The Physiological Society

Magazine

April 1993
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The Physiological Society Magazine

Contents

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Physiological Sciences at Leicester

Physiology started in Leicester in 1965 with the appointment of Ron Whittam as Professor within the Department of Zoology; the Laboratory of General Physiology, as it was initially called, became a separate department in 1968. Twenty five years ago, fashion was somewhat different: today, pressures on departments tend to be more of the merging kind.

The initial department was very small indeed, with only five members of academic staff. The Department grew with the coming of the Medical School, which opened to its first intake of students in 1975. Even now we have only 11 academic staff, including one newly created position in neurophysiology. The Department is therefore fortunate to have as members three (soon to be four) able senior research fellows, who have won awards within the last couple of years from the Royal Society, the Wellcome Trust and the British Heart Foundation. The new MRC-funded Interdisciplinary Research Centre in the Mechanisms of Human Toxicity includes work from the Department as part of its core science programme. The opening of the IRC early this year immediately adds an honorary lecturer and an IRC research fellow to the departmental complement.

Since 1989, departmental research has been organised into research groups concerning ion channels, membrane transport, neurophysiology and clinical physiology. The Department has perhaps recently been best known for its work on ion channels, with a group led by Peter Stanfield and Nick Standen and including Noel Davies, Ian Forsythe and Phil Langton. John Boyle, who joined as a temporary lecturer in 1991, has now moved to a research fellowship in the IRC. The work of the group encompasses studies of ion channels of skeletal and smooth muscle and of central neurones. Noel Davies is leading a collaborative effort with molecular biologists in Bill Brammar's laboratory in the Department of Biochemistry and Ian Forsythe is pursuing rapidly developing work on synaptic mechanisms in the auditory pathway. Nick Standen will be known to many Members of the Society and their students as a recent G L Brown Prize Lecturer. He is also currently Chairman of the Editorial Board of *The Journal of Physiology*. Work in membrane transport includes José Cavieres' studies of membrane ATPases, carried out partly in collaboration with laboratories in Cincinnati and Aarhus; Toby Law's work on the control of cellular volume in kidney and in the central nervous system; and John Tunstall's interests in excitation-contraction coupling.

Asa Blakeley's work on neurotransmission in the sympathetic nervous system formed the initial basis of the neurophysiology group, together with Dick Stephen's on insect sense organs. Neurophysiology was strengthened in 1989 with the appointment to a permanent lectureship of Jon Scott (a former student of David Barker and of Yves Laporte) who is interested in muscle sense organs and in nerve regeneration. Further strengthening came with the recent appointment of Blair Grubb to a newly established lectureship in neurophysiology. He will bring work on spinal mechanisms in nociception to Leicester, together with an elegant technique, developed in Arthur Duggan's laboratory, for identifying the site of release of neuropeptides using an antibody microprobe.

The development of neurophysiology is part of a University strategy to strengthen neuroscience. New appointments and other developments are occurring in various departments in Leicester. The Department was recently instrumental in setting up a neuroscience group in the University to bring about discussion between members of different departments, and the group is ably chaired by Jon Scott. Among its other activities, it has an active programme of plenary lectures, the first in 1991 being given by Colin Blakemore. Its first anniversary lecturer was Anthony Clare; and it recently ran a day-long symposium on vision chaired by Richard Gregory. The clinical physiology group is developing new methods of recording sounds of artificial heart valves, with Dick Stephen's methods recently being featured in the BBC1 programme *Tomorrow's World*. The group is also heavily involved, with the local paediatricians, in investigating physiological indicators of vulnerability to sudden infant death. Stewart Petersen's work on the development of the normal circadian rhythm for body temperature was recently the subject of press releases from the Foundation for the Study of Infant Death and was featured in TV News Bulletins on both BBC and ITN.

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The Department teaches Physiology within the School of Biological Sciences and the Medical School. The School of Biology admits upwards of 100 students a year and all do some Physiology during their first year. We attract between 50 and 70 students into our two second year courses in what is a modular degree, and we take some pride in these courses normally being among the four most popular in second year biology. Some 20-25 students read third year Physiology though generally in combination with courses in Biochemistry, Pharmacology and Zoology. A good number of these students are again going on to higher degrees. This year, for the first time, Leicester is admitting students to read for first degrees in Physiology and in other named subjects. Possibilities of a joint degree with Psychology and of a Neuroscience BSc are being considered.

The Medical School takes some 135 students a year. Here Physiology is taught within an integrated Structure and Function course throughout the first two years, something that works well. The physiological input into the course is helped by the presence of Laurence Howard, a member of the Department of Physiology, as Pre-Clinical Sub-Dean. Also novel in the Medical School is the method of reading for a BSc during an intercalated year by research only, students presenting a thesis during May after a start in September. The standards reached are often extraordinarily high.

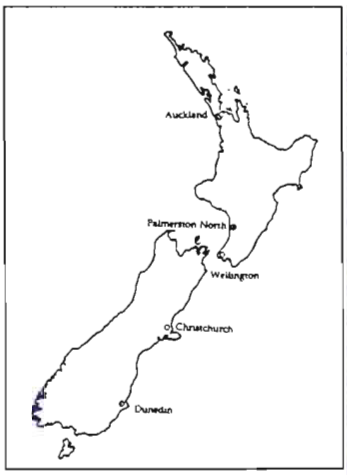
What will happen to Physiology in Leicester over the next 25 years is more open to question, as it may be elsewhere, given the rather low scores achieved by the Physiology unit of assessment in the recent Research Assessment Exercise. Pressures of a merging kind will become real, and may indeed be appropriate. But the future in Leicester will be guided by a determination to defend what is excellent in physiological research and to support and foster what has the promise of excellence. Further, there will be a continued commitment to high quality education and to encourage enjoyment and understanding of a subject many of us find profoundly humanising.

We welcome The Physiological Society to Leicester with all warmth. We hope you enjoy the Meeting and find time also to enjoy the city - Britain's first Environment City.

Peter Stanfield

(See the Events section for details of Designated Sessions to be held at the Meeting, and the Views section for an abstract of the Wellcome Prize Lecture to be delivered at the Meeting).

Physiology in New Zealand - The Physiological Society of New Zealand (PSNZ) in 1992



A few remarks are needed about PSNZ itself to appreciate its members' concerns in 1992. The Society, founded in Dunedin in 1973 at a public meeting called by and chaired by Prof J Hubbard, later the first secretary, will be 20 years old next year. It is an incorporated society governed by a council and chaired by the secretary. The executive officers are elected for four years and there are seven council members elected for three years with two retiring each year. The current secretary is Dr R D Pack and the treasurer is Prof R E Munford, both from the Department of Physiology and Anatomy, Massey University, Palmerston North.

Format of Meetings

The chief activity of the Society is an annual three-day scientific meeting in the university vacation in May. Departments with sufficient physiologists to provide a meeting secretary and the necessary organising committee take turns in hosting the meeting. These are the Physiology Departments of the Universities of Auckland and Otago; the Department of Physiology and Anatomy of Massey University; the Zoology Departments of Victoria University, Wellington, the University of Canterbury, Christchurch and the University of Auckland. The meetings follow a conventional format. An informal get together on the first evening is followed on the next day by oral presentations (15+5 minutes) of research by participants. Organisers try to avoid concurrent sessions so that all participants can learn of each others' activities and, so far, poster presentations have not been held except during joint meetings with other societies. The day ends with the Annual General Meeting followed by a dinner. There are generally no speeches on this occasion and, once the immediate pangs of hunger are satisfied, participants prefer to perambulate from table to table, meeting friends and making new acquaintances. The following day continues the pattern of presentation and that evening is free for members to explore the host city. The meeting terminates the next day, usually at or soon after midday, so that members can reach their homes by the end of the day.

Abstracts of the presentations at a meeting are printed in the Society's proceedings, now in its 12th volume (current editor Prof J D Sinclair). Every three years the Society presents a medal for the most meritorious research done in the preceding three years by a member in New Zealand. The medal is presented at the conclusion of a 50 minute lecture on the topic of the recipient. The lecture is part of the annual meeting programme and is also printed in the proceedings.

The Society also publishes an annual newsletter (current editor Dr P Davie, Department of Physiology and Anatomy, Massey University, Palmerston North). The newsletter carries news of the activities of members and their students in each centre as well as the minutes of the annual general meeting, the accounts of the society, news of scholarships for students, notices of meetings of interest to physiologists and, at the back, the current membership list and the constitution of the society.

The 1992 Annual Meeting

The 1992 meeting, held on 15-17 May at the University of Auckland Medical School, was hosted by their Department of Physiology. This meeting was preceded by and combined with a two day symposium entitled *Exercise, the Physiological Challenge* arranged in honour of Prof J D Sinclair, retiring Foundation Professor of Physiology at the Auckland School and the second secretary of the society. Prof Sinclair was an athlete in his youth and won the New Zealand mile championship in 1948 (a film of the race was shown during the meeting). He retained an interest in exercise for the whole of his working life. Invited speakers included the great New Zealand 1500 metres runner, Peter Snell, now Director of the Human Performance Centre, University of Texas, Dallas; some of Prof Sinclair's ex-students, notably Ingrid Sarelius, now Professor of Biophysics and Physiology at the University of Rochester; well known researchers in the field, such as Prof F Eldridge from the University of North Carolina, Prof J T Shepard from the Mayo Medical School, Prof J H Mitchell from the University of Texas and Prof J Duffin from the University of Toronto; and local experts. The result was a very stimulating two days for a large body of New Zealand physiologists.

Joint Meetings

Every second meeting of the Society is joint, if possible, with another New Zealand or Australian Society. One reason is that many of our members belong to two or more biological societies; another is that usually a more attractive programme can be arranged on these occasions with, for example, invited speakers, symposia, demonstrations of techniques and a trade show. Joint meetings have been held twice with the Australian Physiological and Pharmacological Society (Auckland and Dunedin). On the latter occasion we were joined by the Australasian Neuroscience Society and the Anatomical Society of Australia and New Zealand. New Zealand societies with whom we have had joint meeting include the Endocrinological Society (twice, once with the Diabetic Association as well) and the Biophysics Society. The Endocrinological Society is larger and older than the PSNZ, with many members from the Crown Research Institutes interested in breeding of cattle, sheep, goats and deer.

Bid for 1997 IUPS Meeting

Our Society is affiliated to the International Union of Physiological Societies (IUPS) and made a bid at the last IUPS meeting to host the 1997 meeting of IUPS in Auckland. On this occasion we lost the vote at a council meeting of the IUPS, by the chairman's casting vote, in favour of Leningrad. Currently a committee of the PSNZ is charged with reporting to the 1993 AGM on the question "Should we make a bid for the IUPS meeting in 2001"? Affiliation with IUPS is made through the Royal Society of New Zealand which has been restructured so that societies such as the PSNZ can have representation on the governing body and various subcommittees. This enables our members to play their part in advising the government and the public. Recent questions with which PSNZ members have been involved include the ethics of experimentation and the use of drugs in sport.

IBRO Workshop

The Society has recently become a founder member of the Federation of Asian and Pacific Physiological Societies (FAOPS), which has four yearly meetings alternating with IUPS. The enormous distance between New Zealand and Asian centres and the consequent expense of travelling make it difficult for PSNZ members to play a large part in these gatherings. This year, however, we have played host to a training workshop for Asian physiologists interested in the nervous system. Supported by funds for travel and accommodation from the International Brain Research Organisation (IBRO), 18 postdoctoral students spent a month (November 1992) in physiological laboratories in Dunedin and Auckland, learning techniques that they could take back to their home countries.

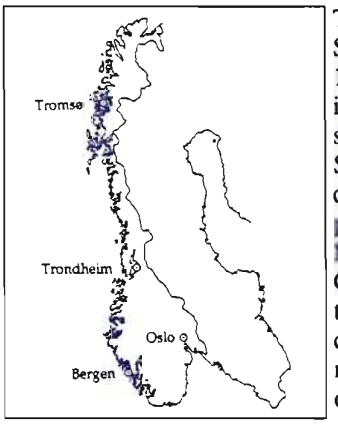
Current issues of concern

The most important current issue of concern to members of PSNZ is their restricted ability to obtain funds to carry out research and fund graduate students. There has been a diminution in sources of funds and the total pool of money available, at the same time as the number of qualified researchers has been increasing. Most members are funded by the Health Research Council, known formerly as the Medical Research Council. This body has received the same annual monetary allocation from Government since 1985, despite rampant inflation in the late 1980s. Members in appropriate disciplines also used to be funded by the Neurological Foundation and the Heart Foundation. The Heart Foundation no longer funds research projects and the Neurological Foundation now confines most of its funding to clinically oriented projects that are likely to be of benefit to patients in the near term. The only consolation is that the Medical and Science Research Committees of the Lottery Grants Board (known colloquially as the "golden kiwi"), which make grants for the purchase of equipment, are currently well supplied with money due to the success of the parent Totalisator Agency Board in stimulating gambling. One new source of funds has appeared. The newly established Foundation for Research, Science and Technology from which members in Crown Research Institutes have to seek grants has, this year, received the Government allocation which used to support postgraduate study and equipment purchase in universities. In return university staff members with any but health related projects may now apply for grants, which may include funding for postdoctoral students, from the Foundation. The first results of this exercise will not be known until May 1993.

Members in clinical departments with joint university and hospital board appointments have the additional burden of trying to do research in face of increased calls on their time due to increased patient numbers and reduced hospital board funding. At the present time hospital boards are funded in proportion to the population served. From July 1993 this money will be given to provider boards which will fund hospitals in their area to carry out specific services. Hospitals in this area will contract to and compete for the funds to carry out particular services. The impending change to an as yet untried system has resulted in a general reduction in morale, particularly as it is not clear how research will be carried out under these circumstances and how joint appointments will be arranged. It appears that 1993 will be an eventful year.

John I Hubbard

Physiology in Norway - The Norwegian Physiological Society



The Norwegian Physiological Society was established in 1970 after existing as an informal Physiology Club for several years. Initially, the Society provided a forum for communication between physiologists at the two largest Norwegian universities, in Oslo and in Bergen. Since then, the Society has grown considerably, with about 350 members distributed throughout the country. Member physiologists are found at the four universities (Oslo, Bergen, Trondheim, Tromsø); the National Hospital and many of the regional hospitals; and at various scientific high schools and other research institutions. Several outstanding, internationally recognised physiology research groups are represented. Major fields of emphasis include cardiopulmonary physiology, neurophysiology, and arctic physiology.

Format of Meetings

The Society has a central steering committee that organises local scientific meetings, administers the Society's finances and maintains professional contact with the larger societies to which we are affiliated, such as the Scandinavian Physiological Society and IUPS. The local meetings are held in Oslo, where the largest number of members is concentrated. These are organised around a particular theme, with two or three evening lectures, most often given by members but on occasion including presentations from visiting researchers. Two such local meetings were held in 1992, one on the topic of the physiological roles of nitric oxide (with guest lecturer Dr Anna Leone from the Wellcome Research Institute) and one in which the three largest biotechnology laboratories in Norway described their research programmes and commercial services.

The major event of each year is the Winter Meeting, usually held over four days in February at a mountain resort in the southern part of Norway. Here we organise a scientific programme that includes a main symposium with an invited speaker from outside Norway. Our guest this year was Dr Niels Secher from the Danish National Hospital, who led a symposium on the topic of exercise physiology. The scientific part of the meeting is restricted to the afternoon and evening while mornings are dedicated to winter sports and leisure activities. The Winter Meeting is very popular and usually attracts members from around the country. The combination of science, skiing, and the comforts and atmosphere characteristic of the Norwegian mountain lodges is typically very pleasurable.

Problems facing The Society

Despite the respectable size of the Society, two factors have limited our activities to this modest level. First, our members are quite widespread geographically; this, combined with the relatively high expense of domestic travel in Norway, prohibits regular centralised meetings. Many of our members prefer to direct their travel budgets towards large, international conferences with greater intellectual payoff. Second, our Society competes with a number of other scientific societies in Norway that represent subfields of physiology. Many members find it more attractive to attend the local meetings that these societies arrange, with the attendant concentration of information within a specific field of interest.

Because of these factors, we have found it very difficult to increase our current activities. Perhaps the greatest problem we face is that Physiology as a well-demarcated field no longer seems to exist. The boundaries between physiology, biochemistry, anatomy, and so on have long since evaporated in the face of increased understanding of physiological systems at the molecular level. Now the information content of even subfields like neurophysiology represent expanses of physiological science so broad that a holistic view is difficult if not impossible to maintain. Consequently, many of our members consider our meetings to be "low return", and concentrate their intellectual investments on more narrowly defined fora.

Improving the appeal of Society's Meetings

Our future goals have been tempered somewhat by the inexorable fragmentation of the field and the concomitant specialisation of most researchers. It is likely that we shall concentrate our efforts not on organising more or larger meetings but rather on co-ordinating the activities of the more specialised societies. In this way, communication of subjects of interest to specialists in different fields can be integrated rather than remain isolated. This policy ought to provide great benefits towards understanding phenomena at a systems level, especially for young researchers who enter fields at such an advanced stage of specialisation that they never realise that what they are studying is in fact part of a system (an unfortunate fate that seems to be especially common among molecular biologists). In parallel with our policy of integration, we are attempting to establish a data network among our members and with the steering committees of the other societies, so that information about various activities and meetings can be rapidly disseminated. Lastly, we wish to maintain an active posture with respect to the recruitment of young students to physiological research. To this end, we have tailored our Winter Meeting specifically to the needs of students. We have directed more of our budget towards financial assistance to participating students and we have organised the programme so that students can obtain practice in the oral presentation of experimental results in a large congress form (10 minutes followed by questions) but before a friendly audience. We also make a point of beginning each symposium with a short introduction of background material so that all participants, regardless of specialisation, understand what are the major questions and points of contention within that research area.

It is probably worth mentioning that our Society very nearly expired a few years ago because of lack of interest. Luckily, by invigorating the Winter Meeting and orienting it to the needs of students, we have managed to inject some new life. But the future of our Society is far from secure and its continued existence will require constant attention to the changing role and definition of physiology as a field. We welcome input from physiological societies in other countries on how to grapple with this problem.

Joel C Glover
(President, Norwegian Physiological Society)

Physiology in Norway - a Member's view

Rebuilding after the war

The present position of Physiology in Norway cannot be fully appreciated without some mention of the situation we found ourselves in after the war and the steps taken since 1945 to restore the profession.

Norwegian physiology was in a really bad state after the war. The university in Oslo, at that time the only university in Norway, had been closed for almost two years by the German occupants, and when the Institute of Physiology reopened it was sadly lacking in staff, equipment and funding. Physiology was far worse off than sister-disciplines such as anatomy. In fact, when the Oslo Institute of Anatomy reopened it did so with both a strong reputation and a well trained staff which included several members with international reputations, among them the late Jan Jansen and Alf Brodal.

The seeds of the rebirth

The miserable state of Physiology in the Oslo Institute and in Norway as a whole started to improve some 10-15 years after the war when, in the 1960s, a number of new appointments were made. The development of modern experimental physiology really took off at about this time. The last 30 years has seen a marked growth in Norwegian Physiology. To a large extent, this growth has been linked to the establishment of three new universities, those in Bergen, Trondheim and Tromsø. All four universities have faculties of medicine, each with a department or a section for physiology. Increasingly, physiological problems are also dealt with in departments of zoology and biology.

A further stimulus to growth has come from the construction of several new multidisciplinary laboratory buildings in which physiological laboratories have been housed together with laboratories of other preclinical disciplines. The last ones to benefit were the Oslo departments, which in 1990 moved from buildings which were 150 years old to a new, modern, well-equipped building.

Benefits of international collaborations

The post-war restoration of Norwegian Physiology owes much to support and influence from other countries, which has come largely through the training of postgraduates, including a number who have since been very influential. For example, on his return from the USA, the Norwegian-born biologist Per Fredrik Scholander stimulated and educated a number of pupils during his four year period as a professor in zoophysiology in Oslo in the 1950s. His strong influence can be traced to several of the most productive physiology groups of today. Several of our other "founding persons" returned to and enlivened Norwegian departments of physiology and experimental medicine after stimulating postgradeate periods in the USA, Great Britain, Sweden or Denmark.

The links with Sweden were and have continued to be very important, with collaborations taking place at many levels and with many a Norwegian physiologist receiving their postgraduate training in the renowned Swedish departments. In this connection, the importance of the Scandinavian Physiological Society must be mentioned. The Society, modelled on The Physiological Society, has been a useful arena for the presentation of research results, through its regular meetings. Also, personal links to the British Society and to British Physiology as well as to American Physiology have been - and still are - of decisive importance for many Norwegian groups.

Current major areas of research interest

Neurobiology

Probably the most successful and most progressive field within Norwegian Physiology is that of neurobiology. Norwegian neurophysiology started its development under Birger Kaada in the early post-war years within the well-established neuroanatomical milieu in Oslo. Today, there are several strong groups within the sister-departments of Neurophysiology and Physiology at Oslo University. Within the thriving Oslo milieu, Jan Jansen Jr and his group have been working on the embryonic development of the nervous system, particularly the development of skeletal muscle innervation, now using chick embryos as their main preparation. Terje Lømo and his group are exploring the neuromuscular junction and its formation, with special interest in the activity-dependent differentiation of types of muscle fibres.

Per Andersen's group is studying signal handling in the hippocampal formation, largely in the brain slice preparations pioneered by the group. One main interest today is the mechanisms behind long term potential (LTP) - first discovered several years ago by Terje Lømo, then a graduate student in Per Andersen's laboratory. With these groups well-funded and living in the same part of the same new preclinical building and close to the laboratories of the neuroanatomists and their electron microscopes, there is at present fruitful and lively activity within neurobiology in Oslo.

Neurobiological research is carried out in other departments as well, and much of it can be traced back to the early start of neurophysiology in the Oslo Department of Anatomy. In the Department of Biology in Oslo, groups led by Per Enger and Kjell Døving are dealing with fish sensory physiology; and, in Trondheim, Hanna Mustaparta has established a group focusing on pheromones in insect sensory physiology. In Bergen, there are groups dealing with several psycho-physiological topics, and with research on sensory mechanisms and signal handling in the field of pain perception.

Cellular physiology

Cellular physiology and the study of sub-cellular mechanisms has had a rapid and marked development within old departments of physiology, anatomy, biochemistry and pathology, as well as in newly established sections or departments of biotechnology or molecular biology. Here borderlines between old disciplines are more than difficult to draw today, as new techniques - and among these the revolutionary ones of molecular biology - are taken in and employed in old as well as in new departments and groups. As examples of topics pursued by persons with a training in physiology or in related fields, one can mention: erythropoiesis, immunology - with the emphasis on lymphocyte populations and activity, endocrinology and haemostatic mechanisms. As an example, one could mention the work of Kaare Gautvik and his group, now in the Oslo Department of Medical Biochemistry, on secretory mechanisms, purification and production of the parathormone.

Integrative physiology

Integrative physiology within the fields of circulation, respiration and renal excretion has had and has kept a fairly solid position,

with active groups at all four universities. A main field of interest in the northernmost university of Tromsø has been cardiac physiology with interests extending to cardiovascular disease. In Bergen, Knut Aukland's group has successfully and systematically dealt with transcapillary water balance, with measurements and evaluations of interstitial pressure and interstitial fluid volume and composition in different tissues. Other groups in the same department are working on adrenergic mechanisms. Several groups, particularly in Trondheim and in Oslo, have made profitable use of the new Doppler ultrasound techniques, after actually participating in the development of high quality Doppler equipment, now under industrial production in Norway.

In the Department of Physiology in Oslo, a group led by Lars Walløe has combined the use of Doppler ultrasound and other techniques in revealing regulatory mechanisms related to cardiac output and its distribution and variation, with measurements of blood flow through various organs and tissues, such as working muscle, skin arterio-venous anastomoses and the splanchnic organs. A group led by Gunnar Nicolaysen has continued the departmental line of interest in pulmonary circulation and has lately - with the elaborate use of injected, tracer-marked beads - studied the surprisingly uneven and heterogenous blood flow through pulmonary as well as through muscular tissue. At the Institute of Experimental Medicine in Oslo, a group led by Fredrik Kiil, who years ago developed a well-functioning artificial kidney, has worked productively on renal excretion as well as on circulatory control mechanisms. Methods developed in the group for dynamic measurement of cardiac dimensions have proved very useful.

The interest in arctic physiology, introduced by the late Per Fredrik Scholander, has been maintained and is presently most effectively pursued at Tromsø. Here, physiological research on arctic birds was established in the early 1970s by Johan B Steen. Today, a wide range of survival strategies and adaptive mechanisms related to arctic and sub-arctic animals are studied by Arnoldus Blix and his group.

Funding

Norwegian Physiology, as most other disciplines within biology and fields of science, has traditionally been funded through three channels: basic funding through the universities, additional and important funding from either the research councils or from some specific funding organisations supporting cancer-related research, cardiovascular research or other types of research in general. The funding situation has, on the whole, been reasonably good, especially for groups or topics that have gained the confidence of granting agencies.

There appear to be two main reasons for concern today, one being a shortage of salaries for permanent staff positions, impeding the recruitment to academic institutions. The other is the problem of getting money for new approaches and topics which are at an early stage of development. Money comes more easily to those with an established and acknowledged standing - and to those working within fields declared to have national priority. There is also some general uncertainty as to future funding, partly because the research councils are being reorganised as from January 1993. Instead of five councils, there will now be one big one, with six sections. Nobody knows how this new system will work - and how money in future will be directed into more specialised funding organisation. It would be fair to say that there is less optimism in Norwegian Physiology today than some ten years ago. But that appears to hold true for most sections of our as well as of other societies.

B A Waaler

Committee News

(The Committee News is compiled by Heather Dalitz)

Election of new Members

The Committee welcomes the following recently elected Members:

Ordinary: P I Aaronson, Michael Ashford, Laura Bennet, A Bradford, Fion Bremner, F L Burton, Peter Cahusac, Lucie Clapp, William Coetzee, Roger Corrall, James Docherty, Y E Earm, Simon Farmer, David Fedida, Daron Fincham, Eliot Forster, Michael Geeves, Alasdair Gibb, Paul Greenhaff, Linda Greensmith, Nina Griffiths, Carole Hackney, Linda Harrison, Patrick Hartigan, Graeme Henderson, T W Higenbottam, E Hillhouse, David Holder, Lesley Houghton, David Ingram, Simon Jarvis, I S Kay, Cornelis Kros, Dimitri Kullmann, Philip Langton, G L Law, Helen Leathard, David Lewis, Giamal Luheshi, Mary MacDermott, Ian McFadzean, Barbara Miller, Victor Moss, David Owen, D F Parker, Suzanne Phillips, C E Pollard, Stephen Publicover, John Rawlings, Frances Rind, Duncan Rogers, Kathryn Ryder, P Sacco, Geoff Sandle, Monique Sarantis, D B Sattelle, Wolfgang Schady, Guy Seabrook, Peter Sneddon, J R Sneyd, Baggi Somasundaram, Marek Szatkowski, J E H Tattersall, Peter Taylor, P D Thompson, Emil Toescu, Paul Trayhurn, Jonathan Treherne, P F Watson, Ursula Wells, E M Winter.

Foreign: J R Blair-West, John Crook, C Dehay, Peter Detwiler, Brunello Ghelarducci, Hugo Gonzalez-Serratos, Owen Hamill, P H Hinckel, J R Hume, W Jänig, S Kasparov, O Kiehn, L Kukstas, Edward Lakatta, Peng Li, P-M Lledo, Christopher McBain, Kenryo Minezaki, Gunnar Nicolaysen, Magda Passatore, Bernardo Rudy, Walter Stuhmer, Tomoyuki Takahashi, Bernd Urban, Miguel Valdeolmillos Lopez, A Varro, Mei-Lin Wu, Wing-Ho Yung, Robert Zorec

New Honorary Members

Richard Keynes had a distinguished undergraduate career at Trinity College, Cambridge. He was a lecturer at the Physiological Laboratory, Cambridge University from 1953 to 1960, then moving to the ARC Institute of Animal Physiology, Babraham, first as head of the Physiology department (1960-64) and later as Director (1964-73). In 1973 he was appointed Professor of Physiology at Cambridge University, a post he held until his retirement in 1987.

Richard Keynes has made substantial contributions to our knowledge about nerve physiology, particularly concerning ion movements at rest and during stimulation. Very early on he used radioactive potassium to trace the movements of this ion across the nerve membrane [*J Physiol* (1951) **113**: 199 and **114**: 119]. His paper with Alan Hodgkin on "Active transport of cations in giant axons from *Sepia* and *Loligo*" [*J Physiol* (1955), **128**: 28] was of immense importance.

To enable Members to refer to articles in previous issues of the Magazine more easily, issues will now be numbered. The numbering sequence has been started at the March 1992 issue (the first produced in the current format), so the numbers of previous issues are as follows:

1 *March 1992 (Newcastle Meeting)*
2 *May 1992 (St Andrews Meeting)*
3 *July 1992 (Oxford Meeting)*
4 *September 1992 (Cambridge Meeting)*
5 *December 1992 (Queen Mary & Westfield Meeting)*
6 *January 1993 (Leeds Meeting)*
7 *April 1993 (Leicester Meeting)*

His work has been recognised in many ways. Elected FRS in 1959, he gave the Royal Society's Croonian Lecture in 1983. He was elected Foreign Member of the Royal Danish Academy of Sciences in 1971 and a member of the American Academy of Arts and Sciences in 1978. He served as a member of The Physiological Society's Committee from 1961 to 1965 and was an editor of *The Journal of Physiology* from 1954 to 1961.

Doug Wilkie has recently retired from the Dept of Physiology, UCL, where he had previously been Jodrell Professor of Physiology and head of department. He is a Fellow of the Royal Society and served on the Committee of The Physiological Society from 1965 to 1969. He is scientifically best known for his research into skeletal muscle. His earlier work began to combine mechanical and energetic measurements. This continued throughout his career and, most recently, he is perhaps best known for the introduction of nuclear magnetic resonance imaging (nmr) into muscle research. This work (which was initially carried out with Joan Dawson and David Gadian) examined muscle fatigue in both frog and human muscle and is the basis of the enormous explosion in the use of nmr in physiology.

Doug has always had wide scientific interests. On the basis of his muscle research he predicted that man-powered (but not horse-powered) flight should be possible. He was a member of the committee which designed the competition which eventually verified the first of these predictions.

Finally, in his role for many years as the leader of the UCL muscle group, Doug is responsible for encouraging many younger scientists in this field.

