### **WILLIAM PICKLES LECTURE 1983**

## Quantity, quality and controversy

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#### **William Pickles**

THE William Pickles Lecture was established to commemorate the life and works of William Pickles, general practitioner, epidemiologist and first President of this College.

Future Pickles lecturers will be as indebted as I am to his biographer, John Pemberton, for a picture of a man whose warmth, humanity and facility for friendship illuminated a life of dedication to the population of a beautiful Yorkshire dale but one which also included major contributions to the study of the epidemiology of communicable disease and the establishment of general practice and social medicine as academic disciplines. In the context of my subject, readers of John Pemberton's book will recognize Pickles as one of the initiators of vocational and continuing education for general practice. Many will admire the encouragement and support provided by his partner during the 1930s which allowed Pickles to spend a month of each year on refresher courses at a variety of hospitals. Those who believe that membership of our own College comes too soon in a professional career will be encouraged by the fact that he did not achieve his ambition of becoming an MRCP until 30 years after graduation.

Pickles' sabbatical periods enabled him to keep abreast of the clinical developments of the time and it

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was clear that this, complemented by his published work, established the personal reputation which led, among other activities, to his membership of the Medical Advisory Council of the Nuffield Provincial Hospitals Trust. In that setting he was in the company of some of the great names of the day—Rock Carling, Henry Cohen, Harry Platt, John Ryal, the first Professor of Social Medicine in Oxford, and James Spence of Newcastle.

#### James Spence

The influence each had upon the others is difficult to estimate but there is no doubt that the deep friendship which developed between Pickles and Spence was particularly important to both. Pemberton tells us that Pickles frequently gave Spence a lift as far as Doncaster on the journeys north after Council meetings. Remembering the condition of the roads and the cars of the time, we must be grateful that they both survived. It is particularly interesting to speculate how much Pickles influenced Spence during those journeys. Were the 'thousand families' which Spence studied in Newcastle his urban equivalent of Pickles' Wensleydale population? When producing his classical definition of the consultation, did Spence have a mental picture of Will in a country cottage? How much of Pickles' optimism for the future of general practice rubbed off on Spence? During the last year of his life, which coincided with Will's first year as President of this College, Spence lectured on institutional medicine.<sup>2</sup> Although the text of the lecture is incomplete, those who remember the state of general practice in the early 1950s will appreciate his far-sighted final recorded remarks, 'I foresee the day when the best of our young men will go into simpler and more satisfying institutions—notably general practice', and rejoice at the extent to which they have come true.

#### Tea parties

The friendship between these two northern family doctors was indirectly responsible for my only meeting with Will Pickles at one of the last doctors' tea parties to take place in Aysgarth. Held on an invariably fine, early summer day, these meetings were attended by doctors from far and wide and from a multiplicity of back-



**Figure 1.** William Pickles (right) outside the George and Dragon.

grounds. Because of the Spence connection Newcastle was always well represented, and I attended as a very junior member of the Department of Child Health. After a lecture by a visiting speaker everyone took tea at the Pickles' home and it is clear from some snapshots taken before the meeting outside the George and Dragon just how much Will enjoyed the occasions (Figure 1), which sadly ended in 1960 when he was 75. A farewell dinner held that year was attended by representatives of all the organizations with which he had been associated. Dr Ollerenshaw of Skipton, a foundation Council member, represented this College and spoke on behalf of the 'inarticulate mass of GPs'. Surely times have changed! Happily, Pickles enjoyed several more years of good health and saw the College achieve its Royal Charter. and was able to read the first William Pickles Lecture delivered by Pat Byrne in 1968. I hope he felt a sense of satisfaction that College membership was finally to be achieved only by examination.

#### Membership examination

In 1954 Pickles had begun the first James Mackenzie Lecture with a quotation from Jane Austen: 'You must employ the material which lies closest to your hand, you must contrive your story out of the simplest everyday matters.' Not even by the wildest stretch of imagination could medical education, vocational training and membership of this College be described as simple everyday matters, but the material closest to my hand describes the membership examination, the number and nature of doctors who have chosen to sit it since it was established in 1965, and in particular what the examination has revealed during the seven years since 1976 when we have been able to relate performance to a variety of candidate characteristics.

