Papers

Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus

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Abstract

Objective: To investigate the working hypothesis that common infections occurring early in life prevent atopy.

Design: Cross sectional, retrospective study of young Italian men with results for hepatitis A serology and atopy.

Setting: Air force school for military students in Caserta, Italy.

Subjects: 1659 male students aged 17-24, most of whom (90%) were from central and southern Italy.

Main outcome measures: Skin sensitisation and specific IgE antibodies to locally relevant airborne allergens; diagnosis of respiratory allergy (asthma or rhinitis, or both); hepatitis A seropositivity.

Results: 443 of the 1659 subjects (26.7%) were positive for hepatitis A virus antibody. Atopy was less common among seropositive than seronegative subjects according to skin sensitization (weal reaction ≥3 mm) to one or more allergens (21.9% (97/443) *v* 30.2% (367/1216), $P < 0.001$); polysensitisation (sensitive to three or more allergens) (2.7% (12/443) *v* 6.4% (78/1216), $P < 0.01$); high specific IgE concentration (9.7% (43/443) *v* 18.4% (224/1216), $P < 0.00005$); and lifetime prevalence of allergic rhinitis or asthma, or both (8.4% (37/443) *v* 16.7% (203/1216), $P < 0.001$). Hepatitis A seropositivity remained inversely associated with atopy after adjusting for father's education, the number of older siblings, and the area of residence (based on the number of inhabitants). The prevalence of atopy was constantly low among seropositive subjects, whatever the number of older siblings; by contrast, it increased with a decreasing number of older siblings among seronegative subjects.

Conclusion: Indirect but important evidence is added to the working hypothesis as common infections acquired early in life because of the presence of many older siblings (among seronegative subjects) or because of unhygienic living conditions (among seropositive subjects) may have reduced the risk of developing atopy.

Introduction

In the Western world the prevalences of allergic rhinitis and asthma have increased significantly in the past decades, especially among younger people.[1] Reasons for such a trend are still poorly understood, but they may be related to a parallel increase in IgE sensitisation towards common airborne allergens.[2]

In a British cohort study Strachan and colleagues observed an inverse relation between the number of older siblings and atopy or atopic diseases and hypothesised that protection from atopy might be exerted by infections acquired early and often during childhood as the result of unhygienic contact with older siblings.[3-6] This hypothesis would be consistent with current expanding knowledge on the regulation of the IgE immune response in humans,[7] which suggests that stimulation of TH1-like lymphocytes by infection could physiologically inhibit the clonal expansion of allergen specific TH2-like lymphocytes at a critical time during infancy.[6 8] On the basis of these and other recent studies, declining exposure to infections early in life has been proposed as the most relevant characteristic of Western lifestyle in determining the increasing prevalence of allergy.[6 9 10]

High recirculation of infectious agents is associated with environmental conditions such as overcrowding, poor hygiene in handling food, and infrequent washing. One of the most reliable markers of being brought up unhygienically or having been exposed to an infectious environment is considered in southern Europe to be the presence of antibodies to hepatitis A virus.[11]

We tested the above working hypothesis by analysing the relation between the presence of hepatitis A antibodies and atopy in a population of 1659 Italian military students whose family structure, residence, father's education, atopy, and hepatitis A serology were already available.[12 13]

Subjects and methods

Population sample

During October 1990 to June 1991 we examined 1887 Italian military students attending the Italian air force's school for non-commissioned officers in Caserta, Italy.

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Allergy and lung function were not assessed before entry, so candidates with allergy had not been excluded. Over 90% of subjects came from central and southern Italy. After giving their informed consent 1815 (96.2%) subjects participated in an epidemiological study on respiratory allergic diseases, whose details have been published elsewhere.[12] Of these, 1268 had also participated in a survey on the incidence of hepatitis A.[13]

This study is a retrospective analysis of data, most of which were acquired in these previous surveys and were further completed by collecting missing information on the family structure of all participants and by testing for antibodies to hepatitis A virus in 391 subjects who had participated only in the allergy study but whose serum samples were still available. We used the same commercial assay on aliquots of serum, which were obtained in October 1990 and had been stored since then at −70°C. The final number of subjects examined in this study was 1659 (mean age 20.7 (SD 1.6)), corresponding to 87.9% of those attending the course. There were no differences in known characteristics between those who did and those who did not complete this study.

Demographic data

Demographic data and information on the family structure, father's education, and area of residence (determined as the number of inhabitants in the area) were ascertained from a standard questionnaire.

Skin tests

A panel of seven airborne allergens (mixed grass pollens, *Parietaria judaica*, *Artemisia vulgaris*, *Olea europaea*, *Alternaria alternata*, *Dermatophagoides pteronyssinus*, and cat epithelium (Standard Quality line, Pharmacia, Uppsala, Sweden) were used for immediate skin prick tests in all the participants, as previously reported.[13] For the purposes of the present study a weal reaction greater than or equal to 3 mm after subtraction of the negative control reaction was regarded as positive.

Table 1 Skin sensitisation to common airborne allergens, specific IgE concentrations, and respiratory allergy in 1659 Italian military students according to presence of antibodies to hepatitis A virus. Values are numbers (percentages) of subjects

	Seronegative (n=1216)	Seropositive (n=443)	Odds ratio (95% CI)
Skin sensitisation			
No of sensitisations:			
1	172 (14.1)	59 (13.3)	1.07 (0.77 to 1.49)
2	117 (9.6)	26 (5.9)	1.71 (1.08 to 2.72)*
⩾3	78 (6.4)	12 (2.7)	2.46 (1.29 to 4.81)**
At least 1	367 (30.2)	97 (21.9)	1.54 (1.18 to 2.01)**
Cumulative weal diameter (mm):			
⩾5	308 (25.3)	76 (17.2)	1.64 (1.23 to 2.19)***
⩾10	169 (13.9)	33 (7.5)	2.01 (1.34 to 3.02)***
⩾15	75 (6.2)	10 (2.3)	2.85 (1.41 to 5.91)**
Prevalence of sensitisation to allergens:			
Dermatophagoides pteronyssinus	229 (18.8)	57 (12.9)	1.57 (1.14 to 2.18)**
Cat epithelium	94 (7.7)	18 (4.1)	1.98 (1.15 to 3.43)**
Mixed grass pollens	174 (14.3)	40 (9.0)	1.68 (1.15 to 2.46)**
Parietaria judaica	103 (8.5)	27 (6.1)	1.43 (0.90 to 2.27)
Olea europaea	32 (2.6)	7 (1.6)	1.68 (0.70 to 4.21)
Artemisia vulgaris	21 (1.7)	3 (0.7)	2.58 (0.73 to 10.90)
Alternaria alternata	22 (1.8)	4 (0.9)	2.02 (0.66 to 6.96)
Specific serum IgE to common inhalants			
Low positivity (log ratio unit >0<1.2)	213 (17.5)	83 (18.7)	0.92 (0.69 to 1.23)
High positivity (log ratio unit >1.2)	224 (18.4)	43 (9.7)	2.10 (1.47 to 3.02)***
Respiratory allergic disease			
Allergic rhinitis (with or without asthma)	187 (15.4)	34 (7.7)	2.19 (1.47 to 3.27)***
Allergic asthma (with or without rhinitis)	51 (4.2)	9 (2.0)	2.11 (0.99 to 4.64)
Total (allergic rhinitis and/or asthma)	203 (16.7)	37 (8.4)	2.20 (1.50 to 3.24)***

*P<0.05.
**P<0.01.
***P<0.001.

Serological assays

Blood specimens were taken from all participants, and serum samples were stored at −70°C. A fluorescence, solid phase multiallergen immunoassay (Phadiatop-CAP, Pharmacia, Uppsala) was used to evaluate the overall degree of IgE sensitisation to inhalant allergens as previously validated in this population sample.[13] The results were expressed as the logarithm of ratio units obtained from the formula: log (fluorescence units of sample/fluorescence units of reference serum).

The semiquantitative interpretation of multiallergen immunoassays has been recently introduced both in epidemiological and in genetic studies on allergy.[13 14]

All serum samples were tested for total antibodies to hepatitis A virus by a commercial immunoenzyme assay (HABA, Abbott, IL). Positivity or negativity was assigned according to the kit's instructions.

