Errors and Misconceptions in Drug Prescribing

LINDA BEELEY, MD, MRCP,
Lecturer in Clinical Pharmacology, University of Birmingham

The information required to ensure that drugs are used with the maximum benefit to patients falls into several categories (Table 1). Pharmacodynamic and pharmacokinetic studies determine the mode of action and the optimum dose regimen of a drug; efficacy is established by clinical evaluation, most commonly now in the form of controlled clinical trials; and identification and quantification of the risks of treatment occur both during the evaluation of efficacy and later as a result of adverse drug reaction monitoring. This information tells us how we should be using drugs and what the potential benefits and risks of treatment might be; and it enables us to propose rational prescribing policies. These will always be to some extent provisional. Drugs and their effects on disease continue to be studied long after they are in regular use, and new information must be translated into appropriate modifications of prescribing. This is especially true of traditional therapy with established drugs, the use of which will have evolved by a process of trial and error without much of the information we now accept as necessary for optimum drug use.

Table 1. Information required for an audit of prescribing.

Pharmacokinetic Optimum dose regimes, etc Therapeutic efficacy Risks of treatment Short and long-term Predisposing factors Cost of treatment	Rational prescribing policy
	Current prescribing practices What are they? Why?

Therapeutic audit is the process whereby we attempt to assess to what extent our use of drugs is rational in the light of available information, and what the benefits and risks are in everyday practice. The purpose of such audit is to bring about changes in drug use where necessary, and this requires that we study also the factors that influence prescribing.

The functions of clinical pharmacology are thus threefold: to provide the information on which rational prescribing is based; to monitor and evaluate new information as it arises and to ensure that, where necessary, it is used to modify prescribing; and to measure and influence the extent to which prescribing is rational and beneficial in everyday practice.

I propose to illustrate this by considering some common errors and misconceptions in the prescribing of potassium supplements to patients receiving diuretics for treatment of hypertension or cardiac failure.

It has been standard practice to give potassium supplements to patients on diuretics ever since the introduction of the first thiazide (chlorothiazide) in 1957. At the time, this appeared entirely rational, as thiazides were known to increase potassium excretion and some patients became hypokalaemic. However, over the past ten years a large amount of published work has cast considerable doubt on the validity of this dogma. Confusion now reigns over the use of potassium supplements and is reflected in irrational prescribing.

A rational prescribing policy for potassium needs to be formulated and I shall discuss how present prescribing habits differ from this and why.

Do Diuretics Produce Potassium Depletion?

There is no question that the thiazides and related diuretics, and the loop diuretics—frusemide, bumetanide and ethacrynic acid—increase the renal clearance of potassium. Acute administration can produce a fall in serum potassium within 24 hours and the magnitude of this is related to the diuresis produced. The long-term effects of diuretics on potassium have been exhaustively studied and disputed over the past ten years, and it is only recently that the facts have become reasonably well-established.

In hypertensive patients treated with thiazides or related diuretics a fall in serum potassium is common[1-4]. It usually occurs early in treatment, within the first two weeks, and is not progressive; but it can develop gradually over a longer period. Although many patients will have a serum potassium level between 3.0 and 3.5 mmol/litre, levels below 3.0 mmol/litre are uncommon. This mild hypokalaemia is associated with only a small reduction in total body potassium of 5-10 per cent, or around 200 mmol of potassium, and larger falls in total body potassium do not seem to occur.

In patients with heart failure the situation is more complex. Patients with severe failure have a total body potassium deficit the magnitude of which increases with the severity of the heart failure. Most of it can be accounted for by the loss of muscle mass[5], though an

intracellular deficit has also been demonstrated[6]. Hypokalaemia is less common than in patients with hypertension and the fall in total body potassium is not related to either hypokalaemia or the use of diuretics[7]. Patients with mild cardiac failure show a much smaller deficit in total body potassium, similar to that found in hypertensive patients.

Factors that Predispose to Hypokalaemia

The Choice of Diuretic

It is a common misconception that the loop diuretics produce a greater fall in serum potassium than the thiazides. In fact, for an equivalent diuretic effect, the opposite is true and this is reflected in the lower incidence of hypokalaemia in patients on long-term treatment with these diuretics[2, 8-10]. The difference is probably related to duration of action and may be one reason why patients with heart failure become hypokalaemic less commonly than those with hypertension.

