# Why do we need randomised controlled trials to assess behavioural interventions?

Judith Stephenson, John Imrie

The value of the randomised controlled trial still generates debate.[1] Although some of the earliest examples of these trials can be found in behavioural and psychosocial research, this is not an area that has adopted readily the randomised controlled trial to assess interventions.[2] Two recent developments have intensified debate about the role of randomised controlled trials—the urgent need to find effective behavioural interventions against HIV[3 4] and the advance of evidence based medicine, which is moving the randomised controlled trial beyond clinical trials into areas such as health promotion. This article considers the merits and limitations of randomised controlled trials in the behavioural area compared with clinical medicine, and asks how these trials can be applied successfully to assess behavioural interventions.

## Summary points

- Merits of randomised controlled trials in behavioural and psychosocial research do not differ fundamentally from those in clinical medicine
- Interventions that target behaviour are often complex and demanding, as are the requirements of good randomised controlled trials to assess their efficacy
- Standardising the content and delivery of an intervention in a trial may be more challenging than justifying randomisation during informed consent
- When blinding of participants and researchers to treatment allocation is impossible, it is important to minimise bias through blinded assessment of the outcome
- The contribution that participant choice makes to the efficacy of an intervention is hard to measure

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## Merits and limitations

The merits and limitations of randomised controlled trials in general have been widely discussed[5 6]; only key points are repeated here. In clinical medicine, the randomised controlled trial is considered the best way of measuring the efficacy of interventions because of its ability to minimise bias and avoid false conclusions. Random assignment of individuals to different treatment groups is the best way of achieving a balance between groups for the known and unknown factors that influence outcome. This may seem to run counter to the traditional medical model of the doctor deciding which treatment is best for each patient, but it is considered ethical only when there is genuine uncertainty about which treatment to offer. By the same token, failure to tackle genuine uncertainty about treatments through randomised controlled trials can be considered unethical because it allows ineffective or harmful treatments to continue unchecked.

### Limitations

Aside from ethical issues, the limitations of randomised controlled trials are relative, and shared to some degree by other study designs. These include cost, feasibility, and relevance to the real world. The effect of an intervention in an ideal research setting (efficacy) may well differ from its effect in the real world (effectiveness). This is particularly true of "explanatory" trials, which are designed to establish a cause and effect relation, but less so of "pragmatic" trials, which aim to mimic real life situations.[7] Efficacy tends to differ from effectiveness because people who give informed consent to enter trials usually differ, in ways that affect outcome, from those who are eligible but decline or are not invited. Furthermore, taking part in research often involves procedures and commitments that are different from routine practice. In this sense, effectiveness cannot be judged from tightly controlled research, but without prior evidence of efficacy, it can be hard to attribute events in the real world to the effectiveness of an intervention (see below).

## What is the debate?

Debate about randomised controlled trials generally takes one of two forms. If it is accepted that the randomised controlled trial is the method of choice for estimating the efficacy of interventions, then debate is confined to the conditions which permit the trial on ethical and practical grounds and make the findings useful beyond the trial itself.[7] If a randomised controlled trial is not possible for ethical or practical reasons,



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Is it the cognitive-behavioural component of the therapy that works, or is non-specific group support more important?

observational studies may be the only way of assessing an intervention, and some of these have undoubtedly been useful. To accept the randomised controlled trial as the best way of gauging efficacy is not necessarily to dismiss other study designs that have the same objective.[1 7 8] For example, no randomised controlled trial of the efficacy of condoms in preventing sexual transmission of HIV has been carried out. Given the seriousness of HIV disease and the consistency of early, albeit inconclusive, studies supporting condom use, such a trial would have been unethical. However, in a well designed prospective study of sexual partners whose HIV status differed, the seroconversion rate was zero between couples who used condoms consistently and about 5% per year in those who did not.[9] Given this evidence of condom efficacy, we can be more confident that the decrease in the rates of sexually transmitted diseases and HIV infection in Thailand is due to the effectiveness of a nationwide campaign that dramatically increased condom use in brothels.[10]

The second form of debate involves more fundamental opposition to randomised controlled trials. In the behavioural and psychosocial field, ethical objections have been raised about withholding interventions that are believed or assumed to be beneficial. In addition, it is argued that randomised trials are not applicable in this field because they ignore the importance of external influences, participant choice, qualitative research methods, and the complexity of behavioural and psychosocial interventions.[11]

## Assessing behavioural interventions

Behaviours and outcomes related to health are clearly influenced by complex social and economic factors.[12] Randomised controlled trials may have little to contribute in terms of explaining how and why these factors affect health and behaviour, but this does not deny their usefulness in testing applied interventions with specific objectives. In fact, randomisation seeks to balance out external influences between groups so that the true effect of an applied intervention is detectable. For example, advertising and pricing policies undoubtedly have a major impact on smoking levels, but the effectiveness of a specific intervention to stop smoking—for example, hypnosis—is best examined by a randomised controlled trial of smokers.[13]

Interventions that target behaviour are often demanding and costly. They generally require several sessions run by highly skilled staff. Without evidence of efficacy, scarce resources might be better spent elsewhere, and the possibility of causing harm should be considered. One study of counselling after an HIV test found that the incidence of gonorrhoea in people who tested negative was twice as high in the six months after testing and counselling than in the preceding six months.[14] Without a control group these findings are hard to interpret, and there are few good trials in this area. The point is that well meaning measures may not work as intended.

Behavioural interventions are often evaluated through uncontrolled, before and after comparisons.[4 15] Dissatisfaction with these comparisons in clinical medicine is partly related to the statistical law known as regression to the mean. If extreme values (for example, of blood cholesterol) are singled out from a distribution, they are likely, for purely statistical reasons, to fall closer to the usual level if measurement is repeated. In the absence of a control group, lower cholesterol concentrations at follow up might merely reflect the laws of statistics but be wrongly attributed to the effect of an intervention.

It is easy to imagine a similar, although non-statistical, phenomenon occurring in a behavioural setting. For example, people are most at risk of contracting a sexually transmitted disease when they are taking greater sexual risks than usual, and are likely to return to their usual level of risk behaviour afterwards. If people with a sexually transmitted disease were recruited to an uncontrolled study of a behavioural intervention, lower rates of sexually transmitted diseases or increased condom use might be expected at follow up, even if the intervention had no effect (particularly if participants were reluctant to disclose high risk behaviour or if the process of diagnosing a sexually transmitted disease and treatment alone had had an impact). Effects of this kind could not be detected without a comparable (randomised) control group receiving standard care but not the intervention of interest.

