O of the 10 plagues visited on the biblical Egyptians, the last was the most terrible; after the rain of frogs, the plague of boils, and the hailstorms came the indiscriminate killing of frogs, the plague of boils, and the most terrible; after the rain of the 10 plagues visited on the

ASSOCIATIONS BETWEEN BIRTH ORDER/SIBSHIP AND DISEASE

Studies of birth order—or sibship size—as a risk factor have a long history and have examined a wide variety of diseases. Thus, for example, the rates of Hodgkin’s lymphoma in young adults,1 2 HBsAg-hepatocellular cancer,3 acute lymphoblastic leukaemia,4 and type 1 diabetes mellitus5 all appear to fall with increasing birth order. In each case the pattern has been assumed to reflect the relatively late age at which children of low birth order (or their mothers during pregnancy) acquire common infections. A similar (but opposite) reasoning has been applied to the observations that children of low birth order are at reduced risks of non-Hodgkin’s lymphoma,7 schizophrenia,8 gastric carcinoma and ulcer,9 acute myeloblastic leukaemia,10 and some congenital heart defects.11 Children of low birth order are more likely to have infantile pyloric stenosis, to be taller,12 to be right handed13 and, if they are male, to be heterosexual;14 these are less easily attributed to patterns of early infection.

Nowhere, however, are the patterns of birth order/sibship size/birth order and childhood allergic disease reported in at least 30 studies and usefully reviewed by Karmas and Botezan.15 As with most of the diseases above, these observations have generally been attributed to different rates and timings of early (unspecified) childhood infection. Indeed, they form the cornerstone of the “hygiene hypothesis” whereby it is proposed that the risks of atopic disease are reduced by early contact with infection,17 a proposal bolstered by the more recent suggestion that children born to Alpine farmers are protected in a similar manner.

ASSOCIATION BETWEEN SIBSHIP SIZE/BIRTH ORDER AND ALLERGIC DISEASE

In this issue of Thorax, Kinra et al16 provide an historical perspective on the associations between allergic disease and sibship size/birth order. Their population comprised 14 000 studies, predominantly male and about 50% of those eligible, who were screened at birth, and then examined at 1, 3, 5, 7, and 10 years of age. The prevalence of self-reported allergic disease was found to be lower among children of larger sibships, even after adjusting for potential confounders such as parental income and education.

Further debate on the explanation for the association between sibship size/birth order and childhood allergic disease

Childhood allergies, birth order and family size

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P Cullinan

Further debate on the explanation for the association between sibship size/birth order and childhood allergic disease

O the 10 plagues visited on the biblical Egyptians, the last was the most terrible; after the rain of frogs, the plague of boils, and the hailstorms came the indiscriminate slaughter of all firstborn animals including children. Incidence of this degree is thankfully rare—but is it possible that the author(s) of Exodus were expressing a subtler truth?
diseases (especially hay fever) with both increasing family size and birth order. Although the differences were small and are readily explained by chance, the effects were strongest in the earliest cohort. If this is explained by greater interfamily differences in infection in that era, then the findings overall are compatible with a “hygiene explanation”. Further support is provided by the finding that allergic diseases were less common among students from less affluent backgrounds, and by a (weak) interaction between birth order (but not family size) and childhood socioeconomic status. The report is valuable because it suggests that the sibship/birth order phenomenon is temporally robust and thus indicative of a relatively era independent mechanism.

HYGIENE HYPOTHESIS

As an explanation of family size effects (especially where these have been related to older siblings) and of other aspects of the epidemiology of childhood allergies (notably its geographical distribution), the hygiene hypothesis is both plausible and parsimonious. There are, however, increasing doubts that it is a complete explanation. First is the very tenacity of the birth order/sibship observation. This, of course, is not in itself a counterargument, but consistency is unusual in the shifting sands of asthma epidemiology. If early contact with infection alone is crucial in the development of childhood allergy, then one might expect the effects of the surrogate of family size to have changed more clearly with shifts in the patterns of early infection. This does not appear to be the case. It is not even clear whether the rates and timings of childhood infections are indeed closely related to family structure in the heavily immunised small family societies where allergic diseases are so prevalent. Even in rural Poland where the prevalence of atopy is extremely low—presumably as a result of extended microbial contact in early life,45 allergies are less likely to “lose” their atopic state and their hay fever than are women who have had no (further) pregnancies.52 Some have suggested that these apparent shifts in maternal immunity are hormone related.53 It remains unclear how and whether they are transmitted to successive children, although there is some evidence that firstborn children respond differently to respiratory allergens encountered in the first few weeks of life.44