Diagnosis of allergic rhinitis and asthma

A clinical diagnosis of allergic rhinitis and asthma was based on history (a standardised questionnaire administered by one of us (PMM)), physical examination, and skin test results, as reported elsewhere.[13] Allergic rhinitis or conjunctivitis was diagnosed in subjects with a history of rhinitis apart from colds, such rhinitis being characterised by rhinorrhoea and sneezing with or without watery, itchy eyes that lasted for three weeks or more during the allergy season or occurred non-seasonally but in association with exposure to specific triggers and that was related to sensitisation to airborne allergens. Allergic asthma was diagnosed in subjects who had a history of repeated episodes of coughing, dyspnoea, wheezing, and chest tightness (or whistling) that were not caused by any organic condition, that occurred during the pollen season or recurrently if the subject was continuously exposed to specific triggers, and that were related to the sensitisation to airborne allergens. We considered asthma or rhinitis to be present if disease was current or if there was a documented history of having had it, or both.

Statistical methods

The association between each study factor and skin sensitisation, serum IgE sensitisation, and respiratory allergic disease was evaluated by estimating the prevalence odds ratio. Confidence limits, χ^2 tests, and test for trends were calculated by EpiInfo. To estimate the independent effect of each study factor on atopy the adjusted odds ratio was calculated by logistic regression analysis using the logistic regression program of biomedical data processing.[15].

Results

In all, 443 of the 1659 subjects (26.7%) had antibodies to hepatitis A virus. Only 97 of the 443 subjects with antibodies (21.9%) had a positive weal reaction to at

least one of the seven aeroallergens tested, compared with 367 of the 1216 subjects without antibodies (30.2%) ($P<0.001$). For each of the allergens tested a positive reaction was likely in subjects without antibodies to hepatitis A virus, with a significant difference for *Dermatophagoides pteronyssinus*, grass pollens, and cat epithelium. Interestingly, differences between the two groups increased with the number of positive reactions. When the total weal reaction was taken into consideration, the difference in the prevalence of positive reactions between the two groups increased with increasing total weal size (table 1).

Figure 1 shows the frequency distribution curves of the overall serum concentration of IgE against common airborne allergens. Interestingly, the frequency distribution curve of the seronegative group but not that of the seropositive group peaked at the higher concentrations of specific IgE. This peak occurred at a log ratio unit of 1.5 (range 1.2-1.8); for simplicity we therefore took a log ratio unit of IgE greater than 1.2 (which corresponded to about log 8 fluorescence units and 10 kU/l of overall specific IgE (data not shown)) to mean a high overall degree of sensitisation to airborne allergens (high specific IgE concentration); this cut off point identified as positive most subjects with polysensitisation and with clinical atopy.[13]

The prevalence of allergic rhinitis or asthma, or both, was significantly higher in the seronegative than in the seropositive group (16.7% *v* 8.35%; odds ratio 2.20 (95% confidence interval 1.50 to 3.24)) (table 1).

A multivariate analysis including several relevant sociodemographic variables, such as father's education, number of siblings, number of inhabitants in the area of residence, and age, is shown in table 2. Subjects who were seronegative for hepatitis A virus were more likely to be affected by atopic sensitisation than those who were seropositive (odds ratio 1.98 (1.37 to 2.86)), after adjustment for the confounding effect of sociodemographic characteristics such as the number of older or younger siblings, age, paternal education, and area of residence (table 2). The number of older siblings was another relevant independent factor inversely associated with the prevalence of atopy, but the number of younger siblings was not significantly associated (table 2).

Table 2 High specific IgE concentration to common airborne allergens in 1659 Italian military students according to presence of antibodies to hepatitis A virus and to relevant sociodemographic factors

	No (%) with log ratio unit >1.2	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Antibody to hepatitis A virus:			
Positive (n=443)	43 (9.7)	1	1
Negative (n=1216)	224 (18.4)	2.10 (1.47 to 3.02)	1.98 (1.37 to 2.86)
No of older siblings*:			
⩾3 (n=115)	10 (8.7)	1	1
2 (n=257)	37 (14.4)	1.77 (0.81 to 3.95)	1.44 (0.6 to 3.07)
1 (n=502)	77 (15.3)	1.90 (0.92 to 4.06)	1.71 (0.85 to 3.47)
0 (n=761)	141 (18.5)	2.39 (1.18 to 4.99)	2.13 (1.04 to 4.37)
No of younger siblings*:			
⩾3 (n=72)	8 (11.1)	1	1
2 (n=297)	38 (12.8)	1.17 (0.50 to 2.87)	1.09 (0.48 to 2.47)
1 (n=674)	130 (19.3)	1.91 (0.86 to 4.42)	1.78 (0.82 to 3.86)
0 (n=591)	88 (14.9)	1.40 (0.62 to 3.27)	1.52 (0.68 to 3.41)
Age (years)*:			
17-18 (n=126)	17 (13.5)	1	1
19-20 (n=661)	114 (17.2)	1.34 (0.77 to 2.32)	1.24 (0.70 to 2.21)
21-22 (n=649)	107 (16.5)	1.27 (0.73 to 2.20)	1.24 (0.70 to 2.21)
23-24 (n=222)	29 (13.1)	0.96 (0.51 to 1.83)	1.02 (0.52 to 1.99)
Paternal education*:			
None (n=123)	19 (15.4)	1	1
Primary school (age 6-10) (n=497)	71 (14.3)	0.91 (0.51 to 1.64)	0.95 (0.54 to 1.66)
Junior high school (age 11-13) (n=673)	116 (17.2)	1.14 (0.65 to 2.00)	1.07 (0.63 to 1.83)
High school (age 14-18) (n=287)	51 (17.8)	1.18 (0.64 to 2.19)	1.01 (0.56 to 1.82)
University (age 19-⩾22) (n=25)	2 (8.0)	0.48 (0.05 to 2.29)	0.45 (0.10 to 2.09)
Residence (No of inhabitants):			
<4000 (n=265)	36 (13.6)	1	1
⩾4000 to <16 000 (n=448)	72 (16.1)	1.22 (0.77 to 1.92)	1.28 (0.82 to 2.02)
⩾16 000 to <64 000 (n=522)	79 (15.1)	1.13 (0.73 to 1.78)	1.31 (0.84 to 2.04)
⩾64 000 (n=424)	80 (18.9)	1.49 (0.95 to 2.32)	1.49 (0.96 to 2.33)

*Data on number of older siblings missing in 24 subjects, on number of younger siblings in 25 subjects, on age in one subject, and on paternal education in 54 subjects.

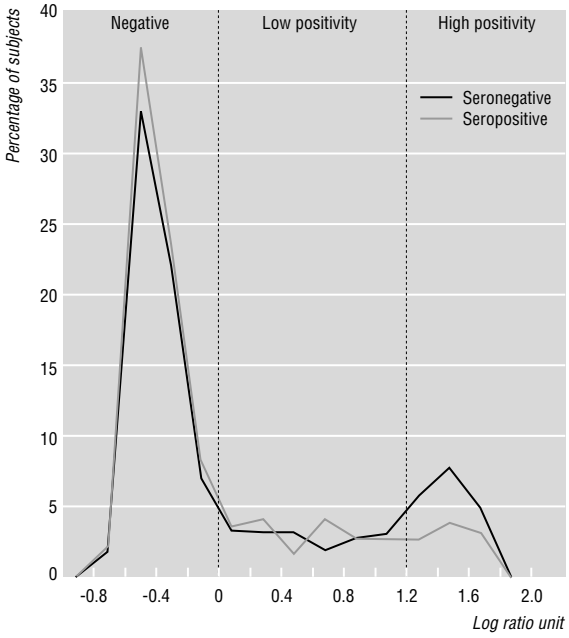

Fig 1 Frequency distribution of overall degree of serum IgE sensitisation to common airborne allergens in young Italian men according to seropositivity for hepatitis A virus

The prevalence of atopy was inversely related to the number of siblings among seronegative but not seropositive subjects (χ^2 test for trend; $P<0.01$) (fig 2). In the seropositive group the prevalence of atopy was around 9% and was independent of the number of older siblings.

Discussion

Inverse association between seropositivity for hepatitis A antibodies and atopy

We found an inverse association between antibodies to hepatitis A virus and atopy in a population of 1659 Italian military students, and this persisted after adjustment for relevant sociodemographic factors, including family size and number of older siblings, age, area of residence (number of inhabitants), and father's education. Lower prevalence of atopy among seropositive subjects had four characteristics.

(1) It was confirmed both from skin sensitisation tests and by serum specific IgE assay.

(2) It was not limited to a single allergen, suggesting a modification in host susceptibility to sensitisation rather than a lower exposure to some specific allergens.