## Randomised controlled trials have limitations

An important limitation to randomised controlled trials in behavioural or psychosocial research relates to "blinding" and participant choice. Blinding to treatment allocation in clinical trials (for example, by using placebos that are indistinguishable from active drugs) is intended to prevent the expectations of patients or researchers from influencing the outcome. In behavioural trials, blinded allocation to treatment may be impossible, but blinded assessment of outcome need not be. For example, in a randomised controlled trial of psychotherapy versus supportive listening in patients with irritable bowel syndrome, both the psychiatrist and the patients knew which treatment group they were in, but the outcomes (psychological and bowel symptoms) were assessed by another psychiatrist and

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a gastroenterologist who were blind to treatment allocation.[16]

**Does choice improve outcome?**

Excluding choice by allocating patients randomly to one or other treatment is seen as a great strength in clinical trials. In behavioural trials, this has brought criticism. Choosing your preferred intervention, it is argued, increases motivation and thereby the success of the intervention.[17] Even if this is true, can such a motivational effect be measured? Some researchers claim it can be measured by comparing outcomes between those who are randomly assigned to a particular intervention and those who choose it.[17] The problem with this is that people who choose an intervention probably differ from those who do not in ways that affect the outcome. For example, in the trial of patients with irritable bowel syndrome, psychotherapy was better than supportive listening at three months, at which time the supportive listening group was offered psychotherapy.[16] The 77% who accepted the offer clearly differed in psychological symptoms—at the point of decision—from the 23% who declined. Other (unknown) factors related to irritable bowel syndrome may also have differed between the two subgroups.

**Inappropriate for exploratory research**

As noted above, randomised controlled trials are not appropriate for exploratory research into factors that determine behaviour related to health. This is the domain of qualitative research.[18] Identifying the cultural context, values, beliefs, and community norms of target groups through good qualitative research is the key to the design and implementation of promising interventions. Examples can be found in the development of behavioural interventions led by peers to reduce the risk of infection with HIV, particularly among hidden or hard to reach groups such as injecting drug users who are not in contact with treatment services, and young gay men.[19 20] Clearly the strengths of qualitative research should not be pitted against those of randomised controlled trials.

**Standardisation is a major challenge**

Standardising the content and delivery of a complex intervention in a randomised controlled trial is a major challenge. More extensive training and monitoring of those delivering the intervention may be needed than in clinical trials. Monitoring can be done through supervision and feedback or, more objectively, by audiotaping or videotaping random sessions by independent assessors. Careful monitoring and qualitative research may explain why complex interventions fail or, conversely, shed light on the factors that lead to behaviour change—the active ingredients.[21] For example, if a support group based on cognitive-behavioural therapy proves effective, is it the cognitive-behavioural component of the treatment that works, or is non-specific group support more important? To be confident about which is most effective would require each component to be tested in additional experiments or a trial with several arms. Both options are usually too costly and too lengthy to be realistic. In terms of assessing healthcare interventions, pragmatic randomised controlled trials may therefore be more appropriate and manageable than explanatory ones, even if they do not identify the active ingredient. By comparison with the effort required to standardise and monitor a complex intervention, the additional effort of justifying randomisation to potential participants is small, while the gain in reducing bias is great.

## Conclusion

The value of the randomised controlled trial in behavioural research does not generally differ fundamentally from its value in clinical medicine. Issues that occasionally arise in other areas, such as lack of opportunity for blinding and complexity of intervention, are particular features of behavioural and psychosocial research. Standardising the content and delivery of a complex intervention may prove more limiting than random allocation. When interventions are complex, pragmatic trials may be more likely to succeed than explanatory ones.

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# Hypertension treatment and control in sub-Saharan Africa: the epidemiological basis for policy

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Although enormous challenges persist in the control of infection in sub-Saharan Africa, non-communicable diseases are also important threats to the health of adult Africans.[1 2] Controversy exists, however, over the priority these conditions deserve in the competition for scarce resources. It has recently been argued that hypertension treatment, for example, should not be attempted in sub-Saharan Africa given the high costs.[3] Unfortunately, these discussions take place in an information vacuum, since it is impossible to define the burden of chronic conditions in societies where health statistics are unavailable.[4] Cohort studies may serve as a proxy for vital statistics and give approximate answers to questions on the usefulness of treatment for chronic disease.[5] Hypertension is particularly suited to this model because it is easily diagnosed, highly prevalent, and information on outcomes is plentiful.

Hypertension is the most common cardiovascular condition in the world and the problem of defining a strategy for control confronts all societies. Hypertension is fully treatable, but social conditions in Africa make the implementation of blood pressure control programmes difficult. Lack of a clear strategy based on evidence has undermined further these efforts. We outline here the epidemiological data on hypertension that are available to guide health policy in sub-Saharan Africa.

## Summary points

- In sub-Saharan Africa it is difficult to formulate and justify policy on treating chronic conditions such as hypertension as there are no health statistics from which to judge likely costs and benefits
- Cohort studies on hypertension in Nigeria and Zimbabwe and epidemiological information show that between 10 and 20 million people in sub-Saharan Africa may have hypertension and that treatment could prevent around 250 000 deaths each year
- Taking account of both relative risk and absolute risk of a cardiovascular event or death, a systolic pressure of 160 mm Hg is recommended as a threshold for treatment in Africa
- The reduction in population attributable risk associated with treatment could be 2% in Africa compared with 0.15% in the Unites States—some 13 times higher
- "Number needed to treat" analysis shows that the costs of drugs to prevent one death would be $1800 (£1104) in Africa and $14 000 to $1m (£8589 to £613 496) in the United States
- This evidence challenges the assertion that treatment for hypertension should not be a health priority in sub-Saharan Africa

## Burden of hypertension in sub-Saharan Africa

Sub-Saharan Africa is a diverse region comprising 47 countries. It is home to approximately 480 million people.[6] Among the elite in African society, the model for hypertension control currently in force in Europe and the United States would be entirely appropriate. However, most Africans (fully 75%) live in rural areas and are marginally integrated into the cash economy, while around 20% live in extreme poverty in cities. The challenge lies in developing effective strategies for these sections of society.