The 'quantity' of my title refers primarily therefore to the number of candidates who have come forward, numbers which have risen from five in the first examination in 1965 to almost 1,000. 'Quality' in this context describes personal characteristics and quality of performance, largely measured through marks achieved. 'Controversy' relates to the fact that, both within the College and without, the membership examination is still, after 18 years, seen as controversial. In the words of a recent *Journal* editorial, 'It continues to be questioned.' I hope it always will, particularly by those for whom questioning implies scientific enquiry and who appreciate the essential interdependence of education and assessment.

Academic institutions, of which this College is an example, exist to establish and maintain standards. To be established and maintained they must be defined. If defined, they are capable of assessment. Although the other functions of an academic institution—education, exhortation and example—are important, only through some form of evaluation is it possible to determine whether standards are being achieved and maintained.

#### What to assess?

Examination of the abilities required to perform a simple task may be simple. When the task is complex, assessment becomes more difficult. If the abilities required for its completion have not been adequately defined, if training programmes designed to develop or enhance those abilities are themselves still in process of development, and if it appears that the job can be satisfactorily completed in a variety of different ways, the task of the assessor is formidable.

For these and other reasons, controversy has been an inevitable accompaniment of the development of an examination in general practice—an area of complex medical activity which had never been examined before. A major achievement of the examiners of this College has, I believe, been their ability to pace developments in general practice and in vocational training and to establish an examination which has a high level of validity and reliability in assessing the attributes required of the doctor completing vocational training and about to enter independent clinical practice.

Although the prime purpose of our examination is the admission of members to the College, it can be seen as a logical conclusion to vocational training. One could argue that it is illogical to complete vocational training without it—'satisfactory completion' is hardly satisfactory in academic terms without some form of evaluation. Indeed, in the absence of appropriate assessment, the establishment of vocational training must be regarded as a well-motivated but uncontrolled educational experiment.

Although one of the first medical examinations in Europe was instituted in the thirteenth century by Royal Decree—'that the King's subjects should not incur danger through the inexperience of their physician'— one of the aspects of our examination which causes controversy is that experience does not guarantee success. The relevance of the examination, therefore, to the

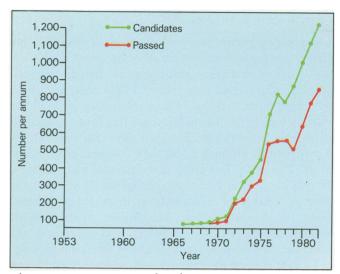


Figure 2. MRCGP examination.

established practitioner has been questioned. Yet how many of us who have been driving reasonably safely for many years would guarantee to be successful if we resat a driving test?

No examination can assess all the attributes required of the good general practitioner. Nor can it ensure that those identified are used. It is possible to assess some, however, and the examination covers as wide a range as possible. Accepting that a quantum of knowledge is necessary for clinical practice, and that the possession of today's quantum reflects an attitude to tomorrow's, the examination does include an MCQ paper. The other two written papers, however, and the two orals are intended to assess the candidate's skills in aspects of hypothesis formation, problem solving, and communication, and attitudes to aspects of patient care, practice organization, and the professional role.

In no way do the aims of the examination differ from those of vocational training, or of good general practice. That preparation for the examination might divert intellectual energy from the prime purpose of training suggests a restricted view of each.

#### The examiners

All the examiners are clinicians in active general practice, most of them are involved in training, all share a view of general practice and its future which requires its practitioners to be well informed, well read, flexible, humane and articulate. Accepting the variety of clinical practice, they welcome originality but expect it to be defended scientifically. They are certainly not involved in the process of rewarding dull conformity. For this reason, no detailed syllabus has been produced—the guidelines plus good training should be sufficient.

Few academic bodies, I believe, expect more of their examiners than this College. Few make fewer assumptions about the ability of their examiners to make educational assessments without appropriate prep-

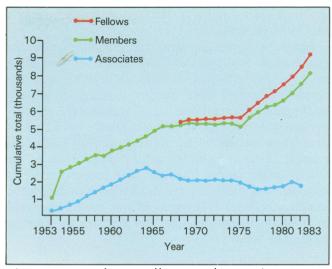
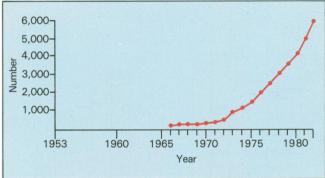


Figure 3. Members, Fellows and Associates.

Figure 4. Members by examination.



