

CAPTURING THE UNEXPECTED BENEFITS OF MEDICAL RESEARCH

Based on the proceedings of a workshop jointly organized by the WHO and the Center for Public Health (CPR) at University College London, on 2 September 2008, including the WHO and chaired by Professor Sir Charles Francis, Medical Director of the British Heart Foundation.

Edited by David Phillips



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Based on the proceedings of a workshop jointly organised by the OHE and the School of Public Policy (SPP) of University College London, on 6 September 2000, hosted by the SPP, and chaired by Professor Sir Charles George, Medical Director of the British Heart Foundation.

Edited by Clive Pritchard



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Office of Health Economics

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FOREWORD

MICHAEL PECKHAM

It has long been known that a medicine may turn out to have an unexpected beneficial effect on an illness other than the one it was originally intended to treat. This is true for long established medicines, for example the cardiovascular benefits of aspirin, and for more recent products, of which Sildenafil (Viagra) is a dramatic example. Such instances are not rare and serendipity has been a highly significant aspect of progress as illustrated by Julius Comroe's (1977) fascinating dissection of the antecedents of some of the seminal advances in medicine.

The fact that drugs or other technologies may work to the advantage of patients, clinicians and industrial producers in unanticipated ways has a number of consequences. Such bonus effects may be overlooked or only brought to light after a long delay. Criteria for accepting new developments into health services may eliminate or discourage treatments that could in the longer term prove to be highly beneficial. Commercial companies having invested heavily in a product, the intended action of which is supported by impressive biochemical and other pre-clinical data, may be blinded to an alternative practical application which runs counter to a logical sequence of steps. The observations of patients may be crucially important in first evoking an unexpected effect. This might be construed as a side effect or complication and then built on to characterise a definitive application.

In 1998 Gelijns and colleagues drew attention to the different mechanisms by which new treatment indications come to light. Elucidation of mechanisms of action after a drug has been introduced into the clinic may lead to recognition of the scope for wider use. Clinical observations may lead to radically new departures as illustrated by the isolation of *Helicobacter pylori* from clinical specimens and the successful medical treatment of peptic ulcer. It is particularly important that the non-linear nature of medical progress highlighted by the example of serendipitous benefits is kept clearly in mind, particularly as we enter the era of rational drug design.

The economics of serendipitous progress present an intriguing challenge. The unanticipated applications of medicines can account

for a substantial percentage of sales revenue. The detection and exploitation of unanticipated benefits is in many instances inefficient. Increasing the efficiency of the processes involved is not only a task for the organisation of commercial companies but also of university structures and clinical research including the meaningful involvement of patients and the groups that represent them. Reaping the unanticipated rewards of clinical interventions is yet one more example of the potential advantages that could be realised by creating novel and stronger connections between different spheres of activity in research, development and health care.

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Chapter 1

Capturing the unexpected benefits of medical research

ANNETINE GELIJNS and ALAN MOSKOWITZ

Introduction

This seminar was organised around a central question: how can one improve the processes by which the unexpected benefits of medical research can be captured? The relevance of this question is uncovered nearly daily, as illustrated recently in a *Wall Street Journal* article entitled: 'Viagra may be effective in treating diabetes ailment.' One can obtain insight into this central question by examining aspects of the innovation process and the organisation of research institutions. In particular, we consider:

- (a) the nature of the uncertainty that is embedded in the innovation process;
- (b) the various pathways by which this uncertainty is diminished and new applications emerge; and
- (c) some ways by which we can capture more fully, and at earlier times, these new indications.

In discussing these issues, it has to be recognised that innovation involves a high degree of serendipity and creativity, which as such cannot be planned, but may be enhanced by incentives, organisational structure, and inter-organisational collaborations. In the words of Pasteur, 'chance favours the prepared mind.'

In considering the spectrum of activities incorporated in R&D, it has become common practice to emphasise the high degree of uncertainty attached to the basic research end of the spectrum, and to contrast this with the supposedly much lower levels of uncertainty that prevail in the realms of applied research and development. However, significant and often neglected uncertainties continue to exist at the end of the R&D process and persist long after new products are introduced into practice.

Of course, it is not uncommon for technologies in other industries to experience considerable improvements in their performance and range of applications after they have been introduced into the market place. A case in point is the laser, one of the most powerful and versatile technologies of the 20th century. Its range of applications since its invention has been truly breathtaking: from navigational instruments, CD players and printers, to medicine. However, perhaps no single application has been more profound than telecommunications, where, together with fibre optics, it is revolutionising transmission. The best trans-Atlantic cable in 1966 could carry simultaneously only 138 conversations; by 1991, however, fibre optic cables could carry nearly 1.5 million conversations. Yet, patent lawyers at Bell Labs were initially unwilling even to apply for a patent on the laser, on the grounds that such an invention had no possible relevance to the telephone industry.

Uncertainties related to medical innovation

In comparison with other industries, however, the degree of uncertainty in medicine appears to be uniquely high. The sources of this uncertainty are twofold: (a) the complexity of the human body; and (b) the heterogeneity of the human population. For example, alpha-blockers were first tested for hypertension. At the time of their introduction, it wasn't known that alpha-receptors existed in the urinary tract as well as in the arterial system and that, therefore, their blockade could constitute a symptomatic treatment for benign prostatic hyperplasia (BPH). Initial trials, which focused on haemodynamics, did not notice its urological value. In fact, it took another 20 years to establish this. The heterogeneity of patients further limits the opportunity to find benefits from new research. Randomised controlled trials often use selection criteria that exclude many patients who might benefit. A case in point is bypass surgery: only 4% to 13% of patients who now undergo this surgery would have qualified for the initial randomised controlled trials that established its efficacy.

The history of medical innovation, therefore, is replete with instances in which new indications have been discovered only after drugs and devices have been introduced into clinical practice. In a *New England*

Table 1.1 Examples of US blockbuster drugs 1993

<i>Generic name</i>	<i>Original indication</i>	<i>Selected secondary indications</i>	<i>US sales</i>
Ranitidine Famotidine Cimetidine	Duodenal ulcer	Zollinger-Ellison syndrome Gastric ulcer GORD Short-bowel syndrome Aspiration prophylaxis	\$5,988m
Enalapril Captopril	Hypertension	Congestive heart failure Diabetic nephropathy	\$3,865m
Nifedipine	Angina pectoris	Hypertension Peripheral vascular disease Oesophageal spasm Intestinal ischaemia Migraine Cerebral-artery spasm Raynaud's phenomenon	\$2,100m

Journal of Medicine 'Sounding Board' article we examined the top 20 blockbuster drugs from 1993 and discovered that by 1995 40% of revenues came from secondary indications (Gelijns et al, 1998). Examples of some of these drugs are listed in Table 1.1.

A similar pattern holds for medical devices. Many devices started life as a research tool, then became diagnostic tools, and later – as they experienced performance improvement – evolved into therapeutic tools. For example, diagnostic cardiac catheters are now being used for revascularisation. Magnetic resonance spectroscopy, which was a fundamental research tool for physics and chemistry, evolved into magnetic resonance imaging (MRI), and recently these machines have become an integral part of complex neurosurgical therapeutic approaches. This range of applications was certainly not foreseen when the original research on MRI was undertaken.

Mechanisms by which new indications are discovered

New indications, whether they are for drugs, devices, or surgical procedures, are discovered via three pathways, which overlap and interact with one another:

- a) new basic science investigation that elucidates mechanisms of action or uncovers fundamental properties of a technology, as was the case with the discovery of the calcium channel blocking properties of nifedipine, which led to a variety of uses related to the control of smooth muscle spasm;
- b) translational research, which identifies new uses, based on known mechanisms of action, or application to closely related disorders or organ systems (for example the modification of gynaecological laparoscopes to gallbladder surgery); and
- c) new clinical observations about previously unrecognised uses or causes of disease, as with the discovery of the role of *Helicobacter pylori* in peptic ulcers, and the subsequent use of antibiotics in their treatment.

Often, the unexpected results of clinical experience pose new questions for basic and translational research, and thereby enrich the ultimate payoff of these types of research. Yet, the process by which this feedback loop occurs often involves long time lags, as was the case for alpha blocking drugs. We have indicated that new indications of use typically come to light as a result of recurring exchanges between different types of researchers: basic, translational, and clinical. Moreover, discovering new indications often requires interactions among researchers from different clinical specialties.

Of late, several pharmaceutical firms have been successful in obtaining multiple indications for use early on in the life cycle of a drug by taking advantage of clinical experience and observational data. These are primarily cases where the new drug is an addition to an existing class of pharmaceuticals, for which there is a literature of observational data. For example, during the development process of Celebrex for arthritis, Monsanto's researchers searched the epidemiological literature for other effects that non-steroidal like drugs could produce.

As a result of this search, they went after familial polyposis, and the drug is currently being tested for Alzheimer's. Most observational databases focus on side effects, which has been a source of new indications in the past. A well-known example is Minoxidil, which had been used in the treatment of hypertension with the side effect of uncontrolled hair growth. This side effect became its next indication with the development of the preparation in topical form for baldness. It might be worthwhile to establish registries of prescribers, which allow for their reporting not only of side effects but also of unexpected benefits. Such registries could also provide a population for hypothesis-directed surveys.

Institutional re-organisation

An important question is what incentives, what institutions, and what policies are likely to lead to a swifter resolution of the uncertainties noted above and to a more rapid discovery of new indications of use? In other words, how can one reduce the time lag between finding original and new indications?

Of major importance is the creation of an institutional environment where dialogues between basic, translational and clinical researchers can take place. Academic medical centres (AMCs) are characterised by substantial organisational complexity. In the US, the medical school, faculty practice plans (the local health care insurers), and the hospital often have relationships that are a mix of co-operation and competition, both for resources as well as for institutional leadership. Historical divisions between hospital and medical schools are still reflected in the administration of research. Commonly, medical schools have associate deans for research, who have a background in laboratory-oriented research. Only recently have AMCs recognised the need for creating specific administrative positions that focus on clinical or patient-oriented research. Given that the entire spectrum of research can be involved in the discovery of new indications, it is necessary to have an administrative structure that reflects this in order to facilitate strategic thinking about exploiting the unexpected benefits of medical research.

Second, we need to create environments that allow for easy interactions among researchers from different clinical specialties. Innovation in academic medicine tends to be the domain of specialty-based divisions. There is little doubt that the organisation of the academic enterprise into disciplines and departments has played a major role in the historic success of universities in contributing to the growth of knowledge. Nevertheless, technological capabilities do not always fall neatly within the boundaries of disciplines and departments. The central issue is how to design institutional arrangements that promote co-operation among disparate disciplines, in the face of organisational and academic incentives that may discourage them.

A development, which may assist in this respect, is the creation of interdisciplinary research centres. A case in point is the Center for Minimally Invasive Therapy that was recently established at the Massachusetts General and Brigham hospitals in Boston. The Center brings together expertise in core technologies, such as lasers, miniaturised sensors, and artificial intelligence, by including faculty of Massachusetts Institute of Technology (MIT) and Draper Labs with a whole range of clinical specialties to enhance the development and application of minimally invasive technologies across many clinical conditions. It also means that firms do not have to contract with 10 different departments within an AMC, but just with one centre. As a number of such interdisciplinary centres have been established recently, it is an appropriate time to evaluate their effectiveness in enhancing the discovery of new indications of use.

In industrial settings, product-related R&D is interdisciplinary in nature and raises no special challenge to the values and priorities of the organisation. Despite this flexibility in structure, few firms span the entire spectrum of clinical and scientific expertise needed for the identification of new indications of use. It will be interesting today to explore how pharmaceutical firms now search for new indications for their products, particularly when there isn't a large literature of related experience. One effective mechanism may be inter-institutional collaborations. For instance, drug and device manufacturers might draw more fully on panels of academic experts at the R&D stage

who would consider how an innovation that is useful for one purpose might prove useful, when modified, for another.

Likewise, a panel of academic experts may be very useful in interpreting the early post-approval experience with a new drug or device. A case in point is bupropion. Initially released as an antidepressant, this drug was serendipitously discovered to reduce the desire to smoke. This clinical observation led to its 1997 approval as a smoking cessation aid.