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Although the relative risk of a cardiovascular event in people with high and normal blood pressure is similar in Africa and the United States, the absolute risk is up to 13 times greater in Africans

### Distribution of hypertension

The prevalence of hypertension is low in rural Africa,[7] and a graded increase is seen in the urban poor and working class.[8–12] Comparing prevalences in studies is difficult, however, as sampling and measurement vary. We recently completed surveys in three communities using a common sampling and measurement protocol (table).[13] In southwest Nigeria, blood pressure in villagers rose modestly with age compared with values in residents of urban areas. Seven per cent of the rural sample had hypertension (defined as blood pressure greater than 160/95 mm Hg or antihypertensive treatment). High blood pressure was more common among the urban poor from Ibadan in Nigeria (17%), and substantially more prevalent in salaried workers in Harare, Zimbabwe (26%). Figure 1 shows the gradual upward

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shift in the distributions of blood pressures across these groups.

### Estimates of preventable deaths

These data represent the principal social strata of African society. They include the range of previous estimates and provide a reference point for considering the burden of hypertension. The estimated distribution of the African population between the three sectors was 75% rural, 20% urban poor, and 5% urban salaried workers and elite. Based on a sub-Saharan population of 500 million, half of whom are older than 25, a hypertension prevalence of 5-10% yields 10-20 million cases. If annual mortality is 2%, and 5% of deaths result from hypertension, then approximately 250 000 deaths each year are preventable.

### Risk factors

In Africa, as elsewhere, obesity and sodium intake are risk factors for hypertension.[12 14–17] In industrialised societies such as the United States, obesity accounts for 25% of cases of hypertension. However, the relative leanness of Africans means that the contribution of obesity to high blood pressure is only around 10%.[15] Psychosocial factors in hypertension have been studied little. Instruments for measuring these factors in African societies have not been developed. No trials of preventive measures that have reduced risk factors for hypertension have been reported from Africa. Drug treatment is therefore the only proved option at present.

### Impact of hypertension on mortality

Although the sequelae of hypertension are predictable,[18] the net impact of high blood pressure on all cause mortality is not. Given the high all cause mortality in Africa, and the small proportion of people who reach an age where sequelae are common, the contribution of hypertension is uncertain. We know of only one prospective study that has been published. In three years of follow up of 1200 adults from the rural district of Igboora-pa, Oyo State, Nigeria, the relative risk of death in people with hypertension was 1.6,[19] a value observed in many other studies.[20] Mortality in this community was high (2.8% per year) and hypertension was associated with a large attributable risk of about 2% per year. It seems unlikely, however, that all of the attributable risk in people with hypertension resulted solely from cardiovascular diseases. Chronic diseases are a predisposing factor for fatal infection, and this could lead to short survival in patients with stroke, heart failure, or renal insufficiency. Under these circumstances prevalence surveys would underestimate disease burden, and prospective risk estimates would exaggerate the cause specific role of hypertension. If this analysis is correct, this interaction between chronic and acute conditions changes considerably the framework within which the value of treating chronic disease in Africa should be viewed.

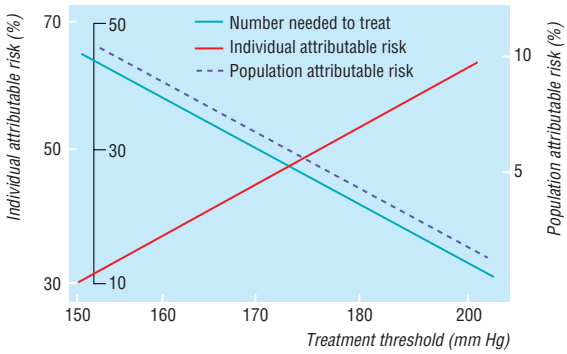


**Fig 1** Probability density distribution of age adjusted systolic blood pressure in three African communities.

Mean blood pressure (mm Hg) and age in three cohort studies in Africa

| | Systolic pressure | | | Diastolic pressure | | |
|---|---|---|---|---|---|---|
| Age group | Rural | Urban poor | Urban workers | Rural | Urban poor | Urban workers |
| 25-34 | 107 | 111 | 118 | 69 | 71 | 73 |
| 35-44 | 113 | 119 | 123 | 73 | 77 | 79 |
| 45-54 | 118 | 131 | 129 | 76 | 81 | 81 |
| 55-64 | 124 | 135 | 139 | 77 | 81 | 87 |
| ≥65 | 129 | 143 | 142 | 75 | 82 | 84 |

Mortality in African adults is unknown and probably varies considerably between regions from 1% to 2.5% per year.[21] Community and hospital studies suggest that 5% to 15% of people die from cardiovascular diseases—mainly stroke and congestive heart failure resulting from hypertension.[2 5 22 23] By combining the data on prevalence and relative risk summarised above, we can also estimate the deaths attributable directly to hypertension from the Igboora-pa study. The annual mortality in people over age 25 was 2.8%, and hypertension was associated with a relative risk of 1.6. Calculation of the population attributable risk confirms that about 5% of deaths can be attributed to hypertension. Given that half of all deaths occur in adults, the overall contribution of hypertension would therefore be around 2.5%. By comparison, a study of global disease burden ascribed 5.8% of deaths at all ages to hypertension.[24]

## Potential for hypertension control with drugs

Who is a candidate for antihypertensive treatment? An answer to this critical question requires information on projected benefit, feasibility, and cost effectiveness of treatment.[24–28] While practical considerations will be paramount in the end, it remains essential to describe the medical consequences of the decision that is taken. The calculations presented here are preliminary ones, intended to place the value of hypertension treatment in context. In particular, they provide a counter argument to the view of some that treating hypertension is not cost effective in Africa, and that support should be removed.[3]

### Analysis by "number needed to treat"

Data on the benefit of drug treatment for hypertension in industrialised countries probably understate its impact. Observational studies in westernised societies since the 1960s do not reflect the natural history of the disease, given its widespread treatment.[29] In trials, some patients in the placebo arm cross over to treatment.[30 31] Indeed, early placebo trials contradict the impression from later trials on "mild" hypertension, and should be

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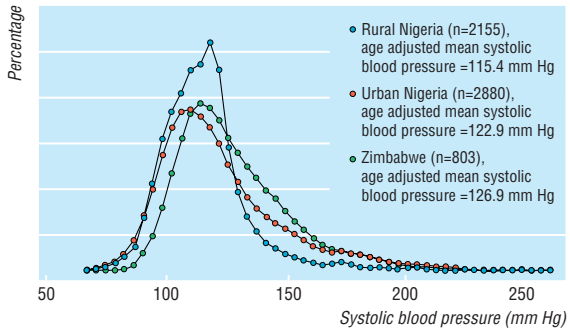


