ORIGINAL ARTICLES

Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood

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Abstract

Background—Apart from heredity, several early life environmental factors are implicated in the development of childhood asthma. Maternal smoking is believed to increase asthmatic symptoms but its influence on the development of allergen sensitisation is debatable.

Study design—A whole population birth cohort was reviewed at ages 1, 2, and 4 years. Of 1218 children seen at 4 years, 981 (80.5%) were skin prick tested with a battery of common food and aeroallergens. Smoking history was recorded at birth and updated at each follow up and its impact on the development of asthma and allergen sensitisation in the children was assessed.

Results—Two hundred and fifty mothers smoked during pregnancy (20.5%) and 307 (25.2%) after childbirth. Maternal smoking in pregnancy was associated with low birth weight (mean (SD): 3.3 (0.5) v 3.5 (0.5) kg; $p < 0.001$). Smoking mothers were more often from lower social classes (31.8% v 16%, $p < 0.001$) and they breast fed their babies for a shorter duration (8.5 (11.4) v 16.6 (15.2) weeks; $p < 0.001$). The difference in breast feeding duration was partly due to a higher proportion of smoking mothers who never breast fed their babies. Although at age 2 years asthmatic symptoms were associated with exposure to maternal tobacco smoke (odds ratio 2.2, 95% confidence interval 1.5 to 3.4; $p < 0.001$), this association was lost by 4 years. However, maternal smoking was a significant risk factor in a subgroup of children with asthmatic symptoms but negative skin prick test. Maternal smoking did not increase allergen sensitisation at age 4 years. No effect of paternal smoking on asthma was observed in the children.

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Keywords: maternal smoking; asthma; allergen sensitisation

Maternal smoking in pregnancy may increase fetal IgE production^{1,2} and early life respiratory infections.³ Its effect on respiratory symptoms in early childhood could in part be through inhibition of fetal (lung) growth during the last trimester.^{4,5} An additional effect of passive smoking after birth on the development of asthma and atopy remains unclear. Martinez *et*

al reported that children of mothers smoking >10 cigarettes/day were 2.5 times more likely (95% confidence interval (CI) 1.42 to 4.59) to develop asthmatic symptoms and had reduced maximal mid-expiratory flow.⁶ An Italian cohort study of preadolescent children reported a high rate of skin prick test conversion from negative to positive among boys exposed to parental smoking (boys 32%, girls 6%; $p = 0.04$).⁷ A study of allergen avoidance in 120 high risk infants in the Isle of Wight showed a marginally increased risk of physician assessed eczema and food intolerance but not asthma in those whose mothers smoked.⁸ No association of parental smoking with atopic symptoms in infancy was found in a feeding trial of 468 children in South Wales.⁹ Zeiger *et al* followed 165 high risk children to age 7 years as part of a dietary intervention study.¹⁰ There was a significantly higher prevalence of aeroallergen sensitisation (odds ratio (OR) 2.9, 95% CI 1.1 to 7.7) but not asthma among the children who were regularly exposed to smoking at home.¹⁰

These studies give mixed results as to the effect of exposure to environmental tobacco smoke on the development of respiratory allergic symptoms and allergen sensitisation in children. A recent meta-analysis concluded that maternal smoking during pregnancy or parental smoking during early childhood is unlikely to increase the risk of allergic sensitisation.¹¹ It is difficult to dissociate the influences of maternal smoking in pregnancy from those of smoking after delivery as most mothers who smoke while pregnant continue their habit after childbirth.³ On the other hand, many women quit smoking for pregnancy and resume after childbirth. In the developed countries maternal smoking is more prevalent among lower social classes.^{12,13} Smoking in pregnancy has been linked to low birth weight and an increased risk of perinatal complications including stillbirth.^{14,15}

Confounding factors such as the association of smoking with reduced production of breast milk and early introduction to a milk formula^{16,17} make valid estimation of the independent effect of maternal smoking very difficult. This report, based on the results of the four year follow up of the Isle of Wight whole population birth cohort, attempts to address the issue of the influence of environmental tobacco smoke on the development of asthmatic symptoms and allergen sensitisation during early childhood.