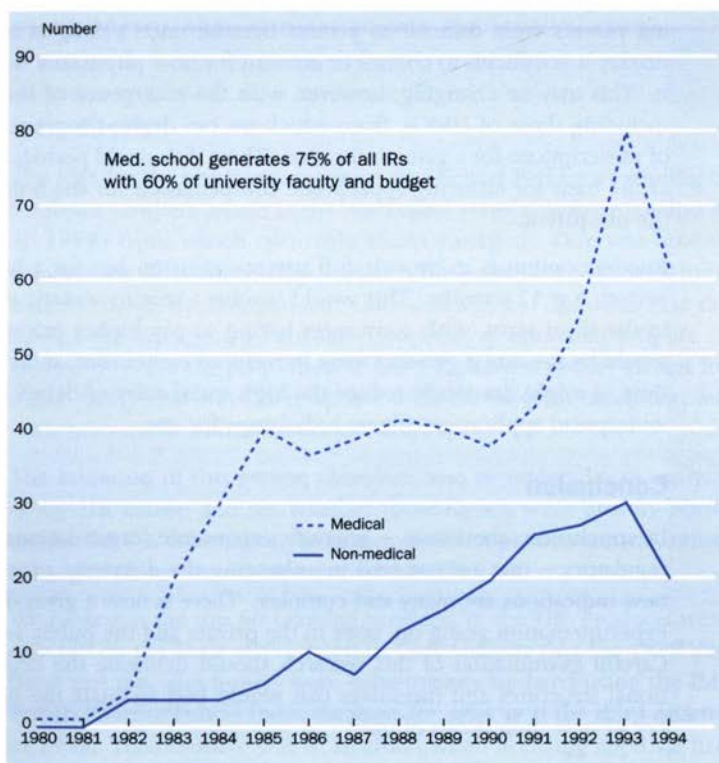
Intellectual property

No discussion of the unexpected benefit of research is complete without consideration of the impact of intellectual property protection. Intellectual property protection remains an important incentive for R&D. The discovery of new indications occurs in a variety of venues, including industry, governmental labs, and academia. Traditionally, academics used to publish such discoveries, but now, at least in the US, they are more likely to patent them. This is part of the general upsurge of university patenting that occurred after the enactment of the Bayh-Dole Act, which gave universities strong incentives to patent the results of federally funded research.

Figure 1.1 shows the growth in invention reports at Columbia University. Faculty members fill these out when they believe that they have created something of commercial value. This figure also shows that the medical centre is the main locus of inventive activity within the university, generating 75% of all invention reports with 60% of the faculty and budget. Patent trends are similar but at a lower volume. At Columbia, licensing revenue, which is concentrated in only a few inventions, amounts to around \$150 million a year. In the US currently over 60% of all university patents are based upon biomedical inventions.

These academic patents also include so-called 'use' patents. For example, Viagra's effect on diabetic gastroparesis was discovered recently at Johns Hopkins and these researchers are now applying for a use patent. The intention of patents, and more specifically of the Bayh-Dole Act, is to induce innovation and technology transfer. It is a major

Figure 1.1 Annual Columbia invention reports



unanswered question, however, whether the widespread patenting of inventions by American universities is a practice that is inducing innovation. Is a use patent necessary to develop the next indication for Viagra? Or is it mainly a mechanism for the university to recoup its investment? The latter may be an important source of research funds for the university but that was not the intention of the Bayh-Dole Act.

From an industrial perspective, if a new indication is discovered close to patent expiry, a firm may not have the incentive to invest in the

clinical trials to garner approval for use, because other manufacturers will reap the benefits. How can we provide incentives? Traditionally, use patents were difficult to protect because once a drug is on the market it is difficult to control or account for how physicians will use it. This may be changing, however, with the emergence of indexes, including those of HMOs, from which we can derive the proportion of prescriptions for a given indication. These data could perhaps serve as the basis for ensuring appropriate compensation for the holder of the use patent.

Another option is to provide full patent extension but for a limited period, e.g. 12 months. This would involve a cost to society, at least in the short term, with consumers having to pay higher prices than would be the case if generics were introduced earlier. But, at the same time, it might drastically reduce the high social costs of delays in the widespread application of new indications for use.

Conclusion

In conclusion, the issues – scientific, economic, organisational and regulatory – that are involved in enhancing the discovery process of new indications are many and complex. There is now a great deal of experimentation going on, both in the private and the public sectors. Careful examination of this research should delineate the organisational structures and incentives that would best facilitate the discovery of new indications of use.

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Chapter 2

Results of a review of leading NHS medicines

CLIVE PRITCHARD, ADRIAN TOWSE and ISLWYN OWEN

Introduction

The idea for the seminar came from Sir Michael Peckham's reading of Professor Gelijns's article in the *New England Journal of Medicine* (Gelijns et al, 1998) from which two main issues emerged. One was how to improve the three routes of potential development for additional indications (basic, translational and clinical research). The other was the size of the unexpected benefits. Gelijns et al estimated a figure of around 40% for the proportion of the US pharmaceutical market for major drugs that was taken up not with the original indication but with subsequent indications or off-label use.

The intention of this review, therefore, was to undertake an analysis of the UK market and see whether those figures were broadly borne out by the UK experience. In principle, if the pharmaceutical industry is global, we would expect that to be the case.

We looked at the top 50 branded products in the UK. Products were selected on the basis of Prescription Cost Analysis data for 1998 and these and the sales figures were subsequently updated using the IMS British Pharmaceutical Index database for sales as at the third quarter of 1999. The objective was to ascertain when licensing approval had been granted for each indication, what proportion of prescribing was for their originally approved indication, and what proportion was for subsequent indications.

Methods

A questionnaire survey was sent to the manufacturers of the top 50 products. These were returned in the first half of 2000. The survey specifically asked for: the listed indications for each of these products; the dates marketing approval was given; and whether there had been any other changes to the authorised uses – was there, for example, a variation in the authorised use?

Table 2.1 The 40 products included in the current analysis

Adalat	Arthrotec	Asacol	Atrovent
Beclazone	Becloforte	Becotide	Bricanyl
Cardura	Ciproxin	Clarityn	Cozaar
Efexor	Flixotide	Gaviscon	Imdur
Imigran	Innovace	Istin	Lamictal
Lamisil	Lipitor	Losec	Lustral
Mixtard Human	Neoral	Prozac	Pulmicort
Risperdal	Serevent	Tenormin	Tritace
Ventolin	Voltarol	Zantac	Zestril
Zocor	Zoladex	Zoton	Zyprexa

The 40 products for which responses were received are listed in Table 2.1. In order to estimate how important secondary indications were for these drugs, the questionnaire responses were compared with data from the IMS Corporation Prescription database on prescribing in the community by indication.

Results

The overall result was that about 62% of prescriptions by value were for original indications, about 15% were for new indications, and about 6% were for unlicensed use. The remaining 17% fell into an 'unknown' category. These comprised firstly of 'unknown' data in the sense that they were for indications outside of the main indications including unlicensed use for the products involved. In some cases, there were up to 50 indications for which the product was reported as being prescribed. Secondly, there were cases where indications that had been listed by the GP did not make sense and could not sensibly be recorded as unlicensed use, indicating a problem with the way that prescribing had been recorded. These also went into the 'unknown' category. Excluding this 'unknown' category, we found that 25% of prescriptions by value were for new or unlicensed indications.

Table 2.2 Prescriptions for subsequent or follow-on indications

<i>Follow-on indications as a proportion of known prescriptions (%)</i>	<i>Number of products</i>
0	19
<10%	5
11-20%	9
21-50%	4
>70%	3

Table 2.2 gives the results on a more disaggregated level, showing that for 19 of the 40 products, no prescriptions for follow-on indications could be identified; all prescriptions were concentrated in the original indications. Of the other 21 products, a wide range was observed for the proportion of prescriptions that were for new indications. Again excluding the 'unknowns' from the percentages, there were five products where the proportion was less than 10%; nine where it was between 11% and 20%; and another four between 21% and 50%. Then there was a group of three products for which over 70% of prescribing was reported as being for new indications rather than the original indication.

Comparisons with the *New England Journal of Medicine* article

Compared with the results presented in the *New England Journal of Medicine* article, our results in aggregate also show that follow-on indications are very important, although we found across all drugs that secondary indications accounted for 25% of sales as compared to the Gelijns et al finding of over 40% of total sales. However within the overall samples there were marked differences in distribution. There were 17 compounds considered in 1993 to be 'blockbusters' in the *New England Journal of Medicine* study and about 90% had important secondary indications. By contrast we found that nearly half of the top 50 selling products did not seem to have any follow-on indications.

However, there are differences in the composition of the two groups of drugs. Only eight of the compounds in the New England Journal of Medicine sample were matched up with compounds that appear in the list of 40 for which UK data were collected. Limiting our sample to these eight products we find that, using our UK data, only one has no secondary indications and, overall, 56% of sales are for new indications and unlicensed indications, adjusting for 'unknown' uses. A more relevant comparison is perhaps between the UK sample and a more recent list of the top 50 selling drugs on a world-wide basis. Of the top 50 global products in 1999, according to IMS data, 18 products are in our sample of 40 and, of these, nine (50%) have obtained no new licensed indications in the UK according to the information listed in the Summaries of Product Characteristics. We found for this subgroup of 18 best selling global products that, using our UK data, sales of subsequent indications accounted for 30% of sales by value – a result above the 25% figure of our overall findings.

Conclusions

Our findings from a small study of leading UK products confirm the findings of the Gelijns et al study of significant unexpected medical benefit from subsequent indications identified post-launch of the products. We found 25% of use by sales of the leading products was for follow-on indications rather than the indication for which the product was initially launched. Amongst the subset of 18 products that are also in the global top 50 products follow-on sales accounted for 30% of the total. We found, however, that the results were skewed with a significant number of products having no subsequent indications and others having very substantial use. This suggests that more research is required to understand the characteristics of those groups of products that do and those that do not have substantial subsequent indications for use.

Some further analysis could be carried out with the UK data that we collected. It would be of interest to address the question of how long it takes a product, on average, from the time when it is originally licensed to when it acquires its subsequent indications. It would also be interesting to look at whether propensity to develop secondary

indications varies by disease area and we could look at whether these products have crossed boundaries between different disease areas, in terms of their secondary indications. The importance of more subtle variations in use changes that were picked up (changes in the authorised use that were not actually changes in the indication) could be explored as could the importance of inappropriate prescribing.

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Chapter 3

Cardio-vascular disease

PHILIP POOLE-WILSON

Introduction

The oldest example of unexpected medical benefit in the area of cardiovascular disease is aspirin. Having initially been used for pain relief, the benefits of this drug are now exploited for the prevention of coronary artery disease. One of the most recent developments, on the other hand, is the belief that statins do not act entirely by reducing cholesterol but also by altering inflammation.

This presentation considers three examples of unexpected medical benefit, the first of which (the ACE inhibitor) can be considered the most pervasive drug of the present time. The second (the beta blocker) is the drug which has upset most prejudices, and the third (heart transplantation) is of topical interest.

Angiotensin Converting Enzyme (ACE) inhibitors – hypertension

There has been awareness of the importance of the renin angiotensin system for many decades, with interest surrounding the possibility of finding a drug to block the conversion of angiotensin I to angiotensin II. This led to a rare example of a drug company setting out to produce such a drug and doing it in a calculated way, assisted by the mathematical construction of molecules. The first drug in the class of angiotensin converting enzyme (ACE) inhibitors came on the market with an indication for hypertension.

ACE inhibitors – heart failure

Because of the prevailing view (not now held) in the 1970s that one of the most important attributes of a drug in heart failure should be vasodilatation (based on studies of nitrates and the unloading of the ventricle), it was reasonable to test ACE inhibitors in this indication. ACE inhibitors were known to reduce blood pressure and to be vasodilators. Having been found to reduce symptoms, an ACE inhibitor duly came on the market for this second indication, namely heart failure.

At the time ACE inhibitors came on to the market in the UK, they were probably used incorrectly. Indeed, they may have come on to the market too quickly and, after causing some severe cases of renal failure and angioneurotic oedema, ACE inhibitors came close to being withdrawn from the market.

One of the most important clinical trials conducted in the last century was the CONSENSUS study in heart failure, in which patients were randomised (for the first year only) to enalapril or placebo. It is the only study in heart failure to have been completed, in the sense that all the patients initially enrolled are now dead, and is therefore one of a small number of studies in which the overall benefit can be observed directly from the trial data. In this case, the ACE inhibitor gave an improvement of about 50% in total patient life years. This was the basis, supported by some other studies, for the widely held view that ACE inhibitors should be used in all patients with heart failure. Table 3.1 shows the results of a recent meta analysis which confirms that view.

ACE inhibitors – Acute Myocardial Infarction (AMI)

Given the evidence on hypertension and heart failure, it is no surprise that other potential indications were considered. An obvious candidate was AMI. One view on this was that ACE inhibitors could be dangerous in the context of myocardial ischaemia due to the lowering of

Table 3.1 Meta-analysis of ACE inhibitor trials in heart failure

<i>End-point</i>	<i>Odds ratio</i>	<i>95% CI</i>	<i>P value</i>
Total mortality	0.77	0.67-0.88	<0.001
Progressive heart failure	0.69	0.58-0.83	
Sudden death	0.91	0.73-1.12	
Fatal myocardial infarction	0.82	0.60-1.11	
Mortality and hospitalisation for congestive heart failure	0.65	0.57-0.74	<0.001

Source: Garg and Yusuf, 1995

blood pressure and therefore the perfusion pressure. Another view was that this pathway, and other pathways modified by ACE inhibitors, would bring about advantages in terms of cell growth and remodelling of the myocardium.