**Fig 2** Individual attributable risk, number needed to treat, and population attributable risk in relation to thresholds for hypertension treatment. Smoothed plots were derived from analysis of adult mortality in Igboora-Pa, Nigeria[19]

considered as the background for policy decisions. In the first Veterans Administration cooperative trial, one of 73 patients taking treatment and 27 of the 70 control subjects had a cardiovascular event.[32–34] The excess in absolute event rates was 28% per year. Under these conditions, four patients would need to be treated each year to prevent one cardiovascular event. In the second Veterans Administration trial, in which patients with diastolic pressures of 90-114 mm Hg were enrolled, the annual cardiovascular event rates were 5.5% in the treated group and 16.7% in the control group, and death rates were 1% and 3% respectively. The corresponding number needed to treat values would be nine each year to prevent a cardiovascular event and 50 to prevent a death. In patients with milder hypertension, however, reductions in mortality were substantially smaller, and the number needed to treat rose to over 1000.[25 35]

## Proposed guidelines for treatment

Choosing an appropriate threshold for treating blood pressure is problematic in Africa. Because resources are scarce, an argument exists for raising the cut off point to reduce the cost. An objective decision, however, requires information that enables benefits to be quantified. The relative risk is the usual basis for determining the treatment threshold. In most studies, the relative risk in people whose blood pressure is greater than 140/90 mm Hg compared with those who have normal blood pressure is around 1.6, and increases 50% with each succeeding 10 mm Hg increase in systolic pressure.[21] If the probability of an event is low, the absolute benefit of treatment is small, no matter what the relative risk. Annual death rates in cohorts in the United States are 0.15% and 0.30% for people with normal and high blood pressures respectively.[21] These rates produce the same relative risk as cardiovascular event rates in people with normal and high blood pressure in Africa (2% and 4% respectively). In the United States, the reduction in attributable risk associated with treatment could be 0.15% at most, while in Africa it could be 2%—some 13 fold higher. This order of magnitude difference in attributable risk is the central problem in assessing the potential benefit of treatment in Africa.

### Absolute versus relative risk

Absolute levels of risk that warrant treatment in Africa are probably in the range of 1%-3%. In the preliminary findings of the prospective study in rural Nigeria, mortality was 2.8% per year in people with normal blood pressure, but 5.1% per year in those with hypertension.[19] If treatment for hypertension eliminated all the excess, then the number needed to treat per year to prevent a death would be 43. Obviously, this estimate is based on the optimistic assumption that 100% control could be achieved, and is an upper bound of what is possible. However, as noted, the Veterans Administration trials gave similar estimates.[32–34]

In other regions of the world, recommendations for treatment are based on relative risks. With the exception of New Zealand, where absolute levels have been introduced,[36] blood pressure thresholds are either 160/95 mm Hg or 140/90 mm Hg.[36] It is assumed that adopting these thresholds in Africa would achieve equivalent benefit. While this is a reasonable assumption in relation to relative risk, the situation in terms of attributable risk could be very different. Taking into account both relative and absolute risk, we believe that a systolic pressure of 160 mm Hg is still currently justified as the threshold. We calculate that the annual mortality in people with blood pressures above this would be around 4%, compared with 1%-2% in those with normal pressures. The number needed to treat to prevent one death would therefore be around 50 each year, and the number needed to treat to prevent a serious cardiovascular complication would be lower.

### Making a compromise

Although benefit at the level of the individual rises as the treatment threshold increases, the benefit at the population level falls (fig 2). A compromise is required which makes treatment worthwhile for individuals, yet still has an impact on public health. The healthcare system must allocate funds to urgent priorities. All of these decisions ultimately require epidemiological data incorporated into the decision making model. An important attribute of the algorithm shown in fig 2 is its potential to determine a useful level of absolute risk (or the number needed to treat) and to calculate from this the blood pressure that should be used as the cut off point. With this approach it is not necessary to rely on relative risk thresholds adopted by external expert panels.

### Costs in relation to numbers needed to treat

Given the data on reductions in mortality associated with diuretic drugs and β blockers, a strong argument exists for using these as standard treatment [30 31 37] Costs in Nigeria are 10-15 cents (US$) per tablet, yielding annual expenditure of $36 (£22) for treatment with one drug only. Assuming a number needed to treat of 50, the cost of drugs alone to prevent one death would be $1800 (£1104) in Africa. In the United States, however, the number needed to treat per year to prevent a death is 1354 for people of similar age, and costs for drugs alone to prevent one death range from $14 000 to $1 million (£8589 to £613 496), depending on the drug used.[25]

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## Conclusions

Complex problems confront any attempt to design a public health strategy to control chronic disease in developing countries, particularly Africa. The obligation for the health professions is to assess potential benefit to patients in the local context, without imposing external standards. For example, the rationale for dismissing the value of hypertension treatment was based on the costs estimated in the United States, which are unlikely to apply in Africa.[3] Only after the health benefits have been defined can useful discussions take place on the social and political possibility that such treatment will be made available. While acknowledging the obstacles to implementing chronic care for asymptomatic conditions in Africa today, the spectre of low cost effectiveness should not foreclose the scientific debate. Otherwise concern over chronic disease in developing countries is little more than hand wringing. Empirical evidence challenges the assertion that hypertension treatment should not be a health priority, suggesting instead that investment in an organised care system would reap large gains in adult health.

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*(Accepted 22 October 1997)*

*One hundred years ago*

## Whisky biscuits

Ardent spirits have been put before the American public in a new form. Whisky can now be eaten as well as drunk. Enticing-looking jelly cakes and biscuits are sold, which have been found to contain a certain amount of whisky, and the United States Board of Health and the Board of Education are reported to have embarked on a crusade against the shopkeepers selling and the bakers manufacturing the whisky bakers' stuff. It is also stated that alcoholic candy, containing an intoxicating proportion of beer, imported from Germany, is being sold in Manchester. (*BMJ* 1898;ii:648)

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*The new genetics*

# The new genetics in clinical practice

John Bell

*See editorial by Gill*

**This is the first of four articles discussing the broader implications of advances in genetics**

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Common diseases are currently defined by their clinical appearance, with little reference to mechanism. Molecular genetics may provide the tools necessary to define diseases by their mechanisms. This is likely to have profound effects on clinical decisions such as choice of treatment and on our ability to characterise more clearly the course of disease and contributory environmental factors. This information also raises the possibility that new therapeutic interventions can be obtained rationally, based on a clear understanding of pathogenesis. Most of these genetic factors will act as "risk factors" and should be managed ethically and practically, as would other risk factors (in hypertension or hypercholesterolaemia, for example). The rapid advances in human molecular genetics seen over the past five years indicate that within the next decade genetic testing will be used widely for predictive testing in healthy people and for diagnosis and management of patients.