The Dose of Diuretic

Diuretic-induced hypokalaemia is dose-related[11]. With the loop diuretics the therapeutic effect (diuresis) is also dose related over a wide range, but the antihypertensive effect of the thiazides shows a flat dose-response curve such that a near maximal effect is achieved with small doses, e.g. bendrofluazide 2.5—5 mg, or chlorthalidone 25 mg daily[11]. Increasing the dose of a thiazide to the top of the recommended range has little further antihypertensive effect but increases the risk of hypokalaemia.

Salt Intake

Dietary sodium restriction was an important part of treatment of heart failure before the introduction of the thiazide diuretics made it unnecessary. There is no longer any place for extreme sodium restriction but in patients with heart failure a moderate reduction of salt intake in patients on diuretics can have an important effect on potassium loss[12] partly by allowing smaller doses of diuretics to be used and partly because renal potassium loss is related to sodium intake. This is particularly true in severe heart failure because the contribution of secondary hyperaldosteronism to potassium loss is also sodium dependent.

The effect of sodium restriction on the development of hypokalaemia in hypertensive patients is unknown.

Potassium Intake and Age

Dietary deficiency by itself probably does not lead to potassium depletion unless intake falls below the level at which renal conservation can compensate, i.e. somewhere between 15 and 30 mmol/day, but reduced intake potentiates the effect of diuretics on potassium. Several studies have shown that the dietary intake of potassium is reduced in the elderly, particularly in elderly women, many of whom have an intake of less than 50 mmol/day[13, 14]. Hypokalaemia is no more common in healthy elderly people[15] but there is some evidence that it develops more readily when they are ill or are treated with diuretics[16, 17].

Other Drugs

The combination of diuretics with other drugs producing potassium loss commonly produces hypokalaemia. Corticosteroids, ACTH and carbenoxolone are the most important ones, and the combination of carbenoxolone and diuretics can produce profound hypokalaemia[18].

Thus, diuretics do produce a fall in serum potassium, particularly in patients with hypertension; but serum levels rarely fall much below 3.5 mmol/litre; and there is no evidence that they are associated with more than a small, and probably unimportant, fall in total body potassium. The total body potassium deficit that occurs in patients with severe heart failure is not a consequence of diuretic therapy.

Does Hypokalaemia Matter?

There is no doubt that severe hypokalaemia, usually associated with potassium depletion, can produce ill-effects (Table 2), but it is less clear how often the hypokalaemia produced by diuretics is harmful. Considering the extensive use of diuretics, there is a remarkable lack of reports of serious adverse effects attributed to hypokalaemia; and in hospital surveys of reactions to diuretics and the studies of patients on long-term diuretics for hypertension it is usually a biochemical finding unassociated with overt symptoms or serious consequences[19-21].

Table 2. Harmful effects attributed to hypokalaemia.

Cardiac effects	ECG changes
	Arrhythmias
	Potentiation of digitalis toxicity
Muscle weakness	
Paralytic ileus	
Nephropathy	
Impaired glucose tolerance	
Miscellaneous symptoms	Constipation
	Malaise
	Anorexia
	Apathy
	Mental confusion
	Weakness

Hypokalaemia produces characteristic ECG changes and can cause cardiac arrhythmias especially in patients with heart disease or receiving digitalis[22, 23]. However, the frequency with which arrhythmias occur in patients with chronic mild hypokalaemia produced by diuretics is unknown. In hypertensive patients given sufficient bendrofluazide to produce hypokalaemia there appears to be a threshold for hypokalaemic ECG changes around 3.0 mmol K^+/litre[24], but whether this is correlated with an increased risk of arrhythmias is also unknown.

Arrhythmias are rarely reported in the many hospital surveys of diuretic-induced hypokalaemia[19, 20] but there is some evidence that hypokalaemia associated with previous diuretic therapy increases the risk of arrhythmias after myocardial infarction [25, 26]. Although it is generally accepted that diuretics increase the risk of digitalis toxicity by producing hypokalaemia the evidence for this is circumstantial and the literature on the subject confusing. Some epidemiological studies of digitalis toxicity have failed to show any correlation with hypokalaemia[27, 28]; others have found an increased incidence of toxicity in patients on diuretics[29] and in patients with hypokalaemia attributed to diuretics[30], with toxicity occurring at lower plasma digoxin levels in hypokalaemic patients[31]. Acute potassium depletion produced by diuretics in patients with severe cardiac failure on digoxin can produce arrhythmias with no change in serum digoxin levels, and the few patients who develop arrhythmias in surveys of diuretic-induced hypokalaemia are usually on digitalis[19]. The exact mechanism involved, the level of hypokalaemia below which the risk of digitalis toxicity is increased, and the role of intracellular potassium depletion have not been established[32, 33]. However, despite the confusion on this subject, there is sufficient evidence to suggest that hypokalaemia should be prevented as far as possible in patients on digitalis and in those with acute myocardial infarction or other serious heart disease.