The Committee welcomes the following newly approved Affiliates

Nikolaos Aggelopoulos, Hossein Bagueri, Richard Barsby, Tracy Birdsey, Andrew Blannin, Deidre Campion, Lorraine Clarson, Michael Cumberbatch, Christopher Darby, David Furness, John Gate, Anne Graham, Kirk Hillsley, Steven Hunter, Egrahimi Ismail, John O'Connor, Gholamreza Olyaei, Carl Petersen, Madeline Semos, Frederick Tattersall, Andrew Turnbull, Edward White, Changhao Wu

Administration & Publications Office, Oxford - changes in staff and Academic Supervisor

Now that the transfer to DTP production of the *Journal* in the Society's Press Office in Cambridge is well under way, the Committee has agreed that there would be technical efficiencies in producing the CRC for the Abstracts and *Proceedings* volumes of the *Journal* in the same place. Diana Greenslade has agreed to move from the Oxford to the Cambridge office in March and any Member with a query concerning an Abstract accepted for publication in the *Journal* should now contact her at the Society's *Journal* office at Cambridge University Press, Shaftesbury Road, Cambridge CB2 2BS, tel (0223) 68713.

Other publications of the Society (Annual Report, Grey Book, *Magazines* etc) will continue to be produced in the Oxford office, and a new Administration & Publications Assistant, Jane Ault, has been appointed to assist with this. After taking science A Levels, Jane obtained a degree in Geology and a higher diploma in administrative procedures which, together with her secretarial training and DTP experience, should stand her in good stead for the broad range of work in the office.

Julian Jack's term of office as Academic Supervisor of the Oxford Office ended on 1 March 1993. Since his appointment in 1990, Julian has overseen the development of the office in terms of the premises, equipment and staff, which now provide a sound and stable base for the Society's administration and many of its publications. The Committee expressed its sincere thanks to him in supervising this major initiative.

Oxford Office staff, past and present, on the occasion of the change of Supervisor

Richard Boyd, formerly Chairman of the Editorial Board of *The Journal of Physiology*, has agreed to be nominated for election to the office of Honorary Committee Secretary at this year's AGM. In the meantime, he has agreed to take over from Julian Jack as the Committee Secretary's nominee as Supervisor of the Oxford Office, with effect from 1 March.

Jane Ault, Administration & Publications Assistant

Diana Greenslade, Publications Assistant

Photography by Ander McIntyre

Above: Julian Jack, outgoing Supervisor

Below: Richard Boyd, incoming Supervisor

Kimberly Kustra, Temporary Assistant

Heather Dalitz, Administrator

Wanted: Congress correspondents - sponsorship available

Any Member or Affiliate who would be willing and able to write an interesting account of his or her scientific and social experiences as a participant at the Glasgow Congress is invited to apply to the Editor of this *Magazine* for sponsorship as a "Congress Correspondent". The Editor can pay up to £100 to each of up to three people towards their travel and accommodation expenses in attending the Congress, payable on receipt of a piece suitable for publication in this *Magazine*. Anyone interested should contact the Society's Administration Office or the *Magazine* Editor in advance of the Congress.

Publication of Contents pages of *The Journal of Physiology* and *Experimental Physiology*

Members who did not have shelf space for the *Journal* in the days when there was no subscription reduction for not receiving Members' copies, may remember that they used to be able to receive instead run-on copies of the Contents & Index pages. This practice was discontinued when the new subscription structure was introduced, partly because of the increased complexity of subscription and mailing administration and partly due to the excessive cost per copy. Since the subscriptions were increased at last year's AGM, the number of Members receiving Members' copies has fallen by about 10%, so that now about 50% of the Society's Members do not receive copies for their personal use. Following receipt of letters such as those from Colin Blakemore and Chris Peers *[see page 13]*, it has now been agreed that the Contents pages of both the Society's journals be published in or with this *Magazine* *[see page 54ff]*. The aim will be to publish the Contents pages of both current and, whenever possible, forthcoming issues of the journals.

Nominations for new Committee Members

The Committee's nominations for the elections at the 1993 AGM are being circulated with this *Magazine*. Members are reminded that nominations for Ordinary membership of the Committee can be made, with the agreement of the nominee, by five Members of the Society. These nominations should be sent to the Committee Secretary, Dr D Cotterrell, The Physiological Society, Multidiscipline Laboratories, School of Medicine, The University, Leeds LS2 9JT. It is the Committee's policy to make fewer nominations than the number of vacancies arising and it hopes that Members will ensure that there is a reasonable field of candidates proposed. All Members standing for election to the Committee will be asked if they are willing to provide a short article containing biographical and bibliographical details and some mention of their contribution to the Society's activities. These statements will then be published in the next issue of the *Magazine* which will appear together with the ballot paper.

Science Policy Sub-Committee

(Members: David Cotterrell, Lynn Bindman, Graham Dockray, David Miller, Laurence Smaje, Nick Standen)

The Committee recently submitted a document on *Science & Technology* in response to William Waldegrave's invitation to comment on ways of achieving a stable and consistent policy for Science research over the next five to ten years. While other organisations such as Save British Science provided detailed statistical information, the Society's submission emphasised matters specific and important to the discipline of Physiology.

The main points made in the document were as follows:

We welcomed the appointment of a Minister for Science and would press him to produce a strategy for support of publicly funded Science against benchmarks of the GDP to keep UK science funding competitive with our EC and North American counterparts.

We welcomed the ACOST report and its recommendations for an increase in the Science base funding which the Minister should strive to implement.

We would urge a commitment to properly funded career and salary structures for Scientists. Morale, motivation and recruitment are low in Science. For the country to retain its international competitiveness the maintenance of quality in Science is imperative. The outcome will be a highly skilled and internationally competitive scientific workforce for the British economy.

We supported the accountability and quality monitoring of Science in Universities and Institutes through research selectivity exercises. The Government should use the mechanisms of accountability to support creativity in Science by a commitment to the re-introduction of the dual support of the Science base in Universities funded both by Government and Research Councils and medical research charities.

We would recommend that overall funding policy should continue to support a balance of both response-mode (ie scientist driven) and directed research. The outcome of this would be an original and increased contribution to both basic and applied knowledge to the country.

We would recommend a commitment to a reduction in bureaucracy in Science and an increased reliance on scientists' professional judgement. The outcome will be increased productivity and creativity from our senior scientists.

Full copies of the submission can be obtained from the Society's Administration Office.

Publications Sub-Committee

(Members: Graham Dockray, John Atherton, Alan Brown, David Cotterrell, Richard Dyball, Jim Gillespie, Cecil Kidd, Gareth Leng, Noel McHale, Ann Silver, Nick Standen, John Widdicombe)

The Committee has agreed to sponsor the publication of a book on women in Physiology in Britain which is being edited by Lynn Bindman, Alison Brading and Tilli Tansey. It is planned that this will be made available for sale at the Glasgow Congress.

It is hoped that copies of the new careers booklet, currently being prepared, will also be on display at the Congress. By contrast with the last edition, the new booklet will be aimed specifically at the 15-18 age group, with the emphasis on encouraging school and college students to specialise in the biological sciences rather than on providing information for university students who have already made that decision.

The Committee has agreed that a special edition of this *Magazine* be produced, solely for distribution to Congress registrants, with the aim of encouraging new Members.

Animal Welfare Sub-Committee

(Members: Janice Marshall, John Atherton, Lynn Bindman, David Cotterrell, David Eisner, Cecil Kidd)

Members of the Sub-Committee are sometimes approached by physiologists who are concerned that their children are receiving one-sided information at school about animal experimentation. The Sub-Committee would like to remind anyone in this situation that the Administration Office is collecting literature which aims to counterbalance the antivivisectionist viewpoint, and that copies of relevant posters and leaflets are available from the office, tel (0865) 798498. For primary school children, AMRIC (12 Whitehall, London SW1A 2DY) produce an attractive, humorously illustrated little booklet, *Imagine what life would be like without animals*. Readers are also reminded that the Research Defence Society runs a speakers' scheme, providing free presentations on this subject to schools; for further information, telephone Simon Brophy at the RDS on (071) 287 2818.

The Sub-Committee is also keen to collect specimens of antivivisectionist literature, including letters in local papers, leaflets and posters etc, and would be grateful if anyone encountering examples could send copies to the Administration Office, PO Box 506, Oxford OX1 3XE.

New Video from AMRIC

Two representatives of the Sub-Committee recently attended the launch of a new video by AMRIC (Animals in Medicines Research Information Centre, sponsored by the Association of the British Pharmaceutical Industry). Aimed primarily at 12-16 year olds, the video takes the form of a kind of *Grange Hill* episode, in which a group of teenagers is doing a project on the subject. Thus, the material on animal experimentation is presented partly as a continuing dramatised debate between the participants and partly as evidence from the people they interview - a cancer nurse, a vet, a research director, a Hodgkin's Disease sufferer and so forth. Emotional and rational arguments are interwoven throughout the film.

One of the author's findings, in visiting schools, had been that schoolchildren felt that one could not be a kind, caring person and also condone - let alone undertake - animal experimentation, and this is one of the themes the video addresses. This oversimplification did arise partly from ignorance (as one actor in the video puts it, "guilty until proven guilty") and when given further information most young people would moderate their views, sometimes a little but sometimes quite substantially. This video aims to present the issue as a very complicated one, with difficult decisions to be made by all concerned, rather than providing easy answers; and therefore to encourage teachers, whether in English, Science or PSE classes, to discuss the issue in a broader and more thought-provoking way.

Copies of the video are available, priced at £15.27 (including VAT), from AMRIC; for ordering details, telephone (071) 588 0841. Alternatively, the Society's Administration Office has copies for loan to Members and departments of Physiology.

Historical Studies & Archives Advisory Sub-Committee and The Paton Fund

(Members: David Whitteridge, Reg Chapman, David Cotterrell, Martin Rosenberg, Julia Sheppard, Tilli Tansey)

The distinguished physician Sir William Osler, elected a Member of this Society in 1910, classified four levels of interest in history displayed in medical men (I think we can safely translate that to include both physiologists and women). The first category was that of complete disinterest; the second stretched to reading articles or even books in the history of their own speciality; whilst members of the third group would do more, engaging in research and producing the occasional paper. The fourth category embraced the tiny minority that became professional historians; as far as I know the present Physiological Society membership includes very few of this class, and fewer, I hope, of the first category. Thus this article is addressed to those with a passing or more focused interest in the history of physiology.

In 1990, the Honorary Member and former Secretary W D M Paton made a donation to the Society, matched by the Committee, to establish a "Historical Resources Fund" to support studies in the history of physiology. The aims of the Fund are to promote the study of physiological experiment and discovery, and, on the founder's advice, a sub-committee was established to oversee the administration of the Fund. After an initial meeting, the sub-committee was reconvened, with broader responsibilities, as an Advisory Sub-Committee on History and Archives. The present constitution is David Whitteridge (Chairman), Tilli Tansey (Secretary), Reg Chapman, David Cotterrell, Martin Rosenberg, and Julia Sheppard, the archivist of the Contemporary Medical Archives Centre of the Wellcome Institute. After two meetings, the areas of interest to the Sub-Committee are acknowledged to be wide-ranging. One main responsibility is that of overseeing the Archives of the Society, recently transferred from Churchill College, Cambridge to the Contemporary Medical Archives Centre. There they are on permanent loan under the care of the CMAC archivists and are currently being catalogued at the Society's expense by Isobel Hunter, a professional archivist. It is hoped that they will eventually be more accessible to serious historical scholars and to Members of the Society who may wish to consult them. Access to the Archives remains as it was in Cambridge, requiring the permission of one of the Officers of the Society, and publication requires authorisation from the Committee. Some files are closed.

Another area of keen interest is that of acquiring and understanding items of physiological equipment that have historical value, either because of their uniqueness or for the very opposite reason - as a record of the routine progress of physiological research and teaching. To a large extent the Society's concerns in this area are mirrored by the interests of the Science Museum, and a joint working party has been established between the two bodies to identify, acquire, document and conserve suitable items of equipment. Asa Blakeley, Angela Drake-Holland, Mary Phillips, Alan Sykes and Tilli Tansey represent the Society in this venture, with members of the Science Museum curatorial staff.

Other activities that currently engage the Sub-Committee include an attempt, with the assistance of the British Medical Association and the National Film Archives, to locate copies of all the

Society's historical films, and to initiate, as soon as possible, a systematic "oral-history" programme amongst Members of the Society.

However, we remain open to any and all suggestions as to how the aims of the Historical Resources Fund, to promote the study of physiological experiment and discovery, might most properly be met, and invite any Member to write to the Secretary of the Sub-Committee (Tilli Tansey, The Wellcome Trust, 183 Euston Road, London NW1 2BE) with suitable propositions or comments.

Till Tansey

Prizes & Prize Lectures Subcommittee

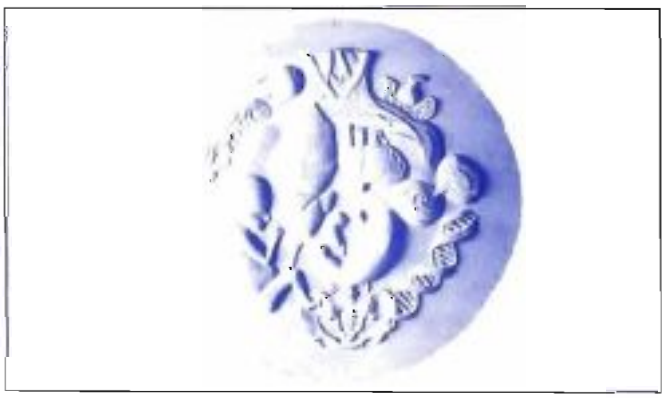
(Members: David Cotterrell, Graham Dockray, Abe Guz, Jim Gillespie, Cecil Kidd, Laurence Smaje, Nick Standen)

The Wellcome Prize in Physiology

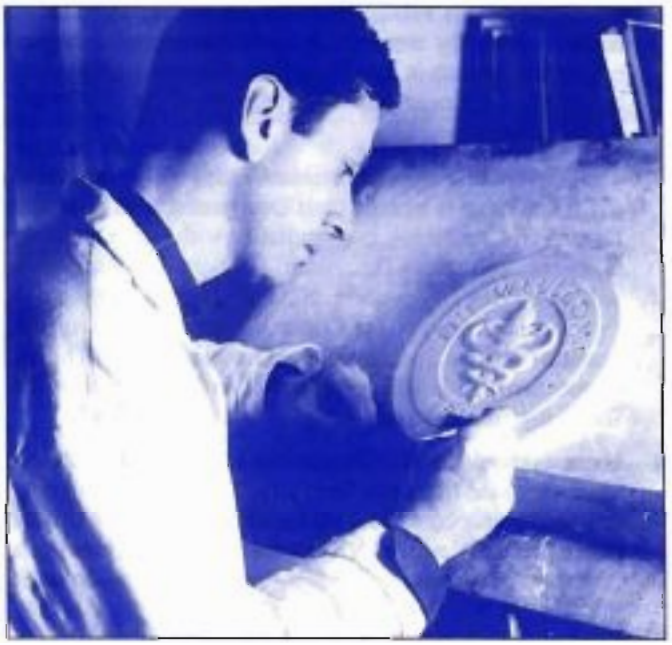
The Wellcome Prize in Physiology was instituted in 1985, to encourage young physiologists and bring their work to general notice. The Prize, awarded biennially, takes the form of a lecture, an award and a medal. Three Wellcome Prize lectures have been given, by Kevan Martin, David Eisner and Andy King, and the fourth Wellcome Prize Lecture is to be given by Hugh Matthews at the Leicester Meeting *[see the Views section for summaries of his talk]*.

A great deal of work and thought has gone into the design of a suitable medal. It was agreed that one side should represent Wellcome, and the other Physiology. The first presented no problems once the Trust's new logo was adopted; however, how does one represent Physiology? As the Committee discovered when it considered suggestions from Members and others for a new Society logo, this is a difficult and contentious challenge!

The Wellcome Trust commissioned January Design (the London consultants who have designed some of the Trust's material, including its new *Science for Life* exhibition book) to work closely with one of the Governors, Sir Stanley Peart, on the conception and design of a medal. January has had wide experience in a range of design areas; but for Mark Pickthall, their Managing Director, who has maintained an interest in science since his schooldays, this was a particularly challenging and enjoyable project. After considering many different concepts, the eventual solution was a design consisting of representations of all the major aspects of physiology. These representations have now been crafted together to produce an interesting and attractive medal.



Once the design of the medal had been agreed, Ian Rank-Broadley (a sculptor well known for his medallic art, with work displayed in the British Museum and the Worshipful Company of Goldsmiths) was commissioned to prepare the models, working from January's original designs. The medal was first modelled in plaster to a size four or five times larger than the finished result



Photograph kindly supplied by January Design

would be, using two plaster moulds to pick up the detail on both sides of the medal. A negative impression was then taken, using a hard resin, and this impression was used as a master in a machine which cuts the reduced impression into a piece of steel, thus producing the dies between which the medal is struck in a press capable of exerting a force of several hundred tonnes. To prevent the metal spreading, the dies are trapped in a cylindrical collar. Striking the medals hardens the metal and during the process it is necessary to soften the metal by annealing it - ie heating and then cooling it in a controlled manner - between the several pressings required. When the desired relief has been achieved and the maker's mark (TF) added, the quality of the silver is then checked at the Assay Office. At this stage, three further distinguishing marks are added: a lion passant, denoting .925 silver; an anchor, being the mark of the Birmingham Assay Office; and a date letter. The desired finish is then applied; in this case, the silver of the medal is lightly oxidised, which turns it to a shade of grey, and then relieved to provide a delicate contrast in order to dramatise the relief.

The Wellcome Trust, January Design and the Committee hope that the first three Wellcome Prize lecturers will agree that these medals are a part of the award worth waiting for. In token of its appreciation of the Wellcome Trust's long-standing support for the discipline of Physiology, the Committee has decided to take the unusual step of presenting the Trust with a bronze Society Dog, in return; this presentation will also be made in Leicester.

Pfizer Prizes

As reported in the September 1992 edition of the *Magazine*, Pfizer offered the Society last year a one-off payment of £10,000 to fund a number of Pfizer Awards. The details of these prizes have now been agreed. Awards, with prizes of £150 each, will be made to postgraduate students for oral Communications presented in the Designated Sessions of the Society's Special Interest Groups, according to the following rules:

1 Up to six Pfizer Prizes will be awarded each year on the basis of oral Communications made in the Designated Sessions of Special Interest Groups.

2 Candidates for a Pfizer Prize should be registered for a higher degree by research in a department of a higher education institute in the UK or Eire. Normally, prizes will be awarded not more than four years from the date of the initial registration.

3 The convenors of Special Interest Groups will be invited to bid for a Prize in one of their Designated Sessions. The Prizes Sub-Committee, in consultation with a representative of Pfizer, will select Designated Sessions in which there will be a Prize competition. Normally, not more than one Prize will be awarded for Communications in a particular Session or to one Special Interest Group each year. The list of successful bids will be published in September for the following calendar year.

4 Entrants should identify themselves when they submit their abstracts to the Meetings Secretary. They may submit only one abstract for consideration for a Prize. When the entrant is not the sole author, the supervisor should provide a statement of the relative contributions made by co-authors.

5 Submissions will be judged by a panel of three, consisting of one nominee each of Pfizer Ltd, the Meetings Secretary and the Special Interest Group convenor. Panel members shall not belong to the same department as any of the entrants.

6 The panel shall meet immediately after the completion of the Designated Session and reach a decision at that time. A majority vote by the panel will be sufficient to make an award. An award will not be made if in the opinion of at least two of the panel members it was not justified by the quality of science in the submitted abstracts.

7 The panel will take account of the quality of the abstracts, oral presentations and discussions.

8 The panel decision will be published by the Meetings Secretary as a written notice displayed at the Registration Desk.

9 Awards will be made at a time and place each year to be decided by the Committee Secretary in consultation with a representative of Pfizer Ltd.

Congratulations

- to Reg Chapman, Dario DiFrancesco and Hans Ussing on their election to membership of the Academia Europaea. The Academia Europaea was established in 1988 and seeks to "respond to the needs and expectations of the countries of Europe".

- to Roger Carpenter on winning the 1992 Glaxo Prize for Biology and Medicine *[see page 25]*

SANDOZ INSTITUTE FOR MEDICAL RESEARCH

VII ANNUAL SYMPOSIUM

MEDIATORS OF INFLAMMATORY PAIN

THE ROYAL SOCIETY

6 Carlton House Terrace, London

21 May 1993

Start 9.00 Close 17.30

Effects of inflammatory products on nociceptors	P Reeh (Erlangen)
Bradykinin in inflammatory pain	*M N Perkins (London)*
Cyclooxygenases in inflammation	T Hla (Rockville)
Neuropeptides in inflammation	*T J Williams (London)*
Mediators of joint inflammation	J Levine (San Francisco)
Sympathetic mechanisms in inflammatory pain	*S H Ferreira (Ribeirao Preto)*
Cytokines in inflammation and hyperalgesia	A McKenzie (Bern)
Neurotrophic factors and nociceptor excitability	*L Mendell (New York)*

Admission to the Symposium will be limited to registrants.
No charge will be made for registration.
Registration forms from: Miss M C Stuart, Sandoz Institute for Medical Research, 5 Gower Place, London WC1E 6BN
Forms to be returned by 23 April 1993

Letters

Society Meetings

Dear Sir,

With reference to the plea from the Meetings Secretary in the January issue of the *Magazine*, we think that there are two main problems: too many Meetings per year and voting with subsequent publication of abstracts.

There should be a maximum of two or possibly three General Meetings a year with several smaller Meetings involving Special Interest Groups. This would have a number of advantages: the Meetings could be held out of term time, therefore student accommodation could routinely be used, leading to reduced Meeting costs to both the Society and the individual. All Members should be able to attend all Meetings, resulting in larger, more knowledgeable audiences.

There should be no second publication of abstracts following the Meeting. The Society could pre-vet abstracts, with selection of work for either oral or poster presentation. Abstracts should be submitted in camera ready form and published four to a page (irrespective of whether actually presented) as a supplement to the *Journal*. In this way, there would be no voting following a presentation and discussions would centre around the scientific content rather than the grammatical content of the presentations, yet still resulting in a citable publication. This would reduce the work load for the Society's administrators and negate the need for the current extra volumes of the *Journal*.

Both of these suggestions would lead to cash savings and, more importantly, to an improved environment conducive to the fostering of scientific relationships.

Malcolm Hunter and Stan White

Publication of Contents Pages of the Society's Journals

Dear Sir,

Under the new arrangements, I, like many other Members of the Society, no longer receive the *Journal*. While I value the bonus in shelf space, I miss the chance to see what is in the *Journal* as soon as each volume appears. Of course, I usually glance at the contents page in the Library, but I sometimes forget or take months to get around to it.

I certainly read the *Journal* less than I used to when it automatically landed on my desk each month. If other Members who no longer take the *Journal* are also looking at it less, this will, in the long run, be bad for the *Journal*, because they won't use it for their own papers.

What about distributing a Contents List for each volume of the *Journal* to all Members, at least to those who take the Notices and Abstracts for Meetings of the Society? To save the costs of postage, these Contents Lists could be mailed with Meeting notices.

Colin Blakemore

Dear Sir,

I decided to cancel my subscription to *The Journal of Physiology* following the increase in subscription costs agreed at the last AGM. I regretted this very much as I found the *Journal* very useful but the approved increase in costs to Members meant that I could no longer afford it. Would it be possible to be sent copies of the *Journal* contents instead? This would be very useful.

Chris Peers

Clinicians in Basic Science Research

Dear Sir,

I have been asked to comment on the articles by Geoff Sandle, George Hart, Praveen Anand and Peter Fentem ("Focus on Clinical Scientists" - December 1992 issue) and a letter giving the perspective from Germany by Alfred Thilmann (January 1993 issue). The Academic Medicine Group has also held a timely one day conference on *"Current opportunities in clinical research"* at the Royal College of Physicians. This Meeting was well attended and was the subject of editorials in both the *British Medical Journal*[1] and *The Lancet*[2]. There is therefore considerable interest in the subject and plenty of material for a vigorous and constructive public debate in which I hope Members of the Society will participate, including via the correspondence pages of this *Magazine*.

Geoff Sandle's article ("Clinicians and Basic Science Research") was detailed, acerbic and enjoyable; it should be recommended reading for any clinician contemplating a research career, in gastroenterology or otherwise.

George Hart ("Some practical problems faced by clinicians doing research in the basic sciences") covered more ground than the title suggests; in particular, he carefully analysed the root causes of many of the problems such as many academic departments being overburdened with routine NHS service commitments, the importance attached to quantity rather than quality of publications, disparities in salaries of academic and "service" clinicians and the serious lack of a (funded) framework for people wanting to train to do both research and clinical practice. His recommendation that research should best be started after clinicians have obtained their MRCP contrasts with the Cambridge philosophy of a unified MB-PhD programme based on the American model of combining a research and clinical career from the outset for a preselected elite. Both sides have distinguished protagonists who uncharacteristically assert the merits of their respective causes in the absence of any comparative follow up results in this country.

Praveen Anand ("Interactions with basic scientists: a neurologist's tale") gave a personal account of his progress in clinical neurochemical research. While triumph over perverse adversity is a clearly necessary and useful personal maxim for clinical scientists, his article did not discuss strategies that might be employed by institutions to break down the barriers between basic scientists and clinicians, thus forming multidisciplinary research groups; there would also be useful spin-offs for teaching. He ended by saying that a niche for an academic clinician would be to conduct clinical trials of new treatments; certainly the flourishing of such units around the country indicates that he is not alone in that belief.

Peter Fentem, wearing his hat as Dean of Medicine, wrote about the Impact of Health Service Reforms on Clinical Medical (undergraduate) Education and only briefly mentioned research; it is a pity that his article was not appropriately extended, as it differs in its focus from the other three articles. Perhaps the Editor should invite him or another dean or a director of medical and dental development to give this important perspective on the issue of clinical scientists. As Peter Fentem points out, importance is translated into monies; the Service Increment for Teaching and Research (SIFTR) is £35,000 for every clinical medical student; postgraduate deans now wield further influence by top-slicing the income of junior hospital staff; the quality of both undergraduate and postgraduate education may be preserved and improved in the new market-based clinical environment.

Keith Peters and Peter Lachmann outlined the current Cambridge viewpoint at the recent conference on current opportunities in clinical research. Unfortunately, due to my current clinical commitments, I missed their talks. They asserted that research training must be for at least three full-time, properly supervised years doing nothing but research, leading to a PhD. The terms "ortho-research" and "meta-research" were introduced. Ortho-research is that research which addresses fundamental questions, and is conducted by clinical scientists for whom research is their major commitment. Meta-research is the rest. By actively nurturing ortho-research, the future clinical scientific elite will be identified and developed, at least in Cambridge. While laudable in its aims, what about those who are unable to participate in such schemes, through lack of either ability or opportunity? A particular problem that was raised was in surgery: Geoffrey Chisolm, a distinguished head of a university department of Surgery and Chairman of the Joint Committee on Higher Surgical Training, said that he could not countenance a "serious" surgeon spending much more than one year away from the scalpel. As such, it introduces a potential schism in the academic clinical community - those for whom research is paramount and others for whom clinical skills are most valued. What a pity that more people do not agree with the middle ground espoused by Sir David Weatherall[3], quoted by George Hart, that the future leaders in academic medicine, rigorously trained both clinically and scientifically, focusing on a limited clinical topic, should excel in both worlds and thereby act as role models for future generations.

The discussion groups were lively. Clinicians in training were deeply concerned about specialist accreditation in that there was a belief that to obtain a senior lectureship, working in a team, one should not have to be as clinically experienced as a candidate for an NHS consultancy, working as a lone specialist. This argument doesn't appear logical: a team is as weak as its weakest link; furthermore, just as there is a danger of clinicians doing second rate science, similarly there is a danger of such academics being regarded as second rate clinicians by their NHS colleagues, their students and potentially by the public. The absence of a well funded alternative career framework for those who wish to pursue a long term research career was highlighted. For example, the MRC, British Heart Foundation, Arthritis and Rheumatism Council and the Wellcome Trust all fund Senior Clinical Fellowships, the holders of which proceed to senior academic appointments; however as Geoff Sandle and others pointed out, the total number available is woefully inadequate. Diana Dunstan, representing the MRC, said that the MRC at least recognised the problem and would shortly be undertaking a nationwide consultative exercise on how best to support a clinical scientific career ladder from the bottom to the top. For such a ladder to function effectively, there must be capacity for lateral movement at each stage, both onto the ladder and, for those whose aptitudes lie elsewhere, off the ladder to be eased back into the NHS or elsewhere.

The director of development and research at the Department of Health, Mike Peckham, described how 1.5% of the NHS budget, some £300m, was going to be spent on R&D. Each NHS region has or will appoint a director of R&D, who will be a senior clinical academic or public health specialist; they will sit on a national council. Their objectives will be to focus on service support and fund allocation for research, manage research and relate the NHS to the science base and vice versa. A second initiative will be to construct regional research databases to inform the council where and when research has been completed, vital to auditing the "R" in "SIFTR".

The final lecture, entitled "Opportunities for Research in the Universities", was given by the Chairman of the Universities Funding Council Medical Committee, Michael Bond. He described how funding for research would be allocated. In the Block grant, 2/3 supports teaching, 1/3 research. The research component is subdivided into DR (support for charity income), JR (a quality factor, depending on the selectivity exercise) and CR (contract research). In addition to the Block grant, there is separate support for teaching undergraduates and postgraduates.

I believe The Physiological Society is well placed to continue as a forum for clinical science in this country. It is not good enough to point to Alfred Thilmann's article and say that other countries have their own problems. It is up to individual Members to enter the debate with vigour and actively participate in the consultation exercises. The outcome should be a self-perpetuating breed of clinical scientists who will have been trained thoroughly, scientifically and clinically, and who can function in a framework designed to support their activity of addressing important questions in medicine and biology.

Avijit Datta

References

1 Smith, R (1993) Academic Medicine: plenty of room at the top. *British Medical Journal* **306**: 6.

2 Editorial (1993) Clinical research: fencing the jumps. *The Lancet* **341**: 23-24.

3 Weatherall D (1991) The physician scientist: an endangered but far from extinct species. *British Medical Journal* **302**: 1002-1005.

Dear Sir,

I was pleased to see Geoff Sandle's article on this important subject in the last issue of The Physiological Society *Magazine*. In his article, he highlights a gap in pre-existing schemes of support that we had already identified. Under the subject of "how to keep going" he talks about the frustration experienced by clinical scientists who have undertaken some research and who wish to remain active in research, particularly across the gap until they are able to compete for a Senior Lectureship or one of the highly prized Senior Clinical Fellowships.

The Wellcome Trust now provides two new schemes of support, in addition to the existing Research Training Fellowships for Medical Graduates, and Senior Clinical Fellowships.

If I may quote from the flysheet advertising these schemes:-

"Research Fellowships for Medical and Dental Graduates

The Trust has schemes of Research Fellowships for Medical and Dental Graduates, designed to provide support at any time in a clinical research career from the completion of general professional training to the stage for appointment to a Senior Clinical Fellowship (whether funded by the Trust or any other body) or to a University Senior Lectureship.