Molecular genetics was originally used in medicine to map and identify the major single gene disorders, such as cystic fibrosis[1] and polycystic kidney disease.[2] The excitement in the field has shifted to the elucidation of the genetic basis of the common diseases. With the help of very large, well characterised family collections, genetic linkages for many of the major causes of morbidity and mortality in Western populations have been identified. The genes and DNA variants responsible for these disorders are now being cloned at an ever increasing pace. Large scale genotyping, increasingly integrated genetic and expressed sequence maps,[3] and large scale sequencing programmes[4] have all contributed to this remarkable evolution in our understanding of how genes might modify our susceptibility to disease.

Considering the current rapid acquisition of genetic information relating to common disease and the dramatic technological developments that continue to fuel the field, it would be surprising if most of the major genetic factors involved in human disease were not defined over the next 5-10 years. This information will form an important template for redefining disease, clarifying biological mechanisms responsible for disease, and developing new treatment for most disorders.

The rapid developments in human molecular genetics have often been underestimated, largely due to a failure to recognise the power of new technologies being applied to the problem. The use of information encoded within the genome for clinical practice has previously been limited by problems of scaling up accurate detection of DNA variation for rapid and inexpensive analysis. The problem will soon be resolved, perhaps by the use of oligonucleotide array technology or "chips."[5] The ease with which this can be accomplished will determine how widespread DNA diagnostics will become, but there is little doubt that the problem is likely to be solved, technologically, in the near future.

The role of genes for susceptibility to disease has been emphasised in clinical medicine; it is now clear that this represents too narrow a perspective for the genetics of the future. Although such genes will be critical for redefining diseases and understanding their pathogenesis, equally important will be loci that determine disease progression, disease complications, and response to treatment.

## Summary points

- Genetic information is likely to transform the practice of clinical medicine
- Genetics will provide a taxonomy of disease that is based on biochemical mechanisms rather than phenotype
- Genetic information will be used to identify individuals who are likely to respond to or suffer toxicity from drugs
- Genetic variation will be another form of "risk factor" and will permit early treatment and directed screening

## A new taxonomy of disease

Perhaps the most important single contribution of the new genetics to health care is that it will create a biological rather than a phenotypic framework with which to categorise diseases. Clinical physiology and biochemistry have provided many insights into the biological disturbances that accompany disease, but it is genetics that is able to identify the pathways that are unambiguously involved in pathogenesis. Such genetic information will eventually lead to the redefinition of disease on the basis of biochemical events rather than phenotype; on molecular events driving biological processes rather than a correlation of clinical syndromes and outcomes.

The ability to redefine common human disease, using genetics to define the biochemical processes responsible for disease, will allow the subdivision of heterogeneous diseases such as hypertension or diabetes into discrete entities. Such subdivision is likely to help explain the wide variation of these diseases, including apparent differences in physiology, clinical course, and response to treatment, and it might also provide a basis for identifying environmental factors that contribute only to certain subtypes of disease. This has already begun in diabetes, where definition of the involvement of HLA genes suggested an immune mechanism in a subset of patients, leading to the subdivision into type I and type II diabetes.[6] More recently, type II diabetes has been subdivided further on the basis of distinct mechanisms involving glucose phosphorylation and insulin (glucokinase) secretion,

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**A new taxonomy of disease: diabetes**

*Type I*
Autoimmune (HLA, INS)

*Type II*
Insulin resistant (INS receptor)
Insulin secretion (glucokinase)
Insulin transcription (?) (HNF1α, HNF4α, IPF)

transcriptional regulation (HNF), and insulin receptor dysfunction.

Disease mechanisms have led to clear definitions of infectious diseases. For example, our understanding of hepatitis has progressed: it used to be viewed as a clinical syndrome with a wide variety of outcomes, and is now seen as a set of quite specific diseases defined by the aetiological agent, each with its own clinical course, prognosis, and (perhaps) response to treatment. An understanding of the biological process underlying the clinical phenotype has been of unquestionable benefit in defining and managing disease, and doctors are unlikely to attempt to manage a jaundiced patient with hepatitis without attempting to define the specific viral agent involved. Similarly, pharmaceutical companies are unlikely to attempt to develop novel vaccines or therapies without precise information about the disease type. Even in a well defined disease such as viral hepatitis, aspects of disease progression such as viral persistence will need to await genetic clarification.

Understanding the biological events and pathways identified by genetics as contributing to disease will lead to clear definition of disease. Such information may become the starting point in the management of most patients.

A new taxonomy of disease based on genetics is already being developed. The first examples of disease definition have come from the loci in common disease that seem to resemble autosomally inherited traits in families. Although these contribute to disease in only a small proportion of affected people, they provide considerable insights into disease mechanisms. Breast cancer (BRCA1, BRCA2),[7,8] colon cancer (FAP, HNPCC),[9] and diabetes (MODY 1, 2 and 3)[10–12] all have such highly penetrant loci, and their elucidation has provided some of the first insights into disease pathogenesis. The controversy over the potential role of impaired insulin secretion versus insulin resistance has been clarified by our understanding of mechanisms that result in each type of pathophysiology (glucokinase mutations versus insulin receptor mutations). Disease genes that contribute a component of susceptibility but require other genetic and environmental factors for disease to occur are also now available for disease definition. Apo E4 involvement in Alzheimer's disease is leading to revelations about its pathogenesis,[13] while angiotensin converting enzyme[14] and angiotensinogen[15] probably contribute to different forms of cardiovascular disease in more predictable ways. The result of these developments is that we are beginning to move toward a refined taxonomy in medicine that is based on biochemical mechanisms and driven by genetics.