Muscle weakness, paralytic ileus and hypokalaemic nephropathy are well-documented consequences of severe potassium depletion and have been described in association with laxative abuse[34] and with carbenoxolone[18, 35, 36]. They have not, to my knowledge, been reported in patients on diuretics alone.

Symptoms attributed to mild potassium depletion in elderly patients include weakness, apathy, confusion, constipation and abdominal distension. Although there is some evidence that these are improved by giving potassium[17] they are difficult to assess and a causal relationship remains unproven.

Deterioration in glucose tolerance is well documented in hypertensive patients on long-term treatment with thiazide diuretics[37, 38], and has been reported, though less frequently, in association with the loop diuretics. The mechanism is not well understood and although it has been suggested that potassium depletion might be responsible, the evidence for this is circumstantial and conflicting. Potassium stimulates insulin secretion experimentally[39], and the impaired glucose tolerance in patients with hypokalaemia due to hyperaldosteronism can be corrected by giving potassium[40]. In one long-term study of hypertensive patients no correlation between deterioration of glucose tolerance and hypokalaemia was found[38], but results from the European working party on hypertension in the elderly suggest that there may be a correlation[37]. Whether or not hypokalaemia is responsible, the deterioration in glucose tolerance is small and probably of minor importance, at least so far as cardiovascular morbidity and mortality are concerned[41].

Thus, there is little evidence that it is necessary to do anything about the mild hypokalaemia usually produced by diuretics. It seems reasonable to try to prevent the serum potassium falling below an arbitrary level somewhere between 3.0 and 3.5 mmol/litre, and particular care should be taken to prevent hypokalaemia in patients with severe heart disease, or who are on digitalis.

Can Hypokalaemia be Prevented by Prophylactic Treatment?

Most of the published evidence suggests that potassium supplements have a limited effect in preventing diuretic-induced hypokalaemia. In patients with hypertension they will produce an increase in serum potassium but this is dose-related and is small with the doses normally used[2, 42, 43]. Under controlled conditions, in patients on 10 mg of bendrofluazide daily, 64 mmol (8 Slow K tablets) daily were required to produce a mean rise in serum potassium of 0.44 mmol/litre while 16 mmol (2 Slow K tablets) increased it by only 0.15 mmol/litre[42]. The results of studies in patients on long-term diuretics are conflicting. Most have found no correlation between serum potassium and the intake of potassium supplements[2, 8, 16, 44, 45, 46], but there is evidence in hypertensive patients that, used in an average dose of 24 mmol daily, they are associated with a modest increase in serum potassium and can reduce the incidence of hypokalaemia[1, 2]. In patients on frusemide in hospital the incidence of hypokalaemia is unrelated to the administration of potassium supplements[20].

Potassium-sparing diuretics are more effective in producing a rise in serum potassium and in preventing diuretic-induced hypokalaemia[46, 48], though there is some evidence that the effect of amiloride may decline over a period of six months[49].

With potassium supplements the increased intake of potassium is balanced by an increased urinary excretion and no change in total body potassium occurs[43, 46, 50]. In patients with hypertension there is some evidence that potassium-sparing diuretics can increase total body potassium[51], but they do not do so in patients with heart failure[46] probably because, at least in severe failure, the deficit is unrelated to diuretic therapy.

Finally, although it seems sensible to try to ensure a reasonable dietary intake of potassium, I am not aware of any evidence that increasing the dietary intake of potassium in patients already on an adequate diet will prevent diuretic-induced hypokalaemia.

Does Prophylactic Treatment Carry Any Risks?

Hyperkalaemia occurs in about 3.5 per cent of hospital inpatients receiving potassium supplements[52] with or without potassium-sparing diuretics, and is one of the commoner causes of life-threatening or fatal adverse reactions to drugs in hospital[52-54]. Of hospital patients on spironolactone, 8.6 per cent develop hyperkalaemia and this increases to 15.8 per cent for patients also receiving potassium supplements[55]. The incidence of hyperkalaemia increases with age and if renal function is

impaired[52, 55, 56] but cardiac arrest and death due to large oral doses of potassium have been reported even in patients with apparently normal renal function[57].