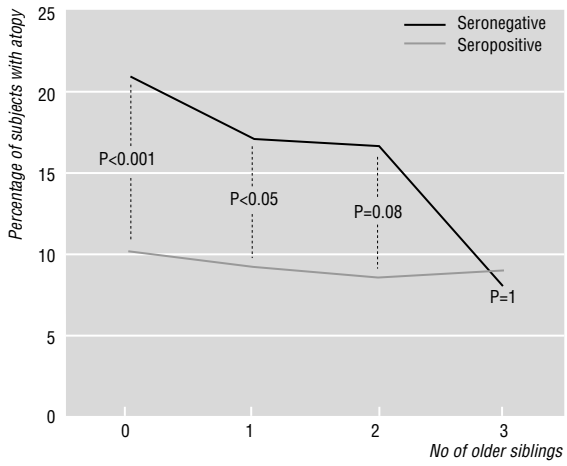

Fig 2 Prevalence of atopy (log ratio unit >1.2) in relation to number of older siblings in seropositive and seronegative subjects

(3) It was more pronounced with higher concentrations of specific IgE or skin test weal sum, thus implying a high specificity.

(4) It was parallelled by a consistently reduced prevalence of allergic rhinitis and asthma, thus implying clinical relevance.

To our knowledge, this is the first observation within one population of a Western country, of an inverse association between serological evidence of a given infection and allergy.

Association and working hypothesis

In the same population we also observed a strong inverse association between the number of older siblings and atopy, and this persisted after adjustment for hepatitis A serology. According to the working hypothesis, these data suggest that hepatitis A is not the only infection associated with low prevalence of atopy. Interestingly, after stratification for hepatitis A serology the protective effect of older siblings disappeared among seropositive subjects.

Taken together, these data suggest two things. Firstly, in people whose living conditions were hygienic enough to prevent infection with hepatitis A virus the presence of older siblings was necessary to reap the benefit of infections at an age early enough to confer protection from atopy. Secondly, in subjects infected by hepatitis A virus, this and other common infections may have been transmitted so frequently and early as to induce protection from atopy, independently from the number of older siblings. Hepatitis A was endemic in Italy during the 1970s, and it was usually acquired early in childhood, most commonly without inducing symptoms[16]; moreover, its transmission was favoured by faecal contamination of the living environment, poor hygienic food handling, day care settings, etc, which all facilitate the transmission of many other infectious agents. Thus, a possible conclusion is that the correlations observed strongly support the working hypothesis even if the temporal relations of hepatitis A with events leading to atopy are not directly shown in our study. Nevertheless, other possible explanations must be considered.

Other explanations

Hepatitis A seropositivity could simply be an indicator of lower exposure to risk factors for atopy (pollution, high indoor allergen concentration, smoke).[17] However, the potential confounding effect of outdoor pollution was indirectly adjusted for by including the number of inhabitants of the place of residence in the logistic analysis; a higher exposure to indoor allergens would have not affected sensitisation to pollen; and active smoking was not associated with atopy (data not shown), though we have no data on passive smoking.

Other studies

Published work shows a consistent inverse relation between current hepatitis A seropositivity and the prevalence of respiratory allergy in different parts of the world, as well as opposite trends over the past decades in Western countries. More interestingly, during the 1970s in the United States the prevalence of hepatitis A seropositivity was high in older people but low in younger people,[18] whereas the opposite was true for atopy.[19] This example suggests how the prevalence of atopy in a given generation of subjects may reflect their overall exposure to common infectious agents (such as hepatitis A virus) during their infancy, as previously postulated.[6] Therefore, as an indicator of exposure to common infections, hepatitis A seropositivity may be useful in testing the working hypothesis in other countries.

Infection(s) that may prevent atopy

Our data do not allow conclusions on the type of infection(s) that reduce the risk of atopy. Interestingly, studies in Guinea-Bissau suggest that measles may prevent atopy.[20] This would imply that a single measles episode is sufficient to influence the immune response to airborne allergens for many years ahead. Although obtained in a completely different population, our data

Key messages

- Young men with antibodies to hepatitis A virus had a lower prevalence of atopy and atopic respiratory diseases, and this was independent of the number of older siblings and other relevant risk factors
- The prevalence of atopy was as low in seronegative as in seropositive subjects only when they had three or more older siblings
- Among seropositive subjects the prevalence of atopy was low, whatever the number of older siblings
- Common infections acquired early in life because of the presence of many older siblings (among seronegative subjects) or because of unhygienic living conditions (among seropositive subjects) may have reduced the risk of development of atopy
- This study adds indirect but important evidence to the hypothesis that improvements in hygiene and reduced recirculation of common infections may be a major cause of the increasing prevalence of atopy and atopic diseases in Western countries

do not refute this conclusion. Indeed, measles might have occurred much earlier than in the remaining population sample in those subjects whose living conditions had also favoured transmission of hepatitis A virus, as well as in subjects who were never infected with hepatitis A virus but had many older siblings.

Nevertheless, our data question whether a more complex and protracted sequence of infectious events, consisting of repeated contacts with various pathogens, is necessary to significantly affect the TH1-TH2 equilibrium in the immune response to airborne allergens. The inverse relation between hepatitis A infection and atopy reported here suggests that infections transmitted through the faecal-oral route might also help to prevent atopy and atopic diseases. Without any more direct evidence, however, the kinds of infections and their possible interaction with processes leading to atopy remain to be clarified.

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Atopic dermatitis and birth factors: historical follow up by record linkage

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Abstract

Objective: To study if factors at birth are associated with later development of atopic dermatitis.
Design: Historical follow up by record linkage from Danish medical birth register. Children were followed up for 5.5 to 8.5 years. Second historical follow up study comprising questionnaire to mothers of singleborn children 6.5 to 9.5 years after birth.
Setting: Private dermatology clinics and dermatology and paediatric departments in the municipality of Aarhus, Denmark.
Subjects: 7862 singletons born in hospital between 1 January 1984 and 31 December 1986 to mothers living in the municipality of Aarhus. Questionnaires sent to 985 mothers.
Main outcome measures: Gestational age, birth weight, parity, and age of mother at the time of birth. Atopy in children diagnosed by specialists in dermatology and physicians. Family size; diagnosis of atopic dermatitis, allergic rhinitis, and asthma; family predisposition; and mothers' smoking habits during pregnancy determined from questionnaires.
Results: Of 7862 children, 403 were diagnosed as having atopic dermatitis by a specialist; the cumulative incidence at age 7 was 5.6%. High gestational age and low parity were associated with an increased risk of atopic dermatitis. Among 985 children atopic dermatitis had been diagnosed by any physician in 184; the cumulative incidence at age 7 was 18.7%. High birth weight, high gestational age, and family history of atopy were associated with increased risk of atopic dermatitis.
Conclusion: In both studies the incidence of atopic dermatitis was associated with high gestational age and in one with high birth weight also. The causes for these associations are at present unknown but may indicate that even during gestation factors associated with atopic dermatitis influence maturation.

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Introduction

Atopic dermatitis is a chronic skin disease of unknown aetiology that is most prevalent in early childhood.[1 2] Recent epidemiological studies have supported an increased incidence of atopic dermatitis.[3-10] Such an

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increase could simply be due to the fact that more children are seen by doctors. The increase has also been related to environmental factors such as pollution and indoor environment, an increase in respiratory infections, and the ingestion of certain foods.[11-13] So far, however, there has been little evidence to support these suggestions. A British national birth cohort of 5 year olds born in 1970 showed an association with more positive health behaviour in parents and in the most advantaged socioeconomic groups, educational level probably being the main factor.[14 15] Recent follow up of a British national birth cohort born in 1958 confirmed an association with a high social class.[16]

In Denmark epidemiological studies of twins have documented an increase in the cumulative incidence of atopic dermatitis at age 7 from 3.2% in 1960-4 to almost 12% in 1979.[17 18] Results have shown that atopic dermatitis is strongly influenced by genetic factors because the concordance rate in monozygotic twins was about 80% compared with about 20% in dizygotic twins.[5 17 18] It is difficult to imagine, however, that changes in the genetics of atopic dermatitis could explain its rapid increase in many countries during the past 30 years.

During the 1980s the age of first time mothers in Denmark increased. Birth weight has increased with the age of the mother as well as with parity.[19] We investigated the influence of specific birth factors, including the age of the mother, gestational age, and birth weight, on the risk of developing atopic dermatitis. We also examined the influence of hereditary factors, smoking during pregnancy, and season of birth. Unfortunately, the Danish medical birth register has no information on social class of the investigated families.