BIOPHOTO ASSOCIATES/SPL

Understanding of how genes might modify our susceptibility to disease is evolving

## Genetic information in clinical practice

### Early diagnosis, patient stratification, and improved management

With an increasing trend to focus healthcare resources so that they are most efficiently used, to develop accurate definition of disease to predict its clinical course, to target other forms of screening, and to choose optimal treatment, it is likely that genetic information will be an essential part of future clinical practice. Already it is possible to identify people at high risk of breast or colon cancer and to focus screening (such as mammography or colonoscopy) or early interventional treatment on these groups. In both breast and colon cancer we understand the genetic basis for about 5% of cases, a sufficiently large number of patients to overwhelm the already stretched genetic screening capacity in the United Kingdom. As we learn more about the effect of individual mutations on phenotype and as we identify more high frequency, low penetrance genes in both of these diseases, the pressure for screening in populations with and without symptoms will increase. Similarly, in diabetes, both the aetiological mutations (HNF, glucokinase)[10,11] and other loci (ACE)[16] contribute to the course of the disease or the frequency of complications; hence these and other genes will be important prognostic indicators for those managing the disease and will need to be tested for. Even relatively simple management decisions regarding individuals at risk of deep venous thrombosis (patients with total hip replacement, or those taking the oral contraceptive pill) may benefit from evaluation of their factor V Leiden status.[17] Decisions about the best treatment (CETP alleles and statins, 5′-lipooxygenase in asthma, or tacrine in Alzheimer's disease) or the side effects of drugs (cytochrome P-450 and flecanide) may rely on genetic stratification.[18] These and many other indications for the use of genetic screening in patients with disease are likely to emerge in the coming years, and the pressure from patients and doctors for such services is likely to increase steadily.

### Discovery and development of drugs

One of the earliest applications of this genetic information will be in the discovery and development of new drugs. Genetics is now widely used to identify new targets for drug designs, and it is increasingly recognised that defining disease populations by genotype will probably correlate with response to drug treatment. The variety of mechanisms that underlie complex disease may account for the wide variations in response seen in clinical practice and the difficulty often encountered in

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**Clinical benefit accruing from genetic studies of disease**

- A new taxonomy of disease based on mechanisms, not phenotype
- New drugs developed rationally from our understanding of pathogenesis
- Drug development and utilisation focused on disease subtypes likely to respond to treatment
- Adverse effects of drugs avoided by genetic screening
- "Risk factor" analysis will facilitate environmental modification, screening, and therapeutic management of people before they develop symptoms

drug development of showing consistent large benefits in trial populations. Wise pharmaceutical companies are already introducing genotyping in their trials to predict response, and eventually this information will be needed to protect individuals from receiving a drug if they are unlikely to respond to it. Effort will also be focused on defining more clearly the basis for severe side effects of drugs and not giving them to people likely to experience side effects. Disease definition and drug response will go hand in hand, and lifelong treatment is unlikely unless an accurate genetic diagnosis provides an indication of response. Development of drugs along genetic guidelines will be a major force driving implementation of genetic screening by healthcare providers, as both response to treatment and complications will have been defined genetically for many new therapeutic agents.

## Genes as risk factors

An indication of how important genetic information will be in defining disease and predicting outcomes in complex diseases can be gained from our knowledge of Apo E4 and Alzheimer's disease. Homozygosity for this allele is associated with a shift of about 20 years in the average age of onset of Alzheimer's disease.[13] These effects are at least as great as other more conventional risk factors in common disease (such as hypertension in hypercholesterolaemia). Although current recommendations suggest that Apo E genotyping be used as an adjunct to diagnosis in cognitively impaired people, it is likely that genetic stratification by Apo E genotype will define drug response, and hence such genotyping may soon be applied in clinical trials and eventually will be more relevant to daily clinical practice.

Examples such as Apo E4 raise the question of whether a genetic susceptibility factor might best be treated as another "risk factor." Other risk factors (blood pressure or cholesterol concentrations) show similar patterns of incomplete penetrance and have been considered for population screening. There is little reason that risk factors based on DNA should not be treated in the same way. Genetic factors that can be used to predict the risk of a population rather than an individual should be viewed in the same way as other risk factors, particularly if safe treatment or environmental modification were available.

This raises the possibility of population screening to detect important susceptibility loci when intervention becomes available. The obvious requirement for such screening would be validation by large scale trials on the benefits of such early detection and treatment. A combination of conventional and genetic risk factors may be optimal for identifying populations at risk. In hypertension or hypercholesterolaemia, risks vary greatly. Treating the extremes of variation has the most favourable cost benefit ratio, but most "at risk" patients fall within the normal range. Genetics could be used to identify those who have additional genetic risks and in whom reduction of these variables might be beneficial, even where such variables might be in the "normal" range. There are some trial data to support such an approach.[19]

## Conclusion

The widespread redefinition of disease through genetics will be accompanied by the use of genetics for prediction and diagnosis and to optimise treatment in most common diseases. This is likely to occur within the next decade. Testing for genetic "risk factors," even in people without symptoms, may develop (as it has for other risk factors), and this information may be used to identify people at increased risk, for early intervention. There is a possibility, however, that DNA diagnostics and pharmacogenomics will be used without proper evaluation—especially as few resources are available for rigorous evaluation and pressure continues to introduce this information in routine clinical practice.

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*Continuing medical education*

# Quality issues in continuing medical education

Hans Asbjørn Holm

The need for continuous learning as part of a doctor's professional career is evident. The best ways of introducing and nurturing this learning have been the subject of much controversy, and the quality of medical education at all levels is being questioned and debated in many countries. This article looks at some trends and issues that are being addressed in order to improve the effectiveness of doctors' continuous learning.

## Contribution of learning theory to medical education

Innovations in undergraduate medical education are influencing the whole spectrum of medical education. So too is the growing literature on adult learning[1–4] and the doctor as learner.[5 6] The works of Schön especially clarify the importance of the professionals' reflection on their everyday practice as a means of continuous change and learning.[7 8]

Clinical problem solving has been identified as the core activity of how doctors learn and keep developing their competence. Creating an environment that provides practitioners with opportunities to explore and understand the personal theories underpinning their own practice is crucial for continuous professional development at all stages.[9]

## Continuing medical education

Although a division of medical education into stages—undergraduate, postgraduate, and continuing medical education (CME)—seems sound from a regulatory and legal perspective, there are no fundamental differences in the way people learn across the continuum. The student often is told what to learn, but the qualified doctor is responsible for directing his or her own (lifelong) learning.[10]

Most doctors work in teams with other doctors, other health professionals, and administrators. Successful functioning depends not only on the doctor but on the performance of the whole team. This multiprofessional team represents a complex learning system which must be reflected in the planning of CME.[11]

## Motivation for continuous learning

What is it that keeps doctors striving to maintain their competence throughout decades of professional life?