What the studies showed was that both points of view were valid. The CONSENSUS II study, where it was given acutely in high doses, was neutral overall but did show harm in elderly females with low blood pressure. In the other studies, patients were given long term therapy beginning late after infarction, or short term therapy beginning in the acute stage; all showed some degree of benefit.

There continues to be a good deal of controversy about when ACE inhibitor therapy should be started in these patients, when it should be stopped, and whether it should be used for all patients with myocardial infarction. Nevertheless, ACE inhibitors have become established therapy for this third indication. Indications four and five (in chronological order), renal failure and diabetic renal failure, do not relate to cardiovascular disease and are not considered further here.

ACE inhibitors – those at risk of cardiovascular disease

Consideration of the next application of ACE inhibitors raises the question of what constitutes an unexpected or further indication. As Table 3.2 shows, the results of the HOPE study were extremely impressive in patients at high risk of cardiovascular events, who are becoming easier to identify. The science behind the idea is that ACE inhibitors have a beneficial effect on the endothelium. Although these results were not confirmed by the QUIET study, there are two other studies still running.

There is no doubt that the HOPE study looked impressive, with particularly favourable results in diabetics. The conclusion that has been drawn from the study is that all people at high risk of a cardiovascular event should be treated with an ACE inhibitor. Does such a conclusion represent a new indication or is it simply that the form of words has changed? For example 47% of the patients in the study had hypertension, 53% had had a myocardial infarct and many had diabetes with the renal abnormalities associated with that. Therefore, for

Table 3.2 The HOPE study*

	ACE inhibitor	Placebo	Relative risk	95% CI	P value
Number of patients	4,645	4,652			
Combined end-point %	14	17.8	0.78	0.70-0.86	<0.001
Total death %	10.4	12.2	0.84	0.75-0.94	<0.005
All death + combined end-point %	18.3	21.9	0.84	0.77-0.91	<0.001
All new heart failure	9.0	11.5	0.77	0.67-0.87	<0.001

Source: Yusuf et al, 2000

Note: *9,297 patients at high risk of cardiovascular events. Ramipril 10 mg od Vit E 400 iu. Mean follow-up 5 years, average age 66 years, 73% male, 80% CHD, 53% MI, 47% hypertension, 65% high cholesterol, 70% compliance. Combined end-point of cardiac death, stroke and myocardial infarction. Stopped early.

the great majority of these patients, an established ACE inhibitor indication was already present. This might be an example where changing the wording broadens the indication for a drug to the benefit of the company, but not necessarily to the benefit of patients.

A general issue about the interpretation of trial data, and one which is well illustrated in the example of ACE inhibitors, is how they relate to the population at large. As Table 3.3 shows, the average age of patients in recent studies of ACE inhibitors in heart disease (mainly heart failure) varies between 59 and 66 years. In comparison, the average age of heart failure patients in the community is 75 years. The mean age in these studies, therefore, is a decade away from that observed in clinical practice. Furthermore, relatively few females were recruited into these studies and the results for females are distinctly unclear. The view that ACE inhibitors should be used in everybody with heart failure is not shared by everyone and is perhaps a view being pushed mainly by commercial rather than patients' interests.

Table 3.3 Characteristics of patients in recent studies of ACE inhibitors in heart disease

	<i>SOLVD prevention</i>	<i>SOLVD treatment</i>	<i>SAVE</i>	<i>CONSENSUS II</i>	<i>AIRE</i>
Number of patients	4,228	2,569	2,231	6,090	2,006
ACE inhibitor	Enalapril	Enalapril	Captopril	Enalapril	Ramipril
Duration (months)	37	41	42	6	15
Age (years)	59	61	59	66	65
Females	11%	20%	18%	27%	26%
Coronary disease	83%	71%	100%	100%	100%
Ejection fraction for inclusion	35%	35%	40%	–	–
Ejection fraction	28%	25%	31%	–	–

Beta blockers – heart failure

The second example of a group of drugs with multiple indications in cardiovascular disease is the beta blockers. Once their effects had been demonstrated in angina and in hypertension, a Swedish group, led by Finn Waagstein, published a paper in 1975 in the *British Heart Journal* alleging they were beneficial in heart failure on the basis of a completely uncontrolled study. The results of the study were greeted with widespread scepticism in the UK and for good reason. In the Xamoterol study in the 1980s, in which a beta blocker was given in the full dose immediately to patients with severe heart failure, mortality was increased.

The stopping of this study because of increased mortality tended to confirm the view that stimulation of the sympathetic system in the treatment of heart failure was important and that blocking it could potentially be harmful. However, this idea has subsequently been shown to be wrong. After the appearance of a number of uncontrolled studies, the results of four large well-designed studies in heart failure, CIBIS II, BEST, MERIT and, most recently, COPERNICUS, have become available.

Table 3.4 The MERIT study

	Placebo	Metoprolol	CR/XL (95% CI)	Relative risk	P value
Deaths total	217/2,001	145/1,990	0.66	0.53-0.81	0.006
Cardiovascular deaths	203	128	0.62	0.50-0.78	0.0003
Sudden death	132	79	0.59	0.45-0.78	0.0002
Worsening heart failure death	58	30	0.51	0.33-0.79	0.002
At 6 months heart rate	-3	-12 beats/ min			
Systolic blood pressure	-3.5	-2 mm Hg			0.013
Drug stopped	15.3%	13.9%	0.90	0.77-1.06	
Annual mortality	11.0%	7.2%			

Source: MERIT-HF Study Group, 1999

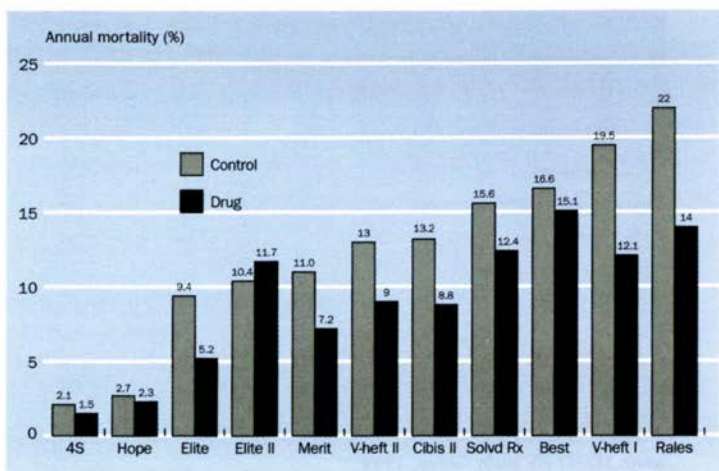
Note: *3,991 patients, average age 64years, 78% male, 66% ischaemic, NYHA II 41%, NYHA III 55%, EF 28%, mean follow-up one year. Stopped early.

Table 3.4 shows the overwhelmingly positive results of the MERIT study, conducted in almost 4,000 patients. In absolute terms, the results are extremely impressive and established that beta blockers were beneficial in the additional indication of heart failure. The lesson to be drawn from this experience is that the benefit arose from a changed understanding of the physiology and, above all, a change in the way in which the drug was used. Increased skill in managing the drug to suit the individual patient, which a general practitioner could not be expected to do, has enabled these additional benefits to be realised. However, the use of beta blockers after acute myocardial infarction may cast some doubt on this simple story, as I now discuss.

Beta blockers – Acute Myocardial Infarction (AMI)

As three trials (the timolol, BHAT and Goteborg studies) have shown, the benefit of beta blockade after AMI is greater in those with heart failure because they are at greater risk, but there are also benefits in

Figure 3.1 Annual mortality in selected trials



those without heart failure. The results suggest that the benefit of a beta blocker in someone with coronary heart disease might not be related to the intrinsic process of heart failure but rather to the presence of coronary heart disease, and it is known that beta blockers are effective in angina.

The one piece of evidence against this view is that relating to mechanisms of action. Although the increase in ejection fraction seen with carvedilol may not be important because of the effect of heart rate, the findings on end-diastolic and end-systolic volume indicate a reduction in the size of the heart. The implication is that there has been a biological process of remodelling, something which has been extensively investigated.

Figure 3.1 shows the annual mortality rates observed in a number of trials. The benefits of the treatment in heart failure are shown by the RALES study which found an annual mortality rate of 22% amongst controls compared with 14% among those receiving drug treatment. In comparison, the 4S study showed a reduction in annual mortality

from 2.1% to 1.5%. In both cases, there is the potential for considerable benefit, in the case of the RALES study because of the greater effect and in the case of the 4S study because of the potentially greater number of patients. These considerations need to be balanced when considering public policy.

Heart transplantation

The final examples in the context of heart failure come from the *British Medical Journal* (BMJ) and the *Sunday Times*. In the BMJ, a German study was reported claiming that it was not possible to show that transplantation was beneficial in patients with heart failure. The conclusion of the BMJ paper, which had some serious limitations and the results of which are similar to those of a paper published 10 years ago, was that only those with severe heart failure benefited.

In practice, however, it is those with severe heart failure who are increasingly being excluded from transplantation. The argument is that donor hearts are precious and therefore should only be used in patients who will achieve considerable benefit. It is thought that by selecting the healthier patients, that is by excluding all those who have liver disease, reduced renal function and so on, the results will be improved.

As shown in Table 3.5, the point made by the BMJ paper is illustrated by the results of an earlier study, in which those undergoing and those not undergoing transplantation had peak oxygen consumption of 17 and 19 ml/min/kg, respectively. These values are indicative of considerable exercise capacity. Those patients recruited into the study summarised in Table 3.5 could, therefore, be viewed as too healthy for transplant. This example highlights the problem, when a new idea comes in, of identifying the appropriate patients to treat and having well-designed studies to support its use.

Left ventricular assist device

Another problem was highlighted by the report in the *Sunday Times* of the Jarvik 2000, a device about the size of a person's thumb, placed in the left ventricle, running round into the aorta. This was put into a

Table 3.5 Transplantation versus medical treatment

	<i>45 had transplantation 22 survived 6 months Group 1</i>	<i>43 ineligible or unwilling 20 survived 6 months Group 2</i>
Ejection fraction (%)	15 to 62	15 to 22
PCP (mm Hg)	15	14
NYHA score	3.4	3.7
6 min walk (m)	1,460	1,430
Peak MVO ₂ (ml/min/kg)	17	19
Peak heart rate (beats/min)	137	145
Peak watts	103	103

Source: Stevenson et al, 1990

Note: 146 patients, 118 discharged from hospital without transplant, 88 stable for one month

patient on 20 June 2000, with the intention of leaving it there permanently, not as a bridge to transplant. Having performed well in one patient, a second implant has been carried out.

If the principle of the device works, as this experience suggests, then it becomes a matter of technology as to how long it will last. It becomes an engineering, not a medical, challenge. The second issue is who should receive the device. The third is how to introduce it into medical practice. Despite raising a number of ethical problems, it appears to be a promising advance which may avoid the problems of transplantation.

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Chapter 4

Viagra

GILL SAMUELS

Introduction

The development of Viagra as a treatment for erectile dysfunction represented the culmination of a research programme involving more than 1,500 people within Pfizer. In 1985, the programme originally began with an idea for developing a novel antihypertensive by potentiating the effect of atrial natriuretic factor (ANF), the intention being to develop a drug with both vaso-relaxant and diuretic effects. The compound which was developed was a very specific and highly potent cyclic GMP phosphodiesterase (PDE) inhibitor able to potentiate the effect of ANF and both the vaso-relaxant and antiplatelet effects of sodium nitro-prusside. Around that time Endothelium Derived Relaxing Factor (EDRF) was shown to be nitric oxide, and we reoriented the clinical research programme towards angina.

Clinical testing in angina

In the early 1990s the compound went into clinical evaluation. It did not have a robust effect in angina but, interestingly, evidence from Phase I studies showed that there were a number of what, at that stage, were thought of as side effects. In a 10-day study, in addition to headache, myalgia and indigestion being reported, some anecdotal reports of erections were received. These occurred only at high dose levels, with other side effects also occurring, and towards the end of the study when the compound was given three times a day.

This finding was of particular interest in the light of some recent evidence in the literature that the non-alpha, non-cholinergic nervous system had as its neurotransmitter nitric oxide and might be involved in the erectile process. There was no knowledge at that stage about the distribution and importance of sub-types of phosphodiesterase, and very few people thought that an oral compound could have a beneficial effect on erectile performance. Nevertheless, it was decided to pursue this possibility and, in 1992, the programme began to focus on erectile dysfunction for the first time.