Subjects and methods

The study cohort included all of the 7862 singleborn children born between 1 January 1984 and 31 December 1986 at the Aarhus Maternity Hospital to mothers living in the municipality of Aarhus. The hospital covers 99% of all births in the municipality. Information about parental age, parity, gestational age, and birth weight was obtained from the Danish medical birth register. Information on deaths and emigration from the region was obtained from the Danish national population register.

The first study included all the children in the cohort, and the diagnostic criterion was a specialist diagnosis of atopic dermatitis. During the summer of 1992 we manually extracted information from the records of the dermatology and paediatric departments and from all the practising dermatologists in Aarhus about all contacts during 1984-92 in which children were diagnosed as having atopic dermatitis. These clinics are free of charge and the only source of specialised services for skin diseases in the municipality. The information was linked to the study cohort file by means of personal identification numbers, and information from the population register was used to identify exclusions (deaths and emigrations from the capture area). The average (range) follow up time since birth was 6.3 (5.5 to 8.5) years.

The purpose of the second study was to investigate further a hypothesis about a decreased risk of atopic dermatitis in preterm children. In this study the diagnostic criterion was the parents' report of a diagnosis of atopic dermatitis given by any doctor. We used a stratified sample of 1060 children from the same cohort, with an overrepresentation of preterm children (gestational age <37 weeks, 19%). The samples of term (gestational age 37-40 weeks, 54%) and post-term children (gestational >40 weeks, 27%) were matched with the sample of preterm children by sex. Families who had emigrated from Aarhus before data collection as well as families in which the child or mother, or both, had died were excluded. In the summer of 1993 questionnaires were sent to the sample families. The questionnaire included questions on atopic dermatitis in the child, other symptoms of atopy, family history of atopy, and mother's smoking habits during pregnancy. The information was linked to the cohort file by means of personal identification numbers. The average (range) follow up time since birth was 6.8 (6.5 to 9.5) years.

Multiple births were left out of both studies because of the influence on gestational age and birth weight.[20-24] The studies were approved by the ethics committee of the County of Aarhus and by the Danish Data Protection Agency.

Statistical analysis

Children who had died or moved outside the municipality and five neighbouring municipalities during the follow up period were considered censored at the time of death or emigration.

The cumulative incidence of diagnosis of atopic dermatitis was estimated by Kaplan-Meier's method, and relative risk estimates were obtained by Cox's regression.

Because of the sampling procedure the cohort in the second study was not representative for the entire cohort regarding gestational age and sex distribution, and the estimate of cumulative incidence was adjusted

Table 1 Cumulative incidence (per 100 children) of diagnosis of atopic dermatitis in both studies

	Age (years)							
	1	2	3	4	5	6	7	8
Study 1	0.5	1.7	2.9	3.7	4.3	4.8	5.6	5.9
Study 2*	6.4	11.7	14.3	16.6	17.1	17.8	18.7	19.6

*Standardised to distribution of sex and gestational age in entire study cohort.

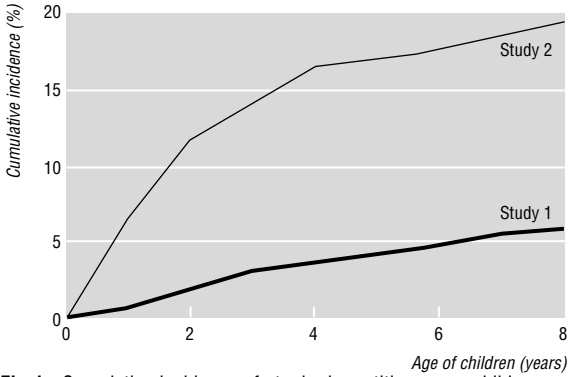

Fig 1 Cumulative incidence of atopic dermatitis among children from 0 to 8 years of age in studies 1 and 2

Table 2 Predictors of specialist diagnosis of atopic dermatitis according to birth factors (Cox's regression analysis) in first study

Independent variable	No of subjects (n=7862)	No with diagnosis (n=403)	Unadjusted		Adjusted*	
			Relative risk (95% CI)	P value†	Relative risk (95%CI)	P value†
Sex of child:				0.31		0.40
Boy	4070	199	1.00		1.00	
Girl	3792	204	1.11 (0.91 to 1.34)		1.09 (0.89 to 1.32)	
Mother's age at childbirth (years):				0.86		0.34
⩽24	2099	101	1.00		1.00	
25-29	3229	165	1.05 (0.82 to 1.35)		1.08 (0.84 to 1.39)	
30-34	1920	112	1.19 (0.91 to 1.56)		1.30 (0.98 to 1.72)	
⩾35	614	25	0.82 (0.53 to 1.27)		1.06 (0.67 to 1.69)	
Parity:				< 0.01		< 0.01
1	4090	224	1.00		1.00	
2	2721	141	0.92 (0.74 to 1.13)		0.86 (0.69 to 1.07)	
3	802	34	0.74 (0.52 to 1.07)		0.69 (0.47 to 1.01)	
⩾4	249	4	0.28 (0.10 to 0.75)		0.26 (0.10 to 0.73)	
Gestational age (weeks)‡:				0.02		0.02
⩽36	306	13	0.99 (0.57 to 1.74)		0.98 (0.56 to 1.71)	
37-38	889	38	0.91 (0.64 to 1.28)		0.91 (0.64 to 1.29)	
39-40	4230	201	1.00		1.00	
⩾41	2410	151	1.34 (1.08 to 1.65)		1.32 (1.06 to 1.63)	
Difference from expected birth weight (g)§:				0.51		0.35
⩽−500	906	41	0.82 (0.58 to 1.16)		0.82 (0.58 to 1.15)	
−499 to −200	1630	78	0.87 (0.66 to 1.14)		0.86 (0.65 to 1.13)	
−199 to 199	2821	154	1.00		1.00	
200 to 499	1487	76	0.92 (0.70 to 1.21)		0.94 (0.71 to 1.23)	
⩾ 500	987	54	0.98 (0.72 to 1.33)		1.02 (0.74 to 1.39)	

*Adjusted for other variables in table.
†Trend test (Cox's regression of ungrouped variables) when applicable.
‡Missing for 27 control subjects.
§Missing for 31 control subjects.

by direct standardisation to the gestational age and sex distribution in the entire cohort.

As gestational age and birth weight are closely correlated, the inclusion of both in a regression analysis gives unstable results that are difficult to interpret. We therefore calculated the expected birth weight according to gestational age and sex from the information in the entire birth cohort and included information on birth weight as the deviation from the expected birth weight in the analysis. The equation obtained by linear regression, expressing birth weight in grams (BW) as a function of sex and gestational age (GA) was: $E(BW) = 32\,027 - 156 \times \text{sex (female)} - 3115.25 \times GA + 98.841 \times GA^2 - 0.96785 \times GA^3$.

The data analysis was performed with SPSS for Windows, version 6.1.3.[25] Probabilities of $<5\%$ were considered significant.

Results

The first study comprised 7862 children. Seventy nine children (mean age 0.7 years) died, 912 (3.7 years) moved out of the study area, and 403 (3.2 years) were diagnosed by specialists as having atopic dermatitis. Table 1 and figure 1 show the cumulative incidence. The incidence was low in the first year of life, 1.2% a year in 1-2 year old children, and about 0.7% a year in 3-6 year old children. At the age of 7 the cumulative incidence was 5.6%.

In the second study we sent out 1060 questionnaires and received 985 replies, yielding a response rate of 93%, equal in the three gestational age strata (data not shown). The parents of 184 children reported a diagnosis of atopic dermatitis given by a doctor. The cumulative incidence is also shown in table 1 and figure 1. The incidence was highest in the first two years of life, about 6% a year, while for 2 to 6 year old children it was 1-2% a year. At the age of 7 the adjusted cumulative incidence was 18.7%.

Table 2 shows the relative risks associated with birth factors in the first study. The sex of the child and maternal age did not significantly influence the risk of atopic dermatitis, but there was a significant inverse relation with parity. Post-term children had a significantly increased risk for later development of atopic dermatitis, but there was an insignificantly decreased risk for preterm children. There was a weakly insignificant relation with birth weight when we controlled for gestational age and sex.

Table 3 shows the relative risks associated with birth factors in the second study. The risk was highest for girls (not significant), and there was no relation with maternal age and parity. There was a significant association with gestational age, with the highest risk among post-term children. Furthermore, there was a significantly increased risk for children with high birth weight compared with expected weight for sex and gestational age. The increased risk for "heavy for dates" children was present in all gestational age strata (data not shown).

Table 4 shows the relative risks associated with family history of allergic disease. The risk was positively associated with all variables, especially atopic dermatitis among the parents. Maternal smoking during pregnancy did not affect the risk of atopic dermatitis.

