Science, medicine and clinical pharmacology

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Introduction

The title of this lecture has been chosen to emphasise the great opportunities open to the clinical pharmacologist by working both with the basic scientist (be he a biologist, chemist or economist) and with the clinician. In doing so, my aim is not to re-open a pointless territorial debate on historical allegiances within clinical pharmacology nor yet to engage in another navel gazing exercise of whither clinical pharmacology.

In his recent presidential address to the American Society of Clinical Pharmacology and Therapeutics [1], Darrell Abernethy entitled clinical pharmacology 'the bridging discipline', linking as it does the structured knowledge of basic science with therapeutic decision making and drug development (Figure 1) and this seems an entirely appropriate assessment of its role. Moreover, among the greatest contributions that the discipline can make may well be those in therapeutic areas where drug treatment is limited and the therapy which is available exhibits a poor risk/benefit profile; infectious diseases such as AIDS, malaria and tuberculosis, not traditional fields of study for the clinical pharmacologist, may illustrate this point well.

The current political and economic climate is not conducive to clinical research, and this includes clinical pharmacology. Every sphere in which the clinical pharmacologist currently operates—be it academia, health service or the pharmaceutical industry—is undergoing change at a breathtaking rate and as a result is full of uncertainty. Referring to universities the *Economist* [2] noted 'Thirty years ago, universities were arguably the most pampered institutions on earth. Governments showered them with money, convinced that they were engines of growth. Intellectuals lavished them with praise, calculating that they were instruments of enlightenment. This mood has vanished. Universities are on the defensive, distrusted by governments worried about losing income and influence. In Britain, the government treats higher education like an inefficient nationalised industry'. This same mood of uncertainty can also be found in the National Health Service [3] and the pharmaceutical industry [4].

To illustrate the role of clinical pharmacology as a linking discipline, I propose to consider four areas

where there are great opportunities for the clinical pharmacologist, the basic scientist and the clinician working together to improve patient care and I shall illustrate these with examples drawn from the work being carried out in the Department of Pharmacology and Therapeutics in the University of Liverpool.

Economics and drug treatment

Pharmacoeconomics is a hybrid term used to denote the application of economic theory to drug treatment and is, in effect, the extension of the science of health economics to the area of therapeutics. Concern about cost effectiveness of medicines within the total health care budget is not new but has mounted over recent years in the UK as in other countries and there have been many governmental policy initiatives aimed at containing drug costs. In the United Kingdom expenditure on medicines currently accounts for approximately 10% of total NHS expenditure, increasing from £1 billion in 1980 to £3.3 billion in 1991. This represents a 59.5% real increase when inflationary factors are taken into account and a 44.7% real increase compared with other costs in the NHS such as pay. Some 80% of the spending on drugs occurs in general practice and in 1992–1993 there was a 14% increase in the drug bill in this section [5].

There are of course, a number of plausible explanations for these increases. In an ageing population, elderly individuals tend to need more drugs. In 1991 the average number of annual prescriptions in the population over 65 years (18.2 per person) was more than double the average for the UK (7.9 per person) and figures for the over 75 year olds are even more striking. The GP contract now encourages screening to discover latent illnesses especially in elderly subjects, and this leads inevitably to an increase in the number of prescriptions written. Technological advances leading to new pharmaceutical products are expensive to fund and drugs such as erythropoietin, granulocyte colony stimulating factor, tissue plasminogen activator and β interferon all represent important therapeutic advances whose research and development costs must be paid for.

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Figure 1 Clinical pharmacology as the bridging discipline (after Abernethy [1]).

The UK Government has responded to these financial problems with a series of initiatives aimed at containing pharmaceutical costs. These include the encouragement of generic prescribing, a restriction in the number of drugs whose cost can be remunerated within the NHS, provision of prescribing analysis and cost (PACT) data to general practitioners and advice on the development of drug formularies and treatment protocols. Other proposals currently under consideration in the UK include the suggestion by the House of Commons Health Committee that cost effectiveness should be demonstrated prior to a drug being reimbursable under the NHS [6]. Such changes must be considered, of course, against a background of regulations introduced by the European Union as a result of the establishment of a single market for pharmaceutical agents. All directives aimed at pharmaceutical pricing and reimbursement should be based on overt principles tenable across the Community.