Early studies in Erectile Dysfunction (ED)

There were a number of challenges in focusing the research programme on erectile dysfunction. For example, there was the role of sexual stimulation and the question of how patients would be monitored during sexual stimulation. There were many unknowns about how questions would be asked of patients in a systematic way, in a clinical setting, to discover whether the Phase I observations were just an interesting clinical anecdote or whether they were dependent on the basic pharmacology of the compound.

The first pilot study was set up late in 1993 amongst a group of patients chosen because they had psychogenic erectile dysfunction. A 25 mg dose was compared with placebo in a cross-over study. Patients were monitored using a daily diary of erections and a rigiscan to monitor the hardness of the penis during visual sexual stimulation. It became clear from this study that what was then called UK-92480 did have an effect on erectile performance in individuals with psychogenic erectile dysfunction.

The compound was generally well tolerated. Five out of 16 patients had myalgia and there was some incidence of indigestion, as was to be expected from the earlier clinical observations. However, questions remaining to be answered were:

- would patients with erectile dysfunction want to have to take a compound three times a day?
- who would want to plan on Monday for an event that might only happen later in the week?
- could a dosing regimen be found that did not cause myalgia?

A second study was conducted again among patients with psychogenic erectile dysfunction, with a single-dose being compared with three doses or placebo. Erections were monitored during visual sexual stimulation, again using the rigiscan. The most interesting finding from this study was that UK-92480, or sildenafil as it was then known, produced a dose-response relationship, an encouraging observation.

The conclusion from the second pilot study was that sildenafil certainly did improve erections in patients with psychogenic erectile dysfunction. Patients recognised the benefit and were asking if they could continue treatment. However, there were a number of questions still to be addressed:

- how relevant were the rigiscan data and visual sexual stimulation?
- how could effective outpatient trials be designed, whereby patients would keep a diary of erectile activity?
- would the compound be effective in the home setting?
- would it work in patients with organic causes of erectile dysfunction?

The actual data on the epidemiology of erectile dysfunction were not particularly clear at that stage, and there were views that psychogenic erectile dysfunction was not very common. Consulting the literature showed that there was a significant incidence of erectile dysfunction, which could be due to psychogenic factors, to organic factors, or could have a mixed origin, with about a third of cases in each category. It was clear that, in order to continue development in erectile dysfunction, it would be necessary to overcome a certain amount of cynicism that an oral compound could have such a specific effect in one particular vascular bed, and efficacy would need to be shown in organic cases. Moreover, there were no agreed diagnostic criteria for erectile dysfunction, no efficacy instruments for outpatient studies and no regulatory guidelines. It was uncertain whether regulators would approve an oral agent for erectile dysfunction. Some data from other companies working in the same therapeutic area, but focusing on different mechanisms of action, suggested that running clinical trials in these areas was a long, resource-consuming and not always a convincing process.

Clinical development from Phase II to launch

Against the potential problems evident at the pilot study phase, encouragement to continue development was forthcoming from a variety of sources, one of the more important being the patients

themselves. It was generally becoming known that erectile dysfunction, whilst unrecognised, was a serious medical condition and could affect people's lives significantly. Positive results had been observed in the pilot studies and no other company had an orally active specific cyclic GMP phosphodiesterase inhibitor of a similar type. Leading urologists were enthusiastic and, after discussing some of the problems with regulators, it was felt that regulatory guidelines would not be a problem in the future. Last, but not least, support was received at a high level within Pfizer.

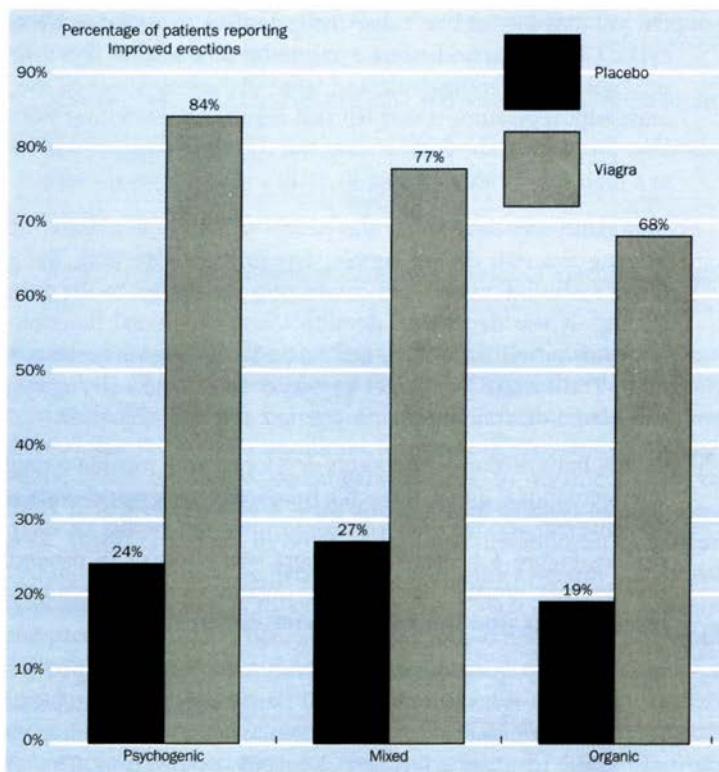
Important decisions about the design of Phase II studies included keeping the trial design simple, avoiding invasive tests, the use of broad inclusion criteria and conducting the studies in the outpatient setting. It was decided to develop a bespoke sexual function questionnaire as well as a diary, and to start long-term extension studies early. The optimal filing strategy was decided, and a strong emphasis was placed on running the programme fast and effectively.

On the basis of simple endpoints developed with outside consultants, the international index of erectile function, now a world-wide accepted standard, was formulated. Confirming the results of early stage studies, Figure 4.1 shows that Viagra was effective in patients with psychogenic erectile dysfunction, organic erectile dysfunction, or those patients who had mixed erectile dysfunction.

In addition to questions on pure erectile performance, patients were asked about orgasm, desire, overall satisfaction and intercourse satisfaction in the questionnaire, which was administered both to untreated healthy men and patients with erectile dysfunction. The effect of Viagra was to restore sexual function to close to normal.

In total, the development programme involved international studies which evaluated between 4,000 and 5,000 individuals. The licensing application was filed with the FDA and in Europe in 1997. The FDA's review resulted in approval being given in March 1998, with European approval following in the autumn of 1998. The compound has proved to be a highly successful, well tolerated first-in-class product.

Figure 4.1 Effectiveness of viagra in erectile dysfunction of varying aetiology



The pharmaceutical company context

In the overall context of a pharmaceutical company's research and development portfolio, finding compounds like Viagra is rare. The attrition rate in the discovery and development process is high, a process that can take between 10 and 15 years. Only one in 12 potential new medicines that enter clinical development reach the market, which means that to bring a new medicine to market successfully requires an average investment of between \$500 million and \$600

million. Viagra is one of a cast of thousands of compounds and has involved a large number of people within Pfizer. Some of those who played key roles in the early discovery and development process are Peter Ellis, who led the biology programme, Nick Terrett who led the chemistry programme, Mike Allen who led the early clinical programme, and Ian Osterloh who led the later clinical programme.

Viagra has been successful because it meets a major medical need that had not previously been well defined. It illustrates the advantages of excellent teamwork between the pre-clinical groups and the clinical groups and of following up all key findings during development. The presence of a toxicology working party and an adverse event working party enabled problems to be addressed immediately and effectively. Perseverance in the face of adversity, and the support received from very high levels in the organisation also proved invaluable. A key lesson from the Viagra story is the need to have a high quality compound when seeking to explore the potential therapeutic significance of an NCE with a novel mechanism of action.

Chapter 5

Photodynamic therapy in the management of arterial disease

STEPHEN BOWN

Introduction

As with the use of ACE inhibitors in cardiovascular disease, a new indication for photodynamic therapy (PDT) has emerged from trying to understand the mechanism of action in the primary indication. The biological effect produced by PDT is the result of a combination of a photo-sensitising drug and low-power, non-thermal, light. It therefore relies on a photo-chemical process, and neither the light on its own nor the drug on its own produces any biological effect. This introduces the complication of having all the problems of introducing new drugs with the need to manage the technology of administering light to the relevant sites.

The first interest in PDT arose from the empirical observation that certain porphyrin derivatives were retained selectively in malignant tissues compared with the adjacent normal tissues in which that tumour had arisen. This finding gave rise to the suggestion that cancers could be selectively destroyed, a possibility which has not been realised in practice. However, scientific discoveries, which have taken much longer to emerge, have shown that the effect of PDT is different from that of most other techniques for localised tissue destruction.

The most important feature of PDT is that there is no heat involved, so that connective tissue is largely undamaged. Although it destroys living cells, collagen, elastin and similar tissue are unaffected. It is therefore possible to achieve extremely good healing. In addition, there is none of the cumulative toxicity associated with ionising radiation and chemotherapy.

Photodynamic Therapy (PDT) in cancer

The implication of the biological effect of PDT is that this type of therapy can be used for local cancer therapy. Once the patient has been photo-sensitised, red light is delivered to the area of the tumour,

the procedure being performed with sedating drugs and local anaesthetic. General anaesthesia is rarely necessary.

In a typical case of a small cancer on the lip, only a small scar was left (where a biopsy was taken to confirm the diagnosis) once the lip had had time to heal following PDT. Regeneration of the lip tissue is extremely good and the results, in terms of healing, were far better than those achieved with surgery and radiotherapy for another nearby lesion treated some years before on the same patient.

Although there is quite a lot of experience using PDT for mouth cancers, it is not yet a licensed treatment for this indication. From this standard indication, the potential for finding other applications of the technique has been explored. The destruction of small areas of cancer, while normal tissues seem to heal safely after the therapy, raised the possibility of being able to destroy microscopic tumour deposits in a surgical bed. The one application that was the initial focus of attention was its use following a radical dissection of the neck. In order to perform the procedure safely, it is essential that all the normal tissues in that area, particularly the carotid artery, can tolerate the treatment.

Animal studies of PDT in normal arteries

Initially, the effects of PDT on the normal artery were explored, mainly in animal studies (pig, rat and rabbit) to assess whether it could be applied safely. Taking the example of a normal iliac artery, it was found that light alone has no effect. In comparison the effects of PDT in normal arteries were:

- the endothelium was denuded but it rapidly regenerated;
- the smooth muscle cells were depleted and took some months to recover;
- special stains for collagen and elastin showed that there was no effect on these tissues;
- there was no reduction in the blood flow and there was no thrombosis;
- when PDT-treated arteries were blown up like a balloon, bursting occurred through the non PDT-treated area rather than the PDT-

treated area; there was no reduction in the bursting pressure and there were no aneurysms.

These results indicated that the treatment was safe to use in the neck, where the main concern was the carotid artery. They also suggested that PDT might be of value in the treatment not only of cancer but also of arterial disease.

PDT in occlusive arterial disease

Currently, one of the major approaches to occlusive arterial disease is balloon angioplasty, which involves sliding the balloon into the obstruction, blowing it up and dilating the lumen. However, there is a high incidence of re-stenosis, which can occur in one of three ways:

- proliferation of the smooth muscle cells in the media, creating tissue in the middle of the artery and thus closing it;
- remodelling, whereby the whole artery appears to shrink – a major cause of re-stenosis only recognised in the last few years;
- instant recoil, whereby the stretched artery simply returns to its original condition by an elastic effect.

The first of these has attracted the most attention in the context of PDT, because it is proliferation of the medial smooth muscle cells, which PDT can kill, that causes the neo-intimal hyperplasia. Therefore, treating the artery at the same time as balloon angioplasty is performed may suppress this re-stenotic mechanism.

An alternative way of preventing re-stenosis in an artery is to insert a stent to hold it open. Although this prevents the artery from recoiling and inhibits negative remodelling, it is now being recognised that intimal hyperplasia will continue when the stent is in place, either through the walls of the stent or round the end. Inserting a stent does not, therefore, solve the problem of re-stenosis from this source, potentially making PDT even more attractive.

Animal studies of PDT in balloon-injured arteries

The first experiments performed on injured arteries, to test whether

the adverse reactions to balloon dilatation could be suppressed, involved the rat carotid artery. In normal animals, the carotid artery was injured by inserting a balloon and dilating it to 1.5 times its normal size. Without treatment, this results in enormous proliferation of the smooth muscle cells compared with the thickness of the underlying media. In contrast, in animals that had PDT immediately after the balloon injury there is no proliferation of these smooth muscle cells; no nuclei were found in the intima or in the media.

Some suppression of this smooth muscle hyperplasia was found in the controls treated with light alone, but this occurred only in the rat carotid and not in the larger arteries in the pigs that were investigated subsequently. It appeared, therefore, that PDT was achieving the suppression of precisely the desired tissue to prevent re-stenosis after balloon angioplasty.