Thus, there is no doubt that potassium supplements and potassium sparing diuretics are potentially dangerous, and this is especially true in patients with poor renal function. Renal function deteriorates with age and it is likely that this contributes to the increased incidence of hyperkalaemia in older patients.

A possible hazard of lesser degrees of hyperkalaemia produced by potassium supplements or by potassium-sparing diuretics relates to the possibility of potentiation of the effect of beta-blockers on potassium. In normal people the serum potassium rises transiently during exercise. This is thought to be due to catecholamine-induced release of potassium from the liver followed by re-uptake, and the latter is mediated via $beta_2$-receptors. Non-selective and, to a lesser extent, selective beta-blockers potentiate the effect of exercise, delaying the recovery of the serum potassium at the end of exercise[58]. The frequency and magnitude of this effect are unknown but it could be important in some patients, especially if already hyperkalaemic as a result of over-enthusiastic use of potassium or a potassium-sparing diuretic, and if they indulge in strenuous exercise.

Intestinal ulceration was originally reported with enteric-coated potassium-containing preparations and was probably due to release of high concentrations of potassium chloride at a localised site. Enteric-coated preparations are no longer marketed and the slow-release preparations now used release potassium gradually during their passage through the gastrointestinal tract. However, ulceration can still occur in patients with delayed transit or obstruction. Thus, Slow-K tablets have produced oesophageal ulceration and strictures in patients with left atrial enlargement due to mitral stenosis[59]; and ulceration, strictures and perforation of the small bowel have been reported with both Slow-K[60, 61] and with Navidrex-K[62].

One important disadvantage of prescribing an adequate dose of a potassium supplement is that it complicates treatment. In general, compliance with treatment falls and the error rate increases as treatment becomes more complex[63]. There is evidence that many patients fail to take potassium supplements[63, 64] and it is a reasonable assumption that the increased number of tablets may increase the risk of non-compliance with their other treatment. The extent to which non-compliance contributes to the failure of potassium supplements to prevent hypokalaemia in long-term studies is unknown.

A Rational Prescribing Policy for Potassium

On the basis of the facts presented above, I suggest that the following points should form the basis of a rational policy for prescribing potassium for patients on diuretics for hypertension or heart failure.

1. Routine prophylaxis against diuretic-induced hypokalaemia is unnecessary and should be reserved for patients at risk.
2. Several simple measures will reduce the likelihood of diuretic-induced hypokalaemia:

   Ensuring an adequate dietary intake of potassium, especially in elderly patients.

   Using small doses of thiazides in hypertension. If control is inadequate a beta-blocker may help to prevent hypokalaemia in addition to its anti-hypertensive effect[65-67].

   Using a loop diuretic rather than a thiazide for patients with heart failure. The diuretic effect of the smallest doses of frusemide or bumetanide is no greater than that of standard doses of thiazides, and potassium loss is less.

   Moderate restriction of the salt intake of patients on diuretics for heart failure. It should be possible to reduce sodium intake to around 70-80 mmol/day by avoiding salty foods and not adding salt at table.
3. Potassium supplements are an inefficient way of preventing or correcting hypokalaemia unless given in doses that are unacceptable to many patients. The use of combined diuretic/potassium preparations (Table 3) is irrational because:

Table 3. Potassium content of some combined diuretic and potassium preparations.

	Diuretic	Dose (mg)	Potassium (mmol)
Burinex-K	Bumetanide	0.5	7.7
Centyl-K	Bendrofluazide	2.5	7.7
Hygroton-K	Chlorthalidone	25	6.7
Lasikal	Frusemide	20	10
Navidrex-K	Cyclopenthiazide	0.25	8
Neo-Naclex-K	Bendrofluazide	2.5	8.4

   The small dose of diuretic they contain is very unlikely to produce hypokalaemia.

   The dose of potassium is too small to prevent or correct hypokalaemia in patients at risk—and may indeed be harmful if it produces a false sense of security in patients who require adequate prophylaxis.

   They are more expensive than the equivalent dose of the same diuretic without potassium.
4. Potassium-sparing diuretics should be used to treat hypokalaemia if it occurs, and for prophylaxis in patients at risk.
5. The risks associated with the injudicious use of potassium supplements and potassium-sparing diuretics are greater than those associated with the degree of hypokalaemia produced in most patients by long-term diuretics.
6. The saving in cost to the Health Service could be considerable if potassium supplements and potassium-sparing diuretics were given only to patients who need them (Table 4).