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Subjects and methods

STUDY POPULATION

After approval of the local research ethics committee, a whole population birth cohort was recruited to study the effect of hereditary and environmental factors on the development of allergic disorders. Between January 1989 and February 1990, 1536 consecutive births were recorded over the whole of the Isle of Wight. The mothers of all the newborn infants were approached prenatally and written informed consent obtained. After excluding perinatal deaths, adoptions, refusals and moves off the island, 1456 babies were available for follow up. The findings at birth and at the ages of 1, 2, and 4 years have been reported.^{12 18–20} At birth, cord serum total IgE was measured in a majority by using an enzyme immunoassay (EIA ULTRA(r), Pharmacia Diagnostics AB, Uppsala, Sweden). At age 4 years, 1218 children were reviewed; cord IgE concentrations were available in 1064 of them. The proportion of children with a positive family history of atopy was comparable for those seen at 4 years and those (n=227) lost to follow up (58.5% *v* 57.1%).

METHODS

The history of atopic disease in the immediate family was taken at birth of the child. Information on tobacco smoking by mother (during pregnancy and later), father, or any other individual inside the house was recorded at recruitment and updated at each follow up. Information on the presence of pets inside the house was obtained. Socioeconomic classes were assigned according to the Registrar General's classification. Details of the occupation of parents were obtained from hospital maternity records. The children were classified by their father's occupation. The mother's occupation was coded if she was a single parent or if her husband was unemployed and she was employed. To assess the effect of social class, classes 1, 2, and 3 were grouped together to form the higher socioeconomic group (professional and skilled workers) and classes 4 and 5 as the lower socioeconomic group (semiskilled, unskilled, and unemployed). These definitions for the socioeconomic groups are the same as those employed at previous follow ups.^{12 18}

At age 4 years, details of environmental factors such as social class, parental smoking, frequent exposure to pets (cat, dog, rodents, birds) at home and elsewhere, housing conditions, number of siblings, position in sibship, and intercurrent illnesses were updated. Data on social class were available for 723 of 1218 children seen at age 4 years.

Skin prick tests

At ages 1 and 2 years, only those manifesting features of allergic disorders were skin prick tested.^{12 18} In contrast, at age 4 years, every child was offered a skin prick test. Eventually, 981 (80.3%) had a skin test with a standard battery of aeroallergens (house dust mite (*Der-matophagoides pteronyssinus*), grass pollen mix, cat and dog epithelia, *Alternaria alternata*, and *Cladosporium herbarum*) and food allergens

(milk, egg, soya, cod, wheat, and peanut), and, as indicated, other allergens were added. Histamine (0.1%) in phosphate buffered saline and physiological saline (0.9%) were used as positive and negative controls respectively. All extracts were from Biodiagnostics, Allergopharma, Germany, except soya which was from ALK, Denmark. The test results were read after 15 minutes, and mean weal diameter (the sum of the longest diameter and the diameter perpendicular to it divided by two) at least 3 mm greater than that with the negative control was taken as a positive result. The methods for assessing weal diameter and the cut off level of 3 mm greater than the negative control for a positive reaction are in line with the current skin prick test recommendations.²¹

Diagnostic criteria for atopic disease

To maintain consistency, the diagnostic criteria were the same as those used in previous reviews. Briefly, a diagnosis of asthma required at least three separate episodes of wheeze per year, each lasting three or more days; eczema constituted recurrent, scaly, pruritic, erythematous rash in a typical distribution lasting more than six weeks; and rhinitis required at least two of three nasal symptoms of discharge, blockage, and recurrent sneezing accompanied by eye symptoms. For asthma, due consideration was given to the presence of typical diurnal variation and to a response to bronchodilator medication. A history of skin rash, respiratory or abdominal symptoms within four hours of ingestion of a particular food on two or more occasions was taken as food allergy.

Statistical analysis

Data was entered into a computer file (SPSS PC+ V4, Chicago, USA); χ^2 with Yates's correction was used to analyse the differences between proportions. For contingency tables with fewer than 10 cases in any cell, Fisher's exact test was used. Group differences in variables exhibiting a continuous distribution were studied by the non-parametric Mann-Whitney U test. Multivariate analysis was performed by stepwise logistic regression. The adjusted OR and 95% CI were calculated for an independent effect of risk factors on the development of atopy.