In further experiments on the coronary arteries of pigs, untreated balloon injured arteries showed a tear in the internal elastic lamina and intimal proliferation. With simultaneous PDT at the time of balloon injury in arteries injured in the same way, with a rupture in the elastic laminae, intimal hyperplasia was found to be much reduced, although not completely eliminated.

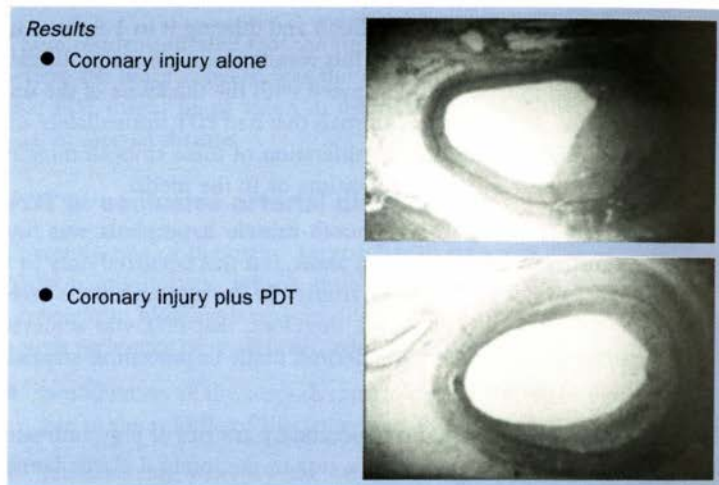
In comparison with the control injured arteries, the area within the external elastic lamina was significantly larger in the injured and PDT-treated arteries, as was the actual lumen. The neo-intimal hyperplasia was less in the PDT-treated cases. Figure 5.1 illustrates the difference between PDT and control arteries in a pig.

Overall, the effects of PDT on balloon-injured arteries are that:

- the endothelium is undoubtedly denuded but it regenerates rapidly;
- the medial smooth muscle cells are destroyed;
- there is much less neo-intimal hyperplasia;
- there is no negative remodelling.

Using PDT, it seems that, in these animal studies, the re-stenosis and contraction that has caused so many problems to cardiologists has been markedly reduced and there is preservation of the arterial lumen.

Figure 5.1 **Effect of PDT in a pig artery**



Source: Jenkins et al, 2000

PDT in stenosed arteries in humans

The results of the first clinical trial on stenosed arteries in humans conducted at the National Medical Laser Centre (probably the first trial undertaken anywhere in the world), have recently been published (Jenkins et al, 1999). The trial was a small pilot study conducted in seven patients with femoral artery stenoses who had had a balloon angioplasty, had re-stenosed within six months of that balloon angioplasty and were undergoing a second angioplasty.

The photosensitising agent ALA (5-Aminolaevulinic acid) was given a few hours prior to the routine angioplasty. Once the balloon angioplasty procedure had been completed, the guide wire was removed and replaced by a thin laser fibre, so that the treated site could be illuminated immediately with low-power red light to activate the photosensitising agent. The balloon angioplasty catheter was of a standard type except that the outer and inner surfaces were required to be transparent, to allow the red light to pass through. In the femoral artery, a 200 micron fibre was used; application of the treatment to

the coronary artery (which is so far only experimental) would require an even smaller fibre with a core of 150 microns.

Using duplex surveillance at six months post-angioplasty, an excellent lumen could be observed with disappearance of the collateral vessels because a good flow had been restored to the main vessel. Although some partial re-stenosis was observed (25% in three patients and 40% in two), at six months none of the seven arteries treated had reached the figure of 50% used as the criterion for re-stenosis in the literature. This was despite the fact that all seven had re-stenosed after the first balloon angioplasty. Moreover, no arterial complications were observed.

The future

Following on from this pilot study, larger studies are planned, initially in peripheral arteries, but with the intention of applying the technique to coronary arteries at a later stage. Evaluating PDT to see if the technique, developed for tumour therapy, will be able to suppress re-stenosis after balloon angioplasty is just one of the results emerging. The experience with PDT illustrates that when a technology is applied directly to an area of tissue, the results are examined in far more detail than is the case of a drug given systemically. Biologically, it is possible with PDT to assess exactly what happens when some light is applied to the treated area. It is when the biology is understood that it is possible to ask 'when is it relevant in the treatment of human disease?' Other potential uses that suggest themselves are the treatment of localised infections, or destroying the endometrium of the uterus, as a simple way of treating menorrhagia. The example of PDT also serves to illustrate the working of multi-specialty units. At UCL, the principles of photodynamic therapy have been applied in a range of clinical specialties in close association with other treatments such as surgery and radiotherapy. Basic scientific studies are also underway to understand more of the mechanisms of PDT and how to deliver and monitor therapy to increase its role as a therapeutic modality.

Acknowledgement

This work is a summary of a series of research projects at the National Medical Laser Centre.

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Chapter 6

Helicobacter pylori

PAUL MOAYYEDI

Introduction – the discovery of *Helicobacter pylori*

The discovery of *Helicobacter pylori* can be attributed to Robin Warren, a pathologist who was convinced that he was seeing bacteria down his microscope at gastric biopsies. Together with a young registrar, Barry Marshall, he set about the difficult task of culturing these organisms.

They were eventually successful after a culture plate was left over a long weekend, the result of Barry Marshall's preference for surfing rather than clearing out his incubator. On his return, he was rewarded with the sight of what we now know as *H pylori*, which requires three to five days to culture compared with two days for other bacteria. Waiting the extra days proved the key to success.

This important discovery, the first time that *H pylori* had been isolated in culture, was reported in the *Lancet* but attracted little interest. Barry Marshall then attempted to fulfil one of Koch's postulates by ingesting the organism. He developed an *H pylori* associated gastritis whereas previously he had a normal stomach.

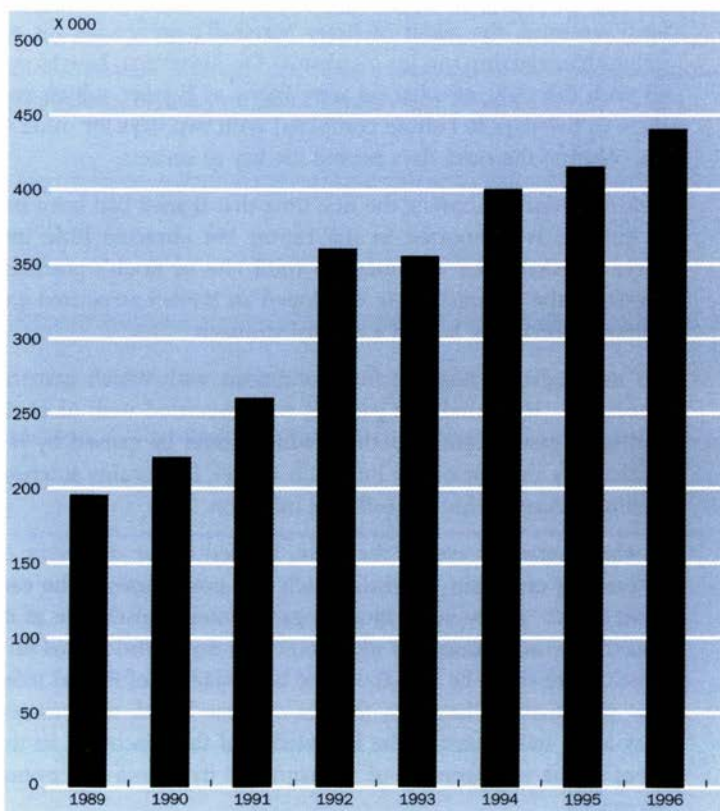
He also began to research into conditions with which gastritis was associated. He found that gastritis was associated with ulcer disease and with gastric cancer, both of which could be caused by *H pylori*. Particularly in light of the link with cancer, he became interested in finding a cure for his self-inflicted infection.

A whole series of events, therefore, has led to the discovery of this interesting organism, *H pylori*, which, we now know, is the cause of most ulcers. A few years ago, the gastroenterologist's rule of thumb was that no acid meant no ulcer; now it is no *H pylori* means no ulcer. Much more could be said about the basic science of *H pylori* infection. The presentation, however, focuses on how health services research may assist in harnessing the knowledge of this discovery, in the two areas of the management of undiagnosed dyspepsia and population screening.

Undiagnosed dyspepsia

A procedure that is often done to diagnose dyspepsia, and to try and rationalise treatment, is endoscopy. Despite it being associated with a considerable morbidity and occasionally mortality, it is also a procedure that is becoming more popular, as Figure 6.1 shows. In England alone, nearly half a million of these procedures are performed each year, at a cost of over £10 million. The reasons for doing this are:

Figure 6.1 Endoscopies conducted in England



- we want to detect cancer early, at a stage where it may be treatable;
- we want to make specific diagnoses; in particular, to find out about peptic ulcer disease;
- we want to reassure people if they do not have these diseases.

Randomised control trials have shown that a strategy of performing endoscopy is more cost-effective than simply giving people dyspepsia treatment, such as H₂ receptor antagonists or antacids.

The discovery of *H pylori* has altered this picture. What is now proposed is that young people with no sinister symptoms are highly unlikely to have gastric cancer. If the problem is an ulcer, a non-invasive test for *H pylori*, either a blood test or a breath test, is sufficient and if the infection is present, any ulcers can be treated with antibiotics – a test-and-treat approach. If there is no infection, the individual can be reassured and treated symptomatically.

That is what the theory would suggest; health services research can attempt to establish whether it works in practice. Three randomised controlled trials have shown that test-and-treat is just as good as early endoscopy, and costs much less. Simple cost minimisation analysis suggests that this strategy should therefore be used rather than endoscopic patients.

A 'real world' example of the introduction of the test-and-treat strategy is that of Leeds General Infirmary, where its use began five years ago. Five years before the introduction of an *H pylori* test-and-treat service the proportion of young people receiving endoscopy had remained stable. This was an ideal context in which to see what impact the new intervention would have on endoscopy workload in a before-and-after study. GPs were told that they could use the new service, as a result of which there was a significant reduction in the number of endoscopies being performed in the young compared with the year before. Overall, there was a 36% reduction in open access endoscopy, representing a significant cost saving to the region.

In addition, as in the randomised controlled trials, a dramatic fall in dyspepsia and associated dyspepsia cost was observed at six months

Table 6.1 *H pylori* and gastric cancer

<i>Study</i>	<i>Odds ratio (95% confidence interval (CI))</i>	<i>% weight</i>
UK	2.99 (1.58, 5.65)	8.2
US (California)	3.63 (1.91, 6.90)	7.4
US (Hawaii)	5.38 (2.11, 13.68)	3.3
Taiwan	1.57 (0.68, 3.60)	6.7
Finland	1.37 (0.64, 2.95)	8.4
Sweden	4.77 (2.29, 9.92)	5.7
Japan	3.32 (1.14, 9.68)	3.6
Norway	2.32 (1.62, 3.34)	31.6
China	1.81 (1.08, 3.02)	17.7
Iceland	1.69 (0.76, 3.74)	7.3
Overall (95% CI)	2.48 (2.02, 3.03)	

Source: Danesh, 1999

compared with the base line. The results of the test-and-treat strategy, compared with a cohort of endoscopy patients matched for age and sex, were impressive.

As with the randomised control trial data, the results of this study should be treated with caution, since much of the benefit is simply a regression to the mean, a phenomenon about which we have known for centuries. However, if 'the art of medicine is to amuse the patient whilst nature cures the disease' (Voltaire), then screening for *H pylori* is as good as endoscopy at amusing the patient. The next challenge is to translate this fully into clinical practice, because there is considerable financial remuneration for doctors in endoscopic patients, especially privately.

Population screening for *H pylori*

What would be the purpose of population screening? Table 6.1 sug-

gests a possible rationale. As well as being associated with ulcer disease, a large number of nested prospective case control studies have shown that *H pylori* is also associated with gastric cancer in the distal part of the stomach. The meta analysis by John Danesh reported here shows a highly significant difference in favour of those infected with *H pylori* getting gastric cancer in later life, with a ratio of about 2.5.

Overall, about one in 30 deaths in men and one in 60 deaths in women in the UK is attributable to *H pylori*, far greater than any other infection in the UK and the western world, and yet it can be simply treated by antibiotics. In the light of these figures, population screening seems a potentially sensible intervention. There is no direct randomised controlled trial evidence, however, that treating the infection will reduce gastric cancer and introducing population screening would be expensive. However, it would help identify not just gastric cancer, but also ulcer disease and, as has already been seen, dyspepsia is an expensive condition to diagnose by endoscopy and to treat. It is possible that, as well as preventing gastric cancer, it will reduce the health and cost burden of dyspepsia in the community. The question is by how much and whether this is economically cost effective?