We did not find any relation between year of birth or month or season of birth and risk in either study (data not shown).

Table 3 Predictors of doctor diagnosis of atopic dermatitis (reported by parents) according to birth factors (Cox's regression analysis) in second study

Independent variable	No of subjects (n=985)	No with diagnosis (n=184)	Unadjusted		Adjusted*	
			Relative risk (95% CI)	P value†	Relative risk (95%CI)	P value†
Sex of child:				0.13		0.09
Boy	569	97	1.00		1.00	
Girl	416	87	1.25 (0.93 to 1.67)		1.29 (0.96 to 1.72)	
Mother's age at childbirth (years):				0.55		0.63
≤24	251	44	1.00		1.00	
25-29	394	73	1.08 (0.74 to 1.57)		1.04 (0.70 to 1.53)	
30-34	259	51	1.15 (0.77 to 1.72)		1.15 (0.75 to 1.77)	
⩾ 35	81	16	1.13 (0.64 to 2.01)		1.12 (0.59 to 2.13)	
Parity:				0.77		0.66
1	508	96	1.00		1.00	
2	348	63	0.96 (0.70 to 1.32)		0.86 (0.61 to 1.21)	
3	98	18	0.97 (0.59 to 1.61)		0.82 (0.48 to 1.40)	
⩾4	31	7	1.17 (0.54 to 2.52)		0.98 (0.42 to 2.28)	
Gestational age (weeks):				0.03		0.03
⩾36	189	30	0.91 (0.60 to 1.39)		0.88 (0.57 to 1.35)	
37-38	93	17	1.05 (0.62 to 1.78)		1.06 (0.62 to 1.80)	
39-40	432	75	1.00		1.00	
⩾41	271	62	1.37 (0.98 to 1.92)		1.35 (0.96 to 1.89)	
Difference from expected birth weight (g)‡:				0.02		0.01
⩾−500	109	17	0.80 (0.47 to 1.36)		0.81 (0.47 to 1.38)	
−499 to −200	211	30	0.73 (0.47 to 1.12)		0.73 (0.47 to 1.12)	
−199 to 199	352	67	1.00		1.00	
200 to 499	190	36	1.00 (0.67 to 1.50)		1.01 (0.67 to 1.52)	
⩾500	122	34	1.52 (1.01 to 2.30)		1.59 (1.05 to 2.42)	

*Adjusted for other variables in table.
†Trend test (Cox's regression of ungrouped variables) when applicable.
‡Birth weight missing for one control subject.

Discussion

Atopic dermatitis is strongly associated with genetic factors as documented in previous and present studies.[5 17 18] Genetic factors cannot explain the rapidly increasing incidence,[17] so we looked at various birth factors and their possible relation to later expression of atopic dermatitis.

The two studies reported here gave essentially the same results concerning the effect of gestational age: a significantly increased risk of developing atopic dermatitis among post-term children. The effect of birth weight was different in the two studies, with no association in the first, whereas the "heavy for dates" children in the second study had a significantly increased risk of atopic dermatitis. The difference might be explained by the fact that the definition of atopic dermatitis was different in the two studies. We conclude that the risk of developing atopic dermatitis is increased for children born post-term (⩾41 weeks' gestation) and possibly decreased for children born preterm. A lack of association between atopic dermatitis and preterm birth, however, has previously been shown.[26] There may also be an independent relation, with birth weight in children born "heavy for dates" having an increased risk of developing atopic dermatitis.

In the second study we studied preterm birth and atopic dermatitis. The sampling principle for this study was somewhat complex by matching the term and post-term samples to the preterm sample by sex. This gave rise to an overrepresentation of preterm children and of boys in all gestational groups. For estimating the overall incidence we standardised the raw estimates to the sex and gestational distribution of the entire cohort. The skewed sample does not introduce bias in the relative risk estimates.

We believe that any selection bias in the second study would probably lead to an overestimate of the overall incidence because of less interest among parents of children without allergic problems. With a participation rate of 93% in all gestational groups, however, selection bias is unlikely to have affected the estimates of overall incidence and relative risk substantially.

The Danish medical birth register is remarkably complete: information on birth weight was missing in only 0.1% and information on gestational age in 0.3% of the children in the cohort. In Denmark, health care is provided free of charge for all permanent residents. Prenatal care is provided by general practitioners and midwives, who predict the date of birth based on the date of the last menstruation. If the gestational age is uncertain, an ultrasound scan may be carried out. Thus, determination of gestational age is as accurate as possible. While measuring birth weight is simple, gestational age may be subject to misclassification.[27] It is unlikely, however, that any misclassification of gestation should be differential, and the same pattern of effect of birth weight was found in all gestational groups in both studies.

Estimates of incidence

The two studies gave rise to very different estimates of incidence. This was expected as only a fraction of children with atopic dermatitis are examined by specialists. The incidence estimate from the first study reflects the incidence of severe cases but is no doubt also influenced by iatrotropic factors—for example, parental

Table 4 Predictors of doctor diagnosis of atopic dermatitis (reported by parents) according to family history (Cox's regression analysis)

Independent variable	No of subjects (n=985)*	No with diagnosis (n=184)†	Unadjusted		Adjusted‡	
			Relative risk (95% CI)	P value	Relative risk (95%CI)	P value
Mother had atopic dermatitis:				<0.01		<0.01
Yes	46	20	2.90 (1.82 to 4.62)		2.42 (1.46 to 4.02)	
No	922	162	1.00		1.00	
Mother had asthma:				< 0.01		0.36
Yes	40	14	2.20 (1.27 to 3.79)		1.32 (0.72 to 2.42)	
No	928	168	1.00		1.00	
Mother had hay fever:				< 0.01		0.07
Yes	117	33	1.73 (1.19 to 2.53)		1.45 (0.97 to 2.18)	
No	851	149	1.00		1.00	
Father had atopic dermatitis:				< 0.01		< 0.01
Yes	23	13	4.30 (2.44 to 7.56)		3.89 (2.15 to 7.03)	
No	945	169	1.00		1.00	
Father had asthma:				< 0.01		< 0.01
Yes	32	16	3.29 (1.97 to 5.50)		2.70 (1.53 to 4.76)	
No	936	166	1.00		1.00	
Father had hay fever:				0.01		0.16
Yes	104	29	1.66 (1.11 to 2.47)		1.37 (0.88 to 2.13)	
No	864	153	1.00		1.00	
Mother smoked during pregnancy:				0.23		0.64
Yes	437	75	0.83 (0.62 to 1.12)		0.93 (0.68 to 1.27)	
No	544	109	1.00		1.00	

*Data missing on one or more variables for 18 subjects.
†Data for mothers with hay fever, father with atopic dermatitis, father with asthma, and father with hayfever missing for two cases.
‡Adjusted for all other variables in table and for variables in table 3.

anxiety. Iatrotropic here refers to the combination of factors that causes parents to bring a child to a doctor. The incidence estimate from the second study probably includes some false positive diagnoses because of overdiagnosis by general practitioners and by the parents mistaking a diagnosis of unspecific dermatitis for atopic dermatitis. On the other hand, false negative diagnoses can no doubt also occur; some mild cases remained undiagnosed or were not recalled. The "true" incidence of a disease like atopic dermatitis cannot be established in studies like ours, and even conceptually it is difficult to distinguish the mildest cases from non-cases.

The observation in the first study of a decreased incidence of atopic dermatitis with parity could reflect the fact that the first child is more likely to develop atopic dermatitis. In a British study hay fever was reported to be inversely related to the number of children in the household. The same pattern was observed for eczema in infancy.[28] Similar gradients in hay fever and eczema with increasing family size were reported at 5 years of age among British children born in 1970.[29] In Denmark average parity did not change essentially during the 1980s. There has been some shifting of parity in different age groups of mothers—that is, first birth has become more common in mothers between 25 and 34 years of age.[19] One could imagine that family size and the age of the mother are dependent on socioeconomic class of the families. In our research we could not take socioeconomic class into consideration. The relative risk estimates, however, may have been subject to information bias because of iatrotropic factors. It is difficult to explain the discrepancy in our results regarding parity. We tend to believe that the decreased incidence of atopic dermatitis with increasing parity in the first but not the second study reflects iatrotropic factors (parental anxiety is highest for the first child) rather than a real difference in incidence.