Research Training Fellowships for Medical and Dental Graduates

These Training Fellowships are for Medical or Dental Graduates early in their academic career. Candidates for this scheme will normally have little research experience, and be considering a serious training in research in an appropriate laboratory. Candidates should not normally be over the age of thirty-four years, and awards are usually for a period of two or three years. Sponsors are invited to submit nominations, which are considered five times each year. Short-listed candidates are interviewed at the offices of the Trust. There are separate schemes available for awards in clinical epidemiology, health services research, mental health and vision research.

Advanced Training Fellowships for Medical and Dental Graduates

This scheme is similar in scope to the Research Training Fellowships for Medical Graduates, but intended for individuals at a slightly more advanced stage in their careers. Many candidates will previously have held a Research Training Fellowship from the Trust or some other appropriate body. Some candidates may wish to re-orient their research after a period in clinical work, or to develop new skills following their earlier period of research training. Support will be available for up to two or three years and the possibility of funding for a period of research abroad will be available. Applications for this scheme will be considered five time a year with applications for the related Research Training Fellowship scheme.

Career Development Fellowships for Medical Graduates

Relatively few of these awards will be available, and they will be for particularly high-flying individuals with an outstanding record of success in their first Research Fellowship. Candidates will be required to convince the Trust that their progress is such that they should have special help to maintain the momenium of their research, whether in their existing laboratory or in another laboratory at home or abroad. These Fellowships will provide support for between two and five years, and candidates will be able to progress without unnecessary interruption to the stage where they can apply for a Senior Clinical Fellowship.

Intending applicants for this new scheme should write to the Trust with a copy of their curriculum vitae, a note on their intended research, and an explanation of why support of this type is particularly desirable in their case."

In his article, Dr Sandle particularly comments on the desirability of spending time abroad, and readers will see from the text of our new advertisement that funding to work abroad is certainly a recognised possibility.

The Wellcome Trust has made another change in its schemes of support for a clinical scientist that may be of interest. Senior Clinical Fellowships are of course highly desirable, and many distinguished clinical scientists have passed through this scheme on their way to very senior academic appointments. However, an established appointment may make pressing demands in terms of teaching, administration and clinical work, and it is a pity when active Senior Clinical Fellows have to partly withdraw from the laboratory bench to undertake more routine duties. The Trust has therefore decided that its Senior Clinical Fellowships can be renewable, so that support can extend for ten years rather than for only five. This should help to keep some of the most active research workers in the place where they belong, with adequate support and with minimum distractions.

The Trust is always keen to develop its schemes of support, and clinicians have a particularly important role to play in many fields of biomedical science. The Trust supports a very large number of clinicians on the various schemes, many of them physiologists, and they will have an important role to play in the future. Anyone with suggestions on ways in which these schemes might be improved is very welcome to write to me and of course we are always interested to hear from intending applicants for the various Fellowships. Such enquiries can be addressed either to me or to my colleague, Miss Sandra Carpenter, at the offices of the Wellcome Trust, 183 Euston Road, London NW1 2BE.

David Gordon
Programme Director

A joint teaching forum organised by the Biochemical and Physiological Societies.

New Directions for Biochemistry and Physiology Teaching

Changing role of the General Medical Council (GMC)

A joint forum to discuss possible future developments in the teaching of basic medical science, was held on Wednesday 16 December 1992 at the Royal Free Hospital Medical School. Over a hundred colleagues attended, representing both sides of the former binary divide, and considerable time was spent in animated discussion of the issues introduced by the four speakers.

The main theme of the afternoon - that of the requirement for change - was introduced by David Shaw, Chairman of the Education Committee of the GMC. He began by concisely describing the historical development of the GMC's role in setting standards for undergraduate medical education and went on to explain how the comprehensive nature of earlier legislation had contributed to the factual overload of the undergraduate curriculum. The 1978 Medical Acts to some extent freed the GMC from the statutory requirement to ensure completeness of training and allowed consideration of what might be educationally most appropriate for students beginning their careers in medicine. The GMC undertakes ten-yearly reviews of medical education, usually resulting in the publication of a series of recommendations. In 1990 a different approach was adopted, with the circulation of a discussion document to foster a wide debate before formulating new recommendations. There are several themes to this document, many of them seeming radical when compared to current undergraduate medical courses. The primary educational aims of the proposals are (1) to reduce the load of factual information now imposed by most curricula and (2) to develop the students' capacity for self-directed learning. Other aims reflect the changes in medicine and public attitudes towards it. The health needs of populations need to be emphasised as well as the diagnosis and management of the diseases of individuals. Training should reflect the changing balance between community care and hospital based provision and training should acknowledge that better informed patients demand better communication skills of their doctors.

Curriculum changes

Within the curriculum there needs to be:

(1) Better integration of information, both horizontally between disciplines and vertically, so that students have early exposure to patients and maintain basic science study late into their training.

(2) Efforts should be made to encourage the skills of learning and to provide early experience of research method.

(3) Thought should be given to the development of a core curriculum, comprising the knowledge and skills necessary to achieve a provisional registration, coupled with periods of "special studies" or "options" which would provide an opportunity for exploration in depth of subjects of particular interest to individual students.

(4) The "core plus options" approach would both reduce factual overload and permit curiosity and research-based learning to produce a cohort of students with varying interests and experience.

(5) Assessment techniques should be improved to support the aims of a closer co-ordination of undergraduate and postgraduate training.

In conclusion, Professor Shaw noted that close collaboration between basic scientists and clinicians in planning the curriculum was now becoming more widely accepted and that the traditional preclinical/clinical divide was becoming blurred as basic scientists contributed to the later stages of training and patients were introduced to students early in their studies. There has also been a shift away from discipline-based courses to those which use an interdisciplinary approach in systems- or topic- based courses leading to greater vertical and horizontal integration of the curriculum.

Case study of a new curriculum

The second session was presented by Peter McCrorie, Curriculum Coordinator for the City and East London Confederation for Medicine and Dentistry (CELC). CELC comprises the clinical schools of St Bartholomew's and the London Hospital Medical Colleges and the Faculty of Basic Medical Sciences at Queen Mary and Westfield College. Dr McCrorie presented the basic medical science components of the CELC curriculum as a case study. This new curriculum, while developed prior to the GMC's discussion document, has nevertheless anticipated some the issues which have subsequently arisen.

Outline of the course: The CELC curriculum is divided into three phases: the first primarily basic medical science; the third clinical training; and the second a transitional phase which includes psycho-social and statistical aspects of medicine, a research project and an introduction to clinical skills. The basic sciences teaching in Phase 1 is systems-based and is arranged as a series of modules (eg Molecules, Cells and Tissues; Alimentary System; Neuroscience; Whole Body and Nutrition), initially designed by a multidisciplinary team including clinicians and students as well as basic medical scientists. The chief benefits of this design process were that areas of overlap in teaching were identified, the curriculum became more integrated and the medical relevance of the material was enhanced.

Integration in the curriculum: Early clinical exposure was improved by increasing the number of patient presentations to about one per week. In these sessions, clinicians present patients or patient histories which help to maintain interest and integrate basic science and clinical information. Vertical integration was also increased by the creation of "academic half days", dealing with topics such as jaundice, hypertension or asthma. These occur in Phase III, as part of the clinical course. The sessions are often organised by groups of students and usually include presentations from both clinicians and basic scientists. It has proved difficult to introduce early exposure to bedside teaching, but the introduction of two weeks of community based study into Phase 1 has allowed students to gain an awareness of the health needs and social issues of the local communities from which the students' future patients will come.

Reduction of factual overload: In an attempt to reduce factual overload, lectures in Phase I were limited to ten per week and reduced to 45 minutes' duration, and there has been a uniform introduction of formal learning objectives for each lecture.

Encouraging learning skills: Active learning was encouraged by setting aside ten hours in each week's timetable for self-directed learning (SDL) exercises, performed as individual private study or as group study and linked to tutorial sessions. SDL exercises included the analysis of patient histories, computer based exercises, data handling, mini-projects, poster preparation, etc. These exercises were intended to increase student capacity for self-learning, critical and logical reasoning skills and to improve student participation in tutorial sessions. Critical and scientific thinking and in-depth study were also developed by the inclusion of a research project (in any area related to medicine) in Phase II, which also introduced a element of choice into the curriculum, adding to that provided by the clinical elective period. However, much remains to be done in developing a core plus options approach.

Improved assessment: The guiding principle here was to match assessment to style of teaching and learning. Thus, systems based courses are examined in collections of systems based papers and reliability has been increased by a shift away from essays to short answer and other forms of assessment. Where teaching uses particular techniques such as televisions for microanatomy, then assessment also uses televised material.

Dr McCrorie stressed that the key to successful reorganisation was to respond positively to the challenge. Interdisciplinary integration can generate new friendships and partnerships between departments, and students gain more enjoyment from a basic medical science course which is interesting and relevant.

An experiment in active learning

Dr McCrorie's session was followed by my own which was intended to highlight the differences in approach of a teacher oriented curriculum as opposed to a student oriented curriculum. Since I was concerned to advance a case for the merits of active learning, I attempted to avoid lecturing to the audience for the whole session; rather, I asked them actively to consider a number of issues in the hope that this would lead to my carefully prepared conclusions. This was the first time that I had tried to use active learning techniques with a non-student audience and I was surprised by how well it seemed to go. I began by asking colleagues to state characteristics of either "good" or "less good" students. This allowed me very quickly to develop the idea that "good students" have a deep approach to learning, are active and acquisitive about knowledge, seeking to extend and integrate knowledge and understanding as they learn. "Less good" students have a superficial approach, often resorting to rote learning and quickly forgetting information once the examinations are over. Students with the deep approach learn better and remember longer.

I then asked the group to describe the advantages and drawbacks of the use of research projects. It became clear that one of the reasons why many students perform so well in project work is that they are actively involved in the project and have responsibility for their own learning. Active participation in the learning process encourages the deep approach and results in better learning.

Active learning and participation can be introduced into almost every component of the curriculum. Practicals can be problem based, lectures can actively encourage student participation and students can be set challenging tasks for their private study time. Most importantly, the tutorial or seminar can be much more than a mini-lecture by the teacher and can provide opportunities for students to interact with each other and to demonstrate their learning. The benefits of active learning are not limited to better learning but communication skills and teamwork are also improved.

What is required to create more active and self-directed learning is not just the application of appropriate techniques (of which there are many) but also an acceptance by teachers that their role in education should shift from that of instructor to one of facilitator - from director to stage manager of the educational process. This helps students to develop the skills which allow them to take responsibility for their own learning.

Changes in North America

The final session of the afternoon was provided by Gordon Moore of Harvard Medical School. Professor Moore described two revolutions in the scientific culture affecting North American and other medical schools.

Separation of research and teaching: For many decades, medical schools have happily combined the roles of research institute and educational college; but nowadays much medical research, both clinical and basic science, requires expertise at the cellular and molecular level and academic staff have become increasingly specialised in these areas. This research revolution has resulted in a disjunction between the needs of the research enterprise - specialisation - and the needs of the teaching enterprise, where a broad general knowledge is most useful. Gordon pointed out that research in subjects such as anatomy has become so specialised that finding anatomists to teach classical anatomy in North America is virtually impossible.

Changing role of the teacher: The second revolution concerns the changing role of the teacher, as increasing interest in active learning processes requires teachers to become facilitators. Typically, the form of active learning being adopted by North American medical schools (Harvard included) is the problem based curriculum in which most if not all student learning is achieved through the study of patient histories and other problems.

A problem-based curriculum: At first sight, these two revolutions would seem to be incompatible with the dual roles of teaching and research within a traditional medical school. Professor Moore demonstrated, however, that the problems of the first revolution could be largely solved by the consequences of the second. His evidence comes from helping to organise the problem based curriculum which formed the New Pathway at Harvard Medical School. He found that student directed learning could well be an answer to increased specialisation in academic staff as well as countering student boredom and passivity. It also helps to solve problems of factual overload of the curriculum since students become experts at deciding how much they need to learn and what skills are required to learn it. The teaching method stresses independent study, so students spend relatively little time in tutorials with staff, allowing many staff to devote themselves to other activities. Since the tutors are intended to act as facilitators of student study and discussion, and not as sources of information, then it doesn't matter too much if tutors are specialists rather than generalists. Most interestingly, what seems to happen is that the tutors learn alongside the students and most have found the process very rewarding. Professor

Moore concludes, therefore, that one way to maintain strong research and teaching in a united institution is to adopt the techniques of student directed and problem based learning.

Impressions of the symposium: The whole afternoon was characterised by a high standard of observant and often witty discussion (very ably chaired by Tim Horder, Preclinical Dean at Oxford) and this was continued at a reception after the sessions. It was not expected that we would arrive at any consensus at the Meeting but it is interesting that the issues of active and student directed learning were features of all of the sessions. David Shaw, who is particularly concerned that there should be a good debate about the future of medical education, felt afterwards that the sessions and discussions were amongst the most animated and useful that he has attended.

The forum seems to have been judged as useful and successful and there is a feeling that similar events in the future would also be worthwhile. It remains only to thank Dr Michael Yudkin (Biochemistry, Oxford) for his help and support as co-organiser, the Biochemical Society for their efficient organisation of the Meeting and the education committees of the two societies who generously funded the event. The papers presented during the course of the afternoon will be published in the Biochemical Society Transactions.

John Patterson

Physiological Limitations of Human High Intensity Exercise

On Wednesday 16 December 1992, the day before the main Scientific Meeting, a Teaching Symposium was held on the Physiological Limitations of Human High Intensity Exercise. The Meeting was organised by David Jones, Duncan Turner and Ron Maughan and attracted an audience of over 200 Members, guests and visitors. There were three overseas speakers, Tony Sargeant from Amsterdam, Hans Hoppeler from Bern and Neils Secher from Copenhagen. The home speakers were Mary Neville from Loughborough; David Jones and Duncan Turner from UCL, London; and Brian Whipp from St George's, London.

Three of the speakers concentrated on maximum sprinting or cycling exercise in which power output falls rapidly to about 50% of the initial value by 30 seconds. Tony Sargeant discussed the contribution different muscle fibre types could make when exercising at different speeds with the interesting conclusion that even at the highest speeds the slow type 1 fibres can make a small but useful contribution. Mary Neville presented some of the work of herself and colleagues on the changes in muscle metabolites as revealed by heroic muscle biopsies taken before and after single and multiple bouts of sprinting. As lunch approached and spirits flagged, David Jones addressed the appropriate question of fatigue, asserting that the loss of power during sprinting was not the result of loss of central drive but could be ascribed to two factors in roughly equal part: loss of isometric force generating capacity and a slowing of the contractile processes.

Fortified by lunch the audience gamely fought to stay awake to hear Hans Hoppeler discuss the factors which limit oxygen uptake in the tissues, the capillary density, myoglobin and mitochondrial content of the muscle fibres. This was followed by Neils Secher, who was concerned mainly with the cardiovascular limitations but had an interesting diversion into the neural control of respiration describing experiments with partially curarised subjects who retained the function of the diaphragm and showed a phase 1 response to the start of imaginary exercise. For many years it has been part of the dogma of exercise physiology that the mechanics of the lung do not present any impediment to exercise. It was with great interest, therefore, that we heard from Brian Whipp that this is not necessarily true and that top athletes exercising maximally may be working very close to or at the limits of their flow-volume curves. Finally, it fell to Duncan Turner to point out that there are many different forms of exercise and that the limiting factors may well differ in each circumstance. He also briefly mentioned the effects of different types of training and the uncertain benefits of training at altitude.

The Symposium began at 10.00 am and finished just before 6.00 pm, a long day, and it says a lot for the speakers especially the latter speakers, that most of the audience stayed to the bitter end. In retrospect, the scope of the meeting was probably too large for anyone to take home a simple message but the variety of topics did have the advantage of introducing many people to new aspects of the field.

This was the second Teaching Symposium organised by the Human Physiology Interest Group; the previous one on Muscle Fatigue was held in Aberdeen nearly three years ago. The proceedings of the two symposia are currently being organised into a new Physiological Society study guide to be published by Portland Press towards the end of the year and it is hoped that the guide will prove valuable for anyone starting to take an interest in human exercise physiology.

David Jones

Designated Sessions at the Leeds Meeting

GI Tract Group:

Leeds was a relatively small Meeting but then the first week of a new term was always going to have an effect on attendance. Nevertheless, a Poster session on Thursday provided nine presentations and, despite the intervening dinner and its usual postprandial effect, the GI Designated Session on Friday was a lively affair. In addition, a number of GI related Communications were submitted for the Autonomic Nervous System Designated Session, illustrating the overlap in some aspects of the different Special Interest Groups. All in all the GI Tract made a significant contribution to the flavour of the Meeting. This was especially so since the 1992 GW Harris lecture was presented by Graham Dockray. Graham focused on the gut endocrine system and specifically demonstrated how he and his colleagues in Liverpool had dissected out the biochemical steps in gastrin synthesis. Also discussed was the control of gastric acid secretion by interactions between histamine and gastrin on the one hand and somatostatin on the other. This example provided insight into the gains to be achieved by the application of molecular probes to whole animal physiology.

The Designated Communication and Posters were a mixed bag and covered many aspects of GI function, including secretion, mobility and absorption, plus a few others. It would be

inappropriate to give details here. However, in answer to the questions relating to the two papers on lung which appeared in the GI session - no it was not a mistake by the Meetings Secretary and yes the absorption of dipeptides by the enterocyte and pneumocyte have much in common.

David Grundy

Comparative and Invertebrate Neuroscience Group

A select audience attended an interesting Designated Session of this Special Interest Group at the Leeds Meeting. Topics covered ranged from the mystery of "apoptosis" or programmed cell death in the thoracic eclosion muscles (used to escape from the pupal case) of the tsetse fly, through the use of fluorescent intracellular dyes to kill identified serotonergic neurones in the cerebral ganglia (or their axons) to investigate their role in the feeding pattern generator of the pond snail, to the effects of halothane on the postsynaptic actions of two neuropeptides common to mollusca and mammals. *Lymnaea* the pond snail also featured in the Demonstrations and Illustrated Communications, including a demonstration of a novel technique for monitoring animal movements without mechanical contact while simultaneously impaling selected neurones, to study their effects on the feeding CPG in a special chamber designed to maintain precise control of the water level during the addition of drugs. A simple computer program for analysing the shapes of action potentials was also demonstrated, using sample APs from physiologically characterised invertebrate neurones. Special thanks to Bill Winlow for his enthusiastic support of this successful session.

A short business Meeting was held after the morning's Communications to discuss ideas and plans for the future. Various suggestions were considered as to the possibility of a change of the group's title or even a merger with another groups, but in the event no particular changes in status or title met with general approval. Given the potential overlap of interests between the several "neuro-" Groups and the two "comparative" Groups, however, Professor Peter Usherwood's suggestion that the convenors of these groups should get together for discussions about their remit and plans for future Designated Sessions was seen as well worth promoting.

Current plans for the Group's activities in 1993 include a one day symposium on the "Comparative Physiology of Motor Control" at the IUPS Congress in Glasgow on Thursday 5 August. Abstracts for Posters whose subject material is related to this Group's interests will be scheduled appropriately. A joint Designated Session with the "Comparative Physiology" Special Interest Group is proposed for the Southampton Meeting on 27-29 September (deadline for abstracts: 9 July).

Finally, congratulations to Dr Catherine R McCrohan, who was elected as the new Convenor of this Group. Future communications about its activities should be addressed to her at the Department of Physiological Sciences, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT fax (061) 275 5600.

Brian Bush

Regulation of sodium pumps in animal cells

Report on a Symposium held at the St Andrews Meeting (June 1992)

This Meeting was organised by J F Lamb (St Andrews) to mark the twentieth anniversary of the first direct evidence for the regulation of sodium pump density by $[Na]_i$, work done in St Andrews. These early experiments followed on from flux measurements in human heart cells and were made possible by the availability of tritiated glycosides. These and later experiments showed that a rise in cell sodium lasting a few hours was sufficient to upregulate the density of sodium pumps in HeLa cells and Giraldi heart cells, and that both transcription and translation were required for this to occur. Since then, much evidence has accumulated about the efferent pathway for upregulation, but little work has been done on the afferent pathway. Most of the Meeting was devoted to the former.

Kathi Geering (Lausanne) and Alicia McDonough (USC, California) described their work on the regulation which occurs around the translational level. They showed that this regulation was both cell and ion specific, so that few general rules emerged. One which did was that either mRNA (α) or RNA (β) can be the limiting factor for the number of functional pumps formed. The α- or the β-subunits can be synthesised in excess, but when uncombined are labile and degraded. When they join up to form a pump this stabilised unit then moves to the plasma membrane. From the plasma membrane the pumps are internalised, as Cook showed some ten years ago.

Geering described the regulatory role of the β-subunit in *Xenopus* oocytes. The β-subunit exists in three forms: β_1 and β_2 in mammalian kidney and brain respectively and β_3 in oocytes. Previous suggestions for their function range from a sort of adhesion molecule to indirect modulation of pump activity. Geering showed that in oocytes the association of the labile α-subunits with a β_1 or β_3-subnit imposes a stable configuration on the α-subnit. This complex leaves the ER and expresses functional pumps in the plasma membrane. This post-transcriptional method of control seems to be important in the early development of *Xenopus* embryos. During early embryonic stages there is an excess of the α-subunit with low concentrations of β_3-subunit. At morula stage 6 polyadenylation of mRNA (β) increases as well as the concentration of β-subunit, followed by an upregulation of Na - K-ATPase activity. Geering suggested that the physiological significance of this is related to the need to change the isoform composition of the sodium pump form α_1-β_3 to α_1-β_1 to set up the first vectorial sodium transport system during blastocoele formation.

Mc Donough, in a lively account of her recent experiments on dissecting the control of pump synthesis at the ribosomal level, showed that ions have cell-specific effects on mRNA (α and β) and their corresponding subunits in cultured kidney (MDCK) cells and rat proximal tubules low $[K]_o$ which raises $[Na]_i$, increases mRNA and the subunit amounts for both α_1 and β_1. Clausen had shown that hypokalaemia *in vivo* reduced the concentration of Na - K-ATPase in skeletal muscle both in man and in rat; an effect which protects the plasma potassium concentration falling too far. Mc Donough now showed that this

effect in muscle and heart was on the α_2 subunit only, and not on the α_1 and β_1 subunits. It is known that a chronic high salt diet decreases renal NaCl reabsorption through a decrease in Na - K-ATPase activity in the renal cortex; McDonough now showed this occurred without any decrease in the α-subunit abundance, but there was a fall in β that paralleled the fall in Na - K-ATPase activity. So the concentrations of β may be a better predictor of functional sodium pumps in the kidney.

Torben Clausen (Aarhus) described early and recent work on the regulation of the Na-K pumps in skeletal muscle. The activity of the pumps can be increased by up to 120 % within minutes by insulin, catecholamines, and calcitonin gene related peptide (CGRP). These actions counteract the effects of exercise on releasing potassium from the muscle. So CGRP may be a local regulator of pump activity during exercise. During fasting, potassium deficiency, hypothyroidism, untreated diabetes, and following hypophysectomy, the concentration of Na-K pumps in muscle decreases. Muscle inactivity decreases and training increases the concentration of Na-K pumps in muscle. This may explain the observation that training reduces exercise-induced hyperkalaemia. Edelman had shown that the major factor regulating the concentration of sodium pumps in skeletal muscle was thyroid hormone. Clausen now showed that thyroid, both in rats and man, varied the pump concentration in muscle *in vivo* over the rage of 100-1000 pmol (g wet wt)$^{-1}$.

The later sessions, chaired by R Oliver (Dundee), were largely devoted to clinical aspects of sodium pump regulation. Erland Erdmann (Munich) described his work on the role of the sodium pump in the human heart. In the failing heart, cyclic AMP-dependent inotropic effects are reduced, possibly due to a decrease in the number of β-adrenoceptors, as well as a reduced concentration of cAMP. Erdmann concluded that the effects of cardiac glycosides are greater in the failing compared with the normal human heart, although the β-adrenoceptors are downregulated in the heart failure. The increased effectiveness may be due to a change in the receptor-effector coupling or to increased sensitivity to ionic changes. Another beneficial effect may be in enhancing contraction coupling or the handling of calcium.

Jeff Aronson (Oxford) described his group's work on the regulation of sodium pumps in human lymphocytes and EB-virus transformed lymphocytes. Transformation of normal lymphocytes leads to a 10- to 20-fold increase in the number of membrane sodium pumps to values of around half a million per cell, values similar to those in cultured human cells. The reasons and mechanism for this are unknown. In these cells, as in others, they found that treatment with low $[K]_o$ initially increases the V_{max} of Rb uptake. Over the next three days, the cells respond by also increasing the B_{max} of ouabain binding. Monensin treatment causes similar effects, consistent with the idea that the stimulus for upregulation is a rise in cell sodium. Similar experiments using Li to produce upregulation. An important observation was that there were differences in the pattern of upregulation due to lithium and low $[K]_o$, suggesting that these two stimuli mediated upregulation of the sodium pump by different mechanisms.

Kjell Kjeldsen (Copenhagen) described work testing the hypothesis proposed by Lamb that digitalis glycosides might increase the concentration of Na - K-ATPase enzyme in the plasma membrane of human myocardium, thereby reducing the inotropic effect of long-term digitalis therapy. Using samples of left ventricular myocardium from humans obtained post-mortem as well as during heart transplantation and tritiated glycoside binding his group found that patients who had been on long term digitalis therapy had around a third of their receptors occupied by glycoside. When this was washed off, the total pump density was significantly lower in the digitalised group as compared with controls. Skeletal muscle glycoside receptors were found to show changes that mirror those found in the heart. From this, they conclude that in human heart and skeletal muscle there is no evidence for upregulation above control level of digitalis glycoside receptor concentration and thus at receptor level no evidence for development of tolerance in response to long term digitalis therapy.

The Meeting was supported most generously by grants from The Physiological Society, the British Heart Foundation and Pfizer Central Research.

Joe Lamb

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FOCUS ON PHYSIOLOGY AND THE MEDIA

(Articles in this section were commissioned by Saffron Whitehead)

Hitting the Headlines (Science and the media)

Science and the media - so what? Sensationalism in the tabloids, misrepresentation or perfect documentation? To be precise, all of this and more. But, as physiologists, do you fear or love the media?

You may personally fear it because of a concern that all journalists are out for the spectacular story. For example, a physiologist may make a simple but astute observation. Disease X is linked with abnormal Y secretions. The media get hold of the story and to make it newsworthy it is packaged under the headline "Hope for X sufferers - new discoveries herald a cure". Scientific credibility may be discredited. One's mistrust of the media is confirmed.

On the other hand, most people love attention and it can be both flattering and irresistible if the press consider one's scientific endeavours to be of interest to a far wider audience than the reprint collectors, readers of dusty journals and members of obscure learned societies. So we may sit in a Catch-22 situation - wanting to feed the media while fearing their response and interpretation.

As a physiologist and a (very) part-time freelance journalist, I have seen both sides of the coin. The respectable media - and I emphasise respectable - want good, scientifically sound stories with a backdrop of general interest. A new discovery may make a subject newsworthy but a new discovery does not necessarily make news. For instance, you may have discovered a new potassium channel but if it can only be related, at the time, to the peristaltic function of the gut then it has little interest to the city commuter on Network South East. On the other hand, if you had discovered a relationship between a chloride channel and cystic fibrosis then the article could be written in the framework of the disease. A subject of much wider public interest than gut peristalsis, even though they both have a common theme of ion channels. Thus it is essential to be able to identify science that is newsworthy and of concern or curiosity to the general public.

At the same time as feeding editors with ideas (some will inevitably be rejected), journalists must seek out the people who can provide them with first hand knowledge of the facts surrounding the story. Scientists rarely refuse to impart their expertise - the compliment outwins any doubt or caution with which they view the media. But one of the real rifts between scientists and journalists comes in the definitive versus the tentative interpretation of results. Scientists love such terms as "this suggests that", "the results imply", "observations support" and "may have a physiological role". Phrases unacceptable to an editor of a newspaper. They want articles to be positive, no wishy washy if-ing and but-ing. Let's face it, a story. An up front problem, the background to the story, the new discovery and a positive conclusion. Scientists are always concerned that the more definitive approach to reporting will be viewed as false claims. Rightly so, but is press coverage better than none?

Unfortunately, not everyone's research is necessarily of media material, but there is a lot one could and should try to publicise. As scientists we will not get support from the general public unless we promote ourselves. One way is through the media. The days of closed intellectual ivory towers are gone.

And those fears of sensationalism are largely unfounded provided the right outlets are chosen. In my experience, most specialised science and health editors or correspondents are extremely perceptive and scientifically literate people. Even if they don't have a string of letters after their name (many do), they know their job and responsibility towards correct and accurate reporting to the general public.

A few scientists actively seek media coverage. Others may live in hope. Most agree that science is poorly represented in the media. Most of us do nothing about it. So, we have asked scientists with media experience, public relations officers who try and bridge the gaps and those who translate science into news to give us their views, their advice and their expertise.

In this issue of the *Magazine* Colin Blakemore shares his experiences in dealing with the media; and Barbara Davies, the Public Relations Manager of the Research Defence Society, explains the ways in which physiologists can channel their work into the public eye. Geoff Watts from BBC Radio 4 tells us how scientists are indoctrinated by the tyranny of the scientific paper; and finally we present an example of how an abstract of scientific work can be re-written so as to make it more accessible to a wider audience. In the next issue of the *Magazine* Pat McCarthy from the Public Relations Unit of the University of London gives a DOs and DON'Ts guide to interviews with the media, Nigel Williams, former Science Editor of *The Guardian*, airs his views on science reporting and there will be two articles about COPUS - the Committee on the Public Understanding of Science.

In this series of commentaries you will find much common ground but to bring home the salient messages there has been no major editing of the submissions. That being said, we thank everyone for their contributions and hope that the articles may prompt some readers to launch their science toward the media as well as the scientific journals.

Saffron Whitehead

Learning to live with the media

As they are inexorably emasculated by Her Majesty's government in the name of competition and accountability, the positive features of the post-war reform of British universities become ever clearer - decent student grants, the dual-support system, concern for the standards of teaching, adequate provision for research. But the respect for academic values that underpinned the policies of the 1950s and 1960s created one unfortunate sequela: science became too remote, unwilling to communicate its aims and achievements to ordinary people. The independence and freedom that we gained encouraged us to believe that our own peers are the only audience worth addressing.

Our self-isolation has stirred suspicions and resentments about science among ordinary people and politicians (who, in the end, pay for the science that we do). Although the rewards for being willing to talk and explain science to non-scientists are not as immediate as publishing a research paper or securing a grant, they are ultimately as important for the good of science as a whole.