Clinical pharmacology has an important role to play in assessing cost and benefit of drug treatment. Purchasers of health care should know which forms of drug therapy are clinically effective, and also which are cost effective, thus demonstrating the need for the clinical pharmacologist to work closely with the health economist. But better methods of assessing cost effectiveness of drug treatment which take into account both medical and economic issues are also needed; in other words health economics relating to drug treatment requires scientific underpinning from clinical pharmacology.

Where should a start be made? Three obvious areas would seem to be with purchasers of health care, in general practice and at the primary/secondary health care interface. The second of these is of special interest. Hitherto hospitals were a major influence on prescribing in general practice. In hospitals the basis of drug pricing differs from that in primary care.

Fundholding general practitioners who represent some 50% of health care purchasing power in the UK are now beginning to dictate therapeutic policy to the hospitals from which they purchase services. Methods of implementing change at the primary/secondary interface include the development of joint drug formularies, the establishment of new pricing arrangements with the pharmaceutical industry to obviate differences between drug costs in hospital and general practice. Dissemination of information on drug cost effectiveness using modern technology, in such a way as to allow its maximum implementation is of critical importance in changing clinical practice. The clinical pharmacologist working with the health economist and the pharmacist is in a strategic position to ensure optimal patient care within the resources available.

Pharmacokinetics and clinical practice

Pharmacokinetics has acquired a reputation in some quarters as a mechanistic exercise whose clinical relevance is limited [2]. Used appropriately however it represents a tool of great value, especially in the context of diseases where effective therapy is constrained by considerations of risk and benefit. The drug treatment of malaria represents such an example.

The world wide importance of malaria needs little reiteration. Review of the global epidemiological situation by WHO in 1991 [8] revealed that of a world population of 5160 million, 10% (490 million) lived in areas, mainly tropical Africa, where the endemicity of malaria had never changed and no national antimalarial programme had ever been implemented. A further 31% (1620 million) lived in areas where control programmes had had some success but transmission had recurred and the situation was deteriorating. The rising costs of insecticides, the development of resistance to organochlorines such as DDT coupled with concern about their environmental toxicity, and burgeoning resistance of *P. falciparum* to most available drugs can be held responsible for this depressing picture. The achievement of malaria eradication in the whole of Europe and most of North America is more than counterbalanced by the increasing number of cases of malaria in the tropics.

Most available antimalarial drugs are old; only halofantrine and artemisinin derivatives have been introduced in the last decade, and the availability and cost of these new drugs remains an important issue in countries with a deteriorating malaria situation and faltering economic prospects. Further, the introduction of new drugs in an uncontrolled manner also poses threats to their long term usefulness due to the rapid acquisition of resistance characteristics by the malaria parasite. More than 90% of global malaria related mortality occurs in young African children where the rising incidence of resistance of *P. falciparum* to chloroquine has resulted in an

increasing use of quinine for the treatment of severe malaria. There is however no consensus as to the dose of quinine which should be given, or its frequency of administration. It is recognised that effective drug concentrations should be attained rapidly and while minor adverse effects such as tinnitus are of little consequence in severe disease, serious adverse reactions such as drug induced blindness which is related to drug blood levels [9], must be avoided wherever possible. Until the 1980s intravenous quinine was given in a manner that had evolved empirically, until White and his colleagues [10] utilising sound pharmacokinetic principles, designed quinine regimens for adults in South East Asia and firmly established the value of loading doses to initiate therapy.