**Self directed learning**

"A process in which learners take the initiative . . . for increasing self and social awareness; critically analysing and reflecting on their work . . . defining their learning needs . . . formulating goals . . . identifying human and material resources for learning . . . choosing appropriate learning strategies . . . and reflecting on and evaluating their learning." [4]

### Summary points

A doctor's desire to be more competent in the delivery of health care is the most important motivating factor for continuous learning and change

Continuing medical education must be planned to meet the needs of doctor and based on both self assessment and peer review

The role of mandatory traditional programmes in maintaining competence is questionable

Medical colleges and societies need to improve their educational competence to be able to deliver high quality continuing medical education

More programmes should be linked to the workplace; they should include group based activities and use quality improvement tools

The driving force among the outstanding doctors interviewed in different working environments by Manning and DeBakey was "their pride in performance—a desire never to be (or to be seen as) professionally inadequate." [12] Similarly, in the physician change study the desire to be more competent in the delivery of health care to patients was the key force for change; regulations had little impact.[13]

Strict legislative and regulatory measures are thus not likely to be an effective way of maintaining professional competence. Reliable and valid identification of those few doctors whose practice falls well below accepted standards requires well planned and rather expensive programmes.[14] These doctors undoubtably present a great challenge to the profession and to the licensing bodies. For them CME is hardly the "cure," and this must be acknowledged.[15]

## Mandatory or voluntary?

In the United States, most boards (licensing authorities) issue specialists with time limited certificates.[16] The need for doctors to get recertified every few years to retain their "board certified" status has fuelled a multibillion dollar enterprise. This consists mostly of didactic courses offered to doctors in need of credit hours to meet recertification requirements.

The rationale for time limited certificates is twofold: firstly, to encourage doctors to learn and keep up to date; secondly, to identify those doctors who continue to meet the specialty boards standards—and those who do not.[16]

In Europe, participation in CME programmes is largely voluntary, but both the European Union of Medical Specialists and the Standing Committee of

**This is the fifth in a series of seven articles looking at international trends and forces in doctors' continuing professional development**

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DAVID HITCH

European Doctors have adopted charters which state that doctors have an ethical obligation or duty to undertake further education.[17 18] The European Union of General Practitioners, "recognising that moral responsibility alone is insufficient," has suggested that doctors should be given incentives to participate in CME activities.[19]

The impact of credit hours of traditional courses on the quality of practice is, however, disputable, and traditional CME may have impeded development of more effective ways of promoting continued learning.[20] In one study the number of reported continuing education hours was found to correlate positively with lower competence.[21] The most important issue in continuing medical education is the quality of the education programmes on offer, not whether they are voluntary or mandatory.

## Competence and accountability

Although competence is often taken as an all embracing term, it is important to distinguish between competence and performance. What the doctor does in day to day practice (performance) does not always corresponds to what he or she is assessed as being capable of doing (competence). No simple and effective way of assessing doctors' competence and performance has as yet been developed. The approach developed by the College of Physicians and Surgeons of Ontario (Canada) is probably the most systematic.[14]

The issue of professional accountability is crucial for doctors. Public expectations and demands are growing, and people expect their doctor to meet set standards. If they do not, it is right for the public to expect these doctors to be identified and removed from practice. The profession needs to acknowledge this fully and implement policies to meet this challenge if it is to escape the imposition of external regulations of doubtful benefit to continued learning. It is therefore important that those responsible for continued medical education ensure that their methods of assessment of doctors' competence and performance are evidence based and promote self directed learning.

## Needs assessment

Identification of learning needs is the basis for planning of continuing education—for individuals, organisations, and the professional organisations responsible for medical training. The medical competence of medical colleges and societies is high, but professional educational expertise has until recently been rather scarce. This may have impeded the planning, implementation, and evaluation of more effective programmes.

Who defines the needs and how they do it is important. Medical audit in its classic form is intended to assess practice against a set of predetermined criteria. It is often carried out as a peer review and is probably more often experienced as a quality control mechanism rather than a basis for defining learning needs. A system of self assessment is preferable if the emphasis is on education and continuous learning rather than the identification of poor performers.

Whether self assessment leads to identification of real needs, and whether these needs can be adequately met by CME, are research issues of interest to the profession and the public.

## Continuous quality improvement

In countries where recertification systems are in place, these are based mainly on documented participation in formal educational activities, while actual performance is seldom subject to assessment. Some organisations, such as the Royal College of Anaesthetists,[23] consider a wider area of activities as eligible for CME credits.

These initiatives reflect a broader understanding of how doctors learn and could be a step towards viewing CME as part of the quality improvement systems that are being developed in hospitals and general practice. There are arguments put forward, however, that the "narrow, professional control of evaluation, buttressed by the quality assurance and monitoring mechanisms of the Colleges, is inappropriate, given the increasingly diverse accountabilities which affect medical professionals." [24]

### Portfolio-based learning

Ten years ago it was shown that doctors could meet specialty board requirements for recertification by set-

**Research issues in self learning**

"There is a need to develop tools to measure or assess the presence of self-reflection or self-learning. The application of such tools, passing methodological criteria hurdles, would ensure that physicians at some internal level: (1) recognize their learning deficiencies in the context of patient care or professionalism; (2) possess the ability to reflect on their practices; and (3) measure these needs against external and internal standards set by peers, regulatory bodies, patients, policies, the literature, and (perhaps most of all) themselves." [22]

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ting up their own learning plans.[25] The Canadian Maintenance of Competence Programme (MOCOMP), a portfolio-based documentation of individual learning, takes this further. It acknowledges that learning takes place daily in the practice environment, and it provides a system for documenting such learning.[26] To facilitate entries and comparison with peers a computerised diary (PCDiary) has been developed.[16]

In Britain, portfolio-based learning has been recommended by a working group appointed by the Royal College of General Practitioners.[27] In the Sheffield region such a programme has already been developed; it consists of a personal education plan, a portfolio to document progress towards attainment of the plan, and mutual support through a co-mentoring group.[28] Evaluation of such programmes is vital to answer the questions such as whether doctors who use PCDiary as a learning portfolio provide a more objective assessment of their practice needs than their colleagues, and whether we can trust self determined needs.