The undeniable success of the anti-vivisectionist movement over the past 20 years is a vivid example of the consequences of academic disdain of public scrutiny. Its progress, despite the weakness of its case, is undoubtedly due in part to the failure of the academic community to think the distortions and misrepresentations worthy of open response. The criminal fringe who resort to bombs and burning and to the "liberation" of laboratory animals are a source of emotional agony and fear to researchers and their institutions. But the greatest threat to research comes from the possibility that the propaganda of this vociferous movement will capture the mood of public opinion, which will then work its democratic magic on the policies of political parties and, through the ballot box, convert the will of a lobbying minority into restrictive legislation. The fight for public support is crucial.

The animal rights issue is the tip of an iceberg of anti-science. In my view, this kind of challenge to science is born out of the scientific ignorance of most of the public, who recognise that science is powerful but who, because they don't understand it, are afraid of it and are easily convinced that all the woes of the world are the products of the unfettered application of science. We shall not dispel such fears by remaining aloof from communication and debate. We have an obligation to respond to the legitimate demands for information and explanation from the public that supports science through its taxes, its purchases and its donations.

Between those who oppose science and the public stand the media. Between the scientists and the public stand the media. If we are to succeed in the defence of our reputation and our right to continue, we must deal effectively with the media.

Not everyone has the inclination to broadcast, write for the press or work with the media. But any scientist should at least be ready and able to give a straightforward account of his or her research in ordinary language. The ability to communicate simply and effectively is surely one of the most valuable lessons that we should learn as we struggle to defend science, the universities and the need for animal experimentation. That means learning the conventions of mass communication and respecting the rights, needs and priorities of the media.

Some suggestions

Dealing with the media involves certain conventions and some simple skills. First a few suggestions for talking or writing about science.

Keep it simple; keep it short

Wasn't it Einstein who said that everything should be made as simple as possible - but no simpler! You must respect the intelligence but the inevitable ignorance of your audience. As you write or speak, ask yourself constantly whether your words would be understood by some sensible but non-scientific colleague or relative.

No compromises. If you can't explain some erudite point concisely, don't try. Just bridge the gap in your argument with a joke about the complexities of science or an appeal to the need for brevity. Metaphors, particularly humorous ones, can be very helpful when describing abstruse facts or mechanisms. So too are references to the relevance of science to normal life. Even quantum mechanics, superconductivity and the sodium pump have everyday consequences.

Any radio or television producer will tell you in his or her more candid moments that audiences remember no more than two or three facts from any programme - even a substantial and well-planned documentary such as *Horizon*. What viewers and listeners do remember is enthusiasm and the sense of commitment. Nothing kills a piece of science broadcasting or journalism more completely than infectious boredom. If you don't look and sound excited by your research you can't blame your audience for thinking it dull. Never forget that the primary objective of public broadcasting is to entertain, not to teach or intimidate.

Respect the media; expect them to respect you

Most people confronted by an enquiry from the media but unfamiliar with their methods suspect that their intention is always to trap their victims and distort their opinions. This kind of misrepresentation does occur, but in my experience it is often as much a product of suspicious or uncooperative behaviour by the interviewee as of malicious intent by the interviewer. You cannot expect to be treated well by the media if you are arrogant to them, refuse to make yourself available to them or show yourself unable or unwilling to respond honestly to their questions.

There is no doubt that the best possible way to deal with the media is to gain their trust before any problem arises. In my experience, newspapers and broadcasters are delighted, even flattered, to be approached by active scientists. Try to make contact with your local newspaper and radio station. Let them know that you are willing to advise or comment on issues relating to your area of science. Go and visit them and get to know their staff personally.

You should try to learn about the methods and needs of the media - not only how to use a microphone or look at a camera, but how to answer questions succinctly and incisively. The techniques of modern broadcasting, for instance, demand that most recorded comments during news bulletins last no longer than about 40 seconds. Successful politicians have to master the art of the "sound bite" and so does anyone else who wishes to utilise the media to his or her advantage. Never lose your temper, even if you are subjected to outrageous abuse. Nothing is more convincing to the audience than someone who stays calm and honest in the face of vilification.

You must respect the absolute deadlines to which the media are chained. Daily newspapers and news broadcasts in particular operate to precise time schedules. If you promise a written contribution or an interview to the media, you must understand these time constraints and be willing to work within them. Also, be prepared to spend sufficient time to do justice to your views and to the professional standards of the media. A few lines in a newspaper article or a few seconds in a television news programme may need hours of preliminary discussion and recording.

On the other hand, you have every right to expect the media to respect you. If you find yourself being harangued or manipulated during an interview, simply complain calmly while the tape recorder or camera is operating. If you feel that you have not answered a question properly or that the direction of an interview or discussion is going in an inappropriate, misleading direction, you should also feel free to say so directly, to ask for the recording to be stopped and to discuss the problem "off the record" before resuming. Don't be afraid to direct the conversation in the direction that you wish it to take.

As a voluntary contributor, you always have the right to ask to inspect any article or broadcast (or at least your quotations or contributions) before it is released and to have your contribution excised or modified if you are not satisfied with the way you have been treated. Your interviewer or producer may object, on the grounds of editorial freedom or time constraints; but the fact is that you can always refuse to contribute unless you are given this privilege, if you feel that it is important. However, you should insist on this arrangement only if you are genuinely worried about the possibility of misrepresentation; and you should not ask for trivial changes in the final material. If you wish to ask for this right, you must do so before you arrange to be interviewed, not after the event. Many journalists will actually welcome an offer from you to look over an article in draft form so as to pick up any factual errors. Remember that you must respond quickly when given this opportunity because of the inevitable deadlines.

The techniques, rights and rules for live broadcasting are, of course, rather different from those for written articles and recorded broadcasts. But the general advice to keep your temper, to be willing to admit ignorance and to challenge the qualifications of your opponents (see below) still apply.

Be prepared

Unfortunately, encounters with the media are sometimes hostile. You may find yourself called to account for the financial cost of your area of research or to say why Britain shouldn't leave research to richer and more profligate nations. And you may find yourself defending animal experimentation, perhaps even as the victim of an anti-vivisectionist campaign.

If you face a personal campaign, or a reporter's interrogation, it may come with little warning. It is essential to have your knowledge and your arguments rehearsed in advance. Even more important, any scientist who uses animals should be secure in his or her own moral position. If you cannot defend your research to yourself, you will not be able to justify it to others. If you supervise the research of students and technicians, you have a responsibility to make them aware not only of the specific issue of animal use but also of their essential role as servants of society. Ask them to be prepared, at any time, to give a brief account in simple language of what they are doing and why. Practise such presentations together in laboratory meetings.

Always be absolutely honest

If media people are good at anything it is smelling a rat. If you avoid questions or are shifty in your replies, you will suffer the same fate as politicians or criminals who behave that way: the media will hound you. No-one should be doing research that they are embarrassed to describe to an ordinary person. Unless you literally have something to hide, you must be prepared to respond to questions about your own work. You must, of course, be aware of the sensitivities of a mass audience. They will not know technical jargon; they will not take for granted the importance of basic research; they will be shocked by tactless description of experimental methods (just as they are shocked by the reality of what goes on in a hospital operating theatre). Keep all these things in mind as you consider how you would describe your work to others.

Honesty extends to admitting ignorance. Don't be tempted to range beyond your areas of knowledge and authority and hence to be trapped into defending work that you know little about. By all means try to inform yourself about other areas of research and about the general issues that are likely to be raised in an interview. If the discussion is about animal experimentation the excellent literature distributed by the Research Defence Society, and by other organizations that the RDS can put you in touch with, can help enormously. If you don't know about a particular topic or don't feel qualified to comment on it, say so. But don't be so cautious and narrow that you end up sounding ignorant or critical of everyone's work but your own.

Be careful to state where your opinion is given as an expert in a particular field and where (if you give it) it is given as a layman. (As an exercise in defining this distinction, imagine how you would respond to questions about cosmetics testing, research on pain in animals, blood sports, zoos and modern intensive techniques for farm animal husbandry).

The need for honesty also extends to the way in which you treat your opponents. Much as they may infuriate and frustrate you, you will gain nothing (except perhaps a summons for defamation) if you make false or exaggerated statements about them or their views. Inform yourself about the laws of libel and slander, in case you find yourself grossly defamed, and don't be afraid to criticise distortion or lies.

Don't be afraid to invoke authority

While modesty is a quality attractive to the media and mass audiences, don't feel forced to be deferential to either reporters or critics of your work. If discussion becomes a matter of simple opposed assertions, don't hesitate to question the authority of your opponent. Ask what training they have in science and particularly what experience and knowledge they have of modern biology. If the discussion concerns animal experimentation, point out the stature of the groups and individuals who have supported public declarations on research involving animals: the British Association Declaration on Animals in Medical Research has been signed by 1000 Professors of Science and Medicine, by 31 Nobel Prize Winners and on behalf of all the Royal Medical Colleges.

Most of all, enjoy yourself. Despite some horrific encounters and some dirty tricks, I have found contact with the media, on balance, a pleasant and stimulating experience. Some of the brightest people I know work in the media and most have pride in their work and a sense of creation just as strong as those of

academic scientists. They have an important job to do and, if we co-operate with them and respect their needs, they will be the best allies we could have.

Colin Blakemore

Some sections of this article are taken from "Neuroscience and the media: the need for communication" *Neuroscience* 1993 (in press).

Getting Media Coverage

Does science get a good press? Yes and no. Some popular reporting of science is good, sensible, straightforward stuff, perhaps with added human interest or a topical angle. But the media thrives on scandal, sensation and, more than anything, bad news. A whiff of controversy about any scientific topic will thus be grasped with glee by journalists. The more sensational reports are invariably written by an ordinary news reporter and the shock horror headline is thought up by a sub editor: they may not even have a science "O" level between them. The original source of the story is often not scientists themselves, but a person or group with an opposing vested interest, perhaps a disaffected employee or a pressure group.

The result, it seems, is a backlash against science. Abandon science and return to nature, these stories tell us, and the world will be a healthier place. After all, was it not chemists who gave us pollution, physicists who produced the nuclear bomb, don't biologists torture animals, and why haven't the medics found a cure for cancer? This anti-science feeling has recently been raised to a slightly more intellectual level with the publication of a couple of books which claim that science somehow damages our spirituality and humanity. This is the "science versus religion" debate in a new virulent form.

So how can scientists or, more particularly, physiologists work with the media to improve the public understanding of science? How can we slow the "science as scapegoat" bandwagon and increase the good, informed reporting of scientific issues? Journalists are not anti-science or scientists, they just know what makes a good story: usually bad news. But surveys show that the public is interested in science, so it should be possible, through the media, to excite people about a new advance in physiology or medicine, a line of research related to a topical issue, even the opening of a new research laboratory.

Of course there are many different types of media, from *The Sun* to *New Scientist*, from *The Big Breakfast* to *Horizon* or *Science Now*. It helps if you know how they approach their subject matter - by reading the newspapers, listening to news and current affairs programmes, watching *Equinox* and *Tomorrow's World*. You have to put yourself in their shoes and ask why their readers, listeners or viewers would be interested, why your subject is important, whether it is topical, whether you are prepared to be challenged if it is controversial.

Let's take a hypothetical case. Your paper on the action of specific monoclonal antibodies against T-lymphocytes in chronic relapsing experimental allergic encephalomyelitis is to be published in a fortnight in *The Journal of Physiology*. You believe that journalists will find this work is newsworthy: it holds promise for an effective treatment for multiple sclerosis before the end of the century. What can you do to achieve wider publicity? You could of course sit back in the belief that a perceptive newspaper journalist will pick up *The Journal of Physiology* in two weeks' time, read your paper and realise how significant your work could be for sufferers of multiple sclerosis.

You would be disappointed. Journalists, even science and medical correspondents, work to tight deadlines (they are forever lecturing PR executives about how busy they are). They do not have time to read the scientific literature and, being generalists, they are unlikely to pick out significant research papers by scanning their titles. Your work will not get publicity just because it deserves it. You have to help.

Whether you are communicating with *The Sun* or with *New Scientist*, there are a few basic factors to bear in mind. With very rare exceptions, news items are written by journalists on the magazine, paper or programme. Longer features are often by freelance contributors and most publications have their favourite freelancers - you will see their byline perhaps once a month. So you will have to rely on a journalist to write about your *The Journal of Physiology* paper and to get the facts and implications right. It will help if you start by writing a short, simple summary of your work and its significance for MS patients. This needs to be about 400-500 words, written in the style of a news item. It should begin by encapsulating the main features, in other words it should begin with the conclusion. Tell the story using simple words (no jargon, but try not to patronise) and short sentences. When you think you have succeeded, test it on a 14 year old and then start again.

This short, simple summary is the basis of the press release, but it is also useful because you have now clarified the most effective way, in your view, of presenting this story in a "user friendly" way to the general public.

So you now have ten days before your paper is due out in *The Journal of Physiology*. What is your next step? You are based at Hatch End University, your work is funded by ARMS (Action for Research for Multiple Sclerosis) and SMERC (Science, Medical and Engineering Research Council). You are a Member of The Physiological Society and the Research Defence Society. At least one of these organisations will have a publicity department and you should now contact them. Your PR or information expert will have the benefit of your summary written in jargon-free language and will be able to assess its news potential. Take their advice. If they think your story looks promising you will be able to work together to try to get news coverage.

Various questions arise at this stage. Timing is important. Ideally, you should release the news to coincide with the publication of your research paper in *The Journal of Physiology*. This means informing the newspapers one or two days in advance of the *Journal*'s publication date, but placing an embargo on the story so it does not appear before the *Journal*. Apart from *The Journal of Physiology*'s publication date, have you considered other events? There is little point in releasing your story to the press if there are other events of scientific or medical importance which will take precedence. You may not have much control here: if a major teaching hospital announces its closure on the same day, then say goodbye to any news coverage of your research. But some events are known about well in advance. If your research paper is published during the week of the British Association Science Festival, all the journalists you want to contact will be busy covering the BA. You will have to think again about timing.

What is the best way of releasing the news? A press release can work well if it is short, well written, has an informative title (no need to attempt headline style - the newspaper sub editors always write their own headlines) and a name and telephone number to contact for further information. You could invite journalists to a press conference, but remember how busy the journalists are - they need to believe this is a story of some significance if they are going to attend.

Have you thought about pictures? Can you find an MS patient who would be willing to be photographed by newspaper photographers? A good picture will add human interest and may even help to get the story into the newspaper. Pictorial interest is essential for television coverage.

Last but not least is the question of targeting. Many people are surprised to discover that journalists working for the same paper do not talk to each other. Do not address your press release or press conference invitation to the editor hoping that it will be passed around until it reaches the appropriate journalist. Your research is of interest to science and/or medical correspondents. Send them each a copy and address it to them by name. Don't forget the Press Association, a particularly valuable source of copy for the regional dailies.

All these questions should be settled by about a week before the publication of your paper in *The Journal of Physiology*. In another couple of days, your press release or press invitation will have been polished, you will have a list of journalists' names and addresses. The journalists will want all the information the day before *The Journal of Physiology*'s publication date, so that their news item can be published on the same day.

There is no guarantee that your story will appear in the newspapers. Space is tight and there are competing stories. If it does appear, do not expect it to be in exactly the same form as written in the press release. It will certainly be edited in some way: it may be completely rewritten, it can be shortened or it can be commented on by other experts in your field. Many journalists have favoured experts whom they contact to find out if a potential story is as significant as the source claims: this is one reason why you should not use hype. The journalist may contact you for further information, to check a particular fact or for a direct quotation. You should be prepared and available.

So the Queen abdicated and there was no coverage of your story. All is not lost. There are other routes which you can follow up with your PR adviser. What about the next *New Scientist*, the next *Science Now* or *Tomorrow's World* programme? Perhaps you can interest a freelance journalist in a feature article for a

PRESS RELEASE
EMBARGO UNTIL 00.01 HRS 7 DECEMBER 1992

"EPIC" WINS TOP BIOLOGY TEACHING AWARD

The 1992 Glaxo Prize for Biology for Pharmacology and Medicine is awarded to Dr R H S Carpenter for development of EPIC Experimental Physiology Instrumentation Computer.

The Glaxo Prize is one of the fourth annual Partnership Awards, a prestigious national event designed to promote and reward innovation and creativity among teachers of Higher Education (HE). The awards are organised by the educational charity The Partnership Trust, and are all sponsored by major companies. Speaker at the winners' reception will be Sir Ron Dearing, Chairman of the HE Council for England.

In awarding the Glaxo Prize, the assessors looked for innovative teaching methods which meet the need for more efficient and effective learning in the biological sciences, and for well organised interaction with industry which helps to reflect the rapidly changing body of content and technique.

EPIC has been developed by Dr Carpenter of the Physiological Laboratory Cambridge University in close conjunction with Cambridge Research Systems Ltd, a company specialising in high-technology computerised solutions for the biosciences.

EPIC provides not only data acquisition and stimulation but also versatile data display, analysis and storage, and performs a wide range of experiments in human physiology, pharmacology, zoology and related subjects. On-screen laboratory notes guide the student, and software options which are not relevant to the current experiment are hidden, ensuring that the technology enhances rather than distracts from understanding of biological principles.

Commenting on the award, the assessors said: "EPIC"... replaces the traditional labour-intensive methods of recording information from physiological preparations... It allows the student to carry out physiological experiments and develop manipulative and analytical skills... It allows a greater degree of independence and thus reduces the supervision required during practical classes."

EPIC is now in its second year of use with undergraduates at the Physiological Laboratory, where it has been received with acclaim by both teaching staff and students. Several other UK universities have already installed EPIC, and Dr Carpenter and Cambridge Research Systems are committed to continued development of the system in line with the needs of the academic community.

For further information, please contact: Carol Luscombe, Manager, Bioscience Division, Cambridge Research Systems Ltd, 80 Riverside Estate, Sir Thomas Longley Road, Rochester, Kent ME2 4BH, tel: (0632) 720707; fax (0634) 720719.

Note to Editors:

The annual Partnership Awards identify examples of innovation and development throughout higher education. They cover a wide range of academic disciplines and each is sponsored by a major UK company. In 1992, twenty-two separate awards will be made. The reception for the winners will be held at the Institute of Directors on 7 December 1992 and will be attended by company heads and leading figures from education and industry. The speaker will be Sir Ron Dearing, Chairman of the HE Council for England.

newspaper or magazine. Perhaps you can find a topical angle during a slack period for news, such as Christmas or the summer parliamentary recess.

Successful or not on this occasion, your effort to communicate your research to a wider public has probably been a stimulating experience. You may want to do more, and there are a variety of options open to you. As reported in the July 92 issue of the Physiological Society Newsletter, the Committee on the Public Understanding of Science (COPUS) is considering setting up a media resource service, comprising a database of scientists in all disciplines willing to talk to journalists. You could perhaps join a school speakers' scheme such as *Talking Point*, or volunteer your services to talk to other groups such as Women's Institutes, Rotary Clubs etc. COPUS also invites applications for Media Fellowships which allow scientists to take up secondments in the print or broadcast media.

A Royal Society report in 1985 said, "It is clearly part of each scientist's professional responsibility to promote the public understanding of science". This responsibility must include bringing the same professional attitudes to communicating science as the scientist brings to science itself.

Barbara Davies
(Research Defence Society)

The Tyranny of the Scientific Paper

Some thoughts on science broadcasting. So, how should I begin...?

"A request was received asking for a contribution to The Physiological Society Magazine. It was considered, and a positive conclusion was reached. The Editor was phoned and advised of this decision."

In truth, if I were to begin like this, and then continue in the same vein, I doubt that anyone would read far beyond those three sentences. So, an alternative: *"The Editor asked me to contribute to The Physiological Society Magazine. I thought about it, decided I would, and phoned to say so."* Much better. But what point am I trying to make? After all, you may say, nobody would actually write in the way I phrased that first version; and certainly nobody would speak like that...

No? Well, perhaps this will seem more familiar: *"The cells were placed in the test tube. Three mls of the first solution were placed in the test tube. Three mls of the first solution were added, and the tube was shaken briskly. A distinct colour change was then observed."*

But people - scientists - don't speak like that, you may insist. Well, after some 15 years spent listening to them through the microphone, I'm here to assure you that they do. Not when talking about the weather, or last weekend's golf, or the price of tomatoes; just when they're talking about science. This bizarre syntax, this sterile, mind-numbing use of the passive voice is the bane of my life as a broadcaster.

It was Peter Medawar who pointed out that the scientific paper, with its neatly compartmentalised sections on "method", "results", "discussion" and the rest of them, is a fraud. The practice of science, he argued, is altogether less tidy, less systematic that the published paper would suggest. The conventions by which scientists report their work to each other may or may not be sensible; that is not my concern. What upsets me is the tyrannical grasp in which the scientific paper continues to hold so many scientists when they are trying to communicate not with their peers, but with an audience unaccustomed to the ways of academics. Such stilted expression renders even simple procedures or ideas harder to follow or, worse, incomprehensible.

This may be the most trying fault of scientists as broadcasters but it is not, I fear, their only one. Another is their too frequent failure to consider the nature of the audience, and the purpose for which they are talking or being interviewed. They are not supposed to be speaking to their fellow scientists; the undotted scientific "i" and the uncrossed technical "t" are of no consequence provided the central ideas and essential caveats are put across. What Dr Snooks in the next lab would like to hear doesn't matter; other channels of communication exist to keep Dr Snooks informed.

Nor does simplification spell automatic trivialisation. To simplify is to isolate and express the essence of an idea or a new development. In writing a report for *Nature* or *The Lancet*, you are writing for a readership who need enough detail to be able to replicate the work for themselves. Radio 4 listeners have no wish to test your methods; excessive detail is merely a distraction from the main thrust of what is being said.

Science is always cautious, provisional, reluctant to claim more than can be demonstrated. Good science broadcasting can and should reflect these virtues. But there is no need to make a meal of it. Small but useful words such as "might", "maybe", "perhaps", and "could" serve quite well to indicate that what is being talked of shouldn't (yet) be taken as ultimate truth.

And then - the biggest problem because it's an unavoidable one - there's terminology. There is no need to say "thorax" when "chest" would do; or "femur" when you could say "thigh bone". A mitochondrion, on the other hand, is a mitochondrion; there is no everyday term for it. So if you really need to refer to this organelle, do so. But then add a quick explanation; something simple and memorable - powerhouse of the cell, source of energy for the cell, or whatever.

Finally, don't go to the other extreme and start displaying what I call the "germs and tummy" syndrome. If you mean bacteria or viruses, say so. These words are not unfamiliar, and to talk all the time of "germs" is to patronise the audience. This is among the worst of all crimes. The BBC Radio Science Unit has occasionally received letters from Radio 3 listeners who feel cheated if they can understand every portion of the programmes they hear. They reason, so far as I can tell, that if as lay people they can grasp everything said by the scientists they're listening to, then they can't be hearing about work at the cutting edge of science. Such work, almost by definition, wouldn't be comprehensible - or so they believe.

Obviously, nobody wants to be utterly at sea; but for some listeners, apparently, to feel that the discussion is sometimes drifting a little beyond their grasp is somehow flattering! No-one ever, on the other hand, finds it flattering to be patronised.

Geoff Watts
(Presenter of "Medicine Now", BBC Radio 4)

1) The abstract of this year's Wellcome Prize Lecture written for an audience of physiologists

Rods and cones, the light sensitive photoreceptors of the vertebrate retina, are well known to adjust their sensitivity in response to changes in steady light intensity, a process known as light adaptation. As the steady light intensity increases, the response to a dim flash of light becomes both smaller and faster as the cell adapts. Such light adaptation is important in ensuring that photoreceptors can operate over a wide range of light intensities. In addition, exposure of a photoreceptor to very bright light results in a profound decrease in sensitivity and speeding of the response which persists thereafter in darkness, an effect known as bleaching adaptation.

In recent years several lines of evidence from a number of laboratories have shown that the concentration of calcium ions within the photoreceptor cytoplasm plays a crucial role in light adaptation. Cytoplasmic calcium concentration is known to be controlled by a balance between the rates at which calcium ions enter and leave the photoreceptor. In darkness, a steady ionic current, partly carried by calcium ions, flows into the photoreceptor across the membrane of the outer segment, the region of the cell specialised to respond to light. These calcium ions which enter the cell are pumped out again, resulting in a stable concentration of calcium within the cell in darkness. Photoreceptors respond to light with a decrease in this inward-flowing current, thereby reducing the rate at which calcium ions enter. But calcium continues for a time to be pumped out, and so the cytoplasmic calcium concentration falls during illumination.

The role of this light-induced fall in calcium concentration has been studied by attempting to stop it from taking place and examining the effect on the electrical response of the photoreceptor to light. If changes in calcium concentration are opposed by incorporating into the photoreceptor cytoplasm a substance which binds calcium, and thus acts as a calcium "buffer", then the onset of light adaptation is slowed also. If the light induced fall in calcium concentration is prevented altogether by using external solution changes to abolish simultaneously both calcium influx and efflux, thereby disabling the mechanism which normally controls cytoplasmic calcium concentration, then all the manifestations of light adaptation are abolished, and the photoreceptor responds over only a very narrow range of light intensities. Such changes in cytoplasmic calcium concentration therefore appear to be necessary for light adaptation to take place. Furthermore, if the cytoplasmic calcium concentration is artifically reduced in darkness then at least some of the manifestations of light adaptation result. These adaptational effects are quantitatively very similar to those that would be produced by light itself, suggesting that changes in calcium concentration are sufficient to cause light adaptation in the absence of light. In addition, recent evidence shows that changes in calcium concentration are important in regulating the light response during the bleaching adaptation which follows exposure to very intense light. Calcium is believed to cause these effects by modulating the biochemical processes which lead to the electrical response to light. Calcium therefore appears to function as the messenger of light adaptation in vertebrate photoreceptors.

Hugh Matthews

2) Initial translation for a wider audience

Calcium sheds new light on adaptation.

Go from a dark dungeon into bright sunlight and there is a temporary loss of vision. The same happens when one goes into the dark room. But soon the eye adapts and we are not blinded by bright sunlight and can see even at very low light intensities.

The ability of the vertebrate retina to operate over a very wide range of light intensities results in part because the light sensitive photoreceptors - the rods and cones - undergo a process known as light adaptation. In other words, they can adjust their sensitivity, or the gain of the transduction process, in response to changes in steady light intensity. Without this adaptation the rods and cones can only respond within a relatively small range of light intensities.

But what is the mechanism that enables this process to occur within the rods and cones? Research from several laboratories over the last few years has begun to shed light on this question and it looks as though calcium plays a critical role.

In the darkness there is a steady inward ionic current, partly carried by calcium ions, which flows across the membrane of the outer (photosensitive) segment of the receptor. As calcium enters it is pumped back out again and in this way the levels of cytoplasmic calcium remain stable. However, when the photoreceptors are stimulated by light, the levels of calcium in the receptor begin to fall. This is because the light has reduced the inward calcium current but the pump continues for a while to push out the intracellular calcium.

Now the link between calcium and light adaptation has been made by investigating the electrical responses of photoreceptors which have been treated with drugs to reduce or block changes in the cytoplasmic calcium concentration.

When a substance which binds calcium, and thus acts as a calcium buffer, is incorporated into photoreceptors, the onset of light adaptation is slowed. More dramatic is the complete abolition of the light adaptation response when both calcium influx and efflux are blocked - the two mechanisms which together cause the fall in calcium concentration in response to light. Under these circumstances photoreceptors are still responsive but only in a narrow range of light intensities. For the final twist in the story, adaptation-like responses can be induced in photoreceptors simply by artificially reducing the cytoplasmic calcium concentration - no light stimulation is required.

More recently bleaching adaptation has also been shown to involve calcium. This effect occurs after exposure to very bright light, and causes a profound drop in the sensitivity of the photoreceptors and a speeding of their responses to light. However, when changes in calcium concentration are prevented, this effect of bleaching on the response is abolished.

Thus changes in cytoplasmic calcium concentration in the photoreceptor are an essential part of light adaptation. Calcium is believed to cause these effects by influencing the biochemical mechanisms which lead to the electrical response to light. It thereby appears to function as the messenger of light adaptation in vertebrate photoreceptors.

Hugh Matthews and Saffron Whitehead

The Wellcome Centre for Medical Science

"Medical research is going through its most exciting time right now" said Sir David Weatherall[1] opening the new Wellcome Centre for Medical Science on 25 November 1992. "And in the next 10-20 years there will be some of the most important developments in the medical sciences that have ever happened. But those developments are complex and some of them have quite serious ethical issues that we have all got to face and what we have got to do is open up a debate with society about how far we want to go. If you want to encapsulate in a simple phrase what the Wellcome Centre is all about it is simply to form links between what is going on in medicine, basic medical research, the press and the public. What are the doctors doing? Where is basic medical research taking us? There are such enormous possibilities in the medical sciences now that we would dearly love to show the excitement of this field to young people. Not necessarily people who are going to be doctors, as biomedical research now covers every aspect of human biology. There is even more to it than that. As well as trying to build up this link with the public we want to teach ourselves, the scientists, how to communicate".

These comments nicely emphasise two of the main aims of the Wellcome Trust's new initiative. The Trust's increased importance on the national scene has led it to recognise a responsibility beyond funding research - a need to alter public opinion towards a more positive attitude to biomedical science and to encourage bright youngsters to think about the possibility of studying science, especially biological science a bit longer. To university perhaps? Or even to undertake research?

An increasingly negative image for science, and national trends in university entrance away from science in general, led the Trust to establish the Centre to help counter these threats to science and indeed in the long run to the well-being of society itself.

The Wellcome Centre comprises several components, the main ones of which are: *Science for Life*, a permanent exhibition explaining the nature of biomedical research; a Scientific Meetings Programme; an Information Service, a Medical Photographic Library; and a Science Policy Research Unit (PRISM, Policy Research in Science and Medicine). I will deal briefly with the first three of these. Future articles will cover other aspects of the Wellcome Centre.

The Science for Life Exhibition

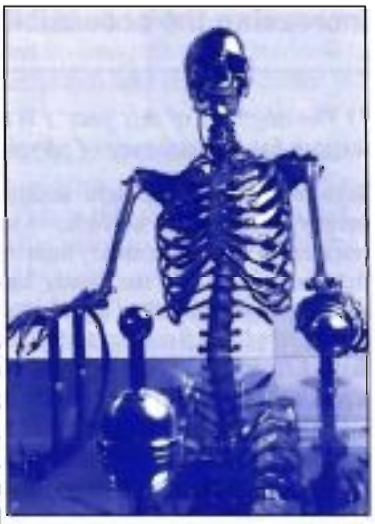
Science for Life is both an explanation and a cele-bration of biomedical science: an exploration of the process as well as the product of research. Designed for educated adults without knowledge of biology and for senior school pupils, it equally seems to entrance those in preceding and succeeding decades (8 to 80 seems to have become the slogan).

Science for Life occupies the east half of the upper ground floor of the

Wellcome Building, some 770 square metres in all (about five times the surface area of the alveoli of the lungs for those of you who have difficulty with these things).