Table 4. Cost of preventive measures.

	Constituents	Daily Dose (tablets)	Approximate annual cost (£)
Neo-Naclex-K	Bendrofluazide 2.5 K^+ 8.4 mmol	1	3.0
Bendrofluazide BP	Bendrofluazide 2.5 mg	1	1.40
Slow-K	K^+ 8.0 mmol	3	5.70
		4	7.60
Dyazide	Hydrochlorothiazide 25 mg Triamterene 50 mg	1	13.00
Moduretic	Hydrochlorothiazide 50 mg Amiloride 5 mg	1	23.00
Aldactide 25	Hydroflumethiazide 25 mg Spironolactone 25 mg	1	31.50
Aldactide 50	Hydroflumethiazide 50 mg Spironolactone 50 mg	1	60.00
Bumetanide-K	Burinex 0.5 mg K^+ 7.7 mmol	1	9.30
Bumetanide	Burinex 1 mg	½	5.70
Lasikal	Frusemide 20 mg K^+ 10 mmol	1	16.50
Lasix	Frusemide 20 mg	1	11.50
Frusemide BP	Frusemide 40 mg	½	4.00

Present Prescribing Habits

Despite the fact that potassium supplements are often ineffective and that most patients on diuretics do not need them, they are still widely used; and routine prophylactic use seems to be common[52, 68]. Their use bears no relation to the dose or type of diuretic used, the amount of potassium is frequently too small to have any appreciable effect, and they are commonly given in the form of a combined diuretic/potassium preparation[68]. In 1978, approximately nine million prescriptions were written for these combined preparations in general practice. Table 5 shows their use in the Queen Elizabeth Hospital where bendrofluazide is the thiazide most commonly used and Navidrex K is the main combined preparation. The number of tablets of Navidrex K dispensed by the pharmacy now exceeds that of bendrofluazide and this is shown also in the results of a one-day survey of diuretic prescribing in the hospital, in which we found that of a total of 25 patients on a thiazide diuretic 17 were having it in the form of a combined preparation.

Table 5. The use of diuretics and potassium supplements in the Queen Elizabeth Hospital, Birmingham.

	Number of Tablets Dispensed by the Pharmacy		
	Bendrofluazide 5 mg	Navidrex K	Slow-K + Sando-K
1977	21,000	6,000	110,000
1978	7,500	8,500	100,000
1979 (projected figures)	5,000	8,000	73,000

One-day Survey of Patients on Thiazides	
Thiazide alone	5
Thiazide + K^+ supplement	3
Navidrex K Centyl K	17
Total	25

In a recent study in Dundee of diuretics prescribed for patients leaving hospital over a period of three months, 70 per cent of patients on a thiazide or a loop diuretic and not on digoxin were receiving either a potassium supplement or a combined diuretic/potassium preparation (personal communication), and similar findings have been reported elsewhere[68].

Why are these combined preparations so popular? There could be many reasons but, assuming that doctors are influenced by the advice they are given, one reason may be that this is conflicting (Fig. 1). Another is that they are advertised on the basis of the assumption that potassium is needed routinely, and that to improve compliance it is an advantage to have them in the same tablet, as this is more convenient for the patient than

Figure 1

'Combination tablets of a diuretic with K should not be used routinely since many patients do not require a supplement and the amount of potassium is too low for many of those who do.' *(Drug and Therapeutics Bulletin*, 1978, **16**, 73.)

'I use cyclopenthiazide/potassium chloride (Navidrex K) 0.25 mg or 0.5 mg each morning . . . in mild failure.' (Hamer, J. (1979), *Medicine*, **19**, 982.)

taking a separate potassium supplement. (It is, of course, no more convenient than taking a diuretic alone.)

I have no direct evidence that the potassium-sparing diuretics are used unnecessarily, but in 1978 approximately four million prescriptions were written for the combined preparations containing a thiazide together with a potassium-sparing diuretic. If many of these were for patients who could have been treated as well with a thiazide alone, the unnecessary cost to the Health Service might have been substantial (see Table 4).

There is evidence[52, 55] that we are not sufficiently aware of the risk of hyperkalaemia. In a survey carried out in the Queen Elizabeth Hospital[56] of drug prescribing for 197 patients with renal impairment we found that 10 patients were receiving potassium or potassium-sparing diuretics despite an elevated serum potassium, and that this often went unnoticed until dangerously high levels were reached (Table 6).