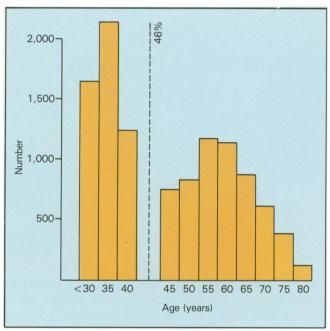
aration and training, and few have been given the opportunity to establish an examination process which has required so much effort in such a short space of time. In assessing the almost 9,000 candidates who have presented since 1965, members of the Panel of Examiners have marked almost 55,000 essay papers, 160,000 pages of modified essay papers, they have constructed over 5,000 multiple choice questions, and have spent over 10,000 hours—equivalent to about six working years—in the process of oral examination. They have also spent the equivalent of over one month in conference and workshop in the process of mutual education.

#### Quantity of candidates

What are the results of their efforts? For the examiners themselves, apart from intellectual stimulation and a sense of achievement: a workload which has increased year by year (Figure 2). In 1980 the record of 1,000 candidates per year was broken; this year we almost achieved that number for the summer examination alone (Figure 3). For the College: a membership including Associates, exceeding 10,000 (Figure 4) with 70 per cent of Members having achieved that status by examination; a membership, 50 per cent of which are under the

age of 40 years (Figure 5). The College is now young; it should be vigorous.

For the academic aspirations of general practice, the examination has provided one method of evaluating some of the effects of vocational training and the characteristics of those doctors entering or already established in general practice. Unfortunately, in comparison with Will Pickles' Wensleydale studies where his population was complete, ours is not. Only half of all trainees currently completing their programme sit the MRCGP examination, although that proportion is increasing, and the 2,758 principals who have taken the examination since 1976 represent only some 10 per cent of those in current practice. Our findings nevertheless have some validity.



**Figure 5.** Age distribution of Members, Fellows and Associates, 1983.

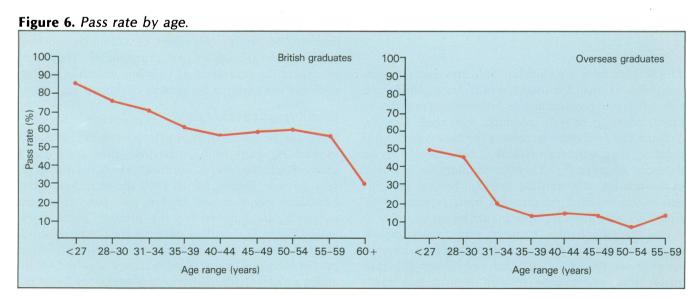
#### Quality of candidates

Categorizing performance on the basis of pass/fail, the first finding which influences all subsequent analysis is the contrast between graduates of British medical schools, who have a pass rate of 73 per cent, and those who graduated overseas, whose rate is just over 17 per cent. A variety of factors influence this finding, age and experience in particular. Figure 6 shows the pass rate by age of British graduates and their overseas contemporaries. Figure 7, however, demonstrates that whereas British candidates had a modal age of 30 years at the time of sitting the examination, those from overseas were significantly older. The higher proportion of women among British graduates also influences the outcome, for women graduates have fared much better than men (Figure 8). Primary and secondary education may also constitute important variables, for, as Figure 9 shows, British graduates born overseas, whose primary and secondary education were more likely to have been overseas, had a lower pass rate than British graduates born in the United Kingdom.

Recognizing additionally that 60 per cent of candidates from overseas had been qualified for more than 10 years and were thus more likely to be principals, that 30 per cent had had no vocational training and that, of those who had, only half had been on three-year schemes, it is clear that they form a special category with special difficulties (Table 1). Age for age, however, overseas graduates follow the pattern established by their UK contemporaries and those with other higher qualifications are more successful in the MRCGP than those without, a pattern which British graduates repeat (Table 2).

#### Previous experience

The possession of a higher qualification may imply extra hospital experience, an attitude to extended training, an ability in examination techniques or a combination of all three. Most postgraduate training for



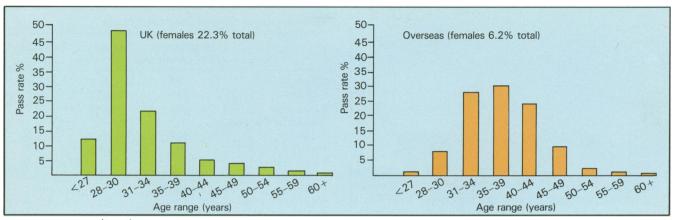
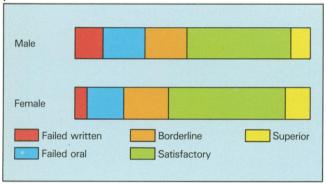


Figure 7. Age distribution.