Winstanley and his group [11] set out to define a regimen for quinine treatment of Kenyan children using the application of the same basic principles as described for Thai adults [10]. Thai regimens were designed to achieve plasma quinine concentrations above 10 mg l^{-1} based on the knowledge of *in vitro* minimum inhibitory concentrations (MIC) of Thai strains of *P. falciparum*. Most African strains however, are more sensitive to quinine than those in Asia, suggesting that lower concentrations might be effective. Further the disposition of quinine is known to vary with age [12]. Winstanley and his group also introduced a new variable by using unbound, rather than total quinine concentrations, to define the regimen and this is logical since it is considered that it is unbound rather than total drug concentration which is therapeutically and toxicologically important. Thus they first defined the distribution and elimination rate constants of quinine in African children who were given the drug as an intravenous bolus, as had White's group in Thailand [10]. They showed that the mean peak plasma quinine concentration was some 43% higher in the African children than in Thai adults, due mainly to a smaller apparent volume of drug distribution and also a longer distribution half-life (Figure 2) [13]. They next showed that, in 60 Kenyan isolates of *P. falciparum*, the mean total concentration of quinine which killed 99% of parasites (that is the MIC_{99}) was 0.89 mg l^{-1} ; in the culture 28% of quinine was free, representing an unbound concentration of 0.23 mg l^{-1} at the MIC_{99} and they took this as the lower limit of their proposed therapeutic range. The upper limit was defined from toxicological data. Quinine has been shown to cause blindness at total concentrations of 10 mg l^{-1} [9] in subjects taking the drug in overdose. These were non-malarious subjects in whom quinine plasma protein binding is low (approximately 20%) compared with patients with malaria where binding proteins (principally α_1 -acid glycoprotein) are greatly increased as part of the acute phase response. The upper limit of the regimen was therefore taken as 2 mg l^{-1} for unbound drug (i.e. 20% of 10 mg l^{-1}). Thus a regimen was defined which incorporated a loading dose, which took into account disease based differences in protein binding, age based differences in drug disposition, and which would maintain

Figure 2 Mean plasma concentrations of quinine following administration of quinine dihydrochloride 4 mg kg^{-1} by intravenous injection over 4 min to seven Thai adults (□) and 12 Kenyan children (◇) with cerebral malaria (from Edwards, Winstanley & Ward with permission [13]).

unbound quinine concentrations within limits of 0.2 to 2.0 mg l^{-1} , and most importantly allowed the drug to be delivered by two intravenous injections per day without the use of infusion devices. Applying similar principles, regimens for intramuscular quinine dosing regimens were also defined. The robustness of this approach has been tested by clinical investigation and pharmacokinetic modelling and its therapeutic value is currently under intensive investigation in Kenya. So far it is proving an important contribution to the paediatric treatment of malaria.

This example demonstrates how the clinical pharmacologist can beneficially apply basic pharmacokinetic principles to a disease where clinical management is difficult and drug choice limited.

Biochemical and cellular pharmacology in disease management

Few diseases have had a greater social, economic or scientific impact over the past decade than AIDS. There are many epidemiological parallels between AIDS and malaria. Both diseases are prevalent in underprivileged parts of the world which cannot afford to purchase drugs; the few drugs which are available to treat these diseases have poor risk/benefit profiles because of limited efficacy, rapid acquisition of resistance and high toxicity. AIDS would thus seem to be an appropriate disease for the clinical pharmacologist to explore in order to improve treatment.

Much is now known about AIDS and the virus which causes it. The clinical manifestations of AIDS are well documented, the biology of HIV (human immunodeficiency virus) is being rapidly unravelled and with a few notable exceptions, most clinical scientists accept that HIV is the cause of AIDS. The aim of therapeutic research in HIV related disease is to discover effective methods of eliminating the virus

from man or at least containing its infectivity using drugs or vaccines but the likelihood of the latter performing either of these tasks currently appears small.

There are several sites in the replicative cycle of HIV at which drugs might in theory be effective (Figure 3) [14]. Of these drugs CD₄ based therapy, TAT antagonists and immune based therapies have proved disappointing for a variety of reasons and while there are great expectations for the success of protease inhibitors, no long term clinical trial data are available at this time to make a judgement and none is yet licensed. Inhibitors of viral reverse transcriptase (RTI) remain the lynch pin of most current anti HIV drug therapy given either singly or in combination. Other important therapeutic approaches in AIDS, of course, include the prevention and treatment of opportunistic infections.

Over the past 5 years, the problems surrounding the use of RTI have become very apparent. Because of the development of resistance, their period of effectiveness is limited and none cures AIDS. Resistance is a problem for both nucleoside and non-nucleoside RTI and its molecular basis is now increasingly understood [15]. All RTIs demonstrate clinical toxicity especially to the bone marrow, some (e.g. didanosine) to the pancreas and others (e.g. zalcitabine) to the peripheral nervous system. Because of this poor risk/benefit profile several clinical issues are therefore currently widely debated.