The way forward, therefore, is to find methods to improve doctors' capacity to define their learning needs, and then to deal with these needs (by asking the right questions and finding the right answers). In terms of continuous quality improvement, this could be seen as a bottom-up approach rather than the top-down approach that is characteristic of traditional CME. Then the key challenge is to establish whether this approach leads to improved performance and improved patient outcome.

## Quality improvement among general practitioners

General practitioners in Europe are introduced to projects representing various methodologies of quality improvement and learning (assessment and audit, guideline setting, and small group peer review and quality circles).[29] Regular and systematic data collection and assessment as part of daily clinical work is, however, still not very well developed.

In Canada, a practice based, small group learning programme for general practitioners has been developed at McMaster University. The programme offers educational material covering a range of topics, mostly based on requests from the participants, and offers training workshops for facilitators. Most of the 2000 or so doctors who have participated in the programme have reported changing their practice as a result (J Premi, personal communication).

In 1995 Danish general practitioners secured funding from their national insurance company for decentralised, group based CME. About 70% of Danish general practitioners are enrolled on a voluntary basis. One of the group members is appointed tutor by his or her peers. The Danish Medical Association offers training for tutors. In addition, each county has one or two specially trained facilitators (recruited from general practitioners in the area) who help the groups in organising their work. Otherwise the groups are self directed and define their own learning needs.

In Norway, more than 95% of eligible laboratories in general practitioners' surgeries are enrolled on a voluntary basis in a quality improvmeent project of laboratory analyses. Every year since inception in 1993, quality has improved. A mentoring service, carried out by specialist doctors and medical technologists, gives feedback to the team working in the surgery on how they work and how they can improve. Currently, the programme is moving further, challenging the doctors to examine the rationale behind their choices of analyses in given cases.[30]

**SATS project, Norway**

Linking continuous quality improvement and continuing medical education: a project aimed at improving care in a general practice setting.

*Example: Acute sore throat*

Objectives: Antibiotics should be prescribed when the clinical picture points to group A streptococcal infection.

Structure: (The indicators describe how the clinic is equipped to facilitate optimal diagnostic procedure.)
Does the clinic have guidelines for the condition?
Is the streptococcal test available, as well as guidelines for its use?

Process:
Is there a positive antigen test or are clinical criteria fulfilled when antibiotics have been given and ICPC (international classification in primary health care) diagnosis is R72 or 76?
If antibiotic other than penicillin V has been prescribed, does the patient suffer from penicillin allergy or relapse?

Results:
Has a relapse been recorded within two weeks?
Has the patient reported being unchanged or worse after 3-4 days despite antibiotic treatment?

Another Norwegian project, SATS (quality indicators in general practice), which also has its parallels in other countries, is aiming at developing continuous quality improvement in primary health care by introducing indicators (pertaining to structure, process, and result) for the assessment of quality and setting of standards in the local practice; developing software to simplify the collection of data and generation of reports from computerised medical records; and supporting peer groups of 5-10 practitioners willing to discuss results, agree on local standards, and plan improvements.[31] Participants earn credits for certification or recertification as general practice specialists.

Although medical decision making is seldom based solely on "pure" evidence, using the best available evidence is a challenge and an ethical obligation that needs to be addressed at all stages of medical education. "Good doctors use both individual clinical expertise and the best available external evidence and neither alone is enough." [32] It is likely that the ability to systematically reflect on clinical problems, which underpins the ideology of the SATS programme, may improve doctors' "reflective competence" in other spheres of their work.

## Conclusions

The challenge of maintaining professional competence in an environment characterised by rapid organizational change, information overload, and increasing public expectations is forcing doctors to think hard about medical education. Adult learning theory and knowledge of how professionals maintain

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and develop competence are placing increased emphasis on self directed learning and pointing to clinical practice and problem solving as key areas of interest. The ability to work in teams is also recognised as essential.[33]

Academic institutions and medical organisations need to improve their educational competence, show a stronger commitment to educational research, and value faculty members who take on these duties. Certification and recertification requirements must be tuned to support continuing professional development and continuing quality improvement if they are not to be rejected. CME must become a more visible, integrated, and well planned activity for which both protected time and adequate funds must be provided.


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*A memorable patient*

## Good luck in your examination

By the time I first met Bill, he had suffered the ravages of severe rheumatoid arthritis for over 20 years. Ever cheerful, he attended the clinic regularly, participating in many of the clinical trials of now established medication, in the course of which he had experienced the all too common side effects of both these drugs and others which had been used to try and control his disease. He had even had his fair share of orthopaedic surgery with indifferent results. Formerly an engineer by trade, he had worked for as long as he could but had been registered disabled for several years.

As the new senior registrar in the department, it was my turn to arrange the patients for the forthcoming student exams. A colleague mentioned to me that Bill always came to the exams and was an exceptionally good patient for those nervous students and ones who might be thought to be on the borderline. This intrigued me and on the day of the exam ushered into him a rather timid student whom we had been concerned would not perform well. I listened outside the curtain of the cubicle with interest. Instead of hearing the faltering tones of a nervous student starting his clerking, I heard Bill's firm voice issue the following commands: "Sit down, shut up, and take notes. My name is Bill, I suffer from rheumatoid arthritis which developed 20 years ago. At that stage, I started with symmetrical swelling of the proximal interphalangeal and metacarpophalangeal joints of my hands."

He then proceeded to give a textbook description of the progression of his disease, the tests that had been done to make the diagnosis, and the range of drugs and orthopaedic procedures to which he had been subjected. His pharmacological knowledge was quite breathtaking, giving a chronological description of all his medication, its attendant side effects, and the appropriate tests needed for its monitoring. He even included remarks concerning the social and psychological effect that the disease had had on him and his family. It was a tour de force which would have graced any rheumatology textbook.

Needless to say, Bill's student got an A. In fact I learnt that Bill's students always got As and it was a matter of pride to him that they did. He took his role as an exam patient extremely seriously, and it gave him pride to feel that he was contributing to the education of young doctors.

Sadly, he was able to do this for only another couple of years, succumbing then to the inevitable consequences of his terrible disease. It was a privilege to have known him and I am sure that there will be a fair number of doctors now practising who will have benefited from meeting this truly memorable patient.

GR Struthers, *consultant rheumatologist, Coventry*

We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from a patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.

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