**Figure 8.** British graduates—overall quality of performance.

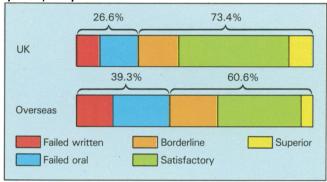


**Table 1.** Overseas graduates. Percentage pass rate by post held.

Trainee $(n = 217)$	26.7	
Assistant $(n = 45)$	22.2	
Hospital $(n = 43)$	14.0	
Principal $(n = 575)$	13.2	
Mean	17.4	

general practice has been justified by Peterson's original association of better practice with duration of postgraduate experience in hospital.3 Figure 10 suggests that, in our examination at least, the difference between any number from one to six years is remarkably small. As only 50 or so candidates had over nine years of hospital experience, that category should perhaps be discounted. Experience in general practice should correlate with success in an examination for general practice, although influenced perhaps by the problem of age. As Figure 11 shows, not only is the pass rate consistent, but the proportion of superior performances among the 'elderly' is encouraging. Experienced practitioners do not find the examination as daunting or inappropriate as some have claimed; on the contrary, others have positively enthused and are almost addicted to repeated successful attempts.4

**Figure 9.** British graduates—place of birth by quality of performance.

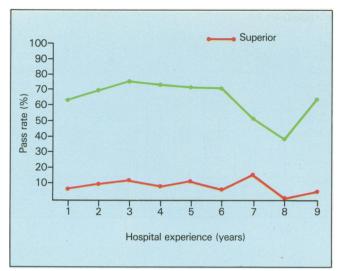


**Table 2.** Qualifications by percentage pass rate in the MRCGP examination.

(	Overseas graduates		British graduates	
-	Percentage possessing qualifications	Pass rate	Percentage possessing qualifications	Pass rate
D.OBST.RCOG	8.7	24.6	52.7	77.1
DCH	6.4	30.0	17.4	78.7
D.OBST.RCOG and DCF	ı 3.3	32.3	12.2	88.3
MRCP	4.4	31.7	5.6	90.8
FRCS	2.0	26.4		_
Mean		17.4		73.1

#### Undergraduate education and postgraduate training

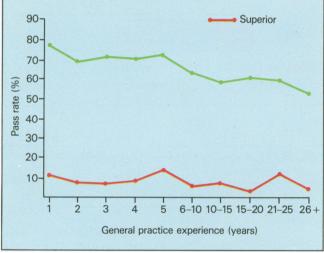
Although the examination will, I hope, continue to be used by experienced general practitioners as a method of self audit, its main purpose is in admitting new Members, most of whom are completing training. The influence of medical school is therefore of considerable interest to deans, and of training region and scheme to regional advisers, course organizers and trainers. A league table of the top medical schools shows the number of candidates, the overall pass rates and the proportion approaching or achieving distinction



**Figure 10.** British graduates — pass rate by years of hospital experience.

Figure 11. British graduates — pass rate by years of

general practice experience.



(Table 3). Table 4 shows those regions with above average pass rates. Five of the regions with the highest pass rates contain seven of the 'best' medical schools. The quality of the entrants to training programmes may therefore be the major factor predicting success. Which is the more important, the medical school or the training region? How do we interpret the fact that in one region the graduates of the local medical school do much better if they leave the region to train, while local graduates who stay put have a significantly higher pass rate than those who move in from other schools? Unless all trainees are assessed before and after their training programme, the complicated questions which these observations raise are incapable of resolution.

#### Age and gender

By December 1982, 60 per cent of candidates for the membership examination were under the age of 30

Table 3. League table of medical schools.

	Number of MRCGP candidates	Percentage pass rate	Percentage superior
Nottingham	47	91.5	2.1
Oxford	101	88.1	21.8
Cambridge	41	<i>87.8</i>	24.4
University College	e,		
London	150	85.3	14.0
Leeds	182	84.1	15.4
King's College,			
London	129	82.9	13.2
Edinburgh	336	81.3	10.7
Sheffield	170	81.2	12.9
Newcastle	295	80.0	12.2
Mean		73.1	9.6

Table 4. UK graduates. League table of regions.