[1] President of the British Association for the Advancement of Science, Regius Professor of Medicine in Oxford and Governor of the Wellcome Trust

A highly interactive area first introduces the visitor to study the structure and function of the human body leading to a section on microscopy using real specimens of normal and diseased tissues. This serves as an introduction to the centre-piece of the exhibition - a giant walk-through cell magnified about a million times. Have you ever wondered what endocytosis and lysosomal digestion sound like? Jim Watson loved it. Lewis Wolpert hated it. Come and find out what you think!



Interactive exhibit from the "Science for Life" exhibition. Photographs courtesy of The Wellcome Trust

The stereotype of the scientist is challenged in a section on the nature of scientific discovery. Visitor becomes scientist using a computer to investigate the cause of a mysterious new disease "green-spot disease". Major achievements in medical science form the scientific meat of the exhibition and repay careful scrutiny. And finally there is a section on funding.

The importance of basic research is emphasised throughout the exhibition and we have attempted to use simple, unpatronising language. The exhibition was designed for educated adults without knowledge of biology and for senior school pupils. An education section coordinates school visits and is attempting to develop an unusual feature - a small laboratory where booked groups can undertake experiments. DNA fingerprinting is already in place and we are in discussion with the Society's Education and Information Sub-Committee with the aim of incorporating a suite of physiological experiments.

Reviews by the press and public have been very positive; to quote Jon Turney in the THES, the exhibition "offer[s] a rare combination of intellectual and aesthetic satisfactions, in a "hands on" setting with a more serious flavour than many of the less ambitious science centres which have sprung up around the country in the last few years".

Scientific Meetings Programme

Facilitating communication between scientists themselves and with the public is one of the aims of the scientific meetings programme.

The **Frontiers of Science** meetings are international in flavour and small (a maximum of about 20 speakers and 10 - 20 further discussants) lasting an intense three days. This format encourages movement in a subject - for example, by agreeing strategies for future development or by seeking to resolve existing conflicts.

Meetings held to date include modern approaches to "Metamorphosis", "Hypoxia: functional consequences of reduced oxygen supply" and "Cholera". Future titles include "Molecular Motors" and "Antibody Engineering".

Suggestions for suitable subjects are always welcome.

Trust funded scientists meetings include interdisciplinary meetings for groups working on different aspects of the same topic; diabetes and red blood cells are examples of recent meetings. In addition, we have held a workshop for our Prize Students in order to help them to communicate their work to other scientists and to the public. This was well received and we plan to extend these courses.

Special interest group meetings for teachers and school pupils, medical charity workers, lawyers, journalists and the general public are planned in order to develop awareness of particular issues and to foster the public understanding of science.

Facilities have been designed for groups from half a dozen or so in seminar rooms to up to 170 in the auditorium.

Information Service

In addition to supporting the *Science for Life* exhibition with a teachers' centre, there is also a collection of non-technical background material on human biology, including videos for the general public.

For the professional user, the Information Service has concentrated its attention on everything to do with biomedical research except the research itself: there is no point in competing with University College Library next door. The Information Service now has some 250 journals and 2,000 books on organisation, management, funding, ethics, biomedical science policy research and the public understanding of science. It is well provided with computers and has access to most standard data bases such as Medline Express, Current Contents (+ abstracts), Health Services Research Database, Current Research in Britain Database, World Research Database, UKOP (Official publications, eg HMSO etc), NERIS (Educational Resources), ECTIS (Higher Education Research) and British Books in Print.

In addition, we are developing two databases of our own, one on sources of Grants funding and another on Research Assistant Vacancies. Once complete, it will be possible to dial up via JANET and use key words to find out the funding agencies most appropriate for your particular needs. Details of the Funding Body can be sought if required and contact names are provided. Secondly, anyone with a grant which includes a research assistant position can enter details onto the Research Assistant Vacancies database and potential candidates can then search it using key words or just by browsing through it. Free to the user, it will be a minimal cost to grant holders - £15 or so per month. These services should be available in the Wellcome Centre in a month or so and on JANET later this year.

Another contribution for those who need to know what is happening in the science policy world is a weekly news round-up - SPIN (Science Policy Information News) which is produced jointly with our Science Policy Research Group PRISM (Policy Research in Science and Medicine).

Next time you are in the Wellcome Building, drop in and see what's in the Information Centre. There are comfortable seats, general journals and newspapers to read as well as the collections mentioned above.

Finally, for those who cannot visit the Centre, an enquiry service is available. The Information service is there to satisfy the needs of the research community and you are encouraged to contact them about any matter related to research other than the science itself.

Laurence H Smaje
Programme Director
Wellcome Centre for Medical Science

Further Information

Science for Life Exhibition

Opening hours:

0945-1700	Mon- Fri
0945-1230	Sat

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Physiological basis of seasonal mortality

Summary of a special lecture delivered at the Queen Mary & Westfield College Meeting (December 1992)

Seasonal mortality may seem an unusual research topic for a department of physiology but, like so many of the major categories of disease, seasonal deaths are turning out to be multifactorial, and with physiology holding the key to much of the causation.

The history is a remarkable one. Excess winter deaths have run at between 50,000 and 150,000 per year ever since British mortality statistics were first collected in the middle of the last century. However, it was only in the 1970s that, for the first time, this huge death rate started to attract either scientific or public and media attention on any major scale. Unfortunately, when it did, there was initially a widespread misconception that these deaths were due to hypothermia. Death certificate statistics show that arterial thrombosis, mainly coronary and cerebral thrombosis, causes over half of the excess deaths in winter in the UK (Bull & Morton, 1978). Respiratory diseases cause about half of the rest, and the remainder are due to a large number of minor causes. Despite the statistics showing at most a few hundred deaths from hypothermia, repeated statements and advertisements assured us that 100,000 elderly British people died of hypothermia every year in their own homes. They were often even said to have frozen to death. As a result, hypothermia became fixed in the public mind, and very widely in the scientific mind, as the cause of our annual winter holocaust.

At the time, the main research interest of our group was in electrophysiology of vascular smooth muscle, but we had been intermittently involved in a number of applied problems of human environmental physiology, including an interesting type of marginal hypothermia that had been causing confusion and memory deficits in North Sea divers. This led to us being asked to look into winter deaths that were widely thought to be due to hypothermia.

The first step was to see whether hypothermia was in fact common, but was simply being missed because people were not taking temperatures, at the right time, with low-reading thermometers. We therefore arranged for every patient coming into The Royal London Hospital in January and February to have mouth temperature measured; if it was below 36 °C, rectal temperature was measured as well. Only three patients out of 982 admitted to hospital in these winter months had temperatures below 35 °C, the official definition of hypothermia. All of these three were very ill for other reasons and all had been recognised already as being hypothermic. A more detailed investigation (Woodhouse *et al*, 1989) of all patients admitted with hypothermia over one year in the entire Royal London group of hospitals, covering most of the East End of London, showed that all of the fourteen patients who had become hypothermic in their own homes had done so after becoming seriously ill from other causes and usually after collapsing on the floor. Another eight patients had become hypothermic outdoors, almost all after alcohol or after a variety of illnesses. Most of Britain's 50,000 excess winter deaths therefore really do seem to be due to arterial thrombosis and not to hypothermia.

In trying to explain why arterial thrombosis should increase dramatically in winter, we made a series of experimental cold exposures on volunteers (Keatinge *et al*, 1984). These involved only mild surface cooling, just enough to cause shivering, and no substantial fall in core temperature. Within 30-60 minutes these produced a series of changes in blood composition which were each of moderate size and which would all have the effect of increasing the likelihood of a thrombosis forming. Red blood cell count (RBC) increased about 10 %; platelet count also increased, though proportionately less. Plasma cholesterol, which rapidly increases platelet stickiness as well as increasing atheroma in arteries in the long term, increased in line with the increase in RBC. These changes were accompanied by a marked increase in blood viscosity, that varied from 20 to 30 % depending on the shear rate used. This increase in viscosity will facilitate the second phase of arterial thrombosis, after a platelet thrombosis has formed, when secondary thrombus is spreading from it. We are now investigating changes in a variety of clotting and thrombolytic factors in the cold. (Syndercombe-Court *et al*, 1993)

So the hypothesis now is that these changes all increase the statistical probability of an arterial thrombus forming; this does not matter much in healthy young adults with arteries that are in good condition, but in elderly people with atheromatous arteries they cause a large number of excess thromboses in winter. In general terms, the changes can be explained by haemo-concentration, associated with a reduction in blood volume needed to match the reduced volume of the circulation following vasoconstriction in the cold. They are therefore part of the normal physiological response to cold. Current studies are largely designed to assess the mechanism of the loss of fluid, as well as to explain the discrepancies between the percentage increases in different blood constituents in the cold.

Since these changes happened in quite short exposures to cold, outdoor excursions could clearly be important in causing them in everyday life. Statistics from Anchor Housing, where homes were well heated throughout the winter, showed that residents of these showed much the same increases in mortality as other elderly people did in winter (Keatinge, 1986). Another indication came from analysis of overall mortality in England and Wales (Keatinge *et al*, 1989) during the 20 years from 1964 to 1984. During this period there was a dramatic increase in central heating, which rose from 13 % of homes to over 66 % of homes. Although excess mortality in winter from respiratory disease fell as central heating increased, excess winter mortality from arterial thrombosis did not, after allowing for effects of influenza epidemics. So the indication was that central heating probably had reduced respiratory deaths in winter but had little effect on the thrombotic deaths that cause most of the mortality.

Outdoor excursions in winter were therefore likely to be the main cause of the persistent high winter mortality from thrombosis. If this was right, it should be possible to produce a fall in the mortality simply by advising elderly people to forget the traditional British belief that plenty of fresh air is healthy in winter, and to take common sense measures to minimise cold exposure outdoors. Five years ago we were able to get a lot of low-key publicity on these lines among elderly people, first through Oliver Gillie in *The Independent*, and then through a

series of radio and television programmes for elderly people at non-peak times. This was later reinforced by advice from the Department of Health carried on main television news broadcasts. Office of Population Censuses and Surveys data for that winter, comparing actual mortality with the mortality predicted from the previous ten years, showed an unprecedented fall in actual as compared to predicted mortality, with deaths 30,000 below predicted level. This happened despite the winter being colder than average and no serious distortion by influenza throughout the 10 year predictive period. This does not, of course, prove that the advice caused the fall but it is at least consistent with it. We need more information about the nature and time course of the changes responsible for thrombotic deaths in winter before a more active and more targeted preventive programme can be advised, but we at least have an indication that current programmes of advice seem to be helping.

A surprising finding (Keatinge *et al*, 1986) was that brief heat stress, with sweating, causes haemoconcentration of a similar kind to cold stress, in this case mainly due to failure to replenish fully the salt and water that is lost in sweat. This in turn can explain marked increases in deaths from arterial thrombosis in heat waves in the USA and other warm countries. Such heat-induced increases are infrequent and moderate, and therefore a minor cause of mortality in Britain, compared to that seen in winter, but they do occur in heat waves every two or three years (MacFarlane & Waller, 1976) in Southern England. The changes in blood composition that occurred during experimental exposure of volunteers to heat differed little from the changes produced by cold, apart from a tendency for platelet count to increase relatively more in the heat than the cold. Statistics for mortality on holidays abroad are not readily obtainable, but we suspect that heat stress is a major cause of arterial thrombosis among elderly British people holidaying in hot countries.

Considerably more information is needed about the everyday activities that carry particular risk of individual cold- and heat-related thrombosis, as well as about the details of the haematological changes and ways in which they can be modified. Until we have this, it is probably unwise to embark on more detailed preventive advice, and almost certainly unwise to embark on preventive mass medication, but it is likely that useful additional measures can be taken on these lines as more information becomes available.

William Keatinge

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How quantitative studies on single capillaries help us to understand the circulation

Summary of a lecture delivered at the Society's Symposium for final year undergraduates (Leeds, December 1992)

When asked to think about the blood flow through a particular organ or tissue, I conjure up a mental picture of the microcirculation in that organ for it is here in the arterioles that blood flow is regulated and distributed and in the capillaries and venules where blood–tissue exchange occurs. Until recently, most of these mental pictures were based on qualitative descriptions of microvascular flow and much of our quantitative understanding of microvascular exchange was derived from indirect measurements (such as the disappearance of tracers from blood). In the past 15 years, however, there has been great interest in making quantitative measurements of flow and exchange in single capillaries. The results of some of these investigations have certainly clarified my own thinking and in this brief review I shall give a small number of examples.

Although it only became fashionable to make quantitative measurements on the microcirculation 10 to15 years ago, two classical series of measurements of this kind were described between 1918 and 1930. The first was carried out by August Krogh in Copenhagen. Using direct microscopic observation of the living microcirculation, quantitative histology, *in vitro* determinations of oxygen diffusion coefficients in tissues and mathematical modelling techniques, he established that O_2 could be supplied from the capillary blood to resting and exercising muscle tissue by diffusion alone. Krogh drew attention to the great increase in the number of capillaries that are perfused when a muscle exercises and how this ensures the oxygen supply to the tissue can meet the increased requirement. It is only within recent years that Krogh's *in vivo* observations have been rigorously repeated and extended. It has been found that the simple interpretation of capillaries being either open or closed had to be revised and that the non-uniform distribution of microvascular perfusion could be considered to result from a distribution of capillary transit tissues.

The second classical series of experiments was carried out by Eugene Landis and he started them when he was a medical student at the University of Pennsylvania. Landis developed a micropuncture technique for measuring capillary pressure, P_c, in single vessels in the frog mesentery. He also devised a method for measuring fluid filtration and reabsorption across the walls of these vessels and, by combining this with measurements of P_c, he was able to provide the first direct proof of Starling's hypothesis of capillary fluid balance. After qualifying in medicine, Landis came to London for a year to work with Sir Thomas Lewis at University College Hospital and, during the winter of 1928/29, he used his micropuncture technique to measure P_c of skin microvessels in normal human subjects. Although Landis himself drew attention to the wide variations in P_c that he recorded, the mean values fitted Starling's hypothesis so well that they immediately became incorporated into the textbooks. With P_c = 35 mmHg at the arterial end of the capillary, 25 mmHg at the mid-capillary level and 15 mmHg at the venous end, the picture of fluid filtering from blood to tissue at the arterial end and being reabsorbed into the blood at the

venous end seemed secure since the proteins of normal plasma exerted an osmotic pressure of 25 mmHg.

What is not emphasised clearly enough in the textbooks is that Landis's figures refer to capillaries in the skin of the hand at heart level. An outstanding question was what happens to P_c in capillaries below the heart. Although Landis had carried out some preliminary experiments on this, surprisingly no-one attempted to follow them up until almost 50 years later when Rodney Levick and I used each other as subjects. We measured P_c in the skin of our toes while lying supine on a laboratory bench, while sitting and during quiet standing. Our data is shown in Fig 1. It is seen that while P_c rises as the foot is lowered below the heart, it does not rise as quickly as the local venous pressure. While the difference between the mean arterial pressure and the local venous pressure in the foot remains fairly constant with changes in position, the difference between P_c and the local venous pressure may be 20-30 cmH_2O in the supine subject but only 2-3 cmH_2O during quiet standing. This shift of P_c towards the local venous pressure is a result of constriction of the arterioles. This is triggered by a local mechanism (which is still not clearly understood) but has two important consequences which minimise fluid loss into the dependent tissues. First is by reducing the rise of P_c (as we have seen) and second by slowing plasma flow through the microcirculation, the transit times become sufficient for plasma proteins to concentrate as fluid is lost in the early part of the capillaries so that the subsequent rise in oncotic pressure acts as a brake on filtration during the later part. As in the glomerulus of the kidney, filtration becomes limited by the rate of plasma flow but while this is high in the glomeruli it is very low in the feet of standing subjects.

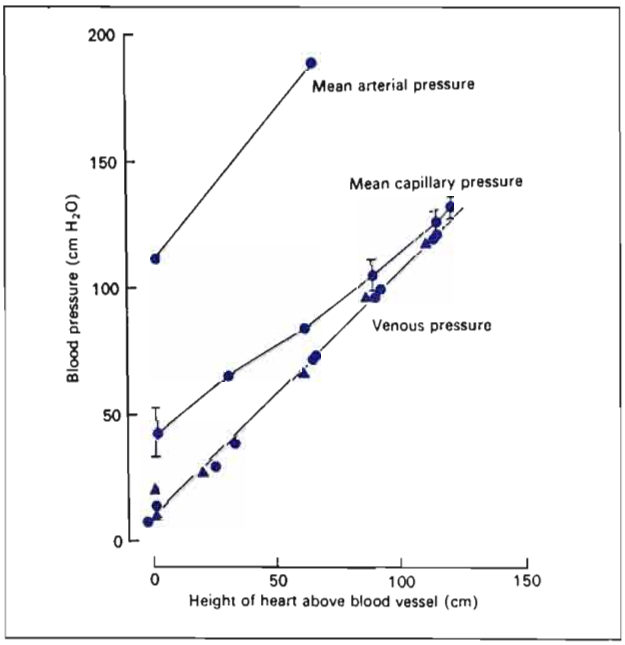

Fig 1 Changes in arterial, venous and capillary pressures in the feet of two normal subjects at different levels below the heart (Levick & Michel, 1978).

The adjustment of the "Starling forces" to minimise fluid filtration when P_c is high is mirrored by changes which limit reabsorption of tissue fluids when P_c is low. This phenomenon became clear to me when my colleagues and I were measuring fluid filtration rates over a range of P_c in single perfused frog mesenteric capillaries. While reabsorption of fluid from the tissues could be demonstrated in these vessels when P_c was less than the oncotic pressure of the perfusate, perfusion for several minutes at the same P_c led reabsorption to diminish until it was undetectable. By vigorously washing the surrounding tissue with protein free fluid and raising the P_c to establish net filtration for a brief period, reabsorption rates at the initial P_c could be restored. It became obvious that during reabsorption protein accumulated in the fluid immediately surrounding the capillary raising the local oncotic pressure and reducing the oncotic pressure difference across the microvessel walls which was responsible for reabsorption. Since capillary walls are finitely permeable to plasma proteins, their concentration difference in the pericapillary fluid is determined by the rate at which they cross the vessel wall and the degree to which they are diluted by the filtration of protein-free fluid. It was possible to write down an equation which described the steady-state relations of fluid balance at any value of P_c and perfusate oncotic pressure depending upon the permeability of the microvascular wall to fluid and protein. The theory was examined in single perfused capillaries by Mary Phillips and myself and we were able to show that the permeability to perfusate macromolecules (as well as their reflection coefficients) could be deduced from measurements of fluid filtration rates at known values of P_c.

The theory gives insight into fluid balance in tissues of intact organs (such as the lung), it negates the classical picture of steady reabsorption at the venous end of capillaries and it raises interesting questions about sustained fluid uptake in tissues such as the kidney and small intestine. When there is adequate lymphatic drainage (eg in the renal cortex and interluminal mucosa), sustained reabsorption can be accounted for, but in the renal medulla (where the presence of lymphatics is disputed) the mechanism of fluid uptake is unclear. For that reason, Dr Peggy MacPhee and I are currently investigating fluid balance in single perfused ascending vasa recta.

Most of the work of my laboratory over the past 20 years has been directed at the question of identifying the permeability pathways through capillary walls and understanding the processes of diffusion and ultrafiltration within them. This has led us to combine techniques for measuring the permeability of single vessels with an examination of the ultrastructure of the same vessels. This work has been reviewed elsewhere (eg Michel, 1988) and I am beginning to hope that the "normal" picture of fluid and solute permeation through vessels with continuous endothelium has been clarified. There are still some major problems to be solved, in particular the passage of macromolecules and the mechanisms whereby permeability increases under patho-physiological (and possibly physiological) circumstances. Like all research, by answering one question we gain sufficient insight to ask several more and I have a feeling that a small number of physiologists will be kept busy making quantitative measurements on single capillaries for a long time to come.

Charles Michel

Suggested Reading

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Cationic amino acid transport: molecular, cellular and physiological studies

Summary of a lecture delivered at the Society's Symposium for final year undergraduates (Leeds, December 1992)

Where does cell physiology stop and molecular biology start? The borderline is in some sense bound to be arbitrary. Perhaps the attitude and hopes of the scientist who is doing the experimental work tell us most about which side of the border he (or she) considers himself to reside. Is he interested in taking the component pieces apart to understand at an atomic level their structure and function; or, alternatively, is the investigator interested in seeing how the component parts of the mechanism interact at a molecular and supramolecular level, to see how function at a cell and tissue level emerges? Recent studies on the mechanism and regulation of transporter proteins in membranes have raised these issues and here I will discuss the specific processes which are involved in movement of cationic amino acids across the cell membrane, particularly in epithelial cells.

Molecular basis

In 1991 two independent studies were published on adjacent pages of *Nature*; they both showed that the transporter responsible for the transport of the amino acids lysine, arginine and histidine was a protein whose gene had already been isolated and sequenced. Thus, the full amino acid sequence of this protein had already been known for several years. This was a surprise because the gene for this membrane protein had been isolated previously on the basis of a quite different biological function, namely that it acted as a receptor for a mouse retrovirus. (It is in science policy to realise that although a great deal of funding had been invested in the search for protein molecules which acted as amino acid transporters in animal cells, this work established this to be a function of a protein whose sequence had already been published; if only those hard-working scientists interested in membrane transport had known what it was! I am sure that there is a more general message here.) The papers by Wang *et al* (1991) and by Kim *et al* (1991) showed, using electrophysiological techniques and flux measurements, that this virus receptor (called EcoR), when expressed in *Xenopus* oocytes, produced transport of this specific group of basic amino acids. The sequence of the protein showed it to have multiple transmembrane domains (probably 12) and it has been suggested (Kavanaugh *et al*, 1993) that the molecule shows internal duplication. There is also homology between this transporter and one other membrane protein of previously unidentified function; this other molecule which had been isolated from activated lymphocytes by MacLeod *et al* (1993) showed striking sequence homology to EcoR. We thought, therefore, that it might be interesting to look at cation amino acid transport in activated lymphocytes.

T cell activation causes rapid expression of the T cell early activation antigen gene and simultaneous expression of lysine transport

Together with Dorothy Crawford (a virologist with an interest in the cell biology of human lymphocytes) we studied the transport properties of activated human peripheral blood monocytes. Using specific lectin mitogens (phytohaemaglutinin (PHA)) for T cells and *Staphylococcus aureus* cowan A (SAC) for B cells, we looked at lysine influx. Fig 1 shows our findings. In activated T cells, the cationic amino acid transport system y^+ was strongly activated within 24 hours and, as shown in Fig 2, when the time course was extended in greater detail obvious stimulation of this system was observed by 12 hours. This time course matches precisely the expression of the T cell gene TEA described by MacLeod *et al* (1990). As discussed below there is also an additional amino acid transport system (given the name y^+L), which is expressed in several cell types and we found also to be present in the T cells. Unlike system y^+, however, system y^+L was activated only slowly and to a much smaller extent than system y^+. When we looked at the activated B cells (which we showed to be appropriately stimulated by monitoring expression of a specific B cell surface molecule, CD23), lysine influx was not altered. We concluded from our work on the lymphocytes that the T cell early activation antigen described by MacLeod and colleagues (1990), was indeed a system y^+ transporter specific to activated T cells. This has now been confirmed by the studies of Kavanaugh *et al* (1993) in which increased amino acid transport was observed following expression of the TEA gene; it also fits with studies by Sarah Chen in my laboratory who has blocked expression of the human H13 gene (the human version of the mouse EcoR) using antisense oligonucleotides and found specific inhibition of lysine transport through system y^+ in activated human T lymphocytes.

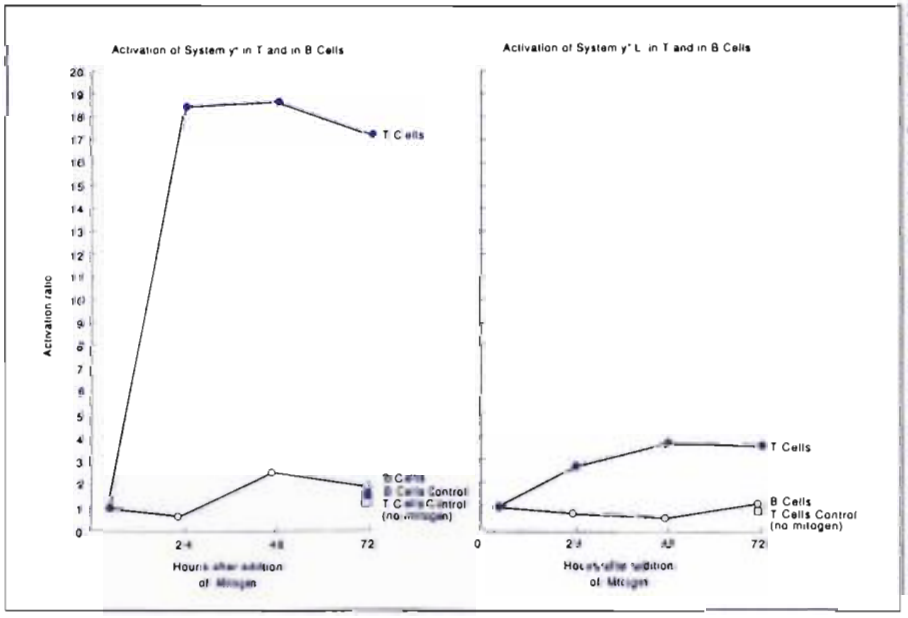
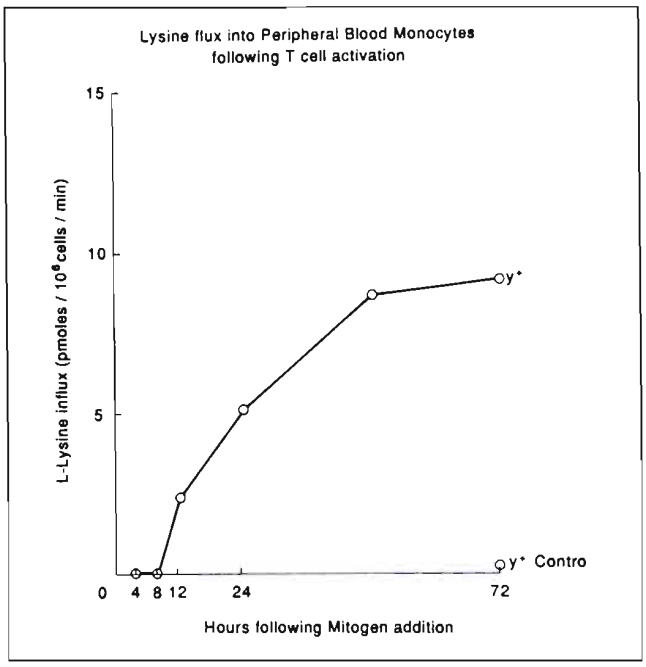


Fig 1 The activation of lysine transport into lymphocytes (T and B cells) from human peripheral blood; the figure on the left shows transport through system y^+ and that on the right through system y^+L. It is clear that in T cells there is very substantial activation of system y^+ which is not seen in B cells.

Fig 2 The time course of activation of lysine influx following T cell activation. This precisely matches the expression of the TEA gene.



A novel system for cationic amino acid transport

The system y⁺L mentioned above was originally described by Devés and her colleagues in human erythrocytes. It was identified on the basis of its extraordinarily high-affinity inhibition by neutral amino acids such as leucine. Thus, as shown in Fig 3, leucine inhibits lysine influx in a biphasic fashion; in erythrocytes at low substrate concentrations approximately half of the flux of lysine can be inhibited by low concentrations of leucine. Using this observation, Devés *et al* (1992) showed that there are two pathways for lysine transport which differ in their kinetic properties and in their substrate specificity. The novel system transports both neutral and cationic amino acids with high affinity, which means that its contribution to total cationic amino acid transport decreases as the concentration of substrate (lysine) increases. Subsequent work by Devés has shown that these two systems can also be separated functionally on the basis of differential sensitivity to inhibition by *N*-ethyl maleimide.

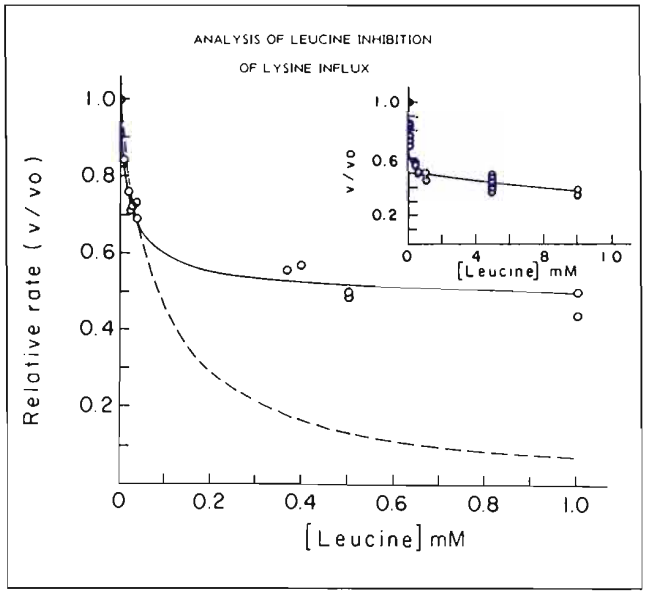


Fig 3 Inhibition by the neutral amino acid leucine of the rate of lysine entry into human red blood cells (expressed as a ratio of the inhibited rate, v, to the uninhibited rate, v_o). Note the biphasic inhibition with one component of lysine influx which is very sensitive to inhibition by leucine. The dotted line extrapolates the predicted inhibition if there were only one transport system; the solid line shows the fit to the data by the two transport system model (with both systems y⁺ and y⁺L).