1 At which stage of the disease (asymptomatic or symptomatic) should RTI therapy be commenced? Various trials give different signals. While the largest study showed no difference in clinical outcome irrespective of whether zidovudine was

started in asymptomatic or symptomatic subjects [16] other studies have demonstrated a preference for early rather than late start of therapy [17, 18].

- 2 What is the optimal dose of a RTI? Therapy with up to 1.5 g zidovudine day⁻¹ has shown no greater efficacy but considerably greater toxicity than doses of 600 mg day⁻¹; there appears to be little rationale for selection of a particular dose [19] and the same argument can be advanced for other RTIs.
- 3 RTIs as monotherapy are now less frequently used than hitherto. If there a good rationale for combination therapy, with what should they be combined?
- 4 Is there a case for stopping RTI therapy in advanced disease, where the risks of toxicity appear to exceed the benefits?

How can the clinical pharmacologist make a contribution to these issues? Monitoring plasma levels of RTIs has not been shown to be helpful in selecting doses with an optimal risk/benefit profile [17, 20, 21]. There is wide interindividual variability in blood levels of RTIs such as zidovudine, but a poor correlation between plasma drug concentration or any other pharmacokinetic parameter with any manifestation of efficacy (direct or surrogate) or toxicity [22]. The possibility remains of course that current dose schedules result in plasma concentrations that exceed the threshold of an observable relationship to efficacy, yet fall below readily definable toxic limits in most patients.

Investigation of the biochemical and cellular pharmacology of RTIs may reveal the reason for this poor correlation and may also indicate a possible scientific basis on which drug doses may be selected.

Figure 3 Diagram of the replicative cycle of HIV-1, showing the sites of action of antiviral agents (from Hirsch & D'Aquila, with permission [14]).

Zidovudine (ZDV) undergoes three routes of metabolism (Figure 4) [23]. Some 70–80% of ZDV is metabolised to inactive glucuronide, and a small percentage undergoes reduction to form aminothymidine (AMT). The other route of metabolism is by intracellular phosphorylation by a series of cellular kinases to form successively ZDV mono, di and tri phosphate (MP, DP, TP). ZDV TP has a selective affinity for HIV reverse transcriptase causing chain termination and reverse transcriptase inhibition where it competes with deoxythymidine TP for binding sites on the enzyme. The therapeutic action of ZDV is probably mediated by intracellular ZDV TP, i.e. the drug must enter infected cells and be phosphorylated by cellular enzymes in order to inhibit HIV replication [24]. However, activity has also been linked separately to the monophosphate (ZDV MP) which may inhibit the phosphorylation of endogenous thymidine [25].

The phosphorylation of ZDV in 12 HIV seropositive patients and 5 HIV seronegative volunteers has been investigated in our laboratory [26]. Each subject was given ZDV 250 mg orally and blood was taken at 1, 2, 4 and 6 h. Plasma and peripheral blood

mononuclear cells (PBMC) were obtained at each time point and individual intracellular ZDV phosphate metabolites as well as plasma ZDV concentrations were measured.

As Table 1 shows, there was no significant difference between plasma levels of ZDV between patients and volunteers. However the extent of ZDV phosphorylation was significantly greater in patients than in seronegative volunteers at each time point chosen. We confirmed the lack of correlation between plasma ZDV and total intracellular ZDV phosphate concentrations, shown previously [27]. Interestingly, concentrations of ZDV-TP were similar in patients and volunteers, the increase in phosphate being primarily due to ZDV-MP. The relationship between total ZDV phosphate AUC(0,6 h) and CD₄ counts was investigated and Figure 5 shows that patients with CD₄ counts of $< 100 \times 10^6 \text{ l}^{-1}$ had higher ZDV phosphate levels, predominantly ZDV-MP than those with CD₄ counts $> 100 \times 10^6 \text{ l}^{-1}$.

These data are open to several interpretations. The higher ZDV phosphate levels found in PBMC from HIV infected patients with more advanced disease may represent an increase in thymidine kinase

Figure 4 Metabolic pathways of zidovudine.