	Number of MRCGP candidates	Percentage pass rate	Percentage superior
Oxford	298	82.9	15.4
Trent	353	· 82.7	11.3
Northern	436	81.4	15.4
SE Scotland	215	80.9	10.2
Avon	294	80.6	13.6
Wessex	279	<i>7</i> 9.9	10.8
Devon	102	<i>7</i> 9.4	6.9
SE Thames	276	<i>7</i> 9. <i>2</i>	8.1
Mean		73.1	9.6

years; 28 per cent were women and the proportion of principals, even young principals, had fallen to 25 per cent. The effect of youth and gender on examination performance has already been noted. The younger and more 'feminine' the entry, the higher will be the pass rate.

#### Does training work?

As 1981 was the last year in which it was possible to enter practice without completing at least a trainee assistantship, we are now past the point at which comparisons can be made between the trained and nontrained. Figure 12 provides the answer to the question 'Does training work?' The overall pass rate of those who were ever trainees is significantly higher (P=0.0001) than the rate for those who were not. The answer to the overall question, 'Does being a trainee work?' is therefore 'Yes'. However, when the results age by age are compared (Figure 13) it is not difficult to see that although in each age group the trained fare better than the non-trained, only 35-39-year-olds show a barely significant difference. As few candidates of this age will present in future, this result is largely academic.

Despite statistical reservations within age groups, vocational training does seem to have some positive effects. The pass rate on the written papers of those who

have been trained is 10 per cent higher than for those who have not. Although the proportion of those in the borderline category is higher among the trained, so are those classified superior—findings which suggest that training does improve performance.

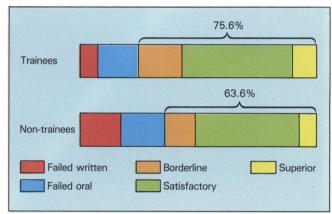
#### Which components in training are important?

In his William Pickles lecture two years ago, Ian Richardson made a plea for further information from the examination. In particular he asked that examiners should identify those aspects of training which appear to be associated with success. The data we have at present can answer only some of his questions. More detailed studies are required.

Do candidates from co-ordinated three-year programmes have an advantage over those whose training experience has been self-constructed? The answer is 'No'. The pass rates are almost identical (Figures 14 and 15) and during some years have favoured the freelance. Do particular hospital posts confer an advantage? Beyond the fact that those with diplomas in Obstetrics or Child Health do well, we do not know. How much does half-day release contribute? Candidates who attended any half-day release session at all were more likely to succeed than those who attended none. But the attenders were more likely to be trainees and to be young. Of the attenders, the pass rate in general increased in proportion to the number of sessions—the optimum being between 60 and 80.

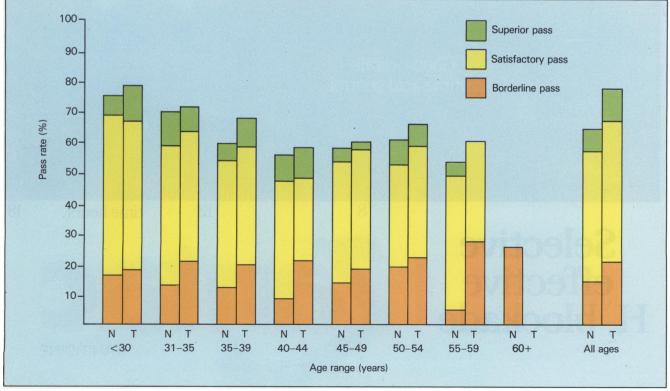
#### Practice characteristics

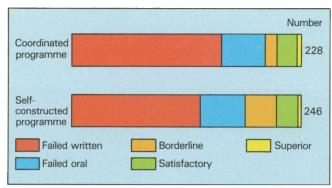
Certain practice characteristics also appear to predict success. The preliminary results of a study being conducted by Ian Stanley on behalf of the Membership Division suggest that well-equipped, well-organized practices produce well-equipped and well-organized candidates. It may be suggested that this is simply the College, through its examiners, rewarding those who respond to its exhortations. Technically of course, this is impossible—for the examiners assess the candidate, not the practice. What seems more likely is that well-organized, well-developed training practices are those



**Figure 12.** British graduates — performance by training.

**Figure 13.** British graduates — performance of the age groups by training. (N = never trained, T = trained at any time.)