The controls for logistic regression analysis were:

Hereditary and developmental factors—these were family history: no atopy in first degree relatives; sex: female; cord blood IgE: <0.5 ku/l; and birth weight: normal (>2500 g).

Environmental factors—smoking: no maternal smoking; pets: no cat or dog in the house; season of birth: spring or summer birth; and method of feeding: exclusive breast feeding for at least three months.

Any other risk factor was studied by substituting it in the model for the relevant factor listed above. For example, the effect of maternal atopy was studied by replacing family history of atopy with maternal history. For any association to be taken as statistically significant an estimated two tailed probability (p) value of <0.05 was accepted.

Figure 1 The proportion of children reviewed at age 4 years who were exposed to tobacco smoking by parents and others at home. Mother, pregnancy: the proportion of children whose mothers smoked during pregnancy. Mother, later: the proportion of children who were exposed to maternal smoking after birth (irrespective of maternal smoking during pregnancy). Father: the proportion of children who were exposed to paternal smoking. Both parents: the proportion of children who had both smoking parents. Others: the proportion of children exposed to smoking by individuals other than their parents at home. Total: the total number of children with any recorded exposure to environmental tobacco smoke after birth (includes smoking by one or both parents and/or other individuals at home).

Results

All individuals smoking more than one cigarette per day on a regular basis were taken as smokers. Smoking by an individual was not considered if it was outdoors only. Figure 1 illustrates the prevalence of smoking among the parents and other individuals. One hundred and ninety two mothers (15.8%) who smoked during pregnancy continued their habit after childbirth. More than a third ($n=465$, 38.2%) of the children seen at age 4 years had been exposed for a length of time after birth to tobacco smoke (fig 1). There was no sex difference in terms of exposure to tobacco smoke at home (53.1% boys, 46.9% girls; not significant), and 350 (28.7%) children had been exposed continually from birth to age 4 years. The recorded number of cigarettes smoked in the house ranged from 1 to 60 with a mean (SD) of 14.4 (10.1) per day. A positive family history of atopy had no bearing on passive smoking among the children as 36.3% children

of atopic families compared with 39.9% children of non-atopic families were exposed to environmental tobacco smoke (not significant). Furthermore, exposure to tobacco smoke was similar among those given skin prick tests at 4 years ($n=981$) and those not skin tested (25% and 26.2% respectively).

Two hundred and sixty nine children had exposure to maternal tobacco smoke during the first six months of life. By age 4 years respiratory allergy was similar among these children to those ($n=38$) who became exposed to maternal smoking after the first six months of life (18.9% v 17.2%).

The relationship of maternal smoking in pregnancy to the findings at birth is described in table 1. Although there was no difference in gestational age, babies born to mothers who smoked during pregnancy had a lower mean birth weight. By age 4 years, the mean height and weight of children born to mothers who smoked during pregnancy was comparable to the mean height and weight of those born to non-smoking mothers (103.9 v 103.5 cm, and 17.5 versus 17.6 kg respectively; both non-significant).¹⁹ Smoking in pregnancy had no effect on cord serum IgE at birth. A possible effect of maternal smoking on crown-to-heel length and head circumference at birth could not be ascertained as data on these fetal growth parameters were not available.

Table 2 shows the relationship of maternal smoking after birth to infant feeding and social class. Maternal smoking was significantly more prevalent among mothers from the lower socioeconomic group. Smoking mothers breast fed their babies for a shorter duration than the non-smoking mothers and they introduced formula milk significantly earlier. The difference in mean breast feeding duration was to some extent due to a higher proportion of smoking mothers who never breast fed their babies. There was, however, no difference in the mean age for introduction to solids (table 2).