The systems y⁺ and y⁺L differ in their response to membrane potential

In our laboratory Dr Neli Eleno has used isolated membrane vesicles to study the effect of membrane potential on the two cationic transport systems. With these biochemically purified plasma membranes it is possible to induce a diffusion potential of known polarity and magnitude and to look at the effect of this potential on transport through the two systems. The trick is either to use ion gradients in which a very permeant ion is chosen (such as the anion SCN^-) or to use ionophores which specifically increase the permeability of the membrane to one particular ion (eg valinomycin which increases K^+ permeability about 10^5-fold). As shown in Fig 4, in epithelial cell membrane vesicles, as in the red blood cell, two systems for lysine transport are seen, one sensitive to inhibition by neutral amino acids (system y⁺L), and the other relatively insensitive to neutral amino acids (system y⁺). Additionally, as shown in the figure, when the membrane potential is altered by addition of valinomycin the contribution of system y⁺ is altered, whereas transport through system y⁺L scarcely changes. These different effects of membrane

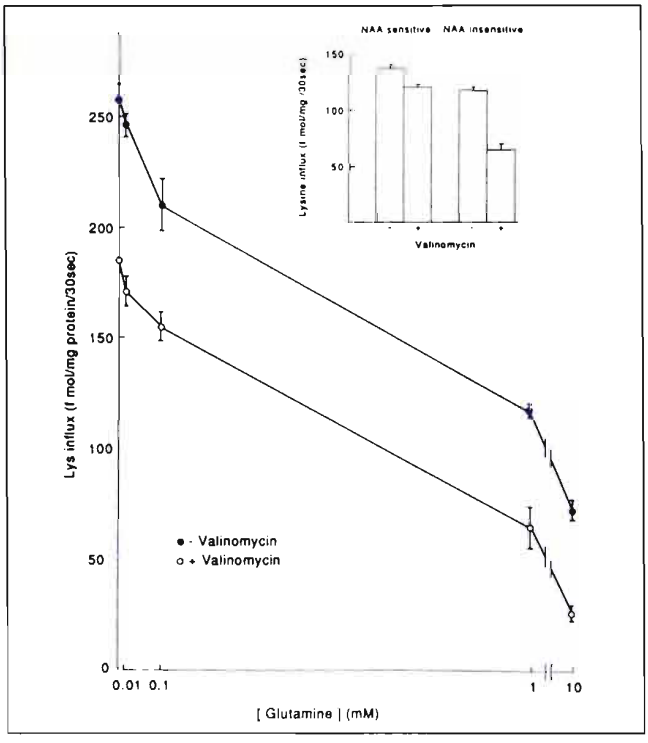


Fig 4 Inhibition of lysine influx into membrane vesicles by the neutral amino acid glutamine. In the presence of valinomycin (upper line) there is a diffusion potential (inside negative). Note that the fractional inhibition of lysine transport is reduced under these conditions, so that, as shown in the insert, the valinomycin-induced membrane potential has little effect on the neutral amino acid sensitive transport system (y⁺L). In contrast, system y⁺ (neutral amino acid insensitive) is substantially reduced by the imposed potential.

potential on the two transporters are of interest both at a molecular level and with respect to function. The most probable explanation for the strong effect of potential on transport through system y^+ is that the lysine binding site for this transporter lies within the membrane proper and thus senses the effect of the membrane potential which therefore alters substrate binding; in contrast, it seems probable that for system y^+L the substrate binding site is nearer the surface of the membrane. Functionally these observations suggest a ready and interesting explanation for findings published more than ten years ago by physiologists interested in transepithelial amino acid transport. Thus Cheeseman (1983) had shown (confirming earlier studies) that neutral amino acids have an unexpected ability to stimulate lysine transport across the small intestine. Fig 5 suggests why this may occur. System y^+, found predominantly in the brush border, enables positively charged amino acids such as lysine to readily enter the epithelial cell down a prevailing electrical gradient (the inside of the cell is typically 40–50 mV negative to the lumen); system y^+L which is insensitive to membrane potential permits efflux of the cationic amino acid in exchange for movement of neutral amino acids. To account for the minimal effect of potential on this system, we have also to postulate that an inorganic ion moves; it seems very likely (see Devés *et al* 1992) that this ion is sodium.

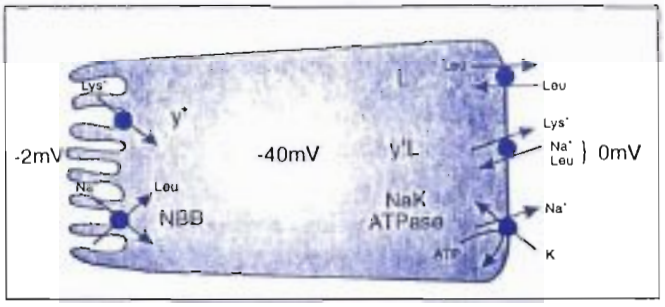


Fig 5 Model of epithelial cell indicating the distribution of membrane transporters responsible for transepithelial transport of cationic amino acids (eg lysine, Lys^+). NBB refers to the neutral brush-border amino acid sodium-dependent transporter. Na^+-K^+ ATPase is the basally located classical sodium potassium pump. Note that the asymmetric distribution of system y^+ (predominant in the brush-border apical membrane) and of system y^+L (predominant in the basal membrane) allows active transepithelial movement of these essential amino acids despite their cationic charge.

Richard Boyd

Acknowledgements

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Editor's note: a summary of another lecture delivered at Leeds, Physiology of the airway mucosa and its relevance to asthma, will appear in the next issue.

Multiple nucleoside transporters in animal cells

Nucleosides perform a multitude of biological functions. Adenosine, for example, acts as a neuromodulator and is involved in the regulation of platelet and neutrophil function, of blood flow in heart and kidney and of lipid biosynthesis in adipocytes. Inosine is an *in vivo* energy source for pig erythrocytes, cells that are unable to metabolise plasma glucose. Other cells require intracellular transport of nucleosides to support anabolic processes, eg intestinal mucosa, bone marrow and certain cells of the central nervous system. In addition, nucleoside transport into target cells is a key determinant of their susceptibility to cytotoxic nucleosides. Such analogues are widely used in cancer chemotherapy, eg cytosine arabinoside, and as antiviral agents, eg acyclovir and azidothymidine. Thus, a clear understanding of nucleoside transport systems is important in unravelling the physiological functions of nucleoside salvage and release from cells, and in the rational design and use of nucleoside drugs in chemotherapy.

The classification of transport systems has been according to their physiological, pharmacological and biochemical properties. More recently, with the increasing application of molecular biology techniques to transporters, carriers have been defined by their amino acid sequence. In this short report, I will highlight the ever increasing heterogeneity that is becoming apparent regarding nucleoside transporters. In addition, I will draw attention to how such diversity could be exploited in the treatment of cancer and viral and parasitic infections.

Facilitated-diffusion nucleoside transporters

Up to about eight years ago, all mammalian cells, with a few special exceptions such as erythrocytes from certain species, were believed to possess a single medium affinity facilitated-diffusion system that exhibited a broad specificity for nucleosides. This system was inhibited by nanomolar concentrations of nitrobenzylthioinosine (NBMPR) resulting from the binding of NBMPR to high-affinity sites on the plasma membrane (K_d ~ 1 nM) (see Jarvis 1991, for review). This NBMPR-sensitive nucleoside transporter from pig and human erythrocytes has been partially or completely purified, and shown to be a heterogeneously glycosylated protein of apparent average M_r 64,000

and 55,000, respectively. Although photoaffinity labelling with [^{3}H]NBMPR has identified the NBMPR-sensitive nucleoside transporters of many other tissues as proteins of similar M_r, it is not known whether such proteins share sequence similarity or merely the ability to bind NBMPR.

Recently, specific polyclonal antibodies have been raised against the NBMPR-sensitive human erythrocyte nucleoside transporter (Kwong *et al*, 1992). Using these antibodies, it has now been possible to examine the relationships between the erythrocyte transporter and those present in other tissues, such as the human placenta (Barros *et al*, 1992). Isolated syncytiotrophoblast brush-border and basal membranes possess similar levels of NBMPR binding sites. However, the anti-erythrocyte nucleoside transport antibodies only recognised brush-border membrane proteins of apparent M_r 55,000 on Western blots with no labelling of basal membrane proteins. The absence of immunoreactive protein from the basal membranes was confirmed by confocal immunofluorescent microscopy, which showed that the brush-border membrane, but not the basal membrane, was labelled in placental sections. These results suggest that at least two isoforms of the NBMPR-sensitive nucleoside transporter are present in human placenta, only one of which is recognised by the anti-erythrocyte nucleoside transporter antibodies. Cloning studies of the kinetically similar passive cytochalasin B-sensitive glucose transporters of mammalian tissues have revealed the existence of a family of glucose transport proteins. Such investigations for passive nucleoside transport systems are still in their infancy but will be required to confirm the possibility of isoforms of the NBMPR-sensitive nucleoside carriers.

Further heterogeneity of equilibrative nucleoside transporters came apparent in the mid-1980s with the recognition of the existence of nucleoside transporters that were resistant to inhibition by nanomolar concentrations of NBMPR. In some cell types, this is the sole nucleoside carrier and such cells lack high-affinity NBMPR binding sites. However, many cell lines possess both passive nucleoside carriers. Detailed studies with rat erythrocytes and Ehrlich ascites tumour cells that express the two transport components have revealed that the affinity of the two systems for certain nucleosides may differ by up to three-fold (Jarvis & Young, 1986; Hammond, 1991). Moreover, the NBMPR-resistant nucleoside transporter in rat erythrocytes is inhibited by external concentrations of the organomercurial, *p*-chloromercuriphenyl sulphonate. In contrast, the NBMPR-sensitive nucleoside transport system in mammalian erythrocytes has been suggested to have a *p*-chloromercuriphenyl sulphonate-sensitive thiol group located within the inward facing conformation of the nucleoside permeation site.

The susceptibility of the NBMPR-sensitive and NBMPR-insensitive nucleoside transporters to inhibition by a variety of other compounds, including the clinically available vasoactive drugs dipyridamole and dilazep has been investigated. The general conclusion is that these compounds, together with other recognised nucleoside transport inhibitors, are more potent inhibitors of NBMPR-sensitive nucleoside influx compared to their capacities to inhibit NBMPR-resistant influx (see eg Griffith *et al*, 1990; Hammond, 1991; Lee & Jarvis, 1988). However, there are two notable exceptions. First, soluflazine, an analogue of lidoflazine, is up to 100-fold more effective as an inhibitor of the NBMPR-insensitive component compared to the NBMPR-sensitive transport system (IC_{50} values of 0.08 and 10 μM, respectively in rat erythrocytes) (Griffith *et al*, 1990). Second, dipyridamole fails to differentiate between the two equilibrative transporters in rat tissues (see Plagemann *et al*, 1988, for review). One explanation of these latter findings is that the NBMPR-sensitive nucleoside transporter in rat tissues has undergone a small structural or conformational change that selectively decreases the transporter's affinity for dipyridamole while leaving its affinity for NBMPR unaltered. As such, dipyridamole is no longer capable of differentiating between the two transporters in rat tissues.

Nothing is known about the molecular properties of the NBMPR-insensitive passive nucleoside transporter. We must await the cloning of this carrier and also nucleoside transporters from rat tissues before we can further determine the extent of the similarities and differences in facilitated-diffusion nucleoside transporters. It seems likely that the NBMPR-insensitive and NBMPR-sensitive nucleoside transporters are the products of distinct genes as cell lines with specific nucleoside transport deficiencies have been generated by mutation techniques (Vijayalakshami *et al*, 1992).

Active nucleoside transporters

Further diversity in nucleoside transport mechanisms has become apparent with the increasing number of reports of Na^+-dependent concentrative nucleoside transporters in both epithelial and non-epithelial cells. Kinetic and substrate specificity studies have revealed the existence of at least three active nucleoside transporters (see Jarvis, 1991 and Table 1). One system, designated N1 or *cif*, accepts mainly purine nucleosides, uridine and deoxyuridine, and nucleosides such as formycin B and guanosine have been used as model permeants. The co-transporter is widespread and has been shown to be present in kidney brush-border vesicles from a variety of species, rat and mouse macrophages, mouse spleenocytes, mouse intestinal enterocytes and rat liver canalicular membrane vesicles. The second system, designated N2 or *cit*, has a substrate specificity for pyrimidine nucleosides, adenosine and analogues of adenosine, and thymidine has often been used as a specific permeant. The N2 nucleoside cotransporter appears to have a narrower tissue distribution and has only been clearly shown to exist in epithelial preparations from kidney and intestine. Human renal brush-border membrane vesicles appear to possess a variant of the N2 system which also accepts guanosine as a substrate (Gutierrez *et al*, 1992). Finally, a broad specificity Na^+-dependent system has recently been reported to be present in choroid plexus from rabbit which I have designated as N3 (Wu *et al*, 1992). This system also differs from N1 and N2 in that the stoichiometric coupling ratio between Na^+ and nucleosides is 2 and not 1 as determined for N1 and N2. The affinity of these co-transporters for permeants is high (generally K_m values of 1 to 20 μM at 20 °C), values one-tenth to one-fiftieth of that of the equilibrative nucleoside transporters. The active nucleoside transporters are also resistant to inhibitors of equilibrative nucleoside transport.

Studies from this laboratory have demonstrated the expression of Na^+-dependent thymidine transport in *Xenopus* oocytes with kinetic properties identical to the N2 transporter following injection of rabbit small intestinal poly(A)$^+$ mRNA (Jarvis & Griffith, 1991). More recently, a complementary DNA encoding a rabbit kidney Na^+– nucleoside co-transporter, SNST1, was isolated by high stringency hybridisation with the rabbit renal Na^+-dependent glucose transporter, SGLT1 cDNA (Pajor & Wright, 1992). The amino acid sequence similarity between the two proteins is high - 61 % identity and 80 % chemical similarity. Expression of SNST1 in *Xenopus* oocytes resulted in Na^+-

Table 1 Properties of nucleoside transporters in animal cells

	Equilibrative		Active		
	NBMPR-sensitive	NBMPR-insensitive	N1	N2	N3
Na^+-dependent	-	-	+	+	+
Inhibitors:					
100 nM NBMPR	+	-	-	-	-
PCMBS (externally located)	-	+	ND	ND	ND
Substrate specificity					
Uridine	+	+	+	+	+
Adenosine	+	+	+	+	+
Thymidine	+	+	-	+	+
Formycin B	+	+	+	-	+
Guanosine	+	+	+	-a	+
Inosine	+	+	+	-	+
Na^+: nucleoside stoichiometry	-	-	1	1	2
Tissue distribution	Most	Most	Kidney Intestine Liver Spleen Leukaemia cells	Kidney Intestine	Rabbit Choroid Plexus

ND, Not determined; a, exception human kidney where guanosine is a substrate.

stimulated uridine uptake and nucleoside-stimulated ^{22}Na uptake. Uridine, 2-deoxyuridine, cytidine, adenosine and guanosine appear to be apparent substrates for the expressed transporter. This specificity is consistent with either the modified N2 carrier characterised in human renal brush-border membrane vesicles or the broad specificity N3 Na^+–nucleoside transporter (see earlier discussion). Northern blots revealed no mRNA in rabbit intestinal mucosa, suggesting that intestinal active nucleoside transport is catalysed by a different gene product(s). Surprisingly, mRNA for SNST1 was abundantly expressed in the heart, although preliminary studies from this laboratory in conjunction with Professor S Nees, University of Munich, have failed to detect Na^+-dependent nucleoside transport activity in guinea-pig cardiomyocytes and coronary endothelial cells. It is anticipated that further genes coding for Na^+-dependent nucleoside transporters will be cloned in the near future.

Nucleoside transport and chemotherapy

The observation of multiple nucleoside transporter systems that differ in their substrate specificities, requirement for Na^+ and sensitivity to transport inhibitors, has potential practical significance for cytotoxic nucleoside chemotherapy. First, NBMPR or alternative nucleoside transport inhibitors could be used to potentiate the accumulation of cytotoxic nucleosides in cells that possess both equilibrative and active nucleoside transporters by blocking efflux of the toxic nucleoside via the former system. Certain tumours have both carrier types. Second, many infections occur intracellularly such as leishmaniasis within macrophages and HIV involving lymphocytes. Thus, facilitated-diffusion nucleoside transport inhibitors could be administered to provide general host protection but would not prevent access of a suitable cytotoxic nucleoside to the cell located organism via the Na^+-dependent nucleoside transporters. Many immune-type cells possess Na^+-dependent nucleoside transport systems. Conversely, the concentrative nucleoside transporters could provide a means by which, for example, marrow bone stem cells can salvage nucleosides while the passive nucleoside transport inhibitors are used to potentiate the activity of *de novo* pyrimidine or purine synthesis inhibitors, such as methotrexate, by blocking the salvage of exogenous nucleosides by a tumour. The ideal nucleoside transport phenotype of such a tumour to be subjected to this treatment would be one in which the NBMPR-sensitive nucleoside carrier predominated.

In conclusion, the findings outlined in this article have illustrated the diversity in the number and types of nucleoside transporter-mediated processes in animal cells. Such heterogeneity has been revealed by a number of approaches, including, (i) kinetic and substrate specificity studies, (ii) the use of inhibitor probes, (iii) replacement of Na^+ in the incubation media to impair Na^+-coupled nucleoside transport, (iv) labelling of carriers with antibodies, and (v) the use of mutation/selection techniques to

generate cell lines with specific transport deficiencies. Further diversity is likely to become apparent with the application of molecular biology techniques. Although considerable progress has been made in describing the types of nucleoside transporters, we are still a long way from understanding the mechanisms of transport and whether the observed diversity in nucleoside transport can be utilised to devise effective therapeutic regimes.

Simon M Jarvis

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Analysis of synaptic kinetics with fast cyclic voltammetry

Knowledge of neurotransmitter receptors has grown explosively in the last two decades. Each known neurotransmitter is now known to act at at least three different receptors; and in the case of serotonin, for example, at least seven receptor subtypes are known to exist. Along with this receptor information explosion, there have been major developments in microanatomical techniques which have challenged our orthodox ideas about axons and dendrites, and have shown that multiple transmitters may reside in a single presynaptic varicosity. However, while these pharmacological and anatomical studies of synaptic transmission have made many advances, physiological analysis has lagged behind. Patch clamp studies have of course greatly increased our knowledge of ion channels in membranes and how transmitters trigger intracellular second messenger systems, but what is missing is precise information about the time course of transmitter release and the ways in which uptake and autoreceptors can control and regulate the transmission process. These processes of "synaptic kinetics" are of fundamental importance in synaptic transmission processes and an understanding of them is essential if we wish to unravel the ways in which multiple transmitters and receptors may interact at a complex synaptic site.

An important question relating to synaptic kinetics concerns the role of uptake processes. Uptake, rather than enzymic inactivation, seems to be the main means of transmitter inactivation in the CNS, and so the kinetics of this uptake may be an important determinant of transmitter action. We can imagine two limiting cases. One is that the uptake process is extremely effective and normally acts within the synaptic cleft to prevent any leakage whatsoever of transmitter out from the cleft. In this model, transmitter would be released and taken back up into the presynaptic endings without any significant diffusion into the extracellular space. Just as the fast-acting acetylcholinesterase at the skeletal neuromuscular junction destroys some synaptically released ACh before it has had a chance to combine with the postsynaptic cholinergic receptors, so might intrasynaptic uptake processes control the access of transmitters to receptors in the CNS. Extrasynaptic receptors would only be activated if the normal balance between uptake and release processes was disturbed in some way and the release processes overwhelmed the uptake. The extrasynaptic (autoreceptors) could then act to downregulate the release process (or upregulate the uptake process) to restore equilibrium. The other limiting case would be when the uptake is slow relative to the diffusion processes around the synapse, and so the concentration of transmitter inside and outside the cleft is controlled mainly by these diffusion processes and not uptake. In this case, transmitter concentration outside the cleft would be monotonically related to that inside, and autoreceptor actions would play an integral part in the normal mechanisms terminating transmitter release. It is obviously important to know which, if either, model best applies at a particular synapse before one can sensibly analyse data involving blockade or enhancement of uptake processes. Furthermore, application of exogenous agonists, whether by iontophoresis or otherwise, is of course initially into the extrasynaptic space. Exogenous agents, therefore, will always activate extrasynaptic receptors before and at a greater intensity than the intrasynaptic ones. This reversal of the normal time course and gradient of receptor activation might have profound effects on the post-synaptic response of the cells. (The above arguments are predicated on the idea that "orthodox" synapses with a close apposition of presynaptic and postsynaptic membranes do indeed exist in the CNS; this idea, however, has been questioned. Some authors believe that some transmitters, in particular amine transmitters like dopamine or serotonin, may be released in a diffuse way into the extracellular space, to act like a "neurohormone" in a restricted region of the CNS.)

These problems of the relative efficacy of endogenous and exogenous transmitter and of the significance of uptake processes can be attacked only if we have a means of measuring the release of endogenous transmitter rapidly and in a spatially specific way. The development of the carbon fibre microelectrode (Armstrong-James & Millar, 1979) and fast cyclic voltammetry (FCV) (Millar *et al*, 1981) has brought us slightly nearer to this goal. FCV is an electrochemical technique that involves oxidation or reduction of a substrate material in an electrolyte solution. Such a material is called "electroactive". Oxidation is loss of electrons, and when an electroactive material is oxidised at an anodic (electron-deficient) electrode in solution the lost electrons

are taken up by the electrode and produce an increase in the anodic current. The electron flow will be proportional to the amount of material oxidised, which in turn will be related to the concentration in the solution. Dopamine is electroactive, and most of the FCV research so far has involved studies on the release of dopamine in anaesthetised animals or in brain slices. Other electroactive materials include noradrenaline, adrenaline, serotonin, certain peptides (for example ADH and the enkephalins) and a few other materials found in the extracellular space of the CNS, for example ascorbic acid and uric acid. Nitric oxide has recently been found to be electroactive and it too can be detected using FCV.

The speed at which the measurement can be made will ultimately depend on the kinetics of the electrochemical oxidation process itself. Fortunately, such electron-transfer reactions (for materials of physiological interest) usually have time constants in the millisecond or sub-millisecond range and so detection on a millisecond time scale is in theory possible. However, to make a new measurement it is necessary to remove the oxidised material left after a preceding measurement, and this is where a major problem lies. Having been driven through one oxidation step, many electroactive materials will then undergo further reactions and adsorb onto the electrode surface. This will poison the surface and prevent further analyses. FCV solves this by driving the voltage at the detecting (working) electrode back to a negative potential immediately after the oxidation has occurred. This normally re-reduces the oxidised material back to its original state, in which form it can diffuse away from the electrode. The electrode therefore does not poison and can be used for another assay immediately. One might think that the easiest way to produce this oxidation/reduction cycle would be to have a bipolar square wave applied to the working electrode. However, there is a problem here of artefactual stimulation. It would obviously be undesirable if a waveform that was designed to analyse the electrochemical environment of the electrode were also to act as an electrical stimulation for the neurones. Square-waves will inject an unacceptably high current into the tissue through a capacitative like that of a tungsten or carbon fibre electrode. The drive waveform normally used in FCV , a triangular "W" shape lasting 15 ms is a compromise between speed of analysis and the need to avoid stimulation of the surrounding cells. But how does one know if the drive waveform has stimulated the cells or not? One answer is to record their electrical activity. The carbon fibre microelectrodes used for FCV have tip diameters of 7-8 µm and can also be used for extracellular multi or single-unit spike recording. Because it is impossible for an amplifier to be simultaneously a voltage amplifier (for spikes) and a current amplifier (for FCV), the electrode must be switched between the two modes of operation. In some commercial FCV amplifiers (eg Millar Voltammeters) this is done automatically. The current amplifier is switched on for 40 ms during each FCV scan. So if, for example, the scans were triggered at two per second, there would be 460 ms in between scans where the electrode would be switched to voltage follower mode for spike recording. Of course, this facility for unit recording is useful in its own right, enabling the researcher to investigate, for example, the response of neurones to a known dose of endogenous or exogenous dopamine (Williams & Millar, 1990).

The carbon fibre microelectrodes cannot be inserted into synaptic clefts, so they can only detect transmitter when it "overflows" from synapses. The fact that the electrodes actually can detect endogenous transmitter in the brain argues that the first model of uptake discussed above (where the transmitter is taken up wholly within the synaptic cleft) must be strictly incorrect. Transmitter must spill out to some extent from clefts after activity, at least when this activity is produced by electrical stimulation of the presynaptic axons. However, although FCV has been highly successful at detecting transmitter release following electrical stimulation of brain tissue, it has so far been unsuccessful (unpublished data) in detecting transmitter overflow following adequate stimulation in anaesthetised animals or in detecting spontaneous transmitter release in freely moving animals. This might mean that the exceptional circumstances of electrical stimulation, involving the synchronous activation of large numbers of presynaptic axons, may produce conditions of transmitter overspill which are not found in normally working synapses. Apart from this restriction to an analysis of electrically stimulated synapses, there are several other problems with FCV. It can be an exasperating technique to use, as electrochemical signals can almost always be obtained from a given experiment; but discovering what they mean in terms of transmitter release is another problem entirely! The speed of the analysis, while it gives the technique a very good time resolution of electrochemical events, often makes it difficult to distinguish between different electrochemical materials. Changes in the tissue unrelated to electroactive transmitters, for example changes in pH or tissue impedance, can mimic or mask the signals from transmitter release. Despite these caveats, however, it is difficult not to be optimistic about the future of FCV research. It appears to offer a tool, albeit an imperfect one, to pierce the shroud of ignorance that covers our knowledge of synaptic kinetics in the CNS.

Julian Millar

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Volume transmission in the spinal dorsal horn: role of neuropeptides in spinal nociceptive

Summary of a lecture given at the Designated Session of the Somatosensory & Motor Physiology Group at the Oxford Meeting (July 1992)

It was long believed that information exchange between neurones would take place at synapses only, where the presynaptic nerve terminal stores transmitter substances in vesicles and comes into close contact (within a few nanometres) with the postsynaptic membrane of the effector cell where there is a high density of specific membrane receptors for the particular neurotransmitter(s). The exocytosis of the neurotransmitter into the synaptic cleft is followed by a rapid inactivation of the transmitter molecules which is a prerequisite for relatively high rates of signal transmission between nerve cells (fast synaptic transmission).

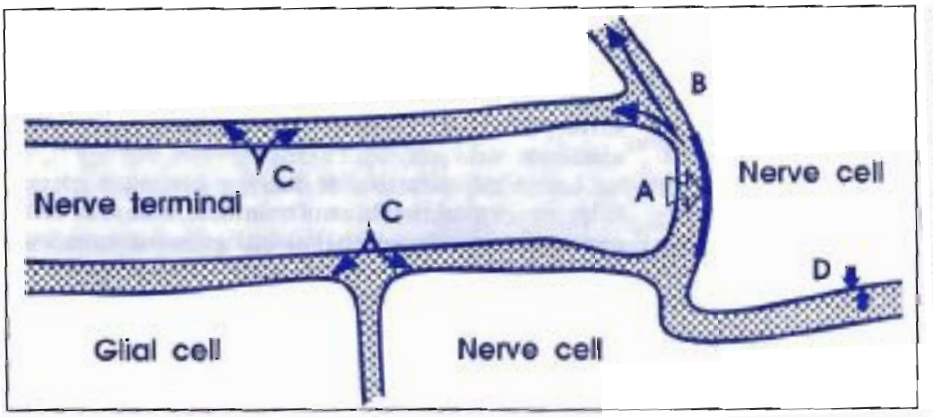

Fig 1 Schematic diagram illustrating some aspects of the concept of "volume transmission". The open arrow at A indicates neurotransmitter release at a specialised synaptic junction. If inactivation mechanisms are saturated, eg by excessive release of transmitter due to long-lasting high-frequency discharges of the presynaptic nerve terminal (grey), neuromediator molecules, such as peptides or monoamines, may diffuse via the extracellular fluid to distant target sites indicated by filled arrows at B. Possibly, neuromediators could also be released from non-synaptic sites (arrows at C). Long-lasting high-frequency discharges of a neuronal population may change the concentration of ions in the extracellular fluid (arrows at D). Ions could then also diffuse to distant target cells.

Recent evidence suggests that neuromediators (neurotransmitter and neuromodulators) which may be released from synaptic and from non-synaptic sites (*boutons en passant*) may diffuse via the extracellular fluid to target cells distant (in the micrometre to millimetre range) from the release sites. This mode of intercellular communication has been termed "volume transmission" (Agnati *et al*, 1986), because here the chemical signals are conveyed via the volume of the extracellular fluid (see Fig 1). Thus, volume transmission summarises all extrasynaptic modes of chemical transmission in the nervous system, including the concepts of paracrine secretion in the brain and local humoral communication (Agnati *et al*, 1986). Chemical signals involved in volume transmission are neuropeptides, trophic factors, inorganic ions, biogenic amines and even classical neurotransmitters if they are diffusely distributed in the extracellular fluid of a particular area of neuronal tissue. For neurotransmitters this may be the case if, after excessive release, inactivation mechanisms are saturated.

Obviously, the concentration achieved several hundred micrometres distant from the release sites will be considerably lower than those concentrations which may be gained within the synaptic cleft. Thus, high-affinity binding sites for neuromediators are the most likely candidates to mediate the effects of volume transmission. Despite the diffuse presence of the chemical signal, binding to high-affinity receptors - which may have a very distinct histological distribution - will result in a high spatial order of action. Volume transmission may be suspected if a ligand/receptor mismatch exists, ie if the histological distribution of storage sites for a neuromediator does not match the distribution of any of its known binding sites and if the chemical signal is present extrasynaptically at biologically effective concentrations.

In the spinal cord a ligand/receptor mismatch exists to some degree for neuropeptides such as the tachykinins (Helke *et al*, 1990) and some neuropeptides can be detected in the interstitial space (Duggan *et al*, 1990) and even in the cerebrospinal fluid after strong and long-lasting excitation of primary afferent nociceptors, eg following trauma or inflammation of peripheral tissues such as skin. This suggests that under certain patho-physiological conditions volume transmission may also play a role in the spinal cord.

To study the effects of volume transmission in the spinal cord, the effects of strong excitation of primary afferent nociceptors may be assessed and compared with the effects of the controlled superfusion of the cord dorsum with the appropriate neuromediator candidates (see Fig 2). For the relatively large cord dorsum of the cat we have constructed a perspex chamber which fits over the dorsal surface of the lumbar spinal cord (Sandkühler & Zimmermann, 1988). Complete sealing is achieved if the chamber is placed on top of a ring of silicone grease. The contents of this chamber can be exchanged completely within seconds through polyethylene tubings without interfering with the quality of the single cell recording underneath the pool. For the relatively small rat spinal cord we have synthesised a special silicon rubber which remains viscous for approximately 20 minutes after all components have been mixed together (Sandkühler *et al*, 1991). During this time, the paste can be applied to the cord dorsum to form a well of any size and shape and with complete sealing. No effects on the impulse conduction in fibres of passage nor on postsynaptic potentials were detected by applying this pool to the cord (Sandkühler *et al*, 1991).

Following superfusion of the rat cord dorsum for 30 minutes with a single dose of ^{125}I-labelled Neurokinin A, significant radioactivity was detected up to a depth of 1.5 mm below the dorsal surface of the cord. Tissue concentrations of [^{125}I]-Neurokinin A in the dorsal horn may be two to three orders of magnitude lower than those in the superfusate. Since significantly less labelling was observed when the cord was superfused with a single dose of 15 or 60 minutes, we always used 30 minute periods for superfusion. Considerable amounts of radioactivity were detected in the urine, especially following the 30 and 60 minute superfusions (Beck *et al*, 1992). We therefore do not recommend continuously exchanging the pool contents or significantly enlarging the exposed cord surface, eg by superfusing the dorsal and ventral cord if a local spinal effect is to be achieved.