In order to evaluate the extent to which dyspepsia might be reduced and the economic importance of doing so, a randomised controlled trial was conducted in Leeds. Subjects between the ages of 40 and 49 were invited to attend their local practice, where their *H pylori* status was determined with a breath test, and a fairly standard treatment for *H pylori* of omeprazole, clarithromycin and tinidazole, or identical placebo, was administered. Participants were followed up for two

Table 6.2 Reduction in dyspepsia with *H pylori* test-and-treat

	<i>Dyspepsia</i>	<i>No dyspepsia</i>
Eradication	247 (28%)	633 (72%)
Placebo	291 (33%)	580 (67%)
		Chi-square $p = 0.015$

Table 6.3 Impact on costs of *H pylori* test-and-treat

	Cost saving (£)	95% CI	P value
Males	26	3 to 48	0.02
Females	-4 (i.e. net cost)	-33 to 25	0.79

years with dyspepsia questionnaires and economic data were also collected from their primary care notes.

A follow up rate of 75% was achieved. As Table 6.2 shows and as was reported in the Lancet (Moayyedi et al, 2000), 28% of those allocated to eradication had dyspepsia for two years, compared with 33% in the placebo group, a statistically significant 5% absolute risk reduction. In other words, 20 people needed to be treated to prevent one case of dyspepsia in the community.

Interestingly, the effect seemed to be limited to men, with a 9% absolute reduction in men, and virtually no reduction in women. Peptic ulcer disease, for reasons that are not clear, is much commoner in men than in women and this perhaps explains this gender difference. The gender difference in the clinical data is reflected in the economic data, which are reported in Table 6.3. There is an average saving of £26 per man across all men (whether or not they had dyspepsia) over the two years, also a statistically significant difference. Again, there was no effect in women.

To investigate the potential importance of these results for a screening programme, the data were explored using a Markov model. The model assumed that *H pylori* screening reduced mortality from distal gastric cancer by 30% and peptic ulcer disease mortality by 30%. On base case assumptions, if 1 million people were screened at the age of 45, running the model over 40 years yields a saving of £6 million and 1,400 years of life at a 5% discount rate. The central estimates suggest that screening for *H pylori* is a dominant strategy (it saves money and saves life) and therefore, in economic terms, should be performed. Moreover, the result was robust to all one-way sensitivity analyses and most two-way sensitivity analyses.

Conclusions

In conclusion, health services research has shown us that all young dyspeptics should be tested, whether or not they have an ulcer, because it is the cheapest strategy and just as effective as early endoscopy. A population screening strategy should also be considered, as it could be the first programme to pay for itself. The efficacy of the strategy still, however, needs to be demonstrated and it should not be forgotten that the estimates were based on a model. As an economist, JK Galbraith said, 'The only function of economic forecasting is to make astrology look respectable'. Firm data are needed before the NHS will realistically consider population *H pylori* screening.

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Chapter 7

Implications for clinical practice and clinical research

KENT WOODS

Introduction

This chapter addresses the subject of the meeting both from the perspective given by a clinical background in cardiovascular medicine and also as director of the NHS Health Technology Assessment Programme.

Taking a narrow definition of truly unexpected benefits, the environment at the interface between clinical research and clinical practice has in the past offered the greatest scope for capturing the unanticipated. However, we should consider the whole innovation process from basic science through to clinical application to seek better ways of identifying the full potential of research findings.

What is an unexpected benefit?

What constitutes unexpected depends on what is known of pathophysiology and of drug mechanisms, both of which evolve over time. In terms of disease mechanisms we can look at the example of the evolving understanding of heart failure, where the empirical evidence from trials of beta blockers and ACE inhibitors has clarified the importance of the renin-angiotensin system and of the sympathetic system. As the understanding of the disease mechanism improves, so the beneficial effects of interventions which interrupt either of those two pathways become less and less surprising.

Secondly, there is knowledge about drug mechanisms. Now that drug discovery is much more focused towards identified targets and pharmacological understanding is much further developed at the point of licensing or marketing than was the case in years past, there is less scope for surprise. Again, beta blockers provide an example, although now a rather distant one. Their blood pressure lowering action emerged only during clinical studies and their mechanism of action

was not well understood when they first came into use for treating hypertension. Precipitation of heart failure was reported as an adverse event in this early work – delaying by many years the recognition of the potential benefit of the careful use of this drug class in patients with poor left ventricular function.

Unpredicted effects that are observed once a drug is in widespread clinical use are, not infrequently, adverse events. They may well relate to a very small subset of patients – perhaps one in 1,000, one in 10,000 or fewer – who would not have been identified in the usual formal randomised trials preceding licensing. The likelihood of their being recognised as drug effects by the clinician depends in part on the distinctiveness of the syndrome that results. There is another category of unanticipated effect which the clinician will not detect, because they require epidemiological techniques of a particularly ambitious, large-scale kind, to identify and measure them.

Epidemiological evidence

An example is the US federally funded Cancer and Steroid Hormone study (CASH) carried out to investigate by case control methods the possible associations between oral contraceptive use and the risk of gynaecological cancers, that is, cancers of the breast, ovary, and endometrium. What was unexpected, but with hindsight might have been expected, was that those studies showed a significant and substantial reduction in the relative risk of endometrial and ovarian cancer in relation to prolonged exposure to oral contraception, related mechanistically to the suppression of cyclical activity in the ovary and endometrium. This study design cannot establish causality because confounding factors can never be wholly excluded. However, the association detected clearly has public health importance and could not have been found by any other research method.

A link between use of hormone replacement therapy (HRT) and reduced risk of acute myocardial infarction (AMI) is another example which stands out from the epidemiological literature as a beneficial association, both from case-control and cohort studies, although again I emphasise that this type of observational research can only

detect associations and not causality. It may be, for example, that women who are at low risk of ischaemic heart disease for other reasons are more likely to use HRT.

A recent case-control study conducted by the Universities of Nottingham and Leicester has been looking at all women who could be identified with AMI under the age of 65 in the East Midlands. In a sample of over 500 cases and over 1,000 controls, an inverse relationship between HRT use and AMI risk is apparent but this must be confirmed by further analysis to control for all known lifestyle and risk profile factors. Thus, potential beneficial effects, which the individual clinician will not identify, can be detected and pursued further by epidemiological means. The link between use of non-steroidal anti-inflammatory drugs and a reduced risk of colorectal cancer and colonic polyps is another example.

In order to mount studies of this scale, there needs to be an iteration between the mechanistic understanding of what treatments are doing and empirical research, but the design of the empirical research has to be appropriate to the problem. Epidemiological studies, randomised trials, and a whole range of study designs may be used. There may, however, have been an over-emphasis to date on randomised trial research as the definitive way of looking at therapeutic effects.

The research chain

The research chain comprises a non-linear process leading from basic research, through translational research and clinical evaluation in randomised trials, into routine practice. The element which is particularly important to understand is the interface between the trials evidence and routine practice. The interface is important because, whether one considers plate tectonics in the Pacific or squamo-columnar junctions in histology, it is at points of interface that unexpected things tend to happen. It is in this area that it may be possible to improve mechanisms for detecting the full therapeutic impact of new drugs.

It is not often possible to study clearly the development of an innovation from the research phase into the clinical application, but the case

of thrombolytic therapy (a cardiovascular example not so far discussed) is an exception. It may not be the most important step forward, since ACE inhibitors could, in the longer term, turn out to be of greater public health impact. However, in contrast with ACE inhibitors, whose impact could be described as a 'loud rumble', thrombolytic therapy has been the biggest 'bang' in cardiovascular therapeutics in the last 20 years. The bang was because the key randomised controlled trials that indicated the advantages of using thrombolytic treatment in AMI appeared in a very narrow window of time from late 1986 through to 1988. Because it was such a well defined time span, one could study the subsequent impact that the new knowledge had on the uptake of thrombolytic treatment in routine practice.

The number of thrombolytic treatment doses being used within the districts of Trent over the time period following the report of these trials in the *Lancet* in 1986-88 showed considerable scatter about the mean. This reflected the fact that different districts took up this innovation at different rates. All the data came from routinely collected NHS sources. It was simply a question of ringing up the pharmacies, finding out what their supply of thrombolytic agents was and, given an easily calculable standard dose, it was possible to monitor the transition from research to clinical use.

Two questions were addressed in considerable detail:

- what are the determinants of the process of diffusion?
- what are the factors which encourage clinicians to take up the results of a clinical trial?

The only strong association found was that between actual participation of districts in multi-centre randomised trials in this phase, and subsequent uptake when the trials had been finished. There was no association between the presence of cardiologists or of tertiary cardiology in the district; but the association between districts contributing patients to randomised trials and subsequently using thrombolytic treatment in later years was very strong. The r^2 value was an impressive 64%.

Trial evidence versus clinical practice evidence

In this example, the transition process is beginning to become apparent at the interface between research and practice. The evidence base at that point will have come from randomised trials looking at selective samples, whereas clinical practice looks at heterogeneous populations. This and other differences are summarised in Box 7.1. Clinical trials assess efficacy, while the clinician is interested in effectiveness. In clinical trials data capture is thorough and extensive. In comparison, data capture in routine practice, particularly on outcomes but also on process, is traditionally poor. The randomised design of a trial will tend to look at a highly specific hypothesis whereas, to look at routine practice and the outcomes that accompany such practice, observational designs will be called for. This is the background in which the transition takes place.

A question to be addressed is what determines whether efficacy converts into effectiveness. An important factor is the widely differing characteristics of patients in the real world and of patients in trials. The age structure is different; co-morbidity is different; concurrent treatment is more complex; disease type and severity are more varied. Effectiveness will only be achieved if there is acceptability to clinicians and patients.

The heterogeneity of clinical populations compared with trial populations can be illustrated with the case of thrombolytics. Properly sampled, it can be seen that a third of patients going into UK hospitals with myocardial infarction are aged 75 or over. In contrast, in the randomised trials against placebo of thrombolytic therapy, only 10% of them are over 75.

Box 7.1 Research versus practice

<i>Research</i>	<i>Practice</i>
Selected sample	Clinical population
Efficacy	Effectiveness
High data capture	Poor data capture
Randomised design	Observational designs

Considering all of the available evidence on the effectiveness of therapy, stratified by age, a large meta analysis published in the *Lancet* (FTT Collaborative Group, 1994) showed that the stratum of age for which there is greatest uncertainty about the beneficial effect is the 75s and over.

The interpretation of these data could run along the following two lines. First, mechanistically, a blood clot in the coronary artery is a problem whether the individual is 95 or 35, and there is no reason why a thrombolytic drug should not be beneficial at either end of the age spectrum. The second, an empiricist's view, would be that in that older age stratum, there is no evidence of benefit over placebo. The confidence intervals around the odds ratio are wide, because there are so few patients in that age group, they overlap with unity and they also overlap with the mean effect for other age groups.

The reason for illustrating this point is that it shows the uncertainty referred to by Annetine Gelijns which persists at the point of introduction of a new therapy, even when the trials base is very large, as is the case in this example. There are very few interventions that have quite the same scale of prior trials experience as the thrombolytic drugs.

There is some clinical database evidence which shows that during the time thrombolytic treatment was being introduced there was an improvement in survival post-myocardial infarction, which was equally present in the elderly and in the young. In other words, effectiveness data, based on real clinical populations, support the mechanistic view that this is a treatment that can be given across the age range.

Implications for clinical practice and research

Considering the implications for clinical practice and research, it is important to recognise that formal randomised trials, which have become the benchmark against which evidence of efficacy is measured, have distinct limitations. They will never give more than partial information and they will never provide all the information that might be of interest. In other words, even when a drug has been very extensively tested in randomised trials, at the point of introduction to

clinical practice and for some time afterwards, large gaps in knowledge will persist. The only way to fill those gaps is to undertake observational studies in the clinical context.

Trial participation

Higher trial participation by patients is required, because if any individual trial just examines a narrow gap in knowledge, more trials are required to make sure the coverage is as full as it can be but, more particularly, higher trial participation by clinicians is needed. This factor facilitates the translation of research into practice because a clinician using a new treatment in a trial context is working in a sheltered environment. The protocol has been rigorously scrutinised. It has been peer-reviewed and has undergone ethical review. There is therefore a surrounding structure which facilitates that clinician experimenting with something unfamiliar.

The trial environment is a very good way in which clinicians learn and acquire the confidence to move on to use innovations in their own routine practice. Anecdotally, when the results of the thrombolytic trials emerged, it was decided at Leicester Royal Infirmary in October 1988 to have a routine policy that every patient coming in with myocardial infarction received a thrombolytic. The first patient treated had an anaphylactic reaction, one of only a tiny number of such events seen in the last 12 years. Had thrombolytic therapy not been an innovation supported by a mass of trials evidence, this single experience might have discouraged any further use.