Further attention to non-infectious explanations for the sibship effects in childhood allergy seems warranted. A useful starting point might be the experience of other diseases: for many years it has been known that the risks of pre-eclampsia and oedema of pregnancy are hormone related.33 It remains to be determined whether the hygiene hypothesis, if at all, is analogous in all respects with the fetal programming hypothesis54 that has been linked to type 2 diabetes in childhood: prospective population-based family study. Bart’s-Oxford Family Study Group. BMJ 2000;321:420–4. 

OTHER POSSIBLE EXPLANATIONS

If variations in the pattern of early infection are not the whole explanation of the sibship effects in childhood allergies, what other explanations are there? Levels of IgE in cord blood are lower in multiparous women, as is the specific reactivity of cord blood mononuclear cells.27–28 These findings may reflect higher rates of in utero infection of women who already have other children or, at least in the latter instance, higher maternal age. Alternatively, they may reflect the maternal experience of pregnancy itself. Pregnancy is an immunological challenge to the mother and child and it may be that the complex mechanisms associated with fetal survival vary systematically with increasing parity. These may, in turn, be reflected by shifts in maternal immunity. Women (but not men) who have had several children are less likely to be atopic, an observation that is not explained by age,59 and they are less likely than nulliparous women to report symptoms consistent with allergic rhinitis60 or conjunctivitis.61 When studied prospectively, women who have had more pregnancies are more likely to “lose” their atopic state and their hay fever than are women who have had no (further) pregnancies.52 Some have suggested that these apparent shifts in maternal immunity are hormone related.53 It remains unclear how and whether they are transmitted to successive children, although there is some evidence that firstborn children respond differently to respiratory allergens encountered in the first few weeks of life.44

Further attention to non-infectious explanations for the sibship effects in childhood allergy seems warranted. A useful starting point might be the experience of other diseases: for many years it has been known that the risks of pre-eclampsia and oedema of pregnancy are hormone related.33 It remains to be determined whether the hygiene hypothesis, if at all, is analogous in all respects with the fetal programming hypothesis54 that has been linked to type 2 diabetes in childhood: prospective population-based family study. Bart’s-Oxford Family Study Group. BMJ 2000;321:420–4.

REFERENCES

Low-dose spiral CT screening for lung cancer

Is screening for lung cancer using low-dose spiral CT scanning worthwhile?

F V Gleeson

The benefits of low-dose spiral CT scanning in screening for lung cancer are still under debate

Intuitively, lung cancer screening using low-dose spiral chest computed tomographic (LDCT) scanning would seem a good bet as it appears to fulfil the necessary criteria for a successful screening programme. Lung cancer is very prevalent; it may be readily detected when asymptomatic using LDCT; it may be cured at an early stage by surgical intervention; and, taking into account the lack of success and the possible costs of investigation and treatment in symptom detected patients, screening with LDCT might prove to be cost effective. For LDCT scanning to be an effective screening tool it must neither lead to an overdiagnosis bias nor to significant morbidity in patients with a false positive screen.

Overdiagnosis bias

The detection of clinically unimportant disease for a particular patient—or overdiagnosis bias—has been postulated as the possible cause for the failure of one of the most analysed chest radiography screening studies performed in the 1970s, the Mayo Lung Project. This screening study, which used the conventional chest radiograph and randomised patients into screened and control arms, was initially reported as showing no mortality benefit between the two groups. A more recent analysis showing no mortality benefit between the two groups. A more recent analysis showing no mortality benefit between the two groups. A more recent analysis showing no mortality benefit between the two groups...
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