Table 3 highlights the lack of association between maternal smoking and the development of respiratory allergic disorders by age 4 years. An inverse association of maternal smoking in pregnancy and/or after childbirth was seen with aeroallergen sensitisation at 4 years. The mean age at the onset of asthmatic symptoms was similar among children whose mothers smoked and those who had non-smoking mothers (18.0 (13.7) v 21.3 (13.9) months, not significant). At age 4 years questions were asked regarding frequency and treatment of asthmatic symptoms. Wheeze and cough were divided into three categories: (1) fewer than three episodes in a year, (2) three to 10 episodes, and (3) frequent (more than 10) episodes. Presence of nocturnal symptoms and exercise induced wheezing were also recorded. Details of asthma treatment included episodic or regular use of bronchodilators, sodium cromoglycate and inhaled or oral corticosteroid. The proportion of asthmatic children with frequent wheeze and/or cough was similar in the group ($n=48$) exposed to maternal tobacco smoke and the group ($n=133$) whose mothers

Table 1 The relationship of maternal smoking during pregnancy to features at birth; values are mean (SD)

	Maternal smoking in pregnancy		p Value
	Yes (n=250)	No (n=968)	
Gestational age (weeks)	39.8 (1.8)	39.9 (1.4)	NS
Birth weight (g)	3290 (500)	3500 (500)	<0.001
Cord IgE (ku/l, n=1064)	0.29 (0.7)	0.32 (0.9)	NS

Mann-Whitney U test; NS = not significant.

Table 2 The relationship of maternal smoking (after childbirth) with infant feeding and social class; values are mean (SD) except where stated otherwise

	Maternal smoking		p Value
	Yes (n=307)	No (n=911)	
Duration of breast feeding (weeks)*	8.5 (11.4)	16.6 (15.2)	<0.001
Proportion of babies never breast fed† (%)	31.6	23.8	<0.01
Age at introduction to formula (weeks)*	6.6 (9.1)	11.8 (11.5)	<0.001
Age at introduction to solids*	13.6 (4.5)	14.9 (4.8)	NS
Lower socioeconomic group‡ (%)	31.8	16.0	<0.001

*Mann-Whitney U test; NS = not significant.

† χ^2 test with Yates's correction.

‡Social classes 4 and 5 according to the Registrar General's classification.

Table 3 Lack of association of maternal smoking with respiratory allergic symptoms and aeroallergen sensitisation at the age of 4 years; values are %

	Maternal smoking		
	In pregnancy (n=250)	After childbirth (n=307)	Any* (n=365)
Asthma			
Yes = 181	24.3	26.5	33.1
No = 1037	19.9	25.0	29.4
Rhinitis			
Yes = 65	21.5	23.1	26.2
No = 1153	20.5	25.3	30.2
Any respiratory symptoms			
Yes = 218	24.8	27.1	33.0
No = 1000	19.6	24.8	29.3
Aeroallergen sensitisation			
Yes = 190	15.3	18.5	21.2
No = 791	21.1	26.5	31.4†

*Any = maternal smoking during pregnancy and/or later.
 χ^2 with Yates's correction.
 †p<0.05.

did not smoke (50% *v* 57.9%, not significant). Eleven of the 48 (22.9%) asthmatic children exposed to maternal smoking had received treatment for asthma compared with 25 of 133 (18.8%) whose mothers were non-smokers (not significant). Similarly, there was no difference between the two groups regarding treatment with anti-inflammatory (corticosteroid, sodium cromoglycate) drugs (seven of 37 (18.9%) *v* 29 of 105 (27.6%), not significant). Nocturnal asthmatic symptoms (39 of 48 (81.3%) *v* 89 of 133 (66.9%)) and wheezing on exertion (three of 48 (6.3%) *v* 1 of 133 (0.8%)) seemed more common in asthmatics exposed to maternal smoking but these differences did not achieve statistical significance.

A strong association between maternal smoking and asthmatic wheeze was observed at ages 1 and 2 years but not at 4 years (table 4).^{12, 18–20} This effect was primarily due to the effect of maternal smoking on non-atopic wheeze. Non-atopic asthmatics were more often exposed to maternal smoking (35.9% *v* 9.7%, *p*<0.05). This was not a predetermined effect as the prevalence of parental smoking was similar among atopic and non-atopic families (36.7% *v* 40%, not significant). Only non-atopic asthma was associated with low (<2500 g) birth weight (8.9% *v* 0%, *p*<0.02). The proportion of children with atopy (positive skin test), among those with asthmatic wheeze, increased as they grew older (1: year 28/93 (30%), 2: years 24/73 (33%), and 3 years: 71/161 (44%)).