Table 1 Concentration of zidovudine (ZDV) phosphate metabolites in peripheral blood mononuclear cells from HIV-seronegative volunteers ($n = 5$) and AIDS patients ($n = 12$) following an oral dose of 250 mg ZDV [26]

Time (h)	Seronegative volunteers			ZDV-MP	AIDS patients	
	ZDV-MP	ZDV-DP	ZDV-TP		ZDV-DP	ZDV-TP
1	0.17 (0.00–9.31)	ND	0.04 (0.00–0.15)	1.20 (0.12–2.46)**	0.06 (0.00–0.12)	0.05 (0.00–0.18)
2	0.11 (0.00–0.28)	ND	0.03 (0.00–0.07)	1.33 (0.45–3.96)**	0.11 (0.00–0.21)	0.06 (0.00–0.22)
4	0.04 (0.00–0.11)	ND	0.02 (0.00–0.05)	0.74 (0.10–1.86)**	0.11 (0.00–0.25)	0.06 (0.00–0.19)
6	0.05 (0.00–0.10)	ND	0.06 (0.00–0.16)	0.43 (0.13–1.20)**	0.07 (0.00–0.21)	0.04 (0.00–0.20)

Results are expressed as mean (with range) in units of pmol/ 10^6 cells. ** $P < 0.01$, significantly different from seronegative volunteers (Mann Whitney U test). MP, monophosphate; DP, diphosphate; TP, triphosphate; ND, not detected.

Figure 5 Total zidovudine (ZDV) phosphate area under ZDV concentration-time curve (AUC(0,6 h)) vs CD₄ counts in 12 HIV infected patients following administration of ZDV 250 mg orally. Inset shows ZDV monophosphate AUC(0,6 h) vs CD₄ counts. (From Barry, Wild, Veal, *et al.*, with permission [26]).

activity or a reduction in intracellular phosphatase enzyme activity. PBMC are composed of various cell types (B and T cells and monocytes) and the extent of phosphorylation has previously been shown to depend on both cell type and activation of the cells [25]. It is possible that the increased phosphorylation in HIV-infected patients, in particular those with low CD₄ counts may be explained by alterations in the circulating cell population as the disease progresses.

The clinical consequences of these observations are also open to conjecture. It has been postulated that the ZDV induced toxicity may be due to an inhibitory effect of ZDV-MP on phosphorylation of endogenous thymidine [25] or on protein glycosylation in cells [28]. It is clinical experience that ZDV haematological toxicity is greater in those patients with low CD₄ counts (and who in our study showed the highest concentrations of ZDV MP). Is ZDV myelotoxicity due to accumulation of ZDV-MP?

Can the measurement of ZDV phosphates form the basis of more rational dosing of ZDV, given either alone or in combination, especially in patients with low CD₄ counts? Paradoxically, it has been shown that in asymptomatic patients that those who responded to therapy as measured by improvement or stability of surrogate cell markers had significantly higher intracellular AUC of ZDV phosphate than those whose markers declined from baseline [28]. This observation was made in patients with higher CD₄ counts ($> 200 \times 10^6 \text{ l}^{-1}$) and the authors warned against extrapolating the results to patients with more advanced disease, the very ones whom we have studied.

It would appear then that the ability to measure phosphorylated metabolites of ZDV (and perhaps those of other RTIs which undergo similar metabolic activation) may represent an important advance in understanding the clinical pharmacology of this group of drugs and may also explain the poor correlation between plasma levels of RTIs and clinical response. Further, it illustrates the importance of utilising bio-

chemical and cellular pharmacological information together with clinical observation to clarify therapeutic possibilities in a disease whose current treatment is suboptimal.

Chemistry and adverse drug reactions

Adverse reactions to drugs range from effects on a single physiological control system to multiple organ failure and their severity can vary from the apparently trivial to the rapidly fatal. Clinical pharmacology is concerned with risk assessment in drug therapy, and as the science of toxicology develops, the pharmacologist evolves new classifications of drug reactions. To the well known classification of Type A (augmented effects of normal drug action and which are also dose related) and Type B (bizarre effects due to effects other than those of a therapeutic nature and which are not dose related) [30] have been added Type C reactions (long term effects, e.g. adaptive changes, rebound phenomena) and Type D reactions (delayed effects such as carcinogenesis and teratogenicity) [31]. Other classifications will evolve as mechanisms of various adverse reactions become better defined.