The functional consequences of the release of numerous neuropeptides and other neuroactive substances into the interstitial space of the spinal cord is not known. The observation, however, that a strong excitation of nociceptors is necessary, both for the induction of some forms of long-term plastic changes in the spinal dorsal horn (Woolf & King, 1990) and for a detectable release of neuropeptides into the extracellular fluid, suggests that volume transmission may be involved in the induction of neuronal plasticity in the spinal dorsal horn. Possibly the synaptic strength within some neuronal pathways is modified as neuropeptides which are endogenously released in the spinal cord such as substance P and calcitonin gene-related peptide are capable of modulating the basal efflux of endogenous aspartate and glutamate (Kangrga & Randic, 1990). Further, substance P

may enhance the excitatory responses of spinothalamic tract neurones mediated by NMDA-receptors (Dougherty & Willis, 1991). Volume transmission of neuropeptides in the spinal dorsal horn should not affect single cells only, but should rather influence the properties of a population of neurones and the function of the neuronal network in the dorsal horn. Opening of a positive feedback loop which involves nociceptive neurones could result in enhanced and prolonged responses to noxious stimulation. Opening of an excitatory connection between multireceptive neurones would result in an additive effect of their receptive fields (Eblen-Zajjur & Sandkühler, 1991).

To test these hypotheses, we have made multiple single neurone recordings in the spinal cord via a single, low impedance tungsten microelectrode in male adult rats under deep pentobarbitone anaesthesia (Fig 2). The shape of each action potential in the multineurone recording was determined on-line by cluster analysis and assigned to individual neurones. The cross-correlograms of the background activity of simultaneously recorded neurones were determined before and after strong excitation of primary afferent nociceptors (heat-induced inflammation of the skin close to the cutaneous receptive fields of the neurones under study). With the skin inflamed 8 out of 18 pairs of neurones had cross-correlograms with bilateral peaks but only 2 out of 62 pairs of neurones when the skin was intact (Eblen-Zajjur & Sandkühler, 1991). In a computer simulation of a simple neuronal network, bilateral peaks in the cross-correlograms could easily be produced by opening a positive feedback loop. Thus, these findings are consistent with the hypothesis that reverberating circuits may be opened in the spinal cord following peripheral trauma.

The cutaneous mechanoreceptive fields of 62 pairs of neurones recorded simultaneously at the same site in the spinal dorsal horn did *not* overlap in 12.6% and partially overlapped in 26.7% of all pairs of neurones tested. With the skin inflamed the receptive fields of *all* pairs of neurones completely overlapped (Eblen-Zajjur & Sandkühler, 1991). This finding is consistent with the hypothesis that stimulation of fine primary afferent not only enlarges cutaneous receptive fields by making subliminal input suprathreshold (Woolf & King, 1990) but also results in additive effects on the receptive fields of neurones located in close proximity to each other (Eblen-Zajjur & Sandkühler, 1991).

An obvious next step is to superfuse the cord dorsum at the recording sites with putative neuromediators of these plastic changes. We have started this series of experiments with the neuropeptide somatostatin, as the role of somatostatin in spinal nociception is highly controversial. Some authors believe it mediates spinal nociception whereas others have reported that it inhibits spinal nociception. In our experiments, spinal superfusion with somatostatin (1 or 100 µM) at the recording sites has to date not produced an expansion of the cutaneous mechanoreceptive fields, nor has it generated bilateral peaks in the cross-correlograms.

To test whether somatostatin mediates the acute effects of nociceptive stimulation we have used two approaches. First, noxious but not innocuous stimulation, eg of the skin of a frontpaw, always produces a strong heterosegmental inhibition of nociceptive responses, eg in the lumbar spinal dorsal horn. To test whether somatostatin may also trigger this heterosegmental inhibition, we superfused the cervical enlargement with somatostatin (1 or 100 µM) while recording noxious radiant heat-evoked responses in the lumbar cord of seven cats, deeply anaesthetised with pentobarbitone. Somatostatin failed to affect nociceptive responses in any of the experiments (Sandkühler *et al*, 1993). We then superfused the spinal cord directly at the recording site. At 61 µM, somatostatin selectively depressed noxious heat-evoked responses (to 59.7 ± 5.1 % of control, n = 8) without changing innocuous brush-evoked responses or background activity (Sandkühler *et al*, 1990). The slope of the stimulus-response functions for graded noxious skin stimuli (42 ° to 52 °C) was reduced to 48.8 ± 9.3 % of control (n =4). Similar results were obtained by superfusion with morphine at 0.3 or 3.0 mM. The effects of morphine, but not of somatostatin, were antagonised by systemic naloxone (2.7 nmol I.V.). Further, we determined the expression of the proto-oncogene *c-fos* with immunocytochemistry (primary antibody at 1:40,000, DAP-method, free floating sections, one hour survival time after a

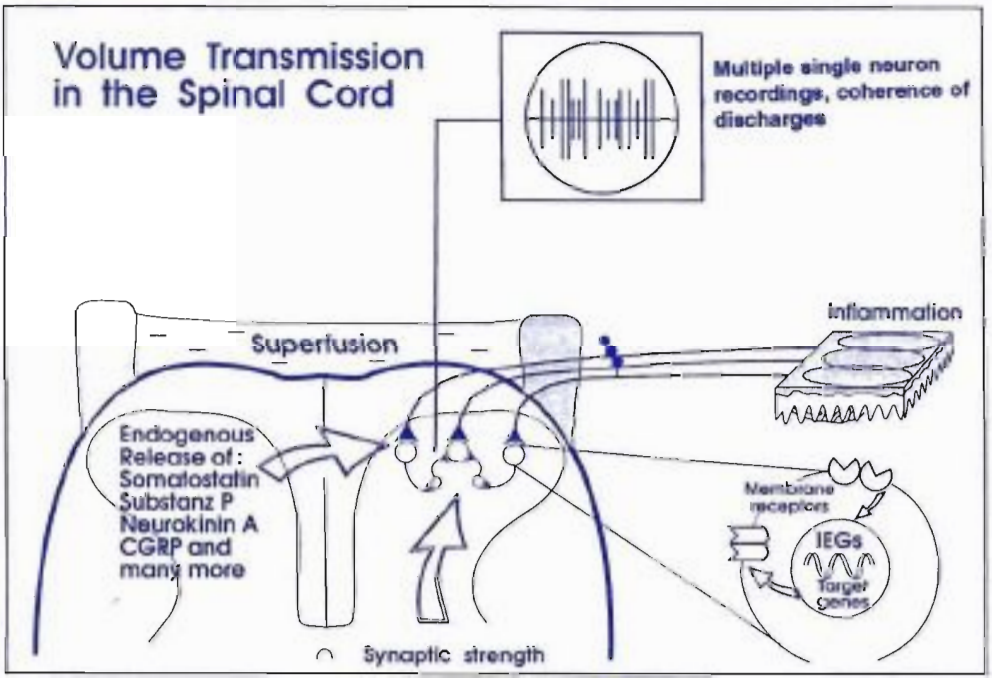

Fig 2 Experimental set-up to study the effects of volume transmission in the spinal dorsal horn. Endogenous release of a mixture of neuropeptides may be evoked by strong excitation of fine primary afferent nerve fibres, eg by inflammation of the skin. The controlled superfusion of the cord dorsum is used to study the effects of selected peptides on the neuronal network underneath. Single and multiple neurone recordings and immunocytochemical detection of products of immediate-early-genes (IEGs) are employed to determine short and long term effects of extrasynaptic neuropeptides in the spinal dorsal horn.

superfusion interval of 30 minutes) in neurones of the rat spinal cord after superfusion of the cord dorsum with artificial cerebrospinal fluid or somatostatin at 10 or 100 μM (Fig 2). No significant differences in the number of *c-fos* positive cells were found in the spinal dorsal horn following artificial cerebrospinal fluid and somatostatin, whereas noxious radiant skin heating or superfusion of the cord dorsum with substance P (100 μM) produced a strong increase in *c-fos* labelling in the superficial and deep dorsal horn (Beck & Sandkühler, 1991). This suggests that somatostatin does not mediate the excitatory effects of noxious skin stimulation. Somatostatin could rather be an inhibitory neuromodulator in the spinal cord, probably released not only from spinal neurones but also from fine primary afferents.

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Are the mechanisms of long-term potentiation involved in learning?

Summary of a lecture delivered at the Society's symposium for final year undergraduates (Leeds, December 1992)

The long-lasting nature of the synaptic change induced in long-term potentiation (LTP) has, ever since its discovery 20 years ago, fuelled speculation that its underlying neural mechanisms might occur during and be necessary for certain kinds of learning (Bliss & Collingridge, 1993). LTP has other properties analogous to memory in addition to its persistence - notably associativity and input-specificity - these being relevant to the conditions under which behavioural learning takes place and to information storage-capacity, respectively. An additional reason for interest is because the idea that changes in synaptic efficacy could be the basis of memory has a long history, having first been mooted in a Croonian Lecture to the Royal Society in 1894 by Ramon y Cajal.

The phenomenon of LTP is well known to physiologists. First reported in detail by Bliss & Lomo in *The Journal of Physiology* in 1973, LTP refers to the long-lasting, synapse-specific enhancement of synaptic efficacy that can be induced by pairing presynaptic activity with postsynaptic depolarisation. A typical LTP experiment consists of three phases: (1) a baseline period of low-frequency stimulation during which the early rising slope of postsynaptic potentials are measured over a defined period (eg 10 minutes); (2) a brief period of high-frequency, high-intensity tetanic stimulation (sometimes as short as 100 ms); and (3) a longer period of low-frequency stimulation during which the consequences of the brief tetanic stimulation are measured (generally for 1-2 hours or, in chronic recording preparations, over days). While first studied *in vivo*, LTP is now commonly studied *in vitro* using slices of hippocampal or cortical tissue. Numerous studies have explored the phenomenon and we now have a reasonably good understanding of the mechanisms of its induction. Several of the physiological characteristics of LTP, such as associativity and input specificity, can be understood in terms of the dual voltage- and ligand-gated properties of the *N*-methyl-D-aspartate receptor. Our knowledge of how LTP is expressed continues, however, to be a focus of dispute and uncertainty.

But does LTP play any role in learning? Or, to put the issue more exactly, are the neural mechanisms underlying the physiological phenomenon of LTP activated during learning and necessary for information storage in the brain? The gist of the idea is as follows. Suppose a rodent wanted to remember where its burrow was located. Different views of and smells from the surrounding environment would, presumably, be represented in certain regions of the brain as distinct patterns of neural activity as the animal explored the scene. Sensory stimulation in the immediate neighbourhood of the burrow would occur at closely related points in time and, through the property of associativity, result in strengthened synapses between co-active neurons. While the functional effect of these changes would, of course, depend very much on the exact neural circuitry in which they occurred, it is reasonable to suppose that one consequence would be that the animal could retrieve a memory of the sensory cues around his burrow from those available some distance away. This capacity to remember what something looks or smells like in the absence of many of the stimuli of which that scene is composed, reminiscent of Hebb's cell-assembly concept (see Milner, 1993), is a crucial constituent of memory and part of any system that the animal might use to navigate accurately back home.

Three main experimental predictions have been examined to test the possible role of LTP in learning: (1) there should be some overlap between the behavioral characteristics of learning and the known physiological properties of LTP; (2) certain types of learning should be impaired when LTP is blocked selectively; (3) LTP-like synaptic changes should occur when animals learn. We shall consider these in turn.

Is there any overlap between the characteristics of learning and the physiological properties of LTP?

One important characteristic of memory is forgetting. LTP also decays to its nominal baseline over time. If LTP is the basis of memory, does its decay underlie the forgetting of information? Barnes (1979) carried out a laboratory study analogous to the problem faced by the animal trying to remember its burrow. Rats were placed once a day on a large circular table illuminated by fairly bright lights and given an opportunity to find a burrow hidden just underneath the edge of the table from where they could escape into the darkness. Initially, the rats would search all over the table until they eventually found and got into the correct burrow but, after a few days, would run straight to it from where they had been released at the centre. All of the rats had previously been implanted with indwelling electrodes in order to induce and record LTP in the dentate gyrus of the hippocampus. Barnes found that rats which showed slowly decaying LTP learned the task faster and better than rats whose LTP was less persistent.

Another important characteristic of learning is that we can only learn so much at one sitting - after a while we saturate and can take in no more. McNaughton *et al* (1986) have described experiments suggesting that this phenomenon might also be explained in terms of LTP. They induced LTP physiologically to its asymptote (ie to the point where no more synaptic increase could be obtained) and then trained their rats to learn a new burrow location in the circle maze task. A control group was subject to similar stimulation of the dentate gyrus except that it consisted of low frequency patterns which did not induce LTP. The results showed that the rats which had their hippocampal synapses saturated had great difficulty in learning the new location of the burrow - prior saturation of LTP had occluded learning. In an ingenious follow-up, Castro *et al* (1989) have reported that if a two-week waiting period intervenes between the saturation of LTP and the subsequent retraining phase of a spatial task, learning then proceeds normally. They argue that the crucial variable is allowing sufficient time for the saturated synapses to decay gradually back to baseline. Unfortunately, work in other laboratories, including my own (Jeffery & Morris, 1983), has had difficulty replicating these occlusion findings. In our hands, repeated episodes of high-frequency stimulation sufficient to produce as much cumulative LTP as that in McNaughton's experiments fail to affect spatial learning. There are several possible reasons for this discrepancy. One is that the difficulty of finding the place in the angular bundle of the perforant path where a large proportion of the afferent fibres can be activated. This is vital because, if only a subset of afferent terminals are saturated, it would not be surprising that learning fails to be occluded by prior saturation of only part of the hippocampus. However, an alternative possibility is that saturating LTP really does have no effect on spatial learning - an implication which would be potentially damaging for the hypothesis. Further research on this conundrum is underway.

Are certain kinds of learning impaired when LTP is blocked selectively?

The fact that most forms of LTP require the activation of NMDA receptors suggests a second avenue for investigation. Morris *et al* (1986) examined this issue using 2-amino-5-phosphonovalerate (AP5), which is a potent and highly selective antagonist of NMDA receptors. Unfortunately, AP5 does not cross the blood-brain barrier very effectively. However, by implanting small osmotic minipumps containing AP5 under the dorsal skin surface and leading a small catheter to the lateral ventricle of the brain, we were able to infuse AP5 directly into the brain over 14 days - hopefully creating a situation where fast neural transmission in regions such as the hippocampus was normal excepting that patterns of activity which would normally induce synaptic changes are unable to do so. During the drug infusion period, we attempted to train these rats in a spatial learning task in which the animals have to swim through cold water in search of a hidden escape platform located at one spot just under the water surface. Normal and control rats learn this water maze task very rapidly, swimming from any starting position directly to the location of the platform. Rats treated with AP5 were impaired. In a series of experiments (see Morris *et al*, 1990), my colleagues and I have investigated the physiological and behavioural selectivity of this AP5-induced learning impairment in various ways. For example, the learning deficit has a similar dose-response profile to that of LTP *in vivo* and occurs at approximately the same extracellular concentration of AP5 *in vivo* as that which blocks LTP in the *in vitro* hippocampal slice. In addition, we have found that AP5 does not impair all learning tasks and, specifically, fails to affect visual discrimination learning. This latter finding has two implications: first, that at the concentrations we are using, the drug cannot be impairing the animals' ability to see or to move around properly and thus the spatial learning deficit cannot be secondary to such changes; second, that LTP might only be involved in selected types of learning - such as those mediated by the hippocampus.

Not all experiments have looked at spatial learning. Rawlins and his colleagues (personal communication) have recently made a direct comparison of AP5 with hippocampal lesions on a range of non-spatial tasks which are differentially affected by hippocampal lesions. Strikingly, they find that tasks impaired by hippocampal lesions are also impaired by intraventricular infusions of AP5, while tasks spared by such lesions are also unaffected by the drug. In another set of experiments, Miserendino *et al* (1990) have examined a phenomenon called "fear-potentiated startle" which is known to depend on circuitry through the amygdala and brainstem. Rats show a pronounced startle reaction to loud sounds; this reaction is amplified if the sound is presented at a time when the rat has otherwise been made fearful, such as by the immediately prior presentation of a second stimulus such as a light previously paired with weak electric shock. These experimenters wondered if the NMDA receptors found in certain regions of the amygdala were responsible for learning this fear-potentiating effect. In a series of studies, they first demonstrated that local infusion of an NMDA antagonist into the amygdala impaired the task and then examined whether this was due to a direct effect upon the learning process or due to various non-associative processes. The results were clear cut: the drug had no effect on sensitivity to light, sound or shock, but did selectively impair learning.

Pharmacological studies have several drawbacks. Despite everyone's best efforts to control for them, there are always side-effects that could be contributing to the behavioural changes observed. This is particularly problematic with NMDA antagonists because of the presence of NMDA receptors in many circuits throughout the brain where they are involved in a myriad of different functions in addition to any role they might have in learning.

A radically different experimental strategy is to make transgenic animals in which proteins which are putatively involved in some critical aspect of LTP have been deleted. Silva *et al* (1992*a*,*b*)

have recently used this gene "knock-out" technique and discovered that mice mutant for the α sub-unit of calcium-calmodulin dependent protein kinase type II (αCAMKII) are deficient in LTP and also display what appears to be a selective learning impairment. Pharmacological techniques are, however, much simpler (and faster) than this molecular engineering approach and the use of other drugs to control LTP than NMDA antagonists (eg glycine agonists and antagonists, inhibition of selected protein kinases, calpain inhibitors, etc) is clearly desirable. If drugs could be found to improve LTP and if these also improved memory, it might even be possible to use these clinically to alleviate at least some of the progressive memory loss seen in such crippling conditions as Alzheimer's disease. There are now some hints that a class of compounds called nootropics may have such properties.

Do LTP-like synaptic changes occur when animals learn?

If learning depends upon synaptic plasticity, LTP-like changes should occur in brain areas such as the hippocampus and the cortex and it should be possible to see and measure them. Unfortunately, matters are not quite so straightforward. One problem is that if the storage capacity of these areas is anything appreciable, which we know it must be to hold a lifetime's worth of information, searching for the synaptic changes caused by a limited set of training experiences in an individual animal is a bit like searching for a needle in a haystack. McNaughton & Morris (1987) have dubbed this puzzle the "Catch-22 problem of learning" - the catch being that if a change is found in the adult brain of vertebrates following a learning experience, it cannot be memory! There are other difficulties with the approach also. One is that there have been recent reports that, in addition to the increases in synaptic strength characteristic of LTP, synaptic weakening may occur with certain patterns of stimulation (Bear & Dudek, 1992). If this is true, finding specific changes in selected synapses using such gross indicators as extracellularly recorded field-potentials looks remote.

The use of an extracellular recording electrode to record selected synaptic changes is a bit like placing a microphone at the centre of the pitch of a football game to record conversations in the crowd. It won't work. But what it will do, and do very well, is give an overall impression of the level of excitement in the crowd - such as after a goal. The life of a laboratory rat is not, shall we say, very exciting, but it does have its moments. And such a moment might be the opportunity to explore an arena stocked full of interesting toys, smells, and things to clamber over. Sharp *et al* (1989) examined what happened to field-potentials during such exploration and found a gradual short-term increase in the size of the synaptic component of field-potentials in the dentate gyrus which then declined to baseline over the next 30 minutes or so. Interestingly, they also found a decrease in the size and latency of cell firing, indicating that the apparent synaptic change was not secondary to some alteration in neural excitability. They suggested that both changes may represent alterations in synaptic efficacy of excitatory and inhibitory feedforward connections associated with learning during exploration. Unfortunately, work by Moser *et al* (1993) has shown that essentially identical field-potential changes occur when the brain is warmed by radiant heat and that behavioural exploration is, surprisingly, associated with an increase in brain temperature of up to 2 °C. Exploration-induced synaptic plasticity appears to be a temperature "artefact". The results of Moser *et al* serve as a salutary reminder that the brain does not exist in isolation from the rest of the body and that neuroscientists must consider the many aspects of the physiology of the body and brain in experiments conducted *in vivo*.

Single-unit recording studies offer another, albeit indirect, way of addressing the question of whether learning is associated with alterations in synaptic efficacy. Do patterns of neural activity which are known to be capable of inducing LTP actually occur? Although it is not possible to examine the specific synaptic consequences of these patterns, their existence would imply that sufficient conditions for LTP to be induced have been met. Otto *et al* (1991) have reported that single units in the CA1 region of the hippocampus display short patterns of burst firing during learning, spaced at what we know to be exactly optimum intervals for inducing LTP. Pavlides & Winson (1989) also saw similar patterns in animals exposed for long periods to areas of a familiar environment where place-cells, which are cells responsive to features of the environment (O'Keefe, 1976), fired frequently. Interestingly, they also found that, during later periods of REM (rapid-eye movement) sleep, these same place cells fired more often than place-cells responsive in other non-visited areas of the environment. This extraordinary finding hints at the possibility that the burst firing is consolidating information in long-term memory and that even rats "dream" about the places they have recently visited! Finally, Cahusac *et al* (1992) have shown that the firing of hippocampal cells to a visual stimulus (as against electrical stimulation of the perforant path) is enhanced following pairings of this stimulus with iontophoretically applied glutamate.

Conclusion

Is LTP involved in learning? The truth is that we still do not know. It does seem that activation of its underlying neural mechanisms is required for certain forms of learning, but such evidence will ultimately only be persuasive when complemented by evidence that synaptic changes accompany such learning. One obstacle to current research is that we are still very ignorant about how information is represented as spatiotemporal patterns of neural activity in the vertebrate brain, and how synaptic plasticity interacts with activity in different neural circuits to realise the particular types of information processing that then occur. Computational models of how the activity of neurons embedded in particular types of neural architecture interact with specific mechanisms of synaptic plasticity will be an important complement to experimental work of the kind summarised above.

Richard G Morris

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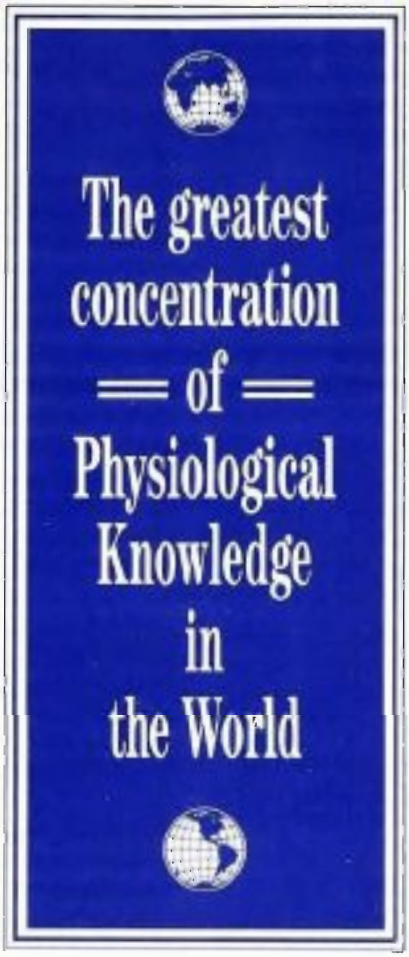
Please enclose two small addressed envelopes with your application. Applications should be sent to:-

Dr D Ogden, Neurophysiology, NIMR, The Ridgeway, London NW7 1AA, UK, fax: (081) 906 4477

L.Aitken (Australia), R.Aldrich (USA), D.L.Alkon (USA), A.Allen (UK), R.J.Alpern (USA), C.Allweiss (Israel), P.L.R.Andrews (UK), B.E.Argent (UK), D.Armstrong (UK), C.C.Ashley (UK), J.Ashmore (UK), G.R.Barnes (UK), K.Beam (USA), J.L.Bert (Canada), B.Bigland-Ritchie (USA), L.J.Bindman (UK), H.Bjurstedt (Sweden), C.Blakemore (UK), S.Bloom (UK), T.I.Bonner (USA), F.Bowser-Riley (UK), C.A.R.Boyd (UK), R.D.H.Boyd (UK), A.M.Brown (USA), D.Brown (UK), H.Brown (UK), J.C.Brown (Canada), B.Bush (UK), M.A.Castellini (USA), J.C.Challis (Canada), E.L.Chambers (USA), J-P.Changeux (France), C.I.Cheeseman (Canada), P.Cohen (UK), J.H.Coote (UK), M.Crompton (UK), V.Crunelli (UK), S.G.Cull-Candy (UK), F.E.Curry (USA), G.F.DiBona (USA), G.J.Dockray (UK), A.Dolphin (UK), A.Doucet (France), R.Dubner (USA), A.W.Duggan (UK), M.Duchen (UK), C.Edwards (UK), S.Egginton (UK), D.A.Eisner (UK), E.Evans (UK), M.Fedak (UK), J.Feldman (USA), W.Ferrell (UK), A.P.Fishman (USA), M.Forsling (UK), E.Frömter (Germany), J.B.Furness (Australia), P.Gaehtgens (Germany), S.Gandevia (Australia), I.M.Garel (France), A.Garner (UK), W.R.Giles (Canada), I.M.Glynn (UK), G.Gold (UK), J.Grantham (USA), R.Green (UK), A.Grigoriev (Russia), D.Grundy (UK), D.Guha (India), M.J.Gutnick (Israel), A.Guz (UK), R.Hainsworth (UK), M.Hanson (UK), A.J.Harmar (UK), D.J.Hartshorne (USA), B.J.Harvey (France), H.W.Heiss (Germany), C.H.Heller (USA), J.Herbert (UK), J.Hescheler (Germany), O.Hikosaka (Japan), S.G.Hillier (UK), P.Hochachka (Canada), E.Hoffmann (Denmark), A.V.Holden (UK), G.Horn (UK), O.Hudlicka (UK), J.Hughes (UK),

SYMPOSIUM ORGANISERS

J.Hutton (USA), H.E.Huxley (USA), M.Imai (Japan), Y.Iwamura (Japan), E.Janowska (Sweden), J.G.R.Jefferys (UK),



INVITED LECTURERS

Sir Bernard Katz, W.Boron, B. Folkow, A. Michelsen, R.F. Schmidt, E.M. Wright

PLENARY LECTURERS

B. Sakmann, S. Brenner, T. Sejnowski, L. Wolpert

E.J.Johns (UK), K.O.Johnson (USA), A.Kaneko (Japan), J.Kaplan (USA), J.S.Kelly (UK), M.Khananashvili (Russia), E.P.Kindwall (USA), M.A.Knepper (USA), T.Kumazawa (Japan), H.Kuriyama (Japan), K.Kurokowa (Japan), T.D.Lamb (UK), J.Lännergren (Sweden), G.M.Lees (UK), G.Leng (UK), D.Louvard (France), L.J.Mandel (USA), C.J.Mathias (UK), C.R.McCrohan (UK), N.G.McHale (UK), J.C.McGrath (UK), D.McQueen (UK), D.Medvedev (Russia), D.J.Miller (UK), B.Milner (Canada), C.Monge (Peru), M.C.Moore-Ede (USA), J.F.B.Morrison (UK), N.G.Moss (USA), L.G.Navar (USA), D.M.Neil (UK), J.Nicholls (Switzerland), P.Nye (UK), R.Olver (UK), R.O'Regan (Ireland), D.Paterson (UK), J.Pearson (UK), O.H.Petersen (UK), D.Pfaff (USA), M-A.Pilot (UK), M.Posner (USA), J.Phillips (UK), D.J.Price (UK), U.Proske (Australia), H.P.Rang (UK), R.Reed (Norway), L.Reuss (USA), D.W.Richter (Germany), T.J.Rink (USA), A.Roberts (UK), N.Rothwell (UK), C.de Rouffignac (France), B.Saltin (Sweden), N.R.Saunders (Australia), A.Scarpa (USA), J.Schrader (Germany), J.R.Seckl (UK), C.P.Sibley (UK), S.Silverstein (USA), E.B.Smith (UK), R.J.Solaro (USA), A.Somlyo (USA), A.P.Somlyo (USA), H.Sparks (USA), N.Spurway (UK), K.M.Spyer (UK), N.Standen (UK), J.Stein (UK), K.Storey (Canada), K.Sudakov (Russia), J.R.Sutton (Australia), C.C.Tisher (USA), R.D.Traub (USA), D.R.Trentham (UK), R.W.Tsien (USA), P.Vanhoutte (USA), R.D.Vaughan-Jones (UK), L.Wang (Canada), M.Ward (UK), J.Waterhouse (UK), E.Weibel (Switzerland), M.Whitaker (UK), J.G.Widdicombe (UK), P.Winlove (UK), C.Woody (USA), C.Woolf (UK), S.Wray (UK), E.Wright (USA), R.Zak (USA), S.Zeki (UK)

XXXII

32nd INTERNATIONAL CONGRESS OF PHYSIOLOGICAL SCIENCES

INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES 1950

TO BE HELD AT

THE SCOTTISH EXHIBITION & CONFERENCE CENTRE AND GLASGOW UNIVERSITY

1st-6th August 1993

REGISTRATION FEE £250 (before 17 April 1993) £300 thereafter. Discount fee for students £125. Fee for person accompanying £100.
For registration forms contact: CEP Consultants Ltd., Dept. IUPS6, 26-28 Albany Street, Edinburgh EH1 3QH. Phone 031-557 2478. Fax 031-557 5749.

IUPS Congress, Glasgow 1993 - Pubs and Clubs in Glasgow

For those long summer evenings after a "surfeit of science" you may want to wind up/down or even continue your discussions at one of Glasgow's pubs or nightclubs. There are certainly plenty to choose from but some have particulars features which merit a special visit.

The City Centre, unsurprisingly the shopping and business heartland of Glasgow, has many upmarket watering holes frequented by the discerning business community. The Horseshoe Bar and Restaurant (Drury Street) has the distinction of having the longest island bar in Europe and its decor includes beautiful etched glass. Appropriately for a bar in the business community, the Drum and Monkey (St Vincent Street) used to be a bank. The bevelled counter still stands, now used to draw beer rather than money - giving a new meaning to "the wages of sin"? Remaining with unusual former lives, De Quinceys (Renfield Street) was once the premises of the Prudential Insurance Company. When the building was renovated, beautiful Victorian tiles were uncovered and were retained as an unusual decorative feature of the new business.

If you prefer a more artistic environment, take a trip east to Glasgow's Merchant City. Babbity Bowster's (Blackfriars Street) has regular poetry readings and performances of folk music. It has pleasant lattice windows and serves huge measures of spirits.

The Rogano (Exchange Place) is special for its 1930s art decor interior, identical to that which graced the Cunard liner, the Queen Mary. This ship is connected with Glasgow because it was built on the Clyde.

For those with a taste for strong ale, the Bon Accord (North Street) at Charing Cross sells many speciality beers. With names like Old Peculiar and Green Man on draft - how can you go wrong?

Near the SECC, and therefore but a stone's throw from the Poster Session, the North Torunda (Tunnell Street) is a restaurant/bar complex built in the converted elevator shaft for the old Clyde Tunnel.