No effect of paternal smoking on the prevalence of respiratory allergic symptoms was observed at any age. At 4 years 18.4% of chil-

dren exposed to tobacco smoke from the father had respiratory allergic symptoms compared with 17.7% of those whose fathers did not smoke (not significant). A similar proportion (17.8%) of children who had no recorded exposure to tobacco smoke till age 4 years, also had respiratory allergic symptoms. In addition, paternal smoking had no influence on allergen sensitisation (paternal smoking *v* no paternal smoking: 17.2% *v* 20.5%, not significant) among the children.

A subgroup of mothers did not smoke during pregnancy but started smoking after the birth of their child (*n*=115). The prevalence of symptoms suggestive of asthma (13.9% *v* 14.2%) and rhinitis (2.6% *v* 5.6%) at 4 years was similar in the children of these mothers to the control group whose mothers had never smoked.

The level of passive exposure to tobacco smoke based on the total number of cigarettes smoked indoors per day did not show a dose-response effect. Asthmatic wheeze was recorded in 18.3% of children with current environmental tobacco smoke exposure of five or fewer cigarettes/day (*n*=128). The corresponding figure for those exposed to greater than 20 cigarettes per day (*n*=176) was 17.1%. Likewise, there was no difference between these subgroups in the proportion who had positive skin prick test responses (18.7% *v* 14.0% respectively, not significant).

Discussion

It has long been recognised that atopy runs in families and this is likely to be due to genetic predisposition.^{18, 22} However, a host of environmental factors may modulate the phenotypical expression of the allergic risk. Active smoking is known to act as an adjuvant towards sensitisation to occupational allergens even in individuals who are otherwise non-atopic.^{23, 24} Zetterstrom *et al* showed that total IgE concentrations increased significantly in rats exposed to tobacco smoke.²⁵ A similar effect has also been described in man.²⁶ More recently Ronchetti and colleagues reported increased allergen sensitisation among preadolescent boys exposed to parental tobacco smoke.⁷ The Isle of Wight study, however, did not confirm their findings. This may in part be due to the fact that Ronchetti *et al* used a complex grading system for the interpretation of skin prick tests. Furthermore, they had included some active smokers in the study population.⁷

In this study salivary or urinary cotinine levels were not measured to corroborate the history of parental smoking obtained at each follow up. This might have influenced the results as there is a tendency to under-report the average number of cigarettes smoked per day. None the less, similar prevalences of maternal smoking, whether assessed by questionnaire or by maternal urinary cotinine concentrations, have been reported previously, suggesting that possible bias due to reliance on smoking history is unlikely.²⁷

As more mothers than the fathers were interviewed, the smoking habit of the fathers

Table 4 Effect of maternal smoking* on asthmatic symptoms among the children at age 1, 2, and 4 years—logistic regression analysis; values are adjusted OR (95% CI)

	1 year	2 years	4 years
Asthma			
Total	2.5 (1.7 to 3.7)#	2.2 (1.5 to 3.4)#	1.2 (0.3 to 2.7)
Atopic	1.3 (0.6 to 2.2)	1.1 (0.5 to 2.0)	1.0 (0.3 to 1.8)
Non-atopic	2.0 (1.3 to 3.0)‡	1.6 (0.9 to 2.4)	1.4 (0.6 to 2.1)
Any atopy	1.5 (1.1 to 2.0)‡	1.3 (1.0 to 1.9)†	1.1 (0.6 to 1.6)

*As at each follow up.

†p<0.05, ‡p<0.001, #p<0.001.

Atopic asthma: asthma with positive skin prick test. Non-atopic asthma: asthma with negative skin prick test.

could have been underestimated. If so, it would explain the lack of effect of paternal smoking on respiratory symptoms of the subjects at each follow up. It is more likely, however, that the association between respiratory symptoms in children and maternal smoking reflects a more intimate contact between the mother and the child. Furthermore, fathers perhaps more often smoke outdoors or away from home compared with the mothers.

Maternal smoking was a significant risk factor for asthma at previous follow ups.¹²⁻¹⁸ This risk for children of smoking mothers declined from 2.5-fold at age 1 year to 1.2-fold at 4 years (table 4). In contrast, no association between maternal smoking and sensitisation to common allergens was observed at any age.¹²⁻¹⁸ By age 4 years, the association of maternal smoking with asthma in the children was lost, with many early life wheezers "outgrowing" their wheeze.²⁰ As maternal smoking during pregnancy was associated with low birth weight, it is possible that early life wheezing in children of smoking mothers may partly be due to relatively small airways. This hypothesis is supported by the observation that babies exposed to maternal tobacco smoke during pregnancy have increased levels of airway resistance at birth as assessed by maximal expiratory flow at functional residual capacity measurements.⁴⁻⁵ Hence it seems plausible that some low birthweight children born to smoking mothers in this cohort lost their wheeze by age 4 years as their lungs and airways matured through catch-up growth.

