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EDITORIAL

Towards testing the Dutch hypothesis from childhood

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Since the 1960s, Dutch investigators have been intrigued by the possibility that some "host" factors, namely increased level of bronchial hyperresponsiveness and atopy, would predispose some individuals to development of chronic obstructive pulmonary disease (COPD) [1]. These "host" factors would have an effect not only on the onset but also on the prognosis of COPD, as assessed by respiratory symptoms and lung function impairment. The most direct method to elucidate the actual course of events in COPD would have been to observe their occurrence in a prospective study of subjects who had not yet developed disabling disease. This could have been achieved, for instance, by following individuals from childhood to adulthood. Such studies were, for a long while, considered as impracticable.

The report in issue No. 6 of the Journal by DE GOOUER *et al.* [2], from the Netherlands, makes an important contribution to the understanding of the Dutch hypothesis mentioned above. The authors evaluated the consequences of prior atopy and bronchial hyperresponsiveness on the change in lung function and respiratory symptoms after 27 yrs, in a population-based sample of 60 subjects, initially aged 8–11 yrs. Childhood atopy was a risk factor for respiratory symptoms in young adulthood but bronchial hyperresponsiveness, as determined by a single challenge, was not. Nevertheless, the asymptomatic hyperresponders in childhood had lower levels of lung function, both in childhood and in adulthood. It has been suggested that bronchial hyperresponsiveness may be due to smaller airway diameter, which may persist during growth, or that bronchial hyperresponsiveness itself may reduce the airway calibre persistently.

Underestimation of the effect of hyperresponsiveness on respiratory symptoms in this study might have been caused by selection bias, due to loss of subjects (85% of the original sample were reinvestigated), who were more diseased than those who were followed-up. But, it also cannot be excluded that an association was not seen because the sample considered was so small that the group at risk of developing COPD was not identified. Boys are more susceptible than girls to develop respiratory symptoms in childhood and possibly later, but the authors did not analyse the relationship of bronchial hyperresponsiveness to respiratory symptoms and lung function according to sex. It may also be that the prognostic value of only one challenge test is meaningless to observe any effect.

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In this study, started 27 yrs ago, it was not possible to evaluate the effects of various factors presently implicated in respiratory disease, such as air pollution, climate, pollen exposure, infections, environmental tobacco smoke exposure during childhood, dietary electrolytes and micronutrients, or occupation, on which the literature of the last decade abounds. Nor was it possible to make detailed studies of "constitutional" (genetic, anatomical, ...) factors. Also, whether symptomatic subjects had taken asthma medication throughout their life, and the effect on respiratory health caused by such treatment were not addressed. The latter might also imply genetic differences in susceptibility to pharmacological agents.

To some extent, these data support the hypothesis that COPD might be due to overall disturbances of airways function associated with childhood allergy. This has already been predicted [3, 4] or observed from other shorter longitudinal population studies conducted among children. Atopy at an early age was an important predictive factor for respiratory symptoms occurring with bronchial hyperresponsiveness and continuing into late childhood among Australian children followed-up for 2 yrs [5]. Similarly, the growth of lung function was impaired after 6 yrs of follow-up in New Zealand children, initially aged 8 yrs, with atopy to house dust mite or cat dander, and with airways responsiveness to methacholine [6].

Among adults, there are ample data which are consistent with the hypothesis that hyperresponsiveness, but not atopy as assessed by skin prick test reactivity, is associated with development of COPD. This was particularly observed among smokers, and persisted even after exclusion of subjects with a history of asthma. No obvious explanation of this finding is as yet available. Smoking may increase bronchial hyperresponsiveness. Alternatively, bronchial hyperresponsiveness may modify the effects of smoking, but may also influence the likelihood of smoking ("the healthy smoker effect"). However, since the level of responsiveness was assessed at the end of the follow-up [7–10], or at the beginning of the survey but already late in life [11–13], inferences concerning the causality of bronchial hyperresponsiveness on decline in forced-expiratory volume in one second (FEV_1) may only be made with caution. Furthermore, the majority of studies which related atopy and bronchial hyperresponsiveness to the occurrence of COPD were conducted in occupational populations, hence the findings cannot easily be extended to general populations. The longitudinal study between childhood and adulthood from the Dutch group reported in issue No. 6 of the Journal is a first attempt to comprehend such phenomena from childhood.

The disparity of results observed between children and adults may be attributable to the fact that the variables under study are different according to age. Lung function impairment is assessed on the basis of a poor growth of lung function in comparison with reference values among children and young adults, and on the basis of lung function decline among adults. Bronchial hyperresponsiveness also varies with time and with the method of exposure during the challenge, and this is a function of age. At present, it is difficult to overcome all of these differences. It has been suggested that bronchial hyperresponsiveness may be "inborn" in children and "acquired" in adults. However, there is now increasing evidence, from different sources, that bronchial hyperresponsiveness could be a transient phenomenon in childhood, becoming more persistent in adults due to the action of some risk factor. Recently, bronchial hyperresponsiveness was found to be associated with parental tobacco smoke exposure in population studies among children [14]. Finally, risk factor exposures are not the same in childhood and later life. As a consequence, no direct comparison can be made.

In the light of overall existing data, allergy and heightened nonspecific airways responsiveness may be independent risk factors in the development of COPD, acting at different periods of life. Both may be the consequence of some other factors, such as allergic or nonallergic airways inflammation. An alternative hypothesis is that, because of some underlying cause, they can be associated with allergic and nonallergic airways inflammation, respectively [15].

The evidence for the role of allergy and airways responsiveness in the development of COPD is far from clear. Additional epidemiological studies considering the role of genetic and environmental factors on growth and decline in lung function are required.

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