Moving west to the Glasgow University area there are many pubs that service the student population. For a taste of the Gaelic way of life try the Uisge Beatha (Woodlands Road). Uisge Beatha (pronounced ushcabe) is Gaelic for "water of life" which of course means whisky. All the barmen wear kilts and a novel decorative feature is the mantelpiece piled with empty shortbread tins.

Byres Road has many pubs up and down its length. Whistler's Mother serves huge cappuccinos. Its walls are plastered with posters and cuttings with a decidedly European theme. Its name may honour the celebrated American artist James McNeill Whistler who was of Scottish descent. Glasgow University was bequeathed the contents of his studio at his death; these are now displayed in the Hunterian Museum. Curlers is conveniently situated next to Hillhead Underground Station. Named after the game (curling), Curlers is a "Glasgow University institution". Its decor has changed several times in the last few years; it currently favours marbled table tops with wrought iron legs. It also has the distinction of being the oldest public house in Byres Road.

The Ubiquitous Chip (Ashton Lane) is one of Glasgow's most famous restaurants. Upstairs from the main restaurant is a wine bar popular with the artistic and academic communities. Cottiers wine bar (Hyndland Street) is a new establishment fast becoming popular. It is part of a complex situated in converted Dowanhill Parish Church.

Nightclubs are located for the most part in the City Centre. Victoria's (Sauchiehall Street) is open 7 days a week until 3.30 am. Mardi Gras (Dunlop Street) has a moving dance floor and is open from 10.30 pm to 3.00 am Friday and Saturday. The Riverside Club (Clyde Street) is a departure from the normal disco and hosts ceilidhs (a great Scottish social institution) from 7.30 pm Friday and Saturday nights. Or if you want to gamble there is a Princes Casino (Sauchiehall Street) which opens its doors at 2.00 pm until 4.00 am every day except Sunday when they open at 7.30 pm.

The West End's most famous nightclub is Cleopatra's (Great Western Road) and is open from 11.00 pm to 3.00 am every day except Tuesday. The Volcano (Benalder Street) specialises in Latin American, reggae and World music.

Many Glaswegians would argue with the choice of pubs and clubs mentioned in this article because it may not include their own particular favourites. You too after visiting Glasgow may also disagree. However, pubs and clubs abound and there is sure to be one somewhere to suit your personality and pocket.

Heather Gibson

Designated Sessions at the Leicester Meeting

Epithelia and Membrane Transport Special Interest Group

The Epithelia and Membrane Transport Group is a new Group formed from the merger of two other Groups in the Society. Both the Epithelial Physiology and the Membrane Transport Groups have had successful Designated Sessions at numerous Society Meetings over the past few years. At the instigation of the Committee, a review of all the Special Interest Groups took place last year and it was decided opportune to merge these two Groups. The proposed merger of the two Groups met with considerable enthusiasm from their respective members, much due to members being comfortable in submitting abstracts to either of these Special Interest Groups. In the past, the Designated Sessions have been considerably lively with a knowledgeable audience willing to discuss the Communications. Therefore, the merger appears an obvious step and it is hoped that the merged Group will build upon the success of the individual Groups.

During the Leicester Meeting, Professor Ron Borchardt from the University of Kansas will be delivering a Plenary Lecture entitled "The use of cultured intestinal epithelial cells (Caco-2) to study the vectorial transport of bile acids". Professor Borchardt has gained immense respect in the field of transport, mainly in an applied area, by his use of cultured gastrointestinal and brain endothelial cells to reconstitute intact epithelia and endothelia *in vitro* in order to uncover basic mechanisms of the barrier properties of these two tissues. At the Leicester Meeting Professor Borchardt's lecture will concentrate on the transport of bile acids across cultured epithelial layers of human intestinal Caco-2 cells. An abstract of Professor Borchardt's lecture is presented below.

At the Meeting there will also be a short business meeting where the future events organised by the Group will be discussed. In particular, it is hoped that members of the Group will provide new ideas for activities of the Group including suggestions for plenary lectures. Also, it would be appropriate to discuss the feeling of the members for the frequency of the Meetings of this Special Interest Group.

Barry Hirst

The use of cultured intestinal epithelial cells (Caco-2) to study the vectorial transport of bile acids

Bile acids are produced in the liver and secreted into the small intestine whereby virtue of their surfactant activity they play a role in the intestinal absorption of lipids. After exerting their action, bile acids are passively or actively transported across the intestinal mucosa and recycled back to the liver. This entero-hepatic recirculation ensures minimal loss of bile acids into the feces and maximal utilization along the entire length of the small intestine. While some of the characteristics of the intestinal bile acid transporter have been elucidated (eg, structural specificity, Na^+ dependency, etc), little information is available concerning the molecular basis of the vectorial transport of this class of molecules across the intestinal mucosa. Recently, a highly polarised human colon carcinoma cell line (Caco-2), has been developed as a cell culture model of the intestinal mucosa and it has proven useful to study nutrients and drugs of the intestinal mucosa and this *in vitro* model has been shown to be useful to elucidate pathways and mechanism of drug and nutrient (eg, bile acids) transport. The transport of taurocholic acid (TA) across Caco-2 cell monolayers was dependent on time in culture and reached a plateau after 28 days, at which time the apical (AP)-to-basolateral (BL) transport was ten times greater than BL-to-AP transport. AP-to-BL transport of TA was saturable and temperature-dependent. V_{max} and K_m for transport were 13.7 nmol/mg protein per min and 49.7 μM, respectively. The transport of TA had an activation energy of 13.2 kcal-mol^{-1}, required Na^+ and glucose. AP-to-BL transport of [^{14}C]-TA was inhibited by the co-administration (on the AP side) of either unlabelled TA or deoxycholate, but it was not reduced by the presence of unlabelled TA on the side of the monolayers (30 min) were approximately equal 54.4 ± 2.7 and 64.6 ± 2.8 fmol/mg protein, respectively). AP and BL uptake of [^{14}C]-TA were inhibited by unlabelled TA and by sodium axide, indicating that AP and BL uptake are carrier-mediated and energy- dependent. The fact that the uptake (AT and BL) of TA did not change under a valinomycin-induced K^+-diffusion potential and that the amount of TA the remained cell-associated after hypotonic lysis of cells preloaded with TA was 70-80%, rules out both membrane voltage and osmotic gradient as driving forces for bile acid uptake. The AP and the BL uptake seem to involve different carrier systems: a) The BL uptakes was more sensitive to inhibition by p-aminohippuric acid (pAH), than the UP uptake; b) Deoxycholic acid inhibited the AP uptake of TA more efficiently than the BL uptake; and c) The AP uptake was more sensitive to inhibition by ouabain than the BL uptake. This study has also shed some light on the properties of the efflux precess(es). For instance, of that TA taken up after incubation with 10 nM for 30 minutes either on the AO or the BL membrane, or both, about 80% underwent BL efflux in 30 min regardless of the route of uptake. The BL efflux was energy-dependent and it was not inhibited by excess unlabelled TA (on the AP or the BL side). These data suggest that bile acid (AP and BL) uptake my be mediated by carrier systems different from those involved in the efflux.

Ronald T Borchardt

Smooth Muscle Special Interest Group

There will be a meeting of this Group at the Leicester Physiological Society Meeting. Both oral and Poster presentations will be given and there will also be a short business meeting of the Group to elect a new convenor.

Susan Wray

The Placental and Perinatal Special Interest Group

The Placental and Perinatal Special Interest Group will meet as planned at the Leicester Meeting. At the last Meeting in Cambridge, we had a two-day meeting over 23-24 September. A Plenary Lecture was delivered by Professor Peter Nathanielsz entitled "The fetal role in the initiation of parturition - neural and molecular messages". This was an excellent lecture in which Professor Nathanielsz reviewed current ideas about the control of uterine activity and the initiation of parturition. During the lecture he spanned a wide range of approaches for studying these processes, ably demonstrating the potential (in the right hands!) for integrating concepts from the cellular to the whole animal. We continue our theme of putting things together at the Leicester Meeting when we hold a joint session with members of the Reproduction and Growth Group of the Nutrition Society. We will have a Plenary Lecture from Dr Pascal Ferre, Director of Research at the Pathology, Metabolic and Hormonal Unit, Inserm Unit 342, Paris. His title will be "Metabolic adaptations during suckling and weaning".

Mark Hanson

Ionic Channels Designated Session

In the forthcoming Leicester Meeting of the Society there will be a Designated Session on Ion Channels in addition to a teaching symposium on Ion Channels. A plenary lecture affiliated with the Ion Channel Special Interest Group will be given by Dr J Peter Ruppersberg. Although still a young scientist, Dr Ruppersberg has contributed much to the pioneering work on the molecular biology of mammalian voltage-gated K^+ channels. He recently moved to Heidelberg to collaborate with Bert Sakmann on NMDA receptors. He will give a talk on "Molecular aspects of voltage-dependent block of ion channels."

Noel Davies

Sight, Sound and Soma: A Sensory Symposium

Physiological Society Symposium at Bristol on Tuesday 4 May, 1993

This one day symposium will bring together young physiologists from the auditory, visual and somatosensory fields. It is aimed at providing an excellent forum for young scientists to talk about their work. Each of ten talks will last for 20 minutes with plenty of time for questions afterwards. As well as providing an opportunity for PhD students and postdocs from related fields of study to meet their peers, we hope the relaxed atmosphere will encourage lively discussion.

The symposium is funded by The Physiological Society and the Department of Physiology, Bristol. There will be a small registration fee to cover lunch and tea/coffee. A meal is also planned for the evening. A similar symposium was organised in this department last year and was a great success.

Anyone interested in attending the symposium should contact either *Jonathan Gale* or *Lesley Anson*, at the address below, for more information and registration details.

Dept of Physiology, School of Medical Sciences, University Walk, Bristol BS8 1TD, tel (0272) 303030 Ext 4854/4859, fax (0272) 303497

Renal Special Interest Group

The next meeting of the Renal Special Interest Group will be held in conjunction with the Southampton Meeting of the Society on 27-29 September 1993. The opening date for abstracts is 28 June, 1993 and the closing date 9 July 1993.

Members may wish to know that the next meeting of the European Kidney Research Forum has been arranged for 23-27 April 1994 at Erlangen Nürnburg.

Dave Potts

NEWS OF SPECIAL INTEREST GROUPS

New Special Interest Group in "Cellular Neurophysiology: Synapses, Circuits and Oscillations"

With the present trend towards specialised sessions at the Society's Meetings, it has become necessary for each field of physiological research to be represented in a Special Interest Group. Sadly perhaps, the days are long gone when we could all consider ourselves to be broad interest physiologists. Cellular neurophysiology, particularly those aspects that relate to synapses and circuitry, is a growing field, but one that is rapidly becoming less well represented at Meetings of the Society. Those who have presented recently have often found that their papers are flanked by communications in widely varying fields or that a parallel session includes work of particular interest. This obviously decreases the enthusiasm in discussion and therefore in submission of abstracts. There are many venues for presentation of work relating to synaptic circuitry and several of my colleagues have indicated scant optimism that interest in the Society can be resurrected now. However, other Groups have extremely successful sessions, with vibrant discussion, serving as a useful forum for debate.

If your interests include, for example, control of presynaptic release, postsynaptic response properties, cable properties of neurones, synaptic plasticity, neuronal circuitry and the mechanisms involved in the generation of oscillations, and you would like to participate in such a Group, please let me, or the Oxford office know of your interest so that you are kept informed of developments and please **plan to submit abstracts for the June/July Meeting at UCL (submit 22 March - 2 April) and/or the September Meeting in Southampton (submit 28 June - 9 July).**

Alex Thompson

Dept of Physiology, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF, tel (071) 431 5269, fax (071) 433 1921

New Special Interest Group in Higher Sensory Functions

As part of the reorganisation of neuroscience Groups within the Society, a new Special Interest Group entitled **Higher Sensory Functions** has been established. This will, in principle, encompass any aspect of sensation and perception. However, given the existing Somatosensory and Sensorimotor Groups, it is anticipated that the new Group will concentrate on vision and audition. As with all Special Interest Groups, one or more Designated Sessions will be organised per year as part of the Society's Scientific Meetings, which I hope will attract a large number of contributions. Funds are also available to organise a Plenary Lecture in association with these sessions.

In order to get the Higher Sensory Functions Group off the ground, we need to establish a mailing list of people who would be interested in hearing about and contributing to events organised through the Group. If you would like to have your name added to this mailing list, then please write to me. Any suggestions for the names of possible Plenary Lectures would also be welcome. If anyone is planning to organise a research symposium in the general area of sensory neuroscience at one of the Society's Meetings, then we should try and arrange this in conjunction with a Designated Session of the Group.

Andrew King

University Laboratory of Physiology, Oxford OX1 3PE, tel (0865) 272523 fax (0865) 272469, email: KINGAJ@UK.AC.OXFORD.VAX

Editor's Note

No notice is carried for more than three successive editions. Notices are starred so that readers can see at a glance whether this is the first (one star) or final (three stars) appearance of the Notice. Notices for the June (UCL) edition should reach the Editor or the Administration Office by 16 April 1993.

British Opioid Colloquium & British Pharmacological Society
OPIOID PEPTIDES AND THEIR RECEPTORS
A Symposium in Honour of Prof H W Kosterlitz
13 April 1993
University of Aberdeen, Scotland
Further information from: Prof A S Milton, Division of Pharmacology, Dept of Biomedical Sciences, University of Aberdeen, Marischal College, Aberdeen AB9 1AS, tel (0224) 273036, fax (0224) 273019 ★★★

Society for Endocrinology/Royal Society of Medicine
TECHNIQUES IN CELLULAR SIGNALLING
16 April 1993
Sheffield
Training course featuring talks on receptor and binding studies, cyclases and cyclic nucleotide assays and G-proteins and many other topics. £25. Further information from: Janet Crompton, Society for Endocrinology, 17/18 North Court, The Courtyard, Woodlands, Almondsbury, Bristol, BS12 4NQ, tel (0454) 619036, fax (0454) 616071 ★

European Tissue Culture Society
UK Branch Workshop
VECTORIAL TRANSPORT IN CULTURED EPITHELIAL & ENDOTHELIAL CELLS
19 April 1993 - Please note the change of date
Newcastle upon Tyne
Further information from: Dr B H Hirst, Dept of Physiological Sciences, Medical School, Newcastle upon Tyne NE2 4HH, tel (091) 222 6993, fax (091) 222 6706 ★★★

Committee for Symposia on Drug Action
MOLECULAR APPROACHES TO DRUG DISCOVERY
19-20 April 1993
The Scientific Societies Lecture Theatre, London W1
Further details from: Barbara Cavilla, Administrative Secretary, 20 Queensberry Place, London SW7 2DZ, tel (071) 581 8333, fax (071) 823 9409 ★

Sandoz Institute for Medical Research
VII ANNUAL SYMPOSIUM - MEDIATORS OF INFLAMMATORY PAIN
21 May 1993
The Royal Society, 6 Carlton Terrace House, London
Deadline for registration: 23 April 1993. Registration forms from: Mrs M-C Stuart, Sandoz Institute for Medical Research, 5 Gower Place, London WC1E 6BN ★ *[Full details on page **]*

International Society of Biomechanics
XIVth CONGRESS
4-8 July 1993
Paris, France
Further information from: ISB 93, Convergences, 120 avenue Gambetta, 75020 Paris, France, fax (010 33) 1 40 31 01 65 ★★★

IUPS CONGRESS
1-6 AUGUST 1993
Further information and registration forms from: IUPS Congress Office, CEP Consultants Ltd, 26-28 Albany Street, EDINBURGH EH1 3QH, tel (031) 557 2478, fax (031) 557 5749.
Correspondence for the Organising Committee should be sent to: IUPS Congress Office, Room F43, Hicks Building, University of Sheffield, Hounsfield Road, Sheffield S3 7RH
Telephone calls to: (0742) 758688, fax (0742) 758688 ★★

IUPS Thermal Physiology Commission
SYMPOSIUM ON TEMPERATURE REGULATION
9-13 August 1993
University of Aberdeen, Scotland
This symposium immediately follows the IUPS Congress in Glasgow. Further information and registration forms from: Prof A S Milton, Division of Pharmacology, University of Aberdeen, Marischal College, Aberdeen, AB9 1AS, Scotland, tel: (0224) 273036, fax (0224) 273019. ★★★

International Society of Arterial Chemoreception
CHEMORECEPTORS AND CHEMOREFLEXES IN HEALTH AND DISEASE
9-13 August 1993
University College Dublin
Further information from: Dublin Chemoreceptor Meeting, c/o Prof R G O'Regan, Dept of Human Anatomy and Physiology, University College, Earlsfort Terrace, Dublin 2, Ireland ★

1993 COMPUTERS IN CARDIOLOGY MEETING
5-8 September 1993
Imperial College, London
Deadline for abstracts: 1 May 1993. Further information from: 1993 Computers in Cardiology Meeting, Centre for Biological & Medical Systems, Mech Eng Building, Imperial College of Science, Technology & Medicine, Exhibition Road, London SW7 2BX, tel (071) 225 8525, fax (071) 589 6897 ★★★

European Placenta Group
Vth MEETING
6-11 September 1993
Manchester Business School
Further information from: Dr C P Sibley, EPG Secretary, Dept of Child Health, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, tel (061) 276 6483/6484, fax (061) 224 1013 ★★★

Marine Biological Association Workshop
MICROELECTRODE TECHNIQUES FOR CELL PHYSIOLOGY
8-22 September 1993
Plymouth
Deadline for applications: 20 April 1993. Further information from: David Ogden, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, fax (081) 906 4477 ★★ *[Full details on page 45]*

The Bayliss and Starling Society
ANNUAL MEETING
13-14 September 1993
Royal Postgraduate Medical School, London
International workshop on biological control systems: Genes, mRNA, regulatory peptides & growth factors. Molecular biology, physiology, pharmacology & clinical applications. Deadline for abstracts: 3 May 1993. Further details from: Kim Cyrus, Endocrinology Unit, 2nd floor, Francis Fraser Building, Royal Postgraduate Medical School, London W12 0NN, tel (081) 740 3242, fax (081) 740 3142 ★

European Working Group on Cardiac Cellular Electrophysiology
17th MEETING
17-19 September 1993
Graz, Austria
Further details from: Prof B Koidl, Karl-Franzens-Universität Graz, Institut fur Medizinische Physik u. Biolphysik, Harrachgasse 21, A-8010 Graz, Austria, or from: Dr H F Brown, University Laboratory of Physiology, Parks Road, Oxford OX3 7TN, tel (0865) 272454, fax (0865) 272469. (Those who have attended any of the last 3 meetings of the Working group will be sent information in April.) ★

APS Conference
PHYSIOLOGY AND PHARMACOLOGY OF MOTOR CONTROL
2-5 October 1993
San Diego, California, USA
Further information from: Miss Linda Buckler, Membership/Meetings Office, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814-3991, USA, tel (010 1) 301 530 7171, fax (010 1) 301 571 1814, E-mail: Linda@APS.MHS.Compuserve.Com ★★★

INTERNATIONAL SYMPOSIUM ON ANAESTHESIA
20-22 October 1993
Beijing, China
Deadline for abstracts: 15 May 1993. Further information from: Mr Zhang Ming, PO Box 300, CICCST, Beijing 100086, China, tel (010 86 1) 8313335, fax (010 86 1) 8316091 ★

INTERNATIONAL CONFERENCE ON GASTROINTESTINAL HORMONES AND GASTROINTESTINAL MOTILITY
25-28 October 1993
Beijing, China
Deadline for abstracts: 15 July 1993. Further details from: Mr Ming Zhang, PO Box 300, CICCST, Beijing 100086, China, tel (010 86 1) 8313335, fax (010 86 1) 8316091 ★

INTERNATIONAL SYMPOSIUM ON QUALITY ASSURANCE PROGRAM IN HOSPITAL
1-3 November 1993
Beijing, China
Deadline for abstracts: 31 May 1993. Further information from: Mr Zhang Ming, PO Box 300, CICCST, Beijing 100086, China, tel (010 86 1) 8313335, fax (010 86 1) 8316091 ★

2ND INTERNATIONAL CONFERENCE ON SPORTS MEDICINE
2-5 November 1993
Beijing, China
Deadline for abstracts: 3 July 1993. Further information from: Dr Jhang Ming, Beijing International Hotel, No 9 Jian Nei Dajie, Beijing, China, tel (010 86 1) 5126688 ext 1534, fax (010 86 1) 8316091 ★

APS Conference
SIGNAL TRANSDUCTION AND GENE REGULATION
17-20 November 1993
San Francisco, California, USA
Further information from: Miss Linda Buckler, Membership/Meetings Office, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814-3991, USA, tel (010 1) 301 530 7171, fax (010 1) 301 571 1814, E-mail: Linda@APS.MHS.Compuserve.Com ★★★

2ND WORLD CONGRESS OF BIOMECHANICS
10-15 July 1994
Vrije Universiteit of Amsterdam, The Netherlands
Deadline for abstracts: 1 December 1993. Further information from: Biomechanics Section, Institute of Orthopaedics, University of Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands, tel (010 31 80) 613366, fax (010 31 80) 540555 ★

Wellcome Centre for Medical Science - one day Open Meetings

The Wellcome Centre for Medical Science, in collaboration with the CIBA Foundation, is organising one day Open Meetings to follow a selection of CIBA Symposia. The calendar for 1992 is as follows:

21 May -	*Neural Tube Defects: Embryology, Epidemiology & Preventions*
23 July -	*Germline Development*
10 September -	*Biological Clocks and Their Adjustment: Molecular, Cellular and Neural Aspects*
29 October -	*Second-Stage, Filtering in Vision*

The meetings will be held in the Auditorium of the Wellcome Trust Building at 183 Euston Road, London NW1 2BE. There is a registration fee of £20 (£10 concessionary rate for graduate students) fore each meeting, which includes refreshments, lunch an documentation. Further information from: Jilly Steward (071) 611 8656 ★

The Krebs Memorial Scholarship

The appeal launched to commemorate the life and work of Sir Hans Krebs by instituting a postgraduate (PhD) scholarship in biochemistry or allied biomedical science, tenable at any British university, has provided sufficient funds to allow a scholarship, equivalent to an MRC Research Studentship, to be awarded in alternate years. The next scholarship will be awarded for 1993/94.

The Scholarship is primarily intended to help candidates who wish to study for the degree of PhD in biochemistry or in an allied biomedical science, but whose careers have been interrupted for non-academic reasons beyond their own control and/or who are unlikely to qualify for an award from public funds. It will cover a personal maintenance grant at an appropriate level and all necessary fees. The Scholarship will be awarded for one year in the first instance but may be renewed up to a maximum tenure of three years.

Applicants will be expected to have made prior arrangements with the university at which they intend to hold the award, and the application must be forwarded through the head of department concerned. Application forms may be obtained from the Administration Manager, The Biochemical Society, 59 Portland Place, London W1N 3AJ.

Whilst the Scholarship is primarily aimed at PhD students, the award of a post-doctoral Fellowships might be considered for a candidate whose circumstances merit such consideration.

The closing date for the next award is 31 March 1993. ★

William Harvey and the Circulation of the Blood

This film, made in 1978 by M de Burgh Daly, Douglas Fisher, Leonard Goodwin and Gweneth Whitteridge, gives a brief account of Harvey's education, and of the theories of the movement of the blood in the body before Harvey's time, before re-enacting Harvey's experiments, described in his De Motu Cordis (1628), that provided proof of his hypothesis of the circulation of the blood. This 16mm film cost £80 plus VAT plus postage.

Two versions are now also available on video (VHS), a long version (approximately 37 minutes; price £40.00 plus VAT plus postage) and a short version (approximately 27 minutes; price £25.00 plus VAT plus postage).

Enquiries and orders should be made to: Dr Michael Clark, Audio Visual Resources Manager, the Wellcome Trust, 183 Euston Road, London NW1 2BE, tel (017) 611 8596/7 ★

Scientific Apparatus Recycling Scheme

The FEBS Council has agreed to support the above scheme which aims to assist the biochemists of Eastern Europe by recycling to them scientific apparatus that is at present surplus to the needs of those in the West. In 1993 a grant was received from the TEMPUS programme of the European Commission (EC) to support a visit to the UK by representatives of the biochemical societies of Hungary and Poland. They visited many laboratories and identified apparatus both small and large that would be useful for the biochemists in their countries. A further grant was obtained from TEMPUS to cover the cost of transport within Europe. The Biochemical Society has kindly made available some spare warehousing at Colchester on a temporary basis. This is being used to assemble and sort the apparatus prior to despatch in bulk to the biochemical societies of many countries in Eastern Europe who are responsible for the distribution within their countries. Items are only sent after their identification as being useful for the recipients. FEBS is paying all the costs involved in the transport of the apparatus to Colchester and usually for transport across Europe although assistance is sometimes provided by the recipient country.

SARS has been warmly welcomed by many laboratories in the UK and requests for apparatus are constantly being received from the East. It is clear that SARS will have to be a long term measure. Attempts are now being made to extend SARS to other potential donor countries. SARS is not limited to university departments and research institutes, for industry and publishers of books and journals are also helping. SARS is also co-operating with the Association of Clinical Biochemists with a view to helping biochemists in the clinics.

Large loads have been sent to Poland, Hungary, Romania and Lithuania. Other loads are being assembled for Latvia and the Czech Republic which will include Slovakia. A reconditioned electron microscope has also been sent to Romania. SARS has now been extended to books and journals. We have in mind that the most valuable are the last ten years of complete runs of good journals but there are requests for much longer runs.

SARS is also now extending to Africa thanks to a grant from The Nuffield Foundation which will enable apparatus to be sent to desperate laboratories.

As SARS Co-ordinator, I would be pleased to hear from anyone who has surplus apparatus, books or journals for disposal. I sometimes have a call for copies of the *Journal of Physiology* which I can send through the Ranfurly Library Service.

Prof Peter N Campbell, Biochemistry and Molecular Biology, University College London, Gower Street, London, WC1E 6BT, tel (071) 387 7050 ex 2169, fax (071) 380 7193 ★

Muscles, Masses and Motion: The Physiology of Normality, Hypotonicity, Spasticity and Rigidity

This book by E Geoffrey Walsh deals extensively with the topic of muscle tone in health and disease and provides both a compendium of current knowledge and a historical overview of the major discoveries from the past. The book is published by MacKeith Press but is being distributed by Cambridge University Press. It runs to 220 pages and there are 196 figures. The current price of the book is £32. ISBN: (UK) 0 901260 97 5; (USA) 0 521 43229 4 ★★★

Forty Years of Membrane Current in Nerve

This co-ordinated set of modern reviews, edited by Daniel Gardner, commemorates the 40th anniversary of the publication of the Hodgkin, Huxley and Hodgkin, Huxley & Katz papers. This special supplement to *Physiological Reviews* is available to non-subscribers for $29 (or $14.50 for APS members) from the American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814-3991, USA. ★★★

Relaunch of *Physiologia Bohemoslovaca* as *Physiological Research*

The Journal is published by the Institute of Physiology, Czechoslovak Academy of Sciences and accepts full papers, short and rapid communications, editorials and mini-reviews. Subjects covered include physiology, pathophysiology, biochemistry, biophysics, pharmacology and allied fields. Further information can be obtained from the Editorial Office, Albertov 5, 128 00 Prague 2, Czechoslovakia. ★★★

Animal Experimentation and the Future of Medical Research

Edited by Dr Jack Botting, Research Defence Society. Proceedings of a Meeting held by the Research Defence Society to examine, from a scientific and medical perspective, the future role of animal experiments in medical research without ignoring the ethical context and justification for that research. Eminent scientists and clinicians who spoke about their fields of work, consider the importance of animal experiments in each case, include: Richard Adrian, D K Peters, David Rees, Sydney Brenner, John Vane, David Hubel, Walter Bodmer. It runs to 96 pages and the current price is £16.95. Published by Portland Press. ★

The Journal of Physiology - Member's Copies

If any person or institution (university or research institute) is interested in acquiring, without cost except for transport, a run of *The Journal of Physiology* from vol 432 (1991) to vol 458 (1992), please write to Dr G Gordon, University Laboratory of Physiology, University of Oxford, Parks Road, Oxford OX1 3PT ★

PHYSIOLOGIST
Dominica, West Indies

Applications are invited for a Physiologist with established teaching commitment and experience. Salary negotiable.

Send CV or contact: Dr Robert Ross or Dr Nancy Perri, Ross University Medical School, 460 West 34th Street, 12th Floor, New York, NY 10001, USA, tel: (010 1) 212 279 5500, fax (010 1) 212 629 3147 ★

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CONFIDENTIAL
THE PHYSIOLOGICAL SOCIETY
APPLICATION FORM FOR AFFILIATION

Photograph of Candidate

Name ..... Date of Birth .....

Qualifications (with name of awarding Institute) .....

.....

Date and Subject of First Degree .....

Present Course or Postdoctoral Position .....

Special Scientific Interest (eg thesis title or postdoctoral project) .....

.....

Scientific Interests (IUPS classifications): Codes (see reverse) ...../...../.....

Special Interest Groups with which you would like to be associated: Codes (see reverse) .....

Laboratory or Institute address .....

.....

Tel ..... Fax .....

Electronic mail address .....

Please delete as applicable:

*I wish to receive Notices, Programmes & Magazines only.

*I wish to receive precirculated Abstracts as well as Notices, Programmes, & Magazines.

I enclose a cheque for £..... payable to The Physiological Society.

I confirm that the information given above is accurate and up to date and that I hereby authorise The Physiological Society to hold this, and such other personal information as is supplied to the Society by me or my authorised agents or representatives in future, in machine-readable form for use for the purposes registered under the Data Protection Act 1984.

Signed ..... Date .....

Members of The Physiological Society who are proposing Candidates should read the Guidelines overleaf and sign the following statement.

I hereby confirm that the Candidate:

(a) is either a post-doctoral worker or registered for a higher degree in Physiology or a cognate subject, and
(b) is a person suitable for admission to Society Meetings.

Signature of Proposer ..... Date .....

Name (in capitals) .....

Tel ..... Fax .....

Address .....

.....

On completion please return this form to: The Administration & Publications Office, The Physiological Society, PO Box 506, OXFORD OX1 3XE, (UK).

GUIDELINES TO MEMBERS OF THE PHYSIOLOGICAL SOCIETY PROPOSING CANDIDATES FOR AFFILIATION

The Committee has authorised the Committee Secretary to consider and accept or reject proposals for Affiliation to the Society as they are received throughout the year, so that these can be processed quickly. The Committee Secretary regards himself as free to withdraw a proposal and return the papers to the Proposer.

Affiliation is for a term of five years in the first instance. Affiliation must be renewed by payment of the appropriate fee at the start of each year (which for this purpose is the academic year, ie October to September). For administrative convenience, Affiliates registered after October will have to pay for the full year. The fees are determined from time to time by the Treasurer; they are currently:-

	UK