Another possible reason for more wheeze in children of smoking mothers during the first two years of life could be a higher risk of respiratory infection. This effect has been suggested by several studies.¹³⁻²⁷ A recent meta-analysis reported a pooled adjusted OR for lower respiratory illness in infancy and early childhood of 1.72 (CI 1.55 to 1.91) if the mother was a smoker.²⁸ In infancy maternal smoking has been linked to the sudden infant death syndrome and to acute bronchiolitis with or without confirmation of respiratory syncytial virus infection.²⁹⁻³⁰ In one study, infants admitted with suspected bronchiolitis were almost three times more likely to have a smoky atmosphere recorded by health visitors at 1 month of age (OR 2.93, CI 1.95 to 4.41).³⁰ It is thus possible that the increased incidence of episodic wheeze and cough in infants exposed to environmental tobacco smoke could in part be due to more frequent and/or severe respiratory infections.

Early in life a child is intimately close to the mother and they virtually share the same environment. By age 4 years one would expect the child to have his or her own bedroom and to spend much less time in close proximity to the mother, resulting in a reduced level of exposure to maternal tobacco smoke. A large American study reported a fall in the odds ratio for current wheeze from 1.9 among infants to 1.07 among teenagers.³¹ The results of this study show the same trend, with maternal smoking being a significant risk factor for asthmatic symptoms at 1 and 2 but not at 4 years.

Although maternal smoking had no effect on respiratory allergic symptoms at 4 years, there was a link between a subgroup of "non-atopic" asthmatic subjects (those with a negative skin prick test response) and maternal smoking.²⁰ At the age of 4 years, this discernible effect of maternal smoking, which is independent of atopic sensitisation, is likely to be due to the associations discussed above. Studies have shown a higher prevalence of childhood asthma among lower socioeconomic classes.¹⁸⁻³¹ This study found that among the 4 year olds, only "non-atopic asthma" was predictably associated with lower socioeconomic group. Furthermore, there was no statistically significant effect of maternal tobacco smoking on various historical indices of the frequency and severity of asthmatic symptoms.

A majority of smoking mothers smoked during pregnancy as well as afterwards. Hence it is difficult to separate the possible in utero effects of maternal smoking from those of smoking after birth. However, no increase in respiratory symptoms was seen among children whose mothers took up smoking only after childbirth. Furthermore, all low birthweight babies (<2500 g) were born to mothers who smoked during pregnancy. These observations suggest a greater impact of maternal smoking during pregnancy.

It is difficult to separate the effect of maternal smoking from that of other early life and social factors. Maternal smoking is more prevalent in lower social classes and so is childhood asthma.⁶⁻¹⁸ Smoking mothers breast feed their babies for a shorter duration.¹⁷⁻²⁰ There may also be differences in family size, sharing of bedroom with siblings, exposure to household pets, and a host of other factors. The potentially deleterious associations of maternal smoking with low birth weight, perinatal morbidity, sudden infant death syndrome, and increased respiratory infections through infancy and early childhood cannot be ignored and clear advice to quit smoking should be given to all expectant and new mothers. However, on the basis of our study there is no evidence that maternal smoking influences the development of respiratory allergic disease or aeroallergen sensitisation at 4 years of age.

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Medical Anniversary

Thomas Forrest Cotton, 4 November 1884

Thomas Forrest Cotton (1884–1965) was born in Quebec and qualified from McGill University in 1909. He trained as a cardiologist with Sir Thomas Lewis at University College Hospital and became a physician at the National Heart Hospital in 1924. He admired his fellow Canadian Sir William Osler so much that he gave a most generous benefaction to the Royal College of Physicians to name the Osler Room there. Readers attending dinners at the college will see his portrait as they enter the Osler Room. He died on 26 July 1965.

—D G James