This offers the prospect of counteracting both microscopic residual disease on peritoneal surfaces and occult liver metastases by achieving high intraportal drug concentrations. Immunocytotoxic detection of isolated tumour cells in the peritoneal cavity may have prognostic significance. In a randomised study of adjuvant treatment in resected stage III or high-risk stage II (T4N0M0) colon cancer, the combination of intravenous and intraperitoneal leucovorin and 5-FU produced a 43% mortality reduction at four years in stage III disease compared to 'standard' therapy with 5-FU and levamisole.

Newer agents are also being evaluated in advanced colorectal cancer. The platinum derivative oxaliplatin (trans-1,2-diaminocyclohexane oxaloplatinum) is active and well tolerated, both as monotherapy and in combination with 5-FU/folinic acid as first- or second-line treatment of patients with metastatic colorectal cancer. Iromotecan ('Campto'), a topoisomerase I inhibitor, is another agent showing early promise as a second-line agent in cases of disease progression following initial 5-FU therapy.

**Aspirin and COX-2**

Epidemiological studies have indicated that regular consumption of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) may lower the risk of the development of colonic adenomas and carcinomas and reduce mortality from colon cancer.19

Prostaglandins are important mediators of normal physiological processes in the gastrointestinal tract. The cyclooxygenase enzymes (COX) have a central role in the biosynthetic pathway of prostaglandins and are inhibited by NSAIDs. Cyclooxygenases exist in two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in the gastrointestinal tract, and is thought to be involved in cytoprotection and mucosal integrity. COX-2 is an inducible cyclooxygenase which is absent in normal intestinal mucosa. COX-2 expression is enhanced by pro-inflammatory peptide mediators (cytokines), inhibited by corticosteroids, and (unlike COX-1) over-expressed in about 85% of colorectal cancers. This has stimulated interest in a role for the newer COX-2 selective inhibitors (eg meloxicam) as tools in research into colorectal carcinogenesis and as potential chemopreventive agents.

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**Clinical research funding: a priority for the Medical Research Council**

**Conference rapporteur: Richard Holt**

This conference was held on 3 November 1999 at the Royal College of Physicians. Delegates attending the Postgraduate Medical Centre at the Freeman Hospital in Newcastle upon Tyne were able to participate with the aid of live video- and audio-links.

Clinical research has undergone radical changes over the last decade. There has been a shift in the focus of research such that there is no longer a place for a full time clinician dabbling in research. To produce internationally renowned research, resources need to be concentrated in areas of academic strengths. Medical science has moved away from the bedside and into the laboratory where powerful molecular techniques have provided new understandings of human diseases. The changes in training patterns brought about by Calman have resulted in a paucity of new medically qualified researchers who are willing to take on the mantle of academic medicine. The future for the entrepreneurial clinician with a brilliant idea but who works outside a centre of excellence, is problematic. Despite the fall in the numbers of medical graduates wishing to take up a career in academia, those who do so face the prospect of
competing for grants in a more and more competitive environment. In response to these changes, the MRC has introduced new research award schemes to meet these challenges.

Although the title of the meeting reflected the priority for the MRC, in reality clinical research funding is a priority for the whole NHS. This was borne out by the number of active and interested participants at this meeting at the RCP on 9 November 1999.

The new MRC research award schemes

Many universities are realising the benefits of having a strategic research plan, with resources targeted to areas of strength and growth rather than spread thinly over a broad spectrum of research. It is no longer possible, or indeed desirable, for every institution to be involved in all areas of research. There are limited resources for which the institutions must compete. The Research Assessment Exercise, which has a large influence on university funding, assesses individual members of each institution for productivity and global competitiveness. The Dearing Report into higher education funding concluded that funding should be directed towards areas and institutions of excellence, and the funding bodies, such as the MRC, have assimilated these recommendations and have realised the need for focussed funding.

Each institution needs to aim for international academic excellence. In order to do this, efforts should be focussed on areas of excellence where a critical mass of people from different disciplines, both basic and clinical, can be assembled. There has to be openness and a willingness to collaborate.

The scientific challenges of the post-genome project era have moved the focus of the MRC strategy towards whole animal physiology and clinically relevant research. In response to these changes, the new MRC research award schemes have been introduced, details of which are available on the MRC website. The aims of the schemes are to promote partnership and collaboration across the basic and clinical science interface and to ensure that appropriate resources are directed towards areas of strength with an adequate infrastructure. The MRC is determined that the review process is seen as transparent and that the performance of the grant making decision process is assessed.

