Biopharmaceutical drug development

Have you ever considered the steps that are required in order to develop and implement a new therapeutic agent? Numerous research papers in QJM have dealt with biomedical aspects of new drugs such as their pharmacology and efficacy in a clinical setting. However, as the review by Mundae and Ostor emphasises, there is much more to this subject. Development of a new therapeutic agent may require 15 years of effort and expenditure of considerable resources. The first and essential step is that of discovery which results from a combination of scientific inquiry and serendipity. Using monoclonal antibodies as an example, the authors proceed to describe the long road whereby a good idea is eventually implemented into clinical practice and commercial success. This involves a preclinical phase whereby a newly formulated drug is studied in order to precisely define its pharmacokinetic and pharmacodynamic properties in terms of therapeutic effect and toxicity. This usually requires testing of lower mammalian species and non human primates. The subsequent clinical phase requires testing under strictly controlled conditions in human subjects. Not surprisingly, this consists of four stages each of which may have a high attrition rate. Development of novel therapeutic agents does not end here however. Most countries have in place highly sophisticated regulatory mechanisms for the release and monitoring of new drugs. Another task is involved with new drug nomenclature with a need for three names: chemical, generic and brand. Then the new agent will need to be successfully marketed and distributed in order to allow the pharmaceutical company to recoup its investment and ultimately to return a profit. One wonders whether the current economic downturn will have any effect on this complex and lengthy process.

Hepatic Encephalopathy

The second review paper deals with a condition that may be difficult to recognise and treat successfully. According to Cash et al, patients with hepatic encephalopathy (HE) may be found “in almost every hospital”. Despite this apparently high prevalence, the condition is not always promptly diagnosed nor is its antecedents adequately identified. As a result, treatment of HE is often sub-optimal. A key message is that, in the authors’ opinion, little progress has been made with respect to the development of new therapeutic options for HE over the last two decades. Numerous reasons are suggested for this which include a dearth of quality clinical trials along with widespread variability of therapeutic approach between treatment centres (which would make critical evaluation of current regimes difficult in any case). However, currently there is sufficient evidence and experience of treating HE to justify a useful algorithm that has been devised by the authors. The review also covers a number of important areas relevant to HE including classification/grading of severity, pathophysiology and treatment. The discussion of pathophysiology is particularly interesting as it is admitted that the precise mechanisms that result in HE are as yet far from being fully understood. The traditionally held view is that HE is caused by a nitrogenous gut-derived substance (most likely ammonia) which results in impaired cerebral function. However, the true picture is probably much more complex with a number of possible co-existing processes playing a pathological role. A number of theories exist including the impact of various neurotransmitters. Until a better understanding of its pathophysiology is achieved, it is unlikely that significant improvements in the management of HE are likely in the immediate future.
Management of low trauma fractures

The economic costs resulting from the morbidity and mortality caused by osteoporotic fractures are significant. Considerable research has already been undertaken in this subject area with resulting advances in both treatment and prevention. It is accepted that previous history of low trauma fracture is highly predictive of future fractures and this risk may be in part be independent of bone mineral density. Many countries have invested in initiatives that aim to reduce the health care burden of low trauma fractures. In the UK, clear and helpful guidance is available from the Royal College of Physicians and the National Institute for Clinical Excellence. Disappointingly, several audits have shown poor compliance by health care professionals with these guidelines. The majority of women in the post-menopausal age group who present with a low trauma fracture are unlikely to receive appropriate preventative treatment. Why is this? The reason is likely to be multi-factorial. Cost is always a constraining factor but as the authors rightly point out, more resource has been directed to diagnosis, treatment and prevention in recent years. It is the view of many that bone disease is currently an “orphan” specialty with care shared by many sectors and disciplines. Sadly, it would appear that there is a lack of clarity regarding the funding responsibilities for management of low trauma fractures between primary and secondary care. This is a pity as this group of patients is in great need of effective recognition and treatment of what is essentially a highly preventable cause of disability.

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