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against Tobacco and was found guilty on 25 June 1996. The advertising campaign was stopped but by then most of the misleading statements had been published.

REFERENCES

1 Davis R M. The ledger of tobacco control: is the cup half empty or half full? JAMA 1996; 275: 1281–84.


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$^a$Relative risk measures the effect of consumption or exposure to a product on the increase or decrease of risk.

The Constitutional Hypothesis Negated by Twins Discordant for Smoking and Mortality

From P H JONGBLOET

Sir—In a recent study$^1$ on smoking-discordant twins undertaken to test the constitutional hypothesis, an elevated risk of death was found among the smokers: for lung cancer (monozygotic (MZ) pairs: RR = 5.0; dizygotic (DZ) pairs: RR = 11.0) and for cardiovascular diseases (MZ pairs: RR = 3.9; DZ pairs: RR = 2.8). This strong association in smoking-discordant MZ twins, as in the population as a whole, would support the causal relation between tobacco and premature mortality and negate the constitutional hypothesis$^2$ that ‘genetic or early shared familial influences underlie this significant association’ or in other words, ‘that the association of tobacco smoking with personality traits would form a synergistic relationship which predisposes to cancer and cardiovascular mortality’.$^2$

This conclusion would only be correct if the phenotype of MZ twin pairs, including personality traits predisposing to smoking, would be exclusively dependent on the shared genome and not on any exogenous factor. There is, however, growing disagreement about whether concordance in MZ twin pairs is due to shared genes or shared environment, and uncritical acceptance of the results of classical twin studies may have misled generations of researchers.$^3$ In this context it is important to notice that in animals, experimentally-induced ageing of eggs before ovulation and/or fertilization resulted in a tendency of axial duplications, taking the form of twins, either of equal size and normal appearance, or of unequal dimensions; this teratogenic component may be apparent either in both embryos or in the smaller one.$^4$–$^6$ The same tendency towards both MZ twinning and developmental abnormalities has also been observed in humans after delayed ovulation.$^7$ These unequal dimensions of MZ embryos could explain why the shorter twin is more likely to die of heart disease than the taller one.$^8$ The same accounts for the well-known low concordance rate of

Department of Epidemiology, University of Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
schizophrenic and other constitutional disorders in MZ twin pairs, and for the high rates of abnormal brain lateralization, besides left-handedness and enlarged cerebral ventricles, in the diseased co-twin. In addition, more often than not, the sick twin has the lower birth weight and the greater number of birth complications; he or she remains smaller, weaker, and slower in development. Additionally, in 9% of the cases the less affected co-twins are said to have reactive psychosis or borderline states, and in 2% neurosis, including character disorders, anxiety states, depressive or somatic neuroses and alcoholism.

A relationship between MZ twinning and personality traits in one or both of the co-twins and its dependence on a non-genetic factor not only discards the predominantly genetic considerations but also emphasizes non-optimal maturation of the oocyte as a possible cause of a constitution characterized by both personality traits and constitutional diseases. The latter include cancer development, as Witschi concluded in his review on overripeness of the egg as a cause of twinning and teratogenesis: 'the persistence of an embryonic appearance of the cells, designated as aplasia or progressive failure of cells to differentiate is the most constant effect produced by overripeness; if combined with considerable growth, it leads to the formation of neoplasm'.

Moreover, the DZ twin pair incidence is modulated by the temporal relationship between follicle growth and rupture which is not as strict, even in spontaneous cycles of healthy volunteers. Asynchrony of follicle maturation and ovulations of up to 81 hours has been registered in induced plural ovulations. Maturation of the oocyte in animals and humans is known to be modulated by maternal factors, such as reproductive age, pregnancy interval, seasonality of conception, endocrinological diseases (diabetes mellitus, thyroid disease), undernutrition, use of drugs, etc. The maturation of the ultimately splitting oocyte leading to MZ twins and of both oocytes to DZ twins thus differs from that in singletons. Intrapair differences, therefore, may be dependent on the intriguing cascade of hormonal events involving optimal and non-optimal maturation of the oocyte(s).

In line with this concept, the mortality among twins has been found to be 1.14 times higher than in the general population, at least in females aged 60-89. Ischaemic heart disease mortality was not higher in a Swedish case-control study among male and female twins aged 46-65. These results, in contrast with the so much greater mortality of younger twins, have been interpreted as a consequence of reaching adulthood and representing healthy survivors who are not directly comparable to singletons born at the same time. 'Constitutional' or germline mutations of the p53 tumour-suppressor gene have been revealed to be present in every somatic cell at birth, and thus from conception. Furthermore, there is growing evidence that adult cardiovascular disease has prenatal origins (the fetal-origins hypothesis). And the manifold reports on dermatoglyphic abnormalities in both cancerous and cardiovascular diseases are all the more argument for embryonic disturbances having their effect in later adulthood. These arguments do not weaken the impact of cigarette smoking, but as the advocates of the constitutional hypothesis state, it cannot be a sufficient cause, but rather one of a whole set of causal determinants, including air pollution, drinking, psychosocial factors, etc. which together are instrumental in causing the disease in question.

In conclusion, the elevated risk of death among smoking-discordant MZ twins does not negate the constitutional hypothesis because twinning and personality variables (and their interaction with smoking) may be dependent on a non-genetic factor, namely, non-optimal maturation of the oocyte. It even substantiates the possibility of a synergistic relationship between personality traits predisposing to cigarette smoking and cancer or cardiovascular mortality.

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3. Phillips D I W. Twin studies in medical research: Can they tell us whether diseases are genetically determined? Lancet 1993; 341: 1008-19; and 342: 52.