**Figure 14.** Overseas graduates — pass rate by training programme.

of trainers who also possess these characteristics and whose enthusiasm for their task is transmitted. as Freeman and his colleagues suggest, to their trainees.5

#### Discriminating questions

Does the examination tell us anything else about candidates or their training experience? I believe it does, for although generalizations are dangerous, certain observations are so consistent that they seem to be fair reflections of the nature of contemporary teaching and early clinical experience. The individual techniques of the examination tell similar tales. In the multiple choice question paper, the type of question which achieves the highest mean mark and which produces the greatest degree of discrimination between the candidates who do well and those who do not are on fundamental clinical topics, such as left ventricular failure, hypothyroidism, hypokalaemia, and cystic fibrosis. You may feel that at the end of four postgraduate years and three years of undergraduate study, it would be alarming if they did not. In general, they and topics from areas of knowledge common to hospital and general practice score highly. Questions concerned primarily with medicine in general practice do less well. Categorization is not helpful, for it is the orientation of the question which is important. Similarly in the modified essay paper, questions based upon knowledge or skills extrapolated from hospital practice produce high mean scores; those requiring the candidate to react to more typical general practice situations, hypothesis formation, problem solving, and patient communication, produce lower scores. Some topics in the essay papers on which candidates do well are management of recurrent pain, breast feeding, alcoholism, prevention of heart disease and nonaccidental injury; others which are more abstract or outside the mainstream of everyday clinical practice do less well. In the orals, examiners have been disappointed by weaknesses in the area of practice organization and in the attitude of some candidates to the ethos of general practice as an independent clinical discipline. Again, while many candidates score highly on technical aspects

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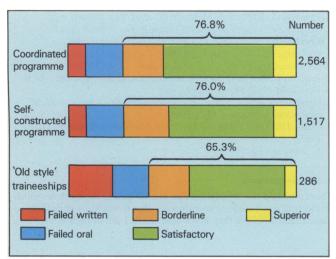
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**Figure 15.** British graduates — pass rate by training programme.

of clinical medicine, its application in the context of general practice has disappointed.

#### Conclusions

Are these findings surprising when we consider the contribution general practice has been able to make to both undergraduate, and, even at this stage, postgraduate education? If the first eight of the nine years it now takes to educate a general practitioner are spent in the context of the laboratory and the hospital, how can we expect orientation to be towards general practice? Herdwick sheep on Lake District fells are heafed. They are born and graze on the same territory, and only feel at home there. Doctors are heafed in hospital. How long do they need to feel at home in the context of practice? This particular controversy has been reopened in the College Journal, where again it was suggested that membership should be deferred until a doctor has had at least a couple of years in general practice. This is a perfectly reasonable argument if we accept that teaching in general practice remains a postscript to an eight-year experience of medical school, hospital wards, and what Dr Griffiths describes as 'body and biochemistry oriented medicine'. But do we accept that this must continue and that in medical school and hospital, learning experiences are incapable of modification? Can we be satisfied if in the fourth postgraduate year, the ninth of medical study, time has to be spent ensuring that doctors possess the basic skills of the consultation, that they can form hypotheses and organize management in physical, psychological and social terms, and that they have developed a philosophy of medicine which balances the value and potential of treatment against the possibilities of prevention and care?

If the effect of vocational training is difficult to demonstrate, it may not just be that the quantity and quality of teaching is too variable. It may be that the task is too great. A recent review of sensitive learning periods<sup>7</sup> re-emphasizes the importance of early influences on the development of attitudes and patterns of behaviour. At present, general practice contributes too little too late. How much better if vocational training completed an educational process which contained coherent, continuing and increasing contributions from general practice throughout, sufficient to ensure that doctors, even before graduation, possessed those attributes we may find undeveloped so much later. Changes in the undergraduate curriculum to achieve these objectives might even be possible.

The most recent Recommendations on basic medical education<sup>8</sup> of the General Medical Council contains 20 aims which will appear familiar to those who know their Future general practitioner or the content of our membership examination. The importance of these aims is that so many are achievable in general practice and so few without its help. In my own school, within a joint Department of Family and Community Medicine, and in collaboration with Paediatrics, Psychiatry, Psychology, Geriatrics, Occupational Health, and Medical Statistics, General Practice has for the past seven years played a central role in an extended two-year course on human development and behaviour which begins on the second day of the first year, and helps students towards achieving at least 16 of those 20 aims.