Variations in practice

A further important consideration is monitored variation in practice. Restricting clinicians to prescribing guidelines may have a potential adverse effect on innovation. There will be, and must be, scope for clinicians to widen indications, and to indulge to some extent in off-label prescribing, provided it is monitored and outcomes are carefully studied. Without that proviso, such prescribing has no informational value at all. With that proviso, the knowledge base can be extended incrementally.

It follows that better data capture is required in the clinical setting. The gathering of data for patients who are receiving 'routine care' is very much seen as an administrative chore. Data collection has largely been for administrative purposes. In fact, it really is a crucial element in therapeutic evaluation. It needs to go much beyond audit; it needs to be a much more analytical and insightful examination of the outcomes of interventions.

There must be a willingness to accept and to apply a wider range of study designs, which will be mainly observational. Many of them will be based on epidemiological principles and analysis. There will then be all the problems of controlling for the case mix, and of confounding, but epidemiologists have been handling these for years. There is nothing very special about tackling problems of confounding from observational data in clinical practice.

Finally, there needs to be an interplay between the empirical research and the mechanistic insights. It is not a linear process of development; it is an iterative process. All of the various possible studies must be constructed in the light of the best available knowledge of mechanisms.

The HTA programme and other initiatives in NHS R&D

The Health Technology Assessment Programme has been running since 1993 within the NHS R&D programme, and is concerned with commissioning research to investigate the effectiveness, cost-effectiveness and broader impact of interventions used in health care. Technology is defined widely to include not just drugs or devices, but the whole range of interventions.

It is very much concerned therefore with the support of research when treatments have either entered practice recently or are well established in practice but have not previously been evaluated. Therefore, there is a role for public investment in HTA, to attempt to flesh out some of the knowledge gaps; but there are other initiatives going on within the NHS R&D environment which will contribute to the chain of research activities. My final comments relate to two of them.

Basic research, historically and functionally, has rested much more with the Research Councils, the university sector and medical research charities than with NHS R&D. Translational research, however, is beginning to receive attention and there is now a commissioned research programme – the New and Emerging Applications of Technology programme – which is starting to put some public funding into translational research. Although this is currently a very small amount of money in relation to the need, at least it is a start.

Clinical evaluation is predominantly funded by the pharmaceutical industry. However, a recent change is the approach to intellectual property generated within the NHS R&D research environment. The first step has been technology audit, to identify existing innovations that remain unrecorded, unused, and unexploited. It is important not only to capture innovation but also to have an intellectual property strategy to protect it and to make sure that it is fully exploited.

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Chapter 8

Implications for Biomedical R&D

DAVID MCGIBNEY

Introduction

A previous CEO of Pfizer, some 20 years ago, made himself unpopular with the discovery scientists by stating that 'drugs are discovered in the clinic, not in the laboratory'. Despite the substantial advances in technology over the last 20 years, this is still the case, a view supported by the preceding presentations.

Despite the advances in technology, and the ability to identify and modulate target molecules very much better, understanding of the role of those targets in a biological system, and the role of that system in the disease itself, is still poor.

The drug development process

In early drug development, three parallel hypotheses are being tested:

- does the drug affect the target?
- is the target important in the biological system?
- is that biological system important in the disease?

It is hardly surprising therefore that the enormous advances in discovery technology have done nothing at all to reduce the attrition that is still seen in pharmaceutical development. Examples of good pharmacological agents from the portfolio at Pfizer which failed because of some of these parallel hypotheses include the PAF-antagonists and the thromboxane synthetase inhibitors. Nor is it surprising that because of the lack of knowledge of these mechanisms across the body there should be a significant incidence of unexpected benefits.

Unexpected benefits

Viagra is an example of a drug where unexpected benefits were spotted early in development. In hindsight, it was relatively easy although,

from the point of view of somebody with responsibility for the clinical research programme, it did not seem easy at the time.

Much less obvious potential benefits of PDE inhibition have only become apparent once the drug has got to the marketplace. A range of non-sexual indications are now being considered, because of anecdotal clinical observation and because the science has moved on, and the role of nitric oxide in other disorders is now much better understood.

Returning to the definition of unexpected benefits, two examples serve to highlight different definitions. Sometimes there can be unexpected favourable consequences of effectively treating the target disease. For example, it may be the case that individuals whose prostatic hypertrophy is improved as a consequence of effective therapy are not admitted to hospital quite so often as a result of falling down going to the bathroom at night.

The treatment of unstable bladder is analogous. Elderly patients who have incontinence, urgency or frequency may have to be admitted to long-term care prematurely, when an effective treatment might not only improve their unstable bladder but also prevent the consequential move to institutional care.

Neither should the changing demography of disease be forgotten. Twenty years ago, fluconazole was being developed for the treatment of vaginal thrush. Subsequently, the scourge of the AIDS epidemic, which was impossible to predict at the time, has meant that one of the main indications for fluconazole is in the prophylaxis of cryptococcal meningitis.

The industry's part in clinical research

I want to focus on some of the points to consider from the standpoint of a pharmaceutical company. The first is good communication with the investigators and, perhaps most specifically, communication with those people who are in touch with the patients, whether it is the study nurse, the technician, or the physician who is undertaking the work. Pfizer's approach is, if possible, to talk to the patients in early

clinical studies. This is facilitated by having a dedicated Phase 1 unit, so that normal volunteer work, and some of the patient work, can be conducted under the company's own auspices. If it is not possible to do that, regular contact is maintained between the in-house Pfizer physician and the investigating physician. In Phase 2 and beyond this direct contact is more difficult, but still important.

Data capture tools or case record forms present a dilemma from the company's point of view. On the one hand, data have to be collected and collated from many thousands of patients. At the same time, data collection instruments that facilitate bulk usage should not mask the anecdote, which is often key to finding an unexpected benefit. Some progress has been made in this area in Pfizer, but much more collaborative work would be beneficial.

Knowing the science and the literature seems obvious, but it is quite difficult in a big organisation with a large team to ensure that everyone who is in contact with the investigators and with the patients is prepared to make the linkages. It is making these linkages between observations and mechanisms which is the difficult part. It is the part where the combination of an alert clinician and an effective multidisciplinary team, committed to exploiting all possible value out of a molecule, can produce great benefit. Annetine Gelijns noted that chance favours the prepared mind. If this is the case, the chances are certainly increased by having many minds prepared.

Safety and efficacy

Every clinical database on a drug filed for registration contains millions of data points from thousands of patients. The database will have been trawled in many different ways from a safety standpoint and a thorough analysis of the primary efficacy end-points will have been carried out. However, exploration of alternative efficacy measures may not be undertaken. Often, the entire focus is on gaining the registration dossier, that is, putting all the data together and filing it. The latitude to be able to undertake additional, more speculative, work at that time is not necessarily available. By the time the dossier has been filed, those involved in preparing the dossier will often be preparing

for regulatory questions or perhaps have moved on to other projects. This is an area where a few well-targeted PhDs could bring enormous benefits to companies and one where companies do not currently perform very well. The appropriateness of pattern recognition software, which is being developed for high-throughput screening and for micro arrays in genomics, has not as yet been explored as a means of picking up patterns in clinical data and is once again an area where additional work could be done.

Selection of research programmes

Moving on to capitalising on any observations or ideas, the points listed in Box 8.1 relate to the role of research management. Being open-minded, flexible and adaptable is a challenge for management anywhere in the world and is true of small companies as well as big companies. In small companies, equity and funding have often been raised on the basis of a single hypothesis with very little data. Under those circumstances, to regroup and to change direction can cause a crisis of confidence and can cause a fall in the stock price. This causes problems for the CEO and, to some extent, restricts the company's activities.

Box 8.1 Capitalising on observations and ideas

- Be open-minded to new observations, hypotheses, linkages and breaking science
- Be flexible and adaptable and avoid the 'Magnus Magnusson syndrome', 'I've started, so I'll finish'
- Take investment risks to follow up on observations and hypotheses
- Sequester some resources to conduct speculative 'probability-adjusting' experiments and take a light-handed approach to governance
- Rapid feedback to discovery if properties seem promising but not optimum
- Remember that a side effect in one indication can be an attribute in another
- Ensure intellectual property issues are cleared up proactively and fairly

In big companies, there are different problems. In Pfizer, there are about 150 different programmes at different stages of development, often incorporating more than one indication. This raises a number of questions:

- how does the company decide where to place its investment?
- how does an individual project clinician attract management's attention?
- what should be the balance of resources between prosecuting a first registration for a new chemical entity and supporting additional investment in exploiting the value from registered molecules?

Each company will have a different answer to these questions, but each research manager knows that there is value being left unexploited both for patients and for companies. One problem is what might be referred to as the 'Magnus Magnusson syndrome', 'I've started, so I'll finish'. An example was Pfizer's neural endopeptidase inhibitor programme in hypertension. The pre-clinical data, in particular, were highly encouraging. Every quarter, management would be shown the most recent data from the clinical programme. In one or two trials there would be a positive result, that is, there would be a drop in blood pressure. By the time nearly 1,500 patients in hypertension had been studied, it was concluded that it did indeed lower blood pressure. However, the reduction was only 5/2mmHg, a clinically insignificant amount. Each trial approximated to the truth – some were positive, most were negative – but the pre-clinical data were so compelling that it attracted attention away from some of the other possible indications for neural endopeptidase inhibition.

The Viagra story proved not to be nearly as easy as it appears in retrospect. The company was committed to the compound being a drug for the treatment of angina and there was disappointment that the haemodynamic changes induced were not sufficiently robust to support this indication. Because the initial side effect which eventually dictated the future development of the drug occurred only at high doses, on multiple dose therapy, and in the presence of other very sig-

nificant side effects, it was thought that the programme was unlikely to succeed.

However, the company persevered, stopped the angina programme and established the dose-response relationship for efficacy and safety in erectile dysfunction. This change probably took 18 months or two years. Making changes in organisations is not easy, even with the most persuasive advocate.

In Pfizer, resources are sequestered to continue work on new indications for marketed products. There is also a process for capturing potential new indications for each molecule, from discovery right through the development process. This life-cycle management has become a core part of the business. Choosing the winning indications in the face of all of the alternatives is a real problem of risk management, irrespective of the resources that can be used. Despite having a budget of close to \$4 billion, ideas will always outstrip resources.

Pfizer's approach is to select the most compelling indications from the point of view of scientific rationale, ease of showing clinical efficacy and commercial return, and then selectively to invest and test the probability of each indication being a success. A dedicated group of both clinicians and pharmacokineticists is charged with running pilot studies in order to test these hypotheses.

Investments are often made in this group well before taking a molecule into a particular therapeutic area. The reason for that is that it is very important to be able to identify surrogates of efficacy. It is impossible, when faced with 2, 5 or 10 potential indications, to have to run 200 patient trials on each of them, moving constantly from one to another. A heavy investment is therefore made in establishing surrogate efficacy endpoints which, it is hoped (and there is a risk associated with this) will guide the choice of which one to continue to invest in.

Without those surrogate efficacy points, no investments would be made. The company cannot afford to invest the requisite amount of money in order to show conventional efficacy in conventionally sized

trials, with such a wide range of indications. Past experience has taught the company that this cannot be allowed to happen.

Intellectual property

Intellectual property has already been discussed. It is a very big issue for all businesses, whether industrial or academic. About 80% of the value of the research-based pharmaceutical industry is determined by its intellectual property (patent protection). The patent gives legal monopoly rights which allow the company to develop and market the product exclusively for the duration of the patent. The compound-of-matter patent provides protection for a compound for about 20 years, but can range up to about 25 years. Use patents – that is, patents relating to the purposes or indications for which the compound is planned to be used – are usually filed at the same time. Pfizer try to ensure that these patents are comprehensive, covering all the possible indications. All patent applications have to fulfil two criteria; firstly, they have to be novel, namely they are not part of the prior art and, secondly, they have to be inventive, in other words, not an obvious extension of the prior art.

In some cases, someone outside the company can have an idea for a new use of one of the company's drugs and file a use patent for that use. That prevents the company from developing, promoting or marketing the drug for the duration of the patent, without some form of licence or without the transfer of intellectual property rights. Dependent on the company's views on the value of that indication, it would hope to be able to come to an arrangement with the owners of that intellectual property, to secure the rights. It will recognise that the other party could not exploit the invention either, since the compound-of-matter patent resides with the company. Usually, a mutually advantageous agreement can be reached.

Implications for R&D

Turning to the implications for biological R&D, it must be recognised that knowledge accumulates slowly and is always incomplete. Everyone, whether inside industry or outside, should be encouraged not to make

negative judgements too early. This is particularly true at the time of registration, where drugs which have clearly passed the hurdle of safety, efficacy and quality may be held up because their comparative position in therapy has not yet necessarily been fully established.

It is important to note that some of the less tangible benefits that clearly differentiate drugs in the marketplace are difficult to show with the type of trials used to produce the data for registration. Those rigorous, usually controlled, trials are used for producing certain kinds of information but the biological equivalent to Heisenberg's uncertainty principle sometimes appears to hold. That is, the process of measurement so disturbs that which is being measured that the results are unrepresentative of the actuality. In other words, when people are watched, they change their behaviour, not surprisingly.

