is due to the fact that we count twice, in the population, factors that contribute together to a sufficient causal complex in the single individual. There is much evidence, indeed, to think that the main causes of cancer are interactions.

Another major issue is whether by the means of the new high-throughput tools of molecular biology we can identify people with a combination of low penetrance polymorphisms, the sum of which substantially increases the risk of cancer. This, again, is probably true, but does not contradict the view that we express. Unless they are in linkage disequilibrium, different genes are independently inherited. Therefore, the probability of having two or more polymorphisms that predispose to cancer is given by the product of separate probabilities. So, even if the level of susceptibility associated with a certain haplotype (due to, say, six different genes) is very high, the probability of having that haplotype is low. In general, the inverse relation that applies between the frequency of a genetic allele in the

population and its penetrance seems to apply also to haplotypes.

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Gnathostomiasis

Sir—Some of our colleagues sent us comments about our clinical picture (March 31, p 1011),[1] and some precision seems to be necessary.

First, we stress that not only the removal of the worm but also anthelmintic drug, especially albendazole, might be useful to treat human gnathostomiasis. Although our patient was unsuccessfully treated with this drug, albendazole has been reported to successfully cure the recurrent migratory swelling of gnathostomiasis.[2] It also seems to favour the migration of the lava to the dermis, which makes the removal of the worm possible.[2,3]

Second, the picture of the larva cross section on the skin biopsy sample sparked off the curiosity of one of our colleagues since the morphology of the larval intestinal canal is one key to identify *Gnathostoma* species.[4] Moreover, serological tools do not allow us to definitively distinguish one species from another within the genus *Gnathostoma*.[5] Thus, careful examination of remaining slides of the skin biopsy suggested this case to be due to *Gnathostoma hispidum*, whose disease cycle is similar to *G spinigerum*.

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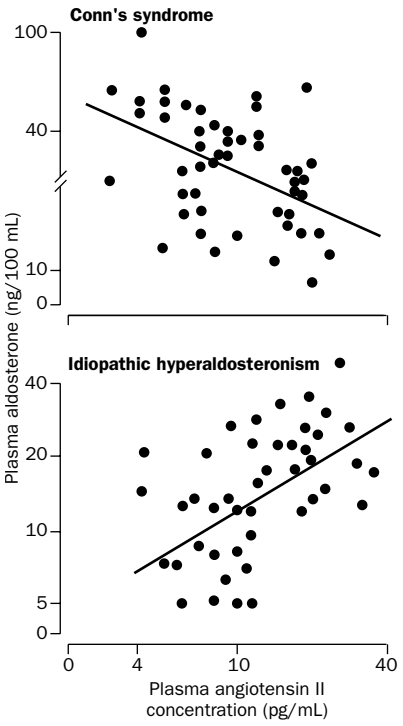
Cautions over idiopathic aldosteronism

Sir—Norman M Kaplan (March 24, p 953)[1] urges caution over the apparent current epidemic of primary aldosteronism. In warning readers that the diagnosis is probably being made overfrequently and, on the basis of inadequate data, he is necessarily obliged to draw attention to earlier published studies

The pathophysiological, statistical, and clinical evidence supporting his case is stronger than he states. Many patients now being diagnosed as having non-tumourous aldosteronism almost certainly have essential hypertension.

In true Conn's syndrome, excess autonomous aldosterone secretion from a unilateral adrenocortical adenoma causes hypertension with increased total body sodium and lessened body potassium content. Concurrent plasma aldosterone has an inverse correlation with angiotensin II concentrations (figure). Plasma aldosterone responds sluggishly to infused angiotensin II. By contrast with normal people, concentration is unaffected or may even fall on orthostasis. Plasma renin is unrelated to age.[2] In so-called idiopathic aldosteronism and in essential hypertension (whether or not plasma renin is low), mean total body electrolytes are normal. Plasma aldosterone and angiotensin II concentrations have significant positive correlation (figure) and aldosterone responds briskly to infused angiotensin II and to orthostasis.



Relation between concurrent basal early morning plasma aldosterone and angiotension II

Aldosterone sensitivity to angiotensin is increased in essential hypertension (this sensitivity of response may be linked to polymorphic differences in the gene coding for aldosterone synthase[3]) and renin concentrations fall with age, whereas basal aldosterone to renin ratios rise and create a superficial resemblance to Conn's syndrome. Furthermore, the histopathology of non-tumourous aldosteronism, bilateral nodular hyperplasia, is non-specific; it also occurs in unambiguous essential hypertension and in some normotensive people.[2] Its relation to aldosterone secretion is unestablished.

Statistical analysis provides further evidence. We and our colleagues analysed a range of variables to calculate Mahalanobis distances for representative populations.[2] The statistic for the idiopathic aldosteronism and essential hypertension groups was similar; the two values were different from that for the Conn's syndrome group. Analysis of the same variables by quadric analysis clearly distinguished Conn's syndrome from idiopathic aldosteronism preoperatively.[4] the linear discriminant[4] and logistic multivariate analysis[5] also distinguish between the syndromes with high probability.

In concurring with Kaplan and colleagues, we reiterate our recommendation that, in patients without adrenocortical tumour, adrenal surgery is best avoided. Medical treatment, including the potassium-sparing drug, amiloride, or aldosterone antagonists such as spironolactone, are preferable.

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Sir—We agree with much of what Norman Kaplan[1] says but have some