One of the most exciting new schemes is the Co-operative Group grant. Across the country, about 50% of applications have been successful. MRC Development grants, such as the one awarded to the Institute of Health of the Elderly in Newcastle, aim to build up research groupings which benefit the institution and the field of research over the fixed tenure of three years. The grants require university commitment with the hope that this creates a strong relationship between the institution and MRC. By the end of the grant tenure, the case for further MRC funding should have been strengthened.

From an academic perspective, Calman training is perceived as rigid, restrictive and unimaginative. As the clinical workload of the trainees has increased, academic productivity has decreased. In the context of the Research Assessment Exercise, this has a deleterious effect on the institution. The MRC is investing heavily in career awards. Last year £30m or between 9.5 and 10% of the MRC annual budget was devoted to career awards. Fifty two Clinical Training Fellowship Awards and ten Clinician Scientist Fellowship Awards were made. In specialties where training is particularly inflexible, notably the surgical specialties, the MRC is establishing links with the Royal Colleges to encourage research in these areas. The MRC has also developed a five year Career Establishment Grant, which is designed to allow an individual holding a secure university appointment to become an independent investigator.

Many of the grant schemes are seen to fund safe predictable research. They may stifle innovative research where few or only preliminary data exist. As grant applications for truly innovative research are difficult to evaluate, the MRC has introduced specific Innovation Grants.

The audience gave these proposals a cautious welcome. There was a perception that it is still too difficult to obtain a first grant. The current approach to awarding grants appears to favour 'big bucks for big boys'. It was suggested that the 'little boys should join the big boys' in order to develop necessary research skills to develop into independent researchers. Holders of MRC Clinical Training Fellowships are more likely to sustain their research efforts if their training was carried out in a centre of excellence.

Experience of a co-operative group grant

There has been much interest in how the new co-operative group grants work.

The aims of the group headed by Professor Shorvon are disease orientated and are focussed around the study of epilepsy. Within the broad aims, the group studies the aetiology, mechanisms, treatment and pathology of cerebral

Conference programme

I The new MRC research award schemes
Professor Alan McGregor, Guy's, King's and St Thomas' School of Medicine, London

II Experience of a cooperative group grant
Professor Simon Shorvon, Institute of Neurology, London

II Clinical research in MRC units and collaborations with the major charities
Professor George Radda CBE FRS, Chief Executive, Medical Research Council

II Matching funding priorities between scientific excellence and clinical need
Professor George Alberti, President, Royal College of Physicians
damage of epilepsy. The group comprises five principal investigators: one basic scientist, one health service researcher, one molecular and clinical geneticist and two clinicians, and 21 other clinical and basic science investigators; five of these are clinical researchers who hold National Training Numbers.

The co-operative grant amounts to £255 thousand, which is a small proportion of the total grants of £4 million held by the group. The investigators hold two initial component grants, five eligibility grants and 18 underpinning grants.

Although in financial terms the co-operative grant does not contribute a large proportion of the total funding held by the group, it brings a number of other benefits. The group provides the intellectual environment necessary for cross-discipline interaction. The mixture of basic and clinical scientists permits the translation of basic science to clinical application and provides a clinical relevance to the basic science. Furthermore, the clinical work can be seen in terms of health service requirements. The interaction between the principal investigators facilitates collaboration across projects. The regular group meetings, at which the latest research is discussed, engender an esprit de corps and help motivate the staff. On a practical level, the group allows economies of scale and sharing of resources. None of these attributes is brought about by the co-operative grant per se, and there is no reason why like-minded researchers cannot form a group. Nevertheless, the grant provides a focus for the research.

The group enhances the profile of the researchers both within and outside the institution. This enhanced profile has several benefits in terms of attracting money, including Cullyer funding, and staff. This is of particular importance with respect to training, which is viewed as a core activity of the group. The group has supported training for PhDs and MDs to the advancement of clinical careers in academic neurology.

There are a few difficulties associated with the running of the group. The success of the group tends to attract new members, and there is pressure to accept members who are not necessarily compatible with the aims of the group. As the groups are based on science and not geography, multi-site groups are allowed if the science will benefit. There are understandable logistical difficulties when this happens. The timing of the underpinning and component grants does not wholly overlap the timing of the co-operative grant and so, as the latter is dependent on the eligibility grants, it could be terminated early if the group failed to maintain sufficient eligibility grants.

The co-operative group is a successful venture which promotes a creative and productive research environment.