Physiology of dermatitis

Atopic dermatitis is somehow linked to a disturbance of the T lymphocyte system. We have previously provided experimental evidence that T lymphocytes in the skin of patients with atopic dermatitis differ in vitro from normal T cells in that they can show cytokine driven growth.[30 31] Our findings provide only circumstantial evidence for possible abnormal maturation of T cells as a central pathophysiological event leading to the development of atopic dermatitis. Our studies of continuous T cell lines established from the skin of patients with atopic dermatitis, however, may be indicators of abnormally mature or immature T lymphocytes.

T lymphocytes mature in the thymus, which contains epithelium from ectodermal tissue.[32] We suggest that a disturbance in the "communication" between epithelium in the thymus and maturing T lymphocytes could lead to an inadequate T lymphocyte selection in the thymus.[33] It is known from studies in mice that about 98% of all pro-T lymphocytes are removed in the thymus through positive or negative selection. We imagine that a defect in this selection process leads to the emission of too many T lymphocytes, which then collect in the skin. This disturbance could be graded so a near complete T lymphocyte selection would lead to mild atopic dermatitis of short duration whereas a more pronounced disturbance would lead to more severe and long lasting atopic dermatitis. The genetic defect could be associated with the ectodermal tissue. If such a genetically determined "ectodermal dysmaturation" is expressed in utero this could be a cause for prolonged gestation.

In conclusion, two studies of a cohort of 7862 single-born births provide evidence for an association between prolonged gestational age and later development of atopic dermatitis. There also seems to be an

Key messages

- This Danish study found that the cumulative incidence of atopic dermatitis at the age of 7 years was 18.7% in 1993
- Children born after term had a significantly increased risk of developing atopic dermatitis
- Children whose birth weight was high for their sex and gestational age also had an increased risk of developing atopic dermatitis
- These findings suggest that a genetically determined predisposition to developing atopic dermatitis is expressed in utero

independent association between "heavy for dates" children in all gestational age groups and atopic dermatitis in children with milder eczema. The causes for these associations, which point towards factors already changing gestation, are at present unknown.

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Conflict of interest: None.

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ONE HUNDRED YEARS AGO

The remuneration of the general practitioner

Sir,—In this Diamond Jubilee of rejoicing, when all sorts and conditions of men are comparing the differences, in the prosperity of all classes of Her Majesty's subjects, between her accession and now, very much to the advantage of the present time, we may very naturally ask ourselves, how has it fared with the general practitioner?

The condition of the working man—and I am mostly concerned with him as I live in his neighbourhood—is vastly improved as to hours of labour, wages, and cheapness of food; he has been relieved of taxation and the education of his children, facts which speak for themselves. Have the fees of the general practitioner risen in proportion, or his position socially improved? Can he make a decent living viewed in the light of the material advances in other classes of the population? I do not think so.

Medical education, like everything else, has marched with the times, and we have greater masters of the physician's and surgeon's art among us than ever before; and general practitioners are turned out better equipped to fight the demon disease; but alas, his fight for existence is ever becoming keener; fresh men start in his neighbourhood and undersell him, even undersell the chemist in the same street in order to gain a livelihood. The struggle is rendered even keener by the action of public dispensaries and hospitals, which give their services to the poor under the guise of charity, and do not blush to compete with the general practitioner.

I do not consider a hospital is a charity unless it gives its services to the poor without payment or reward, but general practitioners have not got a rich treasurer behind them on whom they can draw when their funds are exhausted, but have to plod on and pay rent and taxes, or, if not, become bankrupt; but the hospital may go on, get deeper into dept, and flourish to the disadvantage of the general practitioner. (*BMJ* 1897;ii:55.)

The vexed question of authorship: views of researchers in a British medical faculty

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Abstract

Objective: To assess knowledge, views, and behaviour of researchers on criteria for authorship and causes and control of gift authorship.
Design: Interview survey of stratified sample of researchers.
Setting: University medical faculty.
Subjects: 66 staff (94% response rate) comprising several levels of university academic and research appointments.
Main outcome measures: Awareness and use of criteria for authorship, views on which contributions to research merit authorship, perceptions about gift authorship and strategies for reducing it, and experiences of authorship problems.
Results: 50 (76%) respondents supported criteria for authorship, but few knew about or used available criteria. Of the five people who could specify all three criteria of the International Committee of Medical Journal Editors, only one knew that all criteria had to be met. Forty one respondents (62%) disagreed with this stipulation. A range of practical and academic contributions were seen as sufficient for authorship. Gift authorship was perceived as common, promoted by pressure to publish, to motivate research teams, and to maintain working relationships. A signed statement justifying authorship and a published statement of the contribution of each author were perceived as practical ways of tackling gift authorship. Most researchers had experienced problems with authorship, most commonly the perception that authorship had been deserved but not awarded (49%).
Conclusion: There seems to be a gap between editors' criteria for authorship and researchers' practice. Lack of awareness of criteria is only a partial explanation. Researchers give more weight than editors to practical research contributions. Future criteria should be agreed by researchers and not be imposed by editors.

Introduction

Publication is the key to academic success. In Britain peer reviewed scientific papers are the main determinant of a university's grading in the Higher Education Funding Council's research assessment exercise, which affects income. The pressure to publish is great, as is the temptation to coauthor papers without having made a substantial intellectual contribution ("gift authorship"), factors linked to fraud and misconduct in medical research.[1-3]

In 1985 the International Committee of Medical Journal Editors published criteria for authorship (see box) based on the principle that each author should be able to defend the work publicly.[3] These criteria have been accepted by over 300 journals but are often breached,[4 5] with Goodman's results suggesting that some authors may not fulfil any of the criteria.[5] These findings raise questions about awareness of the criteria and their appropriateness and acceptability to researchers. The idea of assessing researchers' views on authorship was identified and stimulated by the authorship subgroup of LOCKNET, an international network interested in the processes of publishing medical research.[6 7]

Criteria for authorship of the International Committee of Medical Journal Editors

Authorship should be based only on a substantial contribution to:
i Conception and design or analysis and interpretation of data *and*
ii Drafting the article or revising it critically for important intellectual content *and*
iii Final approval of the version to be published

Methods

The objectives of our study were:
- To assess whether researchers knew the criteria for authorship of the International Committee of Medical Journal Editors and, if so, whether they thought they were helpful
- To compare researchers' views on contributions meriting coauthorship with those of the committee, to understand why the guidelines are breached, and to propose criteria supported by researchers
- To ascertain researchers' current practice in relation to coauthorship of academic papers
- To seek views on how the teamwork that does not meet the committee's criteria should be credited
- To explore researchers' perceptions of good and bad practice in relation to coauthorship and on the prevalence and nature of gift authorship
- To assess views on proposed ways of curbing gift authorship.

The need to present our findings at an international conference on authorship[7] imposed strict deadlines for interviewing. We drew up a sample of 70 academic and research staff from the Faculty of Medicine as listed in the University of Newcastle's handbook for 1995-6. As heads of department may influence policy on authorship, we approached all 17 departmental heads designated by the university for interview. To ensure representation of staff with varying experience in publication, we stratified our sampling frame by seniority. A candidate's probability of selection, by random numbers, was proportional to the size of the stratum. We also identified reserves for each candidate.

We invited first choice candidates, by a letter from the dean of medicine and RB, for semistructured inter-

See editorial by Smith and p 1046

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Lois Thomas, *research associate*
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Eileen Kaner, *research associate*
Rosie Stacy, *lecturer in medical sociology*
Pauline Pearson, *lecturer in primary care nursing*
Brian Vernon, *lecturer in the ethics of health care*
Departments of Medicine and Epidemiology, School of Health Sciences, University of Newcastle
Helen Rodgers, *senior lecturer in stroke medicine*
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Table 1 Characteristics of 66 staff from a university medical faculty

Category	No (%) of respondents
Grade of staff:	
Heads of department	17 (26)
Professors, readers, and senior lecturers	19 (29)
Lecturers and senior research associates	10 (15)
Research associates, junior research associates, and demonstrators	20 (30)
Author of published papers:	
No papers	6 (9)
1-10 papers	15 (23)
11-30 papers	12 (18)
31-100 papers	20 (30)
>100 papers	13 (20)

Table 2 Attitudes of 66 staff from a university medical faculty toward criteria for authorship

Attitudes	No (%) of respondents
Believed there should be criteria	50 (76)
Aware of any explicit criteria	32 (49)
Have used any criteria	23 (35)
Heard of the International Committee of Medical Journal Editors	33 (50)
Aware of authorship criteria of International Committee of Medical Journal Editors	16 (24)

views addressing the above objectives. Interviewers, all authors of this paper, were allocated to interviewees of similar status. We conducted the interviews, scheduled for 30-40 minutes, between April and early June 1996.