Drug toxicity may be due to drug or to a metabolite, which can be formed either spontaneously because of the inherent instability of the parent compound or by drug metabolising enzymes. The simplest form of metabolite mediated activity is where the parent drug is a prodrug formulated to enhance bioavailability or to improve access of the active moiety. In such cases drug metabolising enzymes convert the prodrug to a therapeutically active metabolite which leads to predictable therapeutic activity but also predictable (Type A) toxicity. However, of greater toxicological importance are those active metabolites which are implicated in the pathogenesis of Type B adverse reactions and where the active metabolite is usually further metabolised to a stable, inactive metabolite which under normal circumstances is eliminated. When an imbalance occurs between the formation of a metabolite and its detoxification, toxicity may result [32]. If the relevant reactive metabolite binds covalently to essential macromolecules or forms a free radical interfering with normal cellular function, cell necrosis may occur. If the reactive metabolite binds to DNA, genotoxicity and possible carcinogenesis may result. Alternatively, the reactive metabolite can act as a hapten causing immune mediated toxicity which may be due to a specific humoral (antibody) response, a cellular (T lymphocyte) response or a combination of both. The immune response may be directed against the drug, the carrier protein to which the hapten binds or the neoantigen created by combination of the drug and the protein. Subsequent tissue damage is mediated by the four classical general mechanisms of hypersensitivity [33].

Factors influencing individual susceptibility to idiosyncratic drug toxicity are poorly understood but

probably include both metabolic and immunological events [32]. At a clinical level, direct toxicity caused by a chemically reactive metabolite may be difficult to distinguish from that attributable to the secondary immune reaction. On rechallenge, however, the presence of immune factors leads to a more rapid adverse reaction, while with non-immune mediated toxicity, reactions after second exposure have a similar time course as after first exposure [34].

An important example of how understanding the chemical basis of an idiosyncratic adverse reaction may lead to a therapeutic advance is well illustrated with the antimalarial drug amodiaquine. Amodiaquine is a 4-aminoquinoline introduced in the 1960s as a result of the screening programme of the US Army Research Team. It became therapeutically important with the widespread emergence of resistance to

chloroquine, since strains of *P. falciparum* resistant to chloroquine were shown to remain sensitive to amodiaquine. However, in 1986 it was demonstrated that approximately 1 in 2000 subjects taking amodiaquine for malaria prophylaxis developed neutropenia or hepatotoxicity or both [35, 36].

Park and his colleagues have investigated the possible metabolic basis of this adverse drug reaction [37]. Firstly, they have shown that as well as forming a stable, inactive metabolite, desethylamodiaquine, amodiaquine also forms an (unstable, reactive) quinoneimine in liver and in white blood cells (Figure 6) [38]. The fate of this reactive metabolite is either to be conjugated with glutathione and inactivated, or to act as a hapten as outlined above, resulting in possible immune based toxicity. It was shown that patients who developed myelotoxicity or

Figure 6 Proposed metabolic pathway of amodiaquine in man (from Park, Piromohamed, Tingle, *et al.*, with permission [38]).

hepatotoxicity when taking amodiaquine demonstrated high titres of specific antibodies to the reactive metabolite [39]. This provides strong evidence for an underlying immunological basis of the toxicity. Most cases of haematological toxicity or hepatotoxicity following amodiaquine administration have occurred in patients taking the drug for prophylaxis, rather than for therapy of acute malaria where the exposure is shorter. The Liverpool group has now shown that by appropriate fluorine substitution it is possible to alter the chemistry of the amodiaquine molecule, allowing retention of its pharmacological antimalarial action yet changing its pattern of metabolism so that only inactive and not reactive metabolites are formed [40]. Whether this will result in the development of an effective antimalarial agent is under investigation.

A further example of how identification of a functional group responsible for bioactivation of a drug to a toxic metabolite may lead to the design of new compounds retaining therapeutic activity but not causing toxicity is replacement of the nitro group of chloramphenicol by a methyl sulphonyl moiety to form thiamphenicol. This has a similar antibacterial

spectrum to chloramphenicol but has not been reported to cause aplastic anaemia [41].