Our contributions to the clinical curriculum are limited by the usual constraints of time and resource. We hope that our claims for resource are now better understood, while the amount of time we can achieve is dependent upon a variety of factors—not least the academic status of general practice in general and the clinical reputation of local general practice in particular. I believe that the academic status of general practice has been substantially enhanced by the development of our membership examination, for the role of examination in determining standards is well understood by other academics. The clinical reputation of general practice is also being enhanced by those who have completed training and entered partnerships locally.

Given appropriate resources and support, academic departments of general practice should be able to provide a contribution to basic medical education which will allow the aims of the General Medical Council in future to be fully achieved at graduation. When they are, we shall have a population of young doctors whose expectations of vocational training will be extremely high. They will enjoy the assessments which form an integral part of their education—as they in turn will be assessing their teachers. They will value the membership of this College, which at the end of training indicates their degree of competence; and after having settled into practice they will demonstrate their continuing intellectual and professional excitement in a variety of ways not least by having the quality of their work assessed for the purposes of attaining Fellowship.

Some time ago, my colleague Andrew Smith posed for the frontispiece of a book on the clinical care of children.9 At that time, no tradition of teaching or of examining in general practice existed. Twenty years later, I asked him to repeat the pose—to illustrate the continuity of general practice which has concealed its achievements in those fields.

I am optimistic that the interdependence between education and assessment will also continue, and that during the next decade the quantity and quality of those achievements will multiply. Surely that will not be seen as controversial.

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# Beta-blockers after myocardial infarction

 $\beta$ -Blockers offer an important available therapeutic approach for improving long term prognosis among survivors of heart attack, according to participants in a workshop held recently at the National Institutes of Health to examine available evidence from 25 completed clinical trials using various  $\beta$ -blockers. Scientists attending the workshop, sponsored by the National Heart, Lung, and Blood Institute (NHLBI) in May 1982, examined the use of  $\beta$ -blockers as a means of secondary prevention—in other words, of preventing a recurrence and improving longterm survival among patients who had experienced acute heart attacks.

The overall results of all studies reviewed indicated that:

- 1. Long-term administration of  $\beta$ -blockers after myocardial infarction (MI) substantially improves longterm survival.
- 2. Studies have not yet resolved whether the early use of  $\beta$ -blockers during MI favourably affects in-hospital or longterm mortality.
- 3.  $\beta$ -Blockers are safe and well tolerated by most patients, providing there are no standard contraindications to their use.
- 4. Side effects from drugs seldom necessitate permanent withdrawal of the administration of  $\beta$ -blockers. The more cardioselective members of this family of drugs may reduce this problem as well as facilitate the administration of  $\beta$ -blockers in the subset of patients who had experienced MI also suffering from diabetes or chronic obstructive lung or peripheral vascular disease.

5. Given in physiologically equivalent doses under similar circumstances, one  $\beta$ -blocker is probably as effective as another in improving survival and in offering other supposedly beneficial effects. The most prudent approach might be to use those  $\beta$ -blockers for which benefits are most clearly documented—timolol or propranolol. Important questions remain unanswered.

Source: JAMA 1983; 249: 2482. (A detailed summary of the workshop is available from the Information Office, NHLBI, Bldg 31, Room 4A-21, National Institutes of Health, Bethesda, Maryland 20205, USA.)

# Tube-spacer aerosol bronchoconstriction treatment

To assess whether an extension tube between the aerosol source and the patient improves the drug-inhalation therapy in children with acute bronchoconstriction, 20 children were treated under double-blind conditions with placebo or terbutaline delivered by a conventional aerosol or an aerosol with a tube spacer. Both terbutaline treatments resulted in a significant increase in forced expiratory volume in one second, as compared with placebo but treatment with the tube-spacer aerosol produced significantly more improvement than did treatment with the conventional aerosol. The number of errors in inhalation technique was reduced when the spacer aerosol was used, and this reduction may account for the greater improvement in the children treated with the spacer.

Source: Pedersen S. Aerosol treatment of bronchoconstriction in children with or without a tube spacer. *New Engl J Med* 1983; **308**: 1328-1330.