Making the observation is one thing; making the connection is yet another. As a famous Nobel scientist said, 'Research is to see what everyone else sees but thinks what no one else thinks'. This, of course, is the secret. Just making the observation is different from making the linkage.

An earlier question had asked whether there was any evidence to support the contention that people talking together is a good thing. Although Pfizer has no evidence to indicate that this is so, multidisciplinary, cross-functional teams and the philosophy of 'brains rubbing together' form an important part of the Pfizer culture. Whereas, historically, buildings have been designed with biologists on one corridor and chemists on another, they are now built with a single corridor between the two, with common rooms where biologists and chemists can mix together.

In Sandwich over the last 10 years almost £1,000 million has been invested in new buildings, and a range of buildings will be opened over the next year. Each one is designed to facilitate cross-fertilisation between disciplines. Knowledge centres have been created, which are deliberately designed to be attractive to bring people from different disciplines and to create a culture where it is accepted for people to be seen apparently 'just sitting around, chatting'. That is quite a difficult concept in an output-oriented culture.

Finally, there are many more unexpected benefits to come from closer collaboration, meaning a partnership. Most agreements between industry and academia in the past cannot really be characterised as a partnership. Both parties have been in it very much for themselves so there is very much more that the two can achieve together.

Chapter 9

Implications for licensing and post-licensing surveillance

JUNE RAINE

Introduction

The title of this chapter implies a rather simplistic, even a rigid, division of Medicines Control Agency (MCA) tasks between granting marketing authorisations and the use of post-licensing surveillance to restrict use of or to remove products from the market. In practice the MCA has a multifaceted role in helping to capture unexpected benefits. It does not adopt a rigid, bilateral approach, but is concerned with the concept with which everyone is familiar, that medicines evolve once they are on the market. In this context the MCA was contacted recently by the BBC's 'University Challenge' to assist in developing a set of questions to be run on medicines that had developed new uses and new benefits. Three drugs they thought university students would be interested in were Viagra, for erectile dysfunction, minoxidil, for male pattern baldness, and acetazolamide, for mountain sickness.

The purpose of this presentation is, firstly, to consider the regulatory implications for the drug development process from the perspective of a regulator with some important statutory obligations; secondly to explore whether the system inhibits or facilitates capturing unexpected benefits; finally, to consider whether there is scope for change and improvement.

The role of the MCA

The functions of the MCA, which are familiar to those in the pharmaceutical industry but may not be so to those in the academic world or in other industries, are determined by its status as the executive arm of the licensing authority. This authority promotes and protects public health by ensuring medicines meet standards of safety, quality and efficacy both prior to licensing and once on the market. This role was created by legislation post-thalidomide.

Coupled with this role is an obligation to provide accurate, up-to-date information to those who use medicines and those who take them, to support optimal usage. Based in UK law, and subsumed in EC law, the MCA's obligation is to monitor safety. There is no *obligation* to capture benefit; that obligation lies elsewhere.

Pharmacovigilance is the MCA's 'up-front' function when a new medicine comes on to the market. Intensive monitoring takes place in the first two years, with the yellow cards carrying the black triangle to tell practitioners to report. The purpose of that is as an early warning system, to detect early problems and previously unidentified hazards. This monitoring is backed up by the work of the Drug Safety Research Unit, and by company studies, published literature, and a wealth of other sources of data.

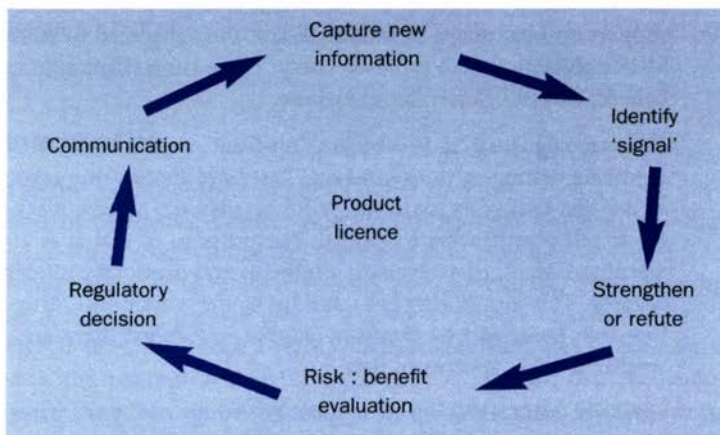
However, behind this 'up-front' post-licensing activity is a more long-term, evolutionary process of capturing information, incorporated in two functions:

- variations, when companies seek updates to marketing authorisations;
- a five-yearly renewal function, where the obligation falls on the licensing authority to re-consider risk and benefit. This involves assessing the proper role of a medicine in therapeutics.

The way that the MCA works can be seen in relation to the product licence, which begins when the marketing authorisation is granted. The cycle, which is illustrated in Figure 9.1, can be summarised as follows:

- capturing new information from that multiplicity of sources, and identifying signals about a drug's effects. Primarily these would be thought of as safety signals but would also include efficacy signals;
- strengthening or refuting those signals by using other sources of information, possibly further trials, and then repeating the risk-benefit evaluation that was considered to be positive at the time of authorisation and making a regulatory decision. Often, in the UK,

Figure 9.1 The post-licensing cycle



this is conducted with the Committee on the Safety of Medicines (CSM) providing the independent expert advice. The decision is then communicated to the company and the medical profession.

Capturing efficacy signals

How can this cycle, which is so critical to public health, be used to capture efficacy signals. Is post-licensing surveillance essentially restrictive? In other words, does it really narrow down the chances of exploiting the benefit from new uses if it whittles down, prunes, restricts or even removes products before yet-to-be discovered benefits can be identified?

The case for the defence is that this is not necessarily implied by post-licensing surveillance. Such surveillance can be seen as a way of optimising exposure, whether that be in terms of dose, or population, so that medicine is forever being more appropriately used, including for a new indication. It may also stimulate targeted development of new drugs to tackle the weaknesses of existing therapies.

An illustration of this is the case of non-steroidal anti-inflammatory drugs (NSAIDs) and the adverse drug reaction (ADR) of gastroin-

testinal (GI) toxicity, on which an enormous amount of work has been done over decades by the MCA and the CSM. Now COX2 inhibitors, which can help to avoid this ADR, are available.

Post-licensing surveillance, when it is effective, can enable risk management goals to be established while a new use is developed. This role has been illustrated with finasteride as its use has moved from treatment for benign prostatic hypertrophy to include use in hair loss. There is also the example of thalidomide which has been authorised in the US for serious skin disorders. The goals of managing safety and risk remain while progress is achieved in capturing additional benefit from a new indication.

Post-licensing surveillance can also provide data to support the wider availability of a drug, thus once again capturing additional benefit, through self-medication. A recent example in the UK is of levonorgestrel, a progesterone-only pill, which has a vast amount of data on its safe use, becoming available on a self-medication basis for post-coital contraception within the space of about six months from its authorisation for prescription use for this indication. This is a clear example of benefit being captured on the basis of post-licensing data. Another example is ibuprofen, a non-steroidal anti-inflammatory drug originally for arthritis, but which has now become available for self-medication for minor indications such as pain.

Lastly, it must not be forgotten that even adverse drug reactions can provide unexpected benefit. Minoxidil is a prime example of this, with the hirsutism observed in its anti-hypertensive use being captured to treat hair loss in a topical delivery system.

These examples help to argue the case for the defence, but the main purpose here is not to defend post-licensing in monitoring safety. Rather, the emphasis is on whether the system focuses too little on capturing new benefit. I have already noted that the obligation is not on the licensing authority. Interestingly, anyone, including parties other than company marketing authorisation holders, can apply to change the legal status of a drug. Whatever the source of a change to the marketing authorisation, introducing a new indication into clinical use relies on the MCA delivering timely variations and timely

updating at five-yearly renewal. Therefore, it is worth considering whether that represents a hurdle to the capturing of unexpected benefit.

Variations in use are notable, principally because there are now many more of what are called 'medically targeted' indications. In comparison with the 30 or 40 new indications per year that used to be recorded, the number is now about 70 or 80 a year. Although they differ in their significance, they are being seen in ever-increasing numbers. For example, reflecting on the welter of activity which Philip Poole-Wilson identifies in his paper, the cardiovascular area is awash with new indications. One way in which the regulatory system can fulfil a facilitating role in this area is in relaying the information to the CSM and transferring new indications into clinical practice. The difference here between the UK and the European system is that the information does not just go to health professionals. Since it is in the patient leaflet, it also goes to the patient, thus facilitating compliance. This activity should also be observed in licensing, in the form of variations.

Learning from experience

In terms of learning from experience, a contrast may be drawn between the stories of two different drugs. The first, which has been rather forgotten, is folic acid. Following on from the research conducted in the 1980s, a government announcement was made in 1992 supporting the use of folic acid by pregnant women, but the product was not available at the right dose and it was not available through general outlets. Hence a woman of child-bearing age could not easily buy it and GPs were being inundated with requests by interested women to know how they could acquire it. Product availability was tackled but overall use by pregnant women remained low. In order to increase take up, the NHS wanted to promote the use of folic acid. The regulatory issue was whether to treat neural tube defects (NTD) as an exception from the advertising ban on neurological disorders. Exemption was granted from the advertising restriction that spina bifida could not be mentioned in publicity material. There is still an issue, however, about whether the public health benefit has been cap-

Box 9.1 What can we learn from experience? Folic acid

1980s – Research identified benefits in prevention of neural tube defect (NTD)

1992 – Government announcement but question mark over availability of product at 4 mg dose GSL

1994 – MCA exempts NTD from advertising restriction on neurological disorders

tured. Recent data indicate that only around a third of women beginning pregnancies are taking folic acid, and infant neural tube defect still accounts for eight in 10,000 deaths. Two decades on from the link being recognised (Box 9.1), it is still questionable whether the benefits are being captured.

A different story can be illustrated with the example of ramipril, where the results of the HOPE trial were published in August 1999 and, by July 2000, guidelines were on doctors' and health authority trusts' desks. Once the variation to amend the licence was agreed by the MCA and agreement reached on the product particulars, the leaflet giving information to patients and guidance to practitioners was disseminated, with the entire process taking less than a year. That is the sort of model that does lead to capturing benefit (Box 9.2).

Turning to the example of the statins, there has been a fascinating study using the General Practice Research Database. The work carried out in Boston examined 30 million years of UK patient experience and the study may be widened in the near future. A significant

Box 9.2 What can we learn from experience? Ramipril

August 1999 – HOPE study published.

June 2000 – Variation to add reduction in myocardial infarction, stroke and cardiac mortality in high risk patients.

July 2000 – National Prescribing Centre guidelines.

increase in bone fractures in people over 50 was observed around the four-month point in those using statins, a finding not seen with fibrates. An animal model has shown effects on bone, indicating the presence of a biological mechanism. The question now is who will do further research – prospective controlled studies, for example – in an area where, in terms of morbidity and mortality, there is considerable public health benefit?

Conclusion

In conclusion, licensed medicines in clinical use generate efficacy signals as well as safety signals. The regulatory process does support the evolution of medicines in their clinical use but, as was said at the outset, there needs to be a co-ordinated approach to capturing benefit. Finally, the MCA has a role in confirming identified benefits when it updates authorisations, as with ramipril and the MCA has a role in communicating to health professionals and patient leaflets. Key questions for the regulatory authorities are:

- should safety and efficacy signals be seen as distinct from one another?
- how does the MCA need to change in order to ensure a more co-ordinated approach to capturing benefits?
- can the MCA support the generation of data on unexpected benefits, for example, using the General Practice Research Database and other sources of data?
- should thought be given to how, practically, to look for the signals of drugs' effects?

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the 1990s, the number of people who have been affected by the disease has increased. In 1990, 100 cases were reported in the Netherlands, in 1995, 160 cases, and in 2000, 200 cases. The number of cases is expected to increase further in the next few years (Van der Wal 2001).

It is important to know the epidemiology of the disease in order to be able to control it. The epidemiology of the disease is determined by the transmission route, the incubation period, the infectiousness of the patient, and the susceptibility of the host. The transmission route is the most important factor in determining the epidemiology of the disease.

The transmission route of the disease is still unknown. It is thought that the disease is transmitted by direct contact with the patient, but this has not been proven. It is also thought that the disease can be transmitted by indirect contact with the patient, but this has also not been proven. The incubation period of the disease is thought to be between 1 and 10 days.

The infectiousness of the patient is thought to be high. It is thought that the patient is infectious from the beginning of the illness until the end of the illness. The susceptibility of the host is thought to be high. It is thought that almost everyone is susceptible to the disease.

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