Table 6. Serum potassium levels in patients given potassium salts or potassium-sparing diuretics.

Serum Creatinine (micromol/litre)	Serum Potassium (mmol/litre)	
	Initial	Highest during Treatment
195	4.4	5.5
196	4.7	5.6
268	4.0	7.9
271	4.9	6.8
327	4.9	5.6
477	4.4	6.0
604	5.7	6.1
715	4.5	8.5
1205	4.5	6.4
1865		6.8

Finally, I suspect that very few patients with heart failure today are given any advice about their salt intake. In a pilot study of the information given to patients receiving diuretics for heart failure in the Queen Elizabeth Hospital we found that only 2 of 18 patients had been given any information about restricting their salt intake, and neither had been given sufficient information to enable them to do this effectively. Since the standard hospital diet provides an average daily intake in excess of 100 mmol of sodium even without added salt, many patients will be receiving considerably more than this unless they are at least advised not to add salt at table. Opinions vary on the importance of salt restriction in patients with heart failure, but there is no doubt that it can reduce both the diuretic requirement and the risk of hypokalaemia[12].

Conclusion

Professor Grahame-Smith quoted Bertrand Russell's dictum 'Vagueness is the rebellion of truth against intellect', referring to the current uncertainties surrounding the use of digoxin. It describes the situation with potassium supplements equally well. I have reviewed the data relating to the 'truth'. The vagueness exists partly because there are still questions unanswered and partly because the traditional dogma seems so eminently reasonable. If diuretics increase the renal clearance of potassium, can it really be true that they do not produce clinically important potassium depletion? Maybe our methods for measuring depletion are inadequate. Are we perhaps wrong in thinking that a loss of 5 per cent of the body potassium or a mild degree of hypokalaemia produce no ill-effects? Maybe these are too non-specific to measure satisfactorily. If more potassium is coming out, surely it must be sensible to put more in? While accepting that some uncertainties remain to be clarified, I believe that much of our vagueness is irrational, based on a number of misconceptions, and sometimes containing errors that have the potential to do our patients more harm than good.

This article is based on a paper read at the College Regional Conference in Birmingham in September 1979.

References

1. Edmonds, C. J. and Jasani, B. (1972) *Lancet*, **2**, 8.
2. Ramsay, L. E., Boyle, P. and Ramsay, M. H. (1977) *Quarterly Journal of Medicine*, **46**, 401.
3. Leemhuis, M. P. and Struyvenberg, A. (1973) *Netherlands Journal of Medicine*, **16**, 18.
4. Wilkinson, P. R., Issler, H., Hesp, R. and Raftery, E. B. (1975) *Lancet*, **1**, 759.
5. Thomas, R. D., Silverton, N. P., Burkinshaw, L. and Morgan, D. B. (1979) *Lancet*, **2**, 9.
6. Edmondson, R. P. S., Thomas, R. D., Hilton, P. J., Patrick, J. and Jones, N. F. (1974) *Lancet*, **1**, 12.
7. Morgan, D. B., Burkinshaw, L. and Davidson, C. (1978) *Postgraduate Medical Journal*, **54**, 72.
8. Anderson, J., Godfrey, B. E., Hill, D. M., Munro-Faure, A. D. and Sheldon, J. (1971) *Quarterly Journal of Medicine*, **40**, 541.
9. Dargie, H. J., Boddy, K., Kennedy, A. C., King, P. C., Read, P. R. and Ward, D. M. (1974) *British Medical Journal*, **4**, 316.
10. Murchison, L. E., Bewsher, P. D. and Seymour, R. (1975) *British Journal of Clinical Pharmacology*, **2**, 87.
11. Bengtsson, C., Johnsson, G., Sannerstedt, R. and Werkö, L. (1975) *British Medical Journal*, **1**, 197.
12. Whight, C., Morgan, T., Carney, S. and Wilson, M. (1974) *Medical Journal of Australia*, **2**, 831.
13. Abdulla, M., Nordén, A. and Jägerstad, M. (1975) *Lancet*, **2**, 562.
14. Judge, T. G., Caird, F. I., Leask, R. G. S. and Macleod, C. C. (1974) *Age and Ageing*, **3**, 167.
15. Leask, R. G. S., Andrews, G. R. and Caird, F. I. (1973) *Age and Ageing*, **2**, 14.
16. Ibrahim, I. K., Ritch, A. E. S., Maclennan, W. J. and May, T. (1978) *Age and Ageing*, **7**, 165.
17. Judge, T. G. (1972) in *Nutrition in Old Age*, p.86, Stockholm: Swedish Nutrition Foundation.
18. Descamps, C., Vandenbroucke, J. M. and Van Ypersele de Stridhou, C. (1977) *British Medical Journal*, **1**, 272.
19. Greenblatt, D. J., Duhme, D. W., Allen, M. D. and Koch-Weser, J. (1977) *American Heart Journal*, **94**, 6.
20. Lowe, J., Gray, J., Henry, D. A. and Lawson, D. H. (1979) *British Medical Journal*, **2**, 360.
21. Beevers, D. G., Hamilton, M. and Harpur, J. E. (1971) *Postgraduate Medical Journal*, **47**, 639.
22. Curry, P., Fitchett, D., Stubbs, W. and Krikler, D. (1976) *Lancet*, **2**, 231.
23. Davidson, S. and Surawicz, B. (1967) *Archives of Internal Medicine*, **120**, 280.
24. Hettiarachichi, J. and Ramsay, L. E. (1979) *Proceedings of the British Pharmacological Society*, September. p.32.