Thus understanding the chemical basis of adverse drug reactions is of great potential value in drug discovery and demonstrates how chemical and clinical pharmacology can combine to improve therapeutic outcomes.

Conclusion

The clinical pharmacologist's goal must be to improve the benefit/risk profile of therapy for patients, and to ensure cost effectiveness. He has an increasing armamentarium at his disposal including the tools of molecular biology and the availability of human tissues. Further, he can call on the collaboration of scientists in many other disciplines to achieve his aims. The need for good clinical pharmacology has never been greater, and the opportunities for success have never been better.

I am grateful to my colleagues in Liverpool whose work I have cited to illustrate the theme of this lecture.

References

- 1 Abernethy D. Presidential address, American Society for Clinical Pharmacology & Therapeutics. *Clin Pharmacol Ther* 1992; **51**: 475–477.
- 2 *Economist*, Dec. 25th 1993, pp. 54–56, Universities—Towers of Babel.
- 3 Ham C. Where now for the N.H.S. reforms. *Br Med J* 1994; **309**: 351–352.
- 4 Sykes R. Innovation in the Pharmaceutical Industry. *Br Med J* 1994; **309**: 422–433.
- 5 Bloor K, Maynard AK. Cost effective prescribing of pharmaceuticals: the search for the holy grail? In *Purchasing & Providing Cost Effective Health Care*, eds Drummond MF, Maynard A. Churchill Livingstone 1993, pp. 198–216.
- 6 House of Commons Health Committee 2nd Report. *Priority setting in the N.H.S.* N.H.S. Drug Budget, H.M.S.O. 1994.
- 7 Dollery CT. The future of clinical pharmacology and therapeutics. *Clin Pharmacol Ther* 1987; **41**: 1–2.
- 8 Onori E, Beales PF, Gilles HM. From malaria eradication to malaria control. In *Essential malariology*, 3rd Edition, eds Gilles HM, Warrell DA. Edward Arnold 1993.
- 9 Dyson EH, Proudfoot AT, Prescott, LF *et al.* Death and blindness due to overdose of quinine. *Br Med J* 1985; **291**: 31–33.
- 10 Davis TME, White NJ, Looareesuwan S, *et al.* Quinine pharmacokinetics in cerebral malaria; predicting plasma concentrations after rapid intravenous loading using a two compartmental model. *Trans Roy Soc Trop Med Hyg* 1988; **82**: 542–547.
- 11 Winstanley PA, Newton C, Watkins WM, *et al.* Towards optimal regimens of parenteral quinine for young African children with cerebral malaria, the importance of unbound quinine concentration. *Trans Roy Soc Trop Med Hyg* 1993; **87**: 201–206.
- 12 Shann F, Stace J, Edstein M. Pharmacokinetics of quinine in children. *J Paediatrics* 1985; **106**: 506–510.
- 13 Edwards G, Winstanley PA, Ward SA. Clinical pharmacokinetics in the treatment of tropical diseases: some applications and limitations. *Clin Pharmacokinet* 1994; **27**: 150–165.
- 14 Hirsch MS, D'Aquila RT. Therapy for human immunodeficiency virus infection. *N Engl J Med* 1993; **328**: 1686–1695.
- 15 Greene WC. The molecular biology of human immunodeficiency virus type I infection. *N Engl J Med* 1991; **324**: 308–317.
- 16 Concorde Coordinating Committee, M.R.C/A.N.R.S. Randomised double blind controlled trial of immediate and deferred zidovudine in symptom free HIV infection. *Lancet* 1994; **343**: 872–881.
- 17 Volberding PA, Lagakos SW, Grimes JM, *et al.* The duration of zidovudine benefit in patients with asymptomatic HIV infection. *JAMA* 1994; **272**: 437–442.
- 18 Cooper DA, Gatell JM, Kroon S, *et al.* Zidovudine in persons with asymptomatic HIV infection and CD4+ cell counts greater than 400/cu.mm. *N Engl J Med* 1993; **329**: 297–303.
- 19 Fischl MA, Parker CB, Pettinelli C, *et al.* A randomised controlled trial of a reduced daily dose of zidovudine in patients with AIDS. *N Engl J Med* 1990; **323**: 1009–1014.
- 20 Collier AC, Tartaglione T, Corey L. A reduced dose of zidovudine in patients with AIDS (letter). *N Engl J Med* 1991; **324**: 996.
- 21 Sale M, Sheiner LB, Volberding P, *et al.* Zidovudine response relationships in early human immunodeficiency virus infection. *Clin Pharmacol Ther* 1993; **54**: 556–566.
- 22 Barry M, Howe JL, Back DJ, *et al.* Zidovudine pharmacokinetics in zidovudine induced bone marrow toxicity. *Br J Clin Pharmacol* 1994; **37**: 7–12.
- 23 Yarchoan R, Mitsuya H, Myers CE, *et al.* Clinical phar-