Clinical research in MRC units and collaborations with the major charities

The MRC aims to promote and support high quality basic, strategic and applied research and related postgraduate training in order to improve human health. To achieve this, it must interact and build strong relationships with the other stakeholders in medical research which include the government, the universities, the clinical community, industry, the public, and – not least – other funding bodies.

The MRC is interested in collaborations with charity funding bodies because it often has goals in common with the charities. There may be overlap in research strategies such as the links between the MRC and British Heart Foundation. Collaboration may facilitate joint action to develop clinical research training, implementation of research findings and communication of research findings to the public. The MRC may underpin basic research and the infrastructure needed to allow for specific grants from charities.

The extent of this collaboration is demonstrated by the fact that 69 of the 76 MRC co-operative grants awarded have charity funded components. This figure remains around 50% even if Wellcome grants are excluded. One of the latest MRC collaborations with the Cancer Research Campaign is a £20m scheme to fund a cancer research centre in Cambridge to drive the application of basic research towards cancer treatment.

The MRC is interested in moving into new areas. It sees the setting up of new MRC units and university centres as an important role for facilitating research in new areas where no appropriate strengths exist in the host institution. The creation of a new unit allows longer-term funding, which facilitates innovative research. The grants are reviewed every five years and the usual life span of a unit is about 19 years. The MRC unit will be closed when it is seen that the research can be done just as well in the university or the research no longer remains at the forefront of science. The units are wide ranging and include environmental epidemiology, health service research, clinical trials, neurosciences and nutrition. MRC units are not confined to the UK, and one of the most successful units is the HIV unit in Uganda.

The MRC believes in career development and has the resources to fund an appropriate candidate from PhD to professorship. One innovative step in career development is the linking of medical research with researchers of disciplines that are not traditionally allied to medicine, such as interactions with physics, engineering and social sciences. By investing in people the MRC hopes to facilitate the reversal of the 'brain drain' and to attract internationally renowned researchers into the UK.

In summary, the MRC is in a position to interact with other parties interested in medical research and has built up strong links with major charities, while MRC units develop research into new areas and provide the security needed to undertake innovative projects.

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of view have problems but there may be common ground such that both can be accommodated.

The principles of scientific excellence are sometimes impossible to apply to human populations because of the difficulties in working with humans. The number of subjects needed and the cost of the studies often make the studies impractical. Even if these difficulties could be overcome, the resource implications for research personnel are prohibitive. Furthermore, there are imprecisions in whole man studies, and human behaviour is often not reproducible. Scepticism engendered by the 'genomaniacs' has led to a cynicism about the relevance of many scientific studies.

Adopting a strategy which is based on need can also be flawed. Although clinical need is a laudable aim, there are challenges in defining need. The process is subject to political bias and can lead to short-termism. The decisions regarding need may be viewed differently by the different stake-holders, which begs the question of who ought to make the decision. In terms of institutions, the Department of Health, NICE and the NHS research and development executive may all wish to be involved. Government ministers may make decisions very different from those of the general public or patients who tend to be more disease focussed. Needs-based research may prove to be intrinsically less interesting to research workers and may lead to recruitment problems, although this may be overcome by involving the researchers in the decision making. The clinical-need approach tends to be narrow and is divorced from basic science. Scientific rigour is frequently lacking as researchers strive to obtain immediate answers which are frequently not forthcoming.

Even where research is perceived as needs-based, there may be other confounding factors depending on the source of funding. The NHS research and development executive may come under undue influence from politicians or healthcare managers, while industry is answerable to its regulating agencies. The MRC remains at the mercy of the vagaries of the peer review system. Even charities often suffer from being advocates of single diseases.

The crux of the issue for clinical research is to find a balance between both approaches. The *sine qua non* is that the science must be of high quality and validity. This may require the concentration of research efforts into centres of excellence, although good thinkers outside these areas should not be forgotten. There needs to be a broad portfolio of problem-directed and curiosity-driven research to allow better opportunities for applied research workers. This will require integrated planning from all involved across disciplines. It is important for those involved in research to explain to the public and paymasters that there is a need for longer-term studies and that research should be focussed on soluble problems.

Although not all clinicians must undertake a higher degree, it is important that all receive training in research methods to allow critical appraisal and appreciation of scientific research. It is anticipated that about 5% of clini-

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**Conclusion**

Research in the UK has undergone radical changes over the last decade. A more open collaborative approach is needed where research funding is directed to centres of excellence. The MRC has developed a number of new grant schemes to move research institutions forward and close links with the charities have been forged through joint ventures. The cooperative group grant has been seen to work in practice. There is now a need to balance clinical need with scientific excellence.

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