25. Duke, M. (1978) *Journal of the American Medical Association,* **239,** 43.
26. Nesje, O. A. (1976) *Journal of the Norwegian Medical Association,* **24,** 1282.
27. Beller, G. A., Smith, T. W., Abelmann, W. H., Haber, E. and Hood, W. B. (1971) *New England Journal of Medicine,* **284,** 989.
28. Evered, D. C. and Chapman, C. (1971) *British Heart Journal,* **33,** 540.
29. Hurwitz, N. and Wade, O. L. (1969) *British Medical Journal,* **1,** 531.
30. Shapiro, S., Slone, D., Lewis, G. P. and Jick, H. (1969) *Journal of Chronic Disease,* **22,** 361.
31. Shapiro, W. and Taubert, K. (1975) *Lancet,* **2,** 604.
32. Steiness, E. and Olesen, K. H. (1976) *British Heart Journal,* **38,** 167.
33. Brater, D. C. and Morelli, H. F. (1977) *Clinical Pharmacology and Therapeutics,* **22,** 21.
34. Cummings, J. H. (1974) *Gut,* **15,** 758.
35. Davies, C. J., Rhodes, J. and Calcraft, B. J. (1974) *British Medical Journal,* **3,** 400.
36. Royston, A. and Prout, B. J. (1976) *British Medical Journal,* **2,** 150.
37. Amery, A. *et al.* (1978) *Lancet,* **1,** 681.
38. Lewis, P. J., Kohner, E. M., Petrie, A. and Dollery, C. T. (1976) *Lancet,* **1,** 564.
39. Randle, P. J. and Hales, C. N. (1972) *Handbook of Physiology* Volume 1, Section 7, p.219.
40. Conn, J. W. (1965) *New England Journal of Medicine,* **273,** 1135.
41. Jarrett, R. J., Keen, H., Fuller, J. H. and McCartney, M. (1977) *British Medical Journal,* **2,** 861.
42. Ramsay, L. E. (1979) *Proceedings of a symposium on potassium and diuretics, Medicine* Meeting, **5,** 13.
43. Schwartz, A. B. and Schwartz, C. D. (1974) *Journal of the American Medical Association,* **230,** 702.
44. Lawson, D. H., Boddy, K., Gray, J. M. B., Mahaffey, M. and Mills, E. (1976) *Quarterly Journal of Medicine,* **45,** 469.
45. Krakauer, R. and Lauritzen, M. (1978) *Danish Medical Bulletin,* **25,** 126.
46. Davidson, C., Burkinshaw, L. and Morgan, D. B. (1978) *Postgraduate Medical Journal,* **54,** 405.
48. Fraser, R., Hettiarachichi, J., Morton, J. J., Ramsay, L. E. and Shelton, J. (1978) *British Journal of Clinical Pharmacology,* **6,** 444P.
49. George, C. F., Breckenridge, A. M. and Dollery, C. T. (1973) *Lancet,* **2,** 1288.
50. Down, P. F., Polak, A., Rao, R. and Mead, J. A. (1972) *Lancet,* **2,** 721.
51. McKenna, T. J., Donohoe, J. F., Brien, T. G., Healy, J. J., St. J., Canning, B. and Muldowney, F. P. (1971) *British Medical Journal,* **2,** 739.
52. Lawson, D. H. (1974) *Quarterly Journal of Medicine,* **43,** 433.
53. Lawson, D. H., Hutcheon, A. W. and Jick, H. (1979) *Scottish Medical Journal,* **24,** 127.
54. Shapiro, S., Slone, D., Lewis, G. P. and Jick, H. (1971) *Journal of the American Medical Association,* **216,** 467.
55. Greenblatt, D. J. and Koch-Weser, J. (1973) *Journal of the American Medical Association,* **225,** 40.
56. Beeley, L. and Brookes, V. (1976) *British Journal of Clinical Pharmacology,* **3,** 970P.
57. Hultgren, H. N., Swenson, R. and Wettach, G. (1975) *American Journal of Medicine,* **58,** 139.
58. Carlsson, E., Fellenius, E., Lundborg, P. and Svensson, L. (1978) *Lancet,* **2,** 424.
59. Collins, F. J., Matthews, H. R., Baker, S. E. and Strakova, J. M. (1979) *British Medical Journal,* **1,** 1673.
60. Farquharson-Roberts, M. A., Giddings, A. E. B. and Nunn, A. J. (1975) *British Medical Journal,* **3,** 206.
61. Heffernan, S. J., Fogarty, O. and Murphy, J. J. (1975) *Journal of the Irish Medical Association,* **68,** 366.
62. Silverman, G. (1976) *Lancet,* **1,** 364.
63. Chaput de Saintonge, D. M. (1978) *Update,* **16,** 635.
64. Stewart, R. and Cluff, L. (1972) *Clinical Pharmacology and Therapeutics,* **13,** 463.
65. Hettiarachichi, J., Ramsay, L. E., Davies, D. L., Fraser, R. and Watson, W. S. (1977) *Clinical Pharmacology and Therapeutics,* **22,** 58.
66. Neuvonen, P. J., Pentikäinen, P. J. and Jounela, A. J. (1978) *British Journal of Clinical Pharmacology,* **6,** 363.
67. Pearson, R. M., Bulpitt, C. J. and Havard, C. W. H. (1979) *Lancet,* **1,** 697.
68. Ramsay, L. E. and Ramsay, M. (1977) *Practitioner,* **219,** 529.