- macology of 3' azido-2',3'-dideoxythymidine (zidovudine) and related dideoxynucleosides. *N Engl J Med* 1989; **321**: 726–738.
- 24 Hao Z, Cooney DA, Hartman NR, *et al.* Factors determining the activity of 2',3'-dideoxynucleosides in suppressing human immunodeficiency virus *in vitro*. *Mol Pharmacol* 1988; **34**: 431–435.
 - 25 Furman PA, Fyfe JA, St. Clair MH, *et al.* Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. *Proc Natl Acad Sci USA* 1986; **83**: 8333–8337.
 - 26 Barry M, Wild M, Veal G, *et al.* Zidovudine phosphorylation in HIV infected patients and seronegative volunteers. *AIDS* 1994; **8**: F1–F5.
 - 27 Stretcher BN, Pesce AJ, Murray JA, *et al.* Concentrations of phosphorylated zidovudine (ZDV) in patient leucocytes do not correlate with ZDV dose or plasma concentrations. *Ther Drug Monit* 1991; **13**: 335–341.
 - 28 Hall ET, Yan J-P, Melancon P, *et al.* 3'-azido-3'-deoxythymidine potently inhibits protein glycosylation. *J Biol Chem* 1994; **269**: 14355–14358.
 - 29 Stretcher BN, Pesce AJ, Frame PT, *et al.* Correlates of zidovudine phosphorylation with markers of HIV disease progression and drug toxicity. *AIDS* 1994; **8**: 763–769.
 - 30 Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In *Textbook of adverse drug reactions*, ed Davies DM. Oxford, Oxford University Press 1977.
 - 31 Grahame-Smith DG, Aronson JK. *Oxford Textbook of Clinical Pharmacology and Drug Therapy*. Oxford, Oxford University Press, 1992.
 - 32 Park BK, Pirmohamed MP, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. *Br J Clin Pharmacol* 1992; **34**: 377–395.
 - 33 Coombes RRA, Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In *Clinical aspects of immunology*, ed Gell PGH. Oxford, Oxford University Press 1968; 575–596.
 - 34 Pirmohamed M, Kitteringham NR, Park BK. The role of active metabolites in drug toxicity. *Drug Safety* 1994; **11**: 114–144.
 - 35 Neftel KA, Woodtly W, Schmidt M, *et al.* Amodiaquine induced agranulocytosis and liver damage. *Br Med J* 1986; **292**: 721–723.
 - 36 Hatton CSR, Peto TEA, Bunch C, *et al.* Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986; **i**: 411–413.
 - 37 Harrison AC, Kitteringham NR, Clarke JB, *et al.* The mechanism of bioinactivation and antigen formation of amodiaquine in the rat. *Biochem Pharmacol* 1992; **43**: 1421–1430.
 - 38 Park BK, Pirmohamed M, Tingle MD, *et al.* Bioactivation and bioinactivation of drugs and drug metabolites: relevance to adverse drug reactions. *Toxic in Vitro* 1994; **8**: 613–621.
 - 39 Clarke JB, Kitteringham NR, Park BK. Detection of antidrug IgG antibodies in patients with adverse drug reactions to amodiaquine. *Int Arch Allergy Appl Immunol* 1991; **95**: 369–375.
 - 40 O'Neill PM, Harrison AC, Storr RC, *et al.* The effect of fluorine substitution on the metabolism and antimalarial activity of amodiaquine. *J Med Chem* 1994; **37**: 1362–1370.
 - 41 Yunis AA. Chloramphenicol toxicity. 25 years of research. *Am J Med* 1989; **87**: 44–48.