JR and RS read the responses to open ended questions. They identified themes, developed a coding frame, and applied it to quantify these responses. For questions where respondents could make more than one comment, the number of comments is reported. Respondents were categorised according to grade at interview. We analysed the quantitative data with SPSS.[8] To examine the effect of seniority, we used the χ^2 test for categorical variables and Kruskall-Wallis analysis of variance for continuous variables.

Results

Nine of the first choice candidates were unavailable: five were no longer in post so reserves were interviewed. In the other four cases, there were difficulties in arranging interviews and no time to approach reserves. We therefore completed 66 interviews (94% response rate). Table 1 shows that the sample achieved a mix of staff and that most respondents had published papers, which was associated with seniority (Kruskall-Wallis $\chi^2 = 44.8$, df $= 3$, $P < 0.01$). The six subjects with no publications were junior researchers.

Table 3 Views of 66 staff from a university medical faculty on the criteria for authorship stipulated by the International Committee of Medical Journal Editors (values are numbers (percentages) of respondents)

Criterion	Agreement with criterion		
	Yes	No	Undecided or other
i Conception and design, or analysis and interpretation (n=66)	54 (82)	10 (15)	2 (3)
ii Drafting the article or revising it critically (n=65)	54 (83)	9 (14)	2 (3)
iii Final approval of version to be published (n=65)	55 (85)	7 (11)	3 (5)
All three criteria must be met (n=66)	20 (30)	41 (62)	5 (8)

Knowledge of criteria for authorship

Table 2 shows that, while most respondents thought that there should be criteria for authorship, only 16 were aware of the guidelines of the International Committee of Medical Journal Editors. Of these 16, four could not specify any of the criteria, one wrongly believing that they involved identifying the percentage input of authors, four specified one criterion, two specified two, and five specified all three. Only one person knew that all three criteria were necessary for authorship.

Views on the criteria

Most respondents agreed with each criterion individually but disagreed that all three should have to be met (table 3). A substantial minority misunderstood the first criterion, taking it to require contribution to all four aspects of a study. This was seen as restrictive and unfair, especially to junior staff. The second criterion was thought to be poorly defined and intellectually unsound. Practical barriers were mentioned in relation to the second and third criteria. Twenty comments indicated that the criteria were too restrictive and that greater flexibility was required. Specific reservations included concerns that they could exclude key players in a research team (nine comments) and that they were out of touch with the realities of modern research (four comments). Some respondents felt that in multidisciplinary research teams it was unreasonable to expect each author to defend every aspect of a paper.

Over half of the respondents thought the committee's criteria were not usually adhered to; 21 comments indicated no surprise. Ten comments indicated that breaching the criteria was wrong or unethical, but 15 comments suggested that non-compliance might reflect flaws in the guidelines and that researchers did not accept their authority. Bending the rules rather than deliberate breaching was said to be more likely (five comments). Difficulties in meeting all three of the criteria and the inevitability of breaching them were identified (11 comments), as were ignorance of the criteria and a perception of their irrelevance (four comments). In discussing why the guidelines might be breached, issues of power, status, and "nepotism" were recognised (22 comments). The pressure to publish was also cited (16 comments), and adding senior colleagues was a strategy for increasing the likelihood of publication (four comments). One respondent likened criteria for authorship to the speed limit on roads: "Good that it's there, but not necessarily adhered to." Others simply did not agree with them: "It's appropriate that they are [breached]," and, "I don't recognise their authority."

Views on grounds for authorship

Almost everyone thought that both major practical and intellectual contributions were definite or possible grounds for authorship (table 4). One research associate explained: "There needs to be a difference between intellectual contribution and the execution of work. You need to have made a contribution to one or the other but it may not be realistic to have both. The criteria seem to overlook the practical, doing the experiments. They seem to say if you have ideas you become an author, if you work in the laboratory 12 hours a day you don't get on. It should be teamwork." However, being head of a department, bringing in

additional money, providing access to research subjects, or preparing diagrams were rarely thought to deserve automatic authorship. Published acknowledgement was the appropriate credit for contributions not meriting authorship.

Views on gift authorship

Table 5 shows that most respondents thought that gift authorship, defined in the questionnaire as when people included as coauthors have not contributed significantly to the research, should be banned. The commonest reasons given for gift authorship were pressure to publish (25 comments), enhancing chances of publication (16 comments), to repay favours, to motivate a team and encourage collaboration (14 comments), and to maintain good relationships (14 comments). Gift authorship was seen as unethical, dishonest, and unacceptable (11 comments) reducing the paper's validity and diluting the input of those who had made major contributions (11 comments). Those who thought that gift authorship should not be banned believed that it aided collaboration (five comments) and that prohibition would be difficult to achieve (six comments). The respondents thought that requiring researchers to sign a statement justifying authorship and to specify the actual contribution of each author were practical and effective strategies for reducing gift authorship (table 5). Limiting the number of publications listed in a curriculum vitae or a system of fixed credits per publication[9] found less favour.

Experiences of authorship

Forty two (64%) respondents had experienced difficulties with authorship, the most common being exclusion from authorship when it was apparently deserved (table 6). Senior staff were more likely to have experienced problems ($\chi^2 = 15.0$, df = 3, $P = 0.001$ for any problems), reflecting that they had coauthored more papers (Kruskall-Wallis $\chi^2 = 44.8$, df = 3, $P < 0.01$). Almost a third of respondents had assigned inappropriate coauthorship. Problems with authorship were memorable and upsetting.

Discussion

While these results should be extrapolated cautiously, our medical school is not atypical and our findings are in accord with quantitative work in other centres and with much comment and analysis.[4 5 10] Our sample included researchers with widely varying seniority and experience of authorship and reflected the range of disciplines in a modern medical school. The high response rate and the frank responses testify that the respondents welcomed debate on authorship. The semistructured format of the interviews allowed for discussion of the responses.

While the researchers supported the idea of criteria for authorship, many did not adhere to those of the International Committee of Medical Journal Editors, partly because these did not fit with their values. Most respondents disagreed that all three of the committee's criteria should be met since this excluded researchers with important but limited roles. Gift authorship was perceived as an unacceptable and unethical practice that was common and difficult to prohibit. It was seen to be encouraged by academic reward systems.

Table 4 Views of 66 staff from a university medical faculty on whether specified contributions alone merited coauthorship of a paper (values are numbers (percentages) of respondents)

	Coauthorship merited		
Contribution	**Yes**	**Not sure**	**No**
Providing statistical advice on ongoing basis	61 (92)	2 (3)	3 (5)
Designing the study	58 (88)	3 (5)	5 (8)
Conceiving the research idea	47 (71)	10 (15)	9 (14)
Collecting data	32 (49)	14 (21)	20 (30)
Obtaining the research grant*	30 (46)	9 (14)	26 (39)
Conducting the literature review	24 (36)	8 (12)	34 (52)
Being head of a research group*	23 (35)	4 (6)	37 (56)
Writing computer programs*	22 (33)	22 (33)	21 (32)
Validating data*	12 (18)	19 (29)	34 (52)
Obtaining additional funding	9 (14)	15 (23)	42 (64)
Providing access to research subjects*	8 (12)	10 (15)	46 (70)
Providing statistical advice on ad hoc basis*	6 (9)	13 (20)	46 (70)
Entering data	5 (8)	10 (15)	51 (77)
Preparing diagrams	4 (6)	6 (9)	56 (85)
Providing access to specialist equipment*	2 (3)	5 (8)	58 (88)
Being head of department	1 (2)	2 (3)	63 (95)
Formatting and proofreading paper	1 (2)	8 (12)	57 (86)

*Missing values.

