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Editorial

PRAGMATISM AND THE DISCOVERY OF DRUGS

Countries throughout the world are grappling with the problem of the increasing costs of providing medical care. Prominent among these is the drug bill. Thus in Switzerland, hardly a poor country, eleven per cent of the eighteen billion pounds annual expenditure on health care is accounted for by pharmaceutical preparations; this has proved too much for the insurers who have increased from 1,500 to 2,300 the list of drugs and other items for which they will not pay.[1] In Italy compulsory price reductions varying from 10 to 60 percent have been imposed. In the UK prescription charges were increased last year by 11·8 per cent, five times the rate of inflation, and this has led to fundholding general practices increasingly substituting generic for proprietary prescriptions. In the USA similar reductive steps in drug prescribing are being undertaken by insuring organisations.

The inevitable outcome of these trends is reduced profits for pharmaceutical companies. As some of these have enjoyed huge successes in recent years, it is tempting to assume that the change in fortune may only be fair, but care and consideration is called for. The most successful companies in the production of new and effective remedies, albeit the most profitable, see writing on the wall and are seeking to protect themselves by diversification. SmithKline Beecham is buying the non-prescription sector of Sterling Winthrop for nearly two billion pounds. It has also linked up with a gene therapy and sequencing company in the USA and another providing screening and counselling services for employees in industry.[2] Not having all one's eggs in one basket is usually laudable but a risk which may have to be addressed is the possible diversion of resources and interests away from the search for new drugs.

In this issue (page 5) Bowman and Harvey describe the several pathways to the discovery of new drugs and the changing methodology of elucidation of their actions and of their production, with the application of biotechnology, computer graphics, molecular biology and gene manipulation. Drug research in the past has been split between academic scientists working in universities or research institutes and the chemists and pharmacologists of the pharmaceutical industries. The former have mostly concentrated on using drugs as tools to elucidate the intrinsic chemical mechanisms of the body and their behaviour in disease, and the therapeutic fruits of the academic studies of the Nobel Laureates, Vane and Black, have been remarkable contributions to human health. Bowman and Harvey point out also that the recognition of multiple properties of nitric oxide, the brain chemical anandamide, factors governing nerve growth and apoptosis have all emanated from academic departments in this decade and have opened great possibilities for the pharmaceutical industry to design, synthesise and develop the most effective and least toxic representations of these agents for therapeutic use. The costs involved in both the academic and industrial sections of such processes are very great; it is fortunate that the interface between academia and industry has strengthened over the years as the financial constraints on universities and medical research councils narrows the prospects for 'venture' funding of research

projects. Bearing on this is the question of the approach to drug research. Should it be problem-focussed or free-ranging? The former inevitably involves determination of therapeutic priorities with all its pitfalls. The latter is expensive, being profligate in resources. For example, the *Rauwolfia serpentine* sold in Indian bazaars for the treatment of insanity was the source of the first tranquilliser, reserpine. Yet less than 10 per cent of the world's 250,000 flowering plant species have been scientifically studied for medicinal potential.[3] Nevertheless compounds originally identified from plants are constituents of drugs which account for a quarter of all prescriptions in the USA.[4] Large pharmaceutical companies using robotic systems can test several hundred thousand compounds in a year as Bowman and Harvey describe, but the process may cost up to a hundred million pounds before even one compound comes up trumps. Even then only one in four such compounds ultimately produce a profit equal to the development costs.

Much of therapeutic history has reflected serendipity rather than structured research.[6] Structured drug discovery starts with basic research into the physiological and pathophysiological mechanisms as mentioned above and then exploits the information so as to encourage or 'structure' serendipity.[6] Much structured research follows upon screening large numbers of molecules which hopefully may lead to the production of compounds which can then be 'improved' by chemists. With the advent of computer technology three-dimensional structures of target proteins and other molecules can be 'built' and structured reserch has taken a half step forward.[7] This step will only be complete when pharmacological activity can be predicted accurately from such models but when this would be achieved is not yet foreseeable. The pharmaceutical industry has emphasised the need for supporting mission-orientated long term basic biomedical research.[8] The evolving technology of drug discovery has been exploited most quickly by new start-up companies founded on collaboration between venture capital and academic research. With only one in a hundred thousand new chemical entities (NCEs) presently achieving product licences such companies are extremely vulnerable since few can achieve the 40 per cent return on investment that venture capitalists appear to require. What should an academic scientist do if he or she discovers an NCE? Patent it? No, according to the Association of British Pharmaceutical Industry which argues that restricted patenting of a developing drug may be unwise.[9] Develop this themselves? This is an attractive option which may explain the large number of start-up companies. Collaborate with a multi-national pharmaceutical company? (Both Vane and Black acknowledged a debt to the pharmaceutical industry for assistance with finance and with ideas promoted within their inter-disciplinary environment).[10, 11] The industry has to be encouraged in these collaborations which should continue to be academically and financially attractive to the scientist.