Away With The Foreigner

The aftermath of rebellion made the Scots less than popular to Londoners in 1747. Just the year for a pamphlet (price sixpence) with the title 'An Address to the College of Physicians and to the Universities of Oxford and Cambridge occasioned by the late Swarms of Scotch and Leyden Physicians'. The author, signing himself AZ, argued that 'Tis owing to this inundation of foreigners that the science of physick itself is brought into so much disrepute; for most of these people are of very narrow fortune, who have been obliged to take up with this obscure method of education'. He wrote of the 'insufficiency or rather absurdity of Scotch degrees' compared to the true learning required to graduate from Oxford or Cambridge. He was not keen on physicians who had bred dissenters and complained that 'irregular physicians (nay even Roman Catholics) are elected to our public hospitals and recommended to all the places of profit in physick (which are very few)'. To emphasise his point he listed all the regular physicians who were, of course, Fellows of the College. He could not understand why anyone should ask for a quack, as they would not choose an attorney to make their clothes or a tailor their will. What is more, he hinted that there were some so steeped in wrong thought that they 'entertain an opinion that the art itself is a cheat and its professors men of ill designs'. So AZ put forward a proposal for suppressing all irregular physicians. He looked to Draconian action by the College of Physicians to fulfil his proposals. It is to be expected that such a xenophobic pamphlet should print below its title 'Written by an Impartial Hand'.

It was true that certain European degrees could be got with money rather than study, and Scotland was not blameless. William Hunter wrote to William Cullen in 1754: 'You no doubt know how comtemtuously the College of Physicians here treated all Scotch degrees indiscriminately . . . and you can hardly be ignorant that . . . the professors shamefully prostitute their degrees still to anyone who can pay them a small sum of money, and procure, perhaps purchase, a recommendation from some necessitous doctor'.

AZ's pamphlet urged that the College should not license doctors with foreign degrees and should take powers to control the entry of students into medicine. Finally, he called on all regular practitioners to apply their own remedy by refusing to consult with irregular practitioners. Considering the unstructured state of medical education and the many surgeons and apothecaries, the College was presented with a task that could not be carried out.