There has long been concern about multiple and unearned authorship. In 1957 Hewitt noted increasing multiple authorship and argued that bestowing unearned authorship was no favour. The second of his 10 commandments for writing is, "Thou shalt not allow thy name to appear as a co-author unless thou hast

Table 5 Views of 66 staff from a university medical faculty on gift authorship and its control (values are numbers (percentages) of respondents)

Statement	**Agreement with statement**
Gift authorship is a problem (n=64)	44 (69)
Perceived prevalence of gift authorship (n=64):	
Very common	18 (28)
Fairly common	24 (38)
Infrequent	10 (16)
Rare	2 (3)
No idea how common	10 (16)
Gift authorship should be banned (n=60)	37 (62)
Practical strategy for reducing gift authorship:	
Signed statement of justification for being an author (n=66)	36 (55)
Statement in publication specifying contributions (n=64)	36 (56)
Limiting number of publications in curriculum vitae (n=63)	25 (40)
System of fixed credits to be shared by authors (n=61)	14 (23)
Most effective strategy for reducing gift authorship (n=60):	
Signed statement of justification for being an author	24 (40)
Statement in publication specifying contributions	24 (40)
System of fixed credits to be shared by authors	10 (17)
Limiting number of publications in curriculum vitae	2 (3)

Table 6 Experiences of 66 staff from a university medical faculty on aspects of authorship

Experience	**No (%) of respondents**
Assigned authorship (n=65)	54 (83)
Any problems with authorship (n=66)	42 (64)
Not included when authorship felt to be deserved (n=66)	32 (48)
Included when contribution did not merit authorship (n=65)	25 (38)
Not aware of being named as an author (n=66)	21 (32)
Assigned inappropriate coauthorship (n=53)	16 (30)
Perception of incorrect placing in authorship order (n=66)	15 (23)

some authoritative knowledge of the subject concerned, hast participated in the underlying investigation, and hast laboured on the report to the extent of weighing every word and quantity therein."[11] This principle is echoed by other writers in the phrases "significant contribution," "intellectual input," and "public responsibility." In 1982 Burman observed no correlation between the number of authors and citation and called for criteria for authorship.[12] He recommended that order be based on contribution, with the head of the laboratory as the last author. The practice of heads of laboratories and departments being coauthors of all papers from their units is now unacceptable.

The criteria of the International Committee of Medical Journal Editors, therefore, were developed on the basis of debated principles, in response to increasing concerns about gift authorship and fraud in science. They have been widely published, but in our study many researchers were unaware of the criteria, tended to misunderstand them, and perceived them as open to misinterpretation. This is partially understandable because, while the criteria are unequivocal, the discussions interpreting them are not. For example, Huth develops the argument for the criteria by emphasising that public responsibility for the content, including intellectual content, is the key to authorship.[13] While technical work, referral of patients, and collection of data alone do not justify authorship, development of the hypothesis, design of the study, and analysis of results may. The detailed discussion contradicts the criteria also given in his text (pages 229 and 44), showing that the criteria alone do not cover adequately a complex matter. Huth's discussion is closer to the views of researchers than the criteria.

Criteria for authorship need to accord more with researchers' values, particularly giving more weight to important practical contributions, which nearly all guidelines consider unworthy of authorship. Researchers views were similar to those of Staheli, who noted that substantial contribution is the key, that excluding key contributors is unethical, and that coauthors include those whose ideas started the study and those who gathered data.[14]

Problems not addressed by the current guidelines of the International Committee of Medical Journal Editors include ordering of authors and failure to gain authorship when deserved. Most writers on authorship agree that the first author is the one most closely associated with the work. The special status of the last author is recognised by several writers, but the general view is that the order of authors should reflect the rank order of contribution. The Council of Biology Editors recommends each journal specify the criteria for order of authorship.

Our data should help researchers and editors develop a shared understanding. The strategy for communicating and implementing the criteria of the International Committee of Medical Journal Editors has largely failed. New initiatives should engage researchers and meet their legitimate needs. Future guidelines should be developed collaboratively and not be imposed on researchers by editors.

We thank the respondents for being so frank; Professor George Alberti, Dean of Medicine, for support; Dr Richard Smith for calling for the study; Drs Nigel Unwin, Neville Goodman, and other colleagues in the authorship subgroup of LOCKNET for ideas; an anonymous referee whose comments reshaped the paper; and Pat Barkes and Suzanne Young for secretarial support. The order of the authors reflects peer group views on overall academic and practical contribution to this paper and is therefore rank order. The questionnaire is available from JR.

Conflict of interest: RB was the convenor of the authorship subgroup of LOCKNET.

Funding: Resources were provided by the three departments of the School of Health Sciences of the Medical School.

Key messages

- We assessed the views of 66 medical researchers on criteria for authorship and gift authorship
- There was lack of awareness of the criteria for authorship stipulated by the International Committee of Medical Journal Editors
- While the concept of criteria for authorship was supported, current criteria were not adhered to, partly because they did not accord with researchers' values
- Gift authorship was perceived as a common problem encouraged by the systems for evaluating research and developing careers
- Future criteria should be agreed by researchers and editors and should give weight to important practical contributions to research

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Correction

Lifetime socioeconomic position and mortality: prospective observational study

An editorial and an authors' error occurred in this paper by George Davey Smith and colleagues (22 February, pp 547-52). In the abstract the penultimate sentence of the results paragraph should have read: "Fathers having a manual [not non-manual, as published] occupation was strongly associated with mortality from cardiovascular disease: relative rate 1.41 (1.15 to 1.72)." The legend of table 3 should have read: "Age adjusted death rates (per 10 000 person years [not 1000 person years, as published]) over 21 years of follow up according to cumulative social class."

H_2 blockers in the intensive care unit: ignoring the evidence? Telephone survey

D L A Wyncoll, P C Roberts, R J Beale, A McLuckie

Stress ulcers are gastroduodenal erosions that occur commonly in critically ill patients. Although once thought to be due to excess acid production, they are now thought to result from gastric mucosal ischaemia and the value of using pH altering drugs to prevent them has been questioned.[1] Cook *et al* showed that only critically ill patients who have a coagulopathy or who are ventilated for more than 48 hours are at increased risk of developing serious bleeding due to stress ulceration.[2] Prophylaxis is usually with either an H_2 receptor antagonist or sucralfate, and these agents appear equally efficacious in terms of reducing bleeding complications.[3] A recent meta-analysis has, however, shown that sucralfate is associated with a lower incidence of pneumonia and mortality than H_2 receptor antagonists.[4] In spite of this, patients referred to Guy's from other intensive care units have often received H_2 receptor antagonists for prophylaxis, and this survey was undertaken to quantify the extent of this practice.

Methods and results

In March 1996 we performed a structured telephone survey of 67 intensive care units in the Thames regions. If respondents were too busy to provide accurate information a repeat call was made. Four questions were put to the senior nurse or doctor in charge: (1) Does your intensive care unit have a protocol for stress ulcer prophylaxis? (2) Which agent is used most commonly for prophylaxis in your unit? (3) How many patients are there in your unit today? (4) How many of these patients are receiving sucralfate, an H_2 receptor antagonist, omeprazole, no prophylaxis?

On the day of the audit 312 patients were in the 67 units: 118 (38%) patients were receiving an H_2 receptor antagonist, 82 (26%) sucralfate, 3 (1%) omeprazole, and 110 (35%) no prophylaxis (one patient was receiving both sucralfate and an H_2 receptor antagonist.) The 28 units that had a protocol for stress ulceration prophylaxis were more likely to prefer sucralfate to H_2 receptor antagonists than those without a protocol, as were the 13 teaching hospitals (table1).

Table 1 Reported usage of stress ulcer prophylaxis agents. Values are numbers (percentages) of intensive care units using each agent

Intensive care units	H_2 receptor antagonists	Sucralfate	Equal use of both agents	X^2
Protocol (n = 28)	9 (32)	19 (68)	0	8.89 (P<0.01)
No protocol (n = 39)	22 (56)	9 (23)	8 (21)	
Teaching hospital (n = 13)	3 (23)	10 (77)	0	5.8 (P<0.02)
District hospital (n = 54)	28 (52)	18 (33)	8 (15)	

Comment

Serious bleeding due to stress ulceration is defined as a drop in haemoglobin of greater than 20 g/1 accompanied by either haemodynamic instability or the need for blood transfusion.[2] Although the incidence of bleeding is declining, it is associated with a mortality approaching 50%. This reduction may be due to pharmacological prophylaxis, but other factors such as improved resuscitation and early enteral nutrition are likely to be equally important.

Several adverse effects have been linked to the use of H_2 receptor antagonists in intensive care units, particularly an increased incidence of nosocomial pneumonia, which is associated with a mortality of 40-70% in critically ill patients.[5] By raising intragastric pH, H_2 receptor antagonists promote bacterial colonisation and overgrowth within the stomach, and hence provide a potential reservoir of infection for the respiratory tract. Sucralfate does not raise intragastric pH but enhances mucosal blood flow, stimulates bicarbonate and mucous secretion, and may be bactericidal.

Our survey shows that many intensive care units, particularly those in district hospitals and those without a protocol for stress ulcer prophylaxis, continue to use H_2 receptor antagonists in preference to sucralfate. Given the known detrimental effects of H_2 receptor antagonists, it is disappointing that their use is so prevalent. If the principles of evidence based medicine were followed this would no longer be so, and the morbidity and mortality of critically ill patients might be reduced.

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