It is no longer profitable to produce a drug belonging to an existing class with only a small advantage over its competitors in efficacy, as purchasers would not buy it. There could be a commercial argument for producing such drugs if it is assumed that a market exists for cheaper drugs even if they displayed less efficacy. But the present trend, in which sales may be influenced as much by price as by efficacy and safety, could cause industry to focus on research and development (R and D) strategies away from the production of truly novel agents, because of the dangers from constraint on profits. Between ten and fifteen years of R&D have to be funded before a 'block-busting' NCE can reach the

market. The strategic risks of developing them becomes greater; the first drug of a completely novel class may fail to prove a hypothesis, and the second of a novel class of drugs on the market could have no sales at all. Many R&D based companies decide that the risk to benefit ratio is no longer worthwhile and concentrate on generic substitutions. To prevent the decline in the number of worthwhile drugs reaching the market the financial risks of development need to be lessened, possibly by lengthening patent life to protect against generic competition or by an increase in the profit from those discoveries which are manifestly therapeutic successes and, less desirably, by shortening the development or regulatory approval times. In the resolution of the Catch 22 situations described above, much depends on fostering continued collaboration between industry and the research institutes of universities and governments. In the USA important biotechnology companies have refused to enter into cooperative research and development agreements (CRADA) with the National Institutes of Health (NIH) laboratories because the NIH had a policy by which the government could fix a 'reasonable' price upon any product arising out of the collaboration. While the object was to limit the federal outlay, it inevitably limited the returns to the development and production companies and now venture capital organisations have declined to invest in companies that have such CRADAs.[12] It should be possible to agree a formula by which the price of the products of proven efficacy provide profit margins agreeable to all parties without being unreasonable. In respect of the UK National Health Service a pharmaceutical price regulation scheme controlling the capital return of companies on NHS sales has been agreed.[13]

Above all however, if the frontiers of medicine are to continue advancing, the free range of basic studies of molecular and physiological mechanisms including those which have traditionally been conducted in the laboratories of universities and academic research institutions have to be adequately funded. Such studies provide the bedrock from which the pharmaceutical industry launches its own endeavours. Failure to achieve continued and adequate financial support at the academic level could result in therapeutics simply marking time. Notwithstanding the considerable financial support already given by the pharmaceutical industry to all levels of science ranging from that of education in schools to fellowships, facilities and equipment for universities and research institutes, agreements in academic and industrial partnerships should result in a proportion of commercial profits being ploughed back into the laboratories conducting basic scientific inquiry. Governments are unlikely to earmark for this purpose the financial gain to the nation from successful pharmaceutical exploration. To an extent this is already met in some of the arrangements between companies and academic institutions in the research and science parks developed on or near the campus of universities and medical schools. The return to the universities may be as a result of their direct investment in manufacturing companies exploiting the successful outcomes of basic research or from the patents and technology licensing, or from a pre-arranged percentage share of profits. In many cases there are also arrangements for sharing the academic and company facilties and R&D scientists and technicians. The introduction into universities and hospitals of a market philosophy seriously threatens this country's eminent place in medical research. Teaching and district hospitals conducting research may find it rewarding as well as expedient to explore arrangements with industry. The essential principle that

basic research remains a feature of academic institutions would not then be wholly lost to pragmatism.

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Leading Article

THE DISCOVERY OF DRUGS

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EARLY MEDICINES

Anthropologists are unaware of any human culture that did not instinctively, and hopefully, turn to natural products in an attempt to alleviate its suffering. Thus, it appears that Man always has taken 'medicines' in the hope of putting right what has gone wrong with him, of enabling him to escape mentally from depressing surroundings, or of heightening religious or mystical experiences. And so we can imagine the first *Homo sapiens*, or even their ancestors, grubbing around among the leaves and roots in the hope of finding a cure for their ills. Sooner or later of course, by sheer coincidence, something that seemed to help would be found, and the treatment would then become part of folklore.

As long ago as 30,000 BC, Australian aboriginals probably knew of the medicinal properties of acacia, eucalyptus oil, and the corkwood tree (which contains hyoscine). In 2700 BC, the Chinese emperor Shen Lung described the uses of rhubarb, tea, and Ephedra species (which contain ephedrine). The medicinal uses of opium, pomegranate (for round worm infestation), powdered liver (for night blindness—contains vitamin A), *Hyoscyamus*, castor oil, figs and senna are described in an Egyptian papyrus of 1550 BC found by Gorg Ebers at Thebes over 120 years ago. Theophrastus in Greece in about 320 BC added mustard, tar ointments, male fern (for tapeworm), aloes and the Mediterranean mandrake to the list. The last, despite its reputedly magical properties, contains no more than hyoscine and related alkaloids. Dioscorides, in the first century AD, collected medicinal plants during his travels as a surgeon in Nero's army. He described 500–600 such plants in a well documented herbal but, generally speaking, there was nothing new compared with those of his predecessors. The same seems to be the case even in the writings of Nicolas Culpepper, the famous 17th century herbalist. In the 12th century, Arabian medicine made use of colchicum for gout and Roger of Salerno described the use of burnt sponge (containing iodine) for the treatment of goitre. In the 16th century, Dutch sailors discovered that lemons prevented the development of scurvy and this concept, using limes instead of lemons, was taken up by the Royal Navy. Hence British sailors, and subsequently all of us, became 'limeys' to our American cousins.

Historically, the practice of medicine was often tied up with religion; many ancient physicians were also priests. The religious aspects led to a number of rather bizarre philosophies, amongst which was the Doctrine of Signatures which held that a merciful god had provided medicinal plants with a sign, or signature, in their appearance, which would indicate their curative properties to the cognoscenti. Hence hepatica (with liver-shaped leaves) and pulmonaria (with alveolar-like leaf markings) were erroneously adduced to be useful in liver and lung diseases respectively. Generally speaking, the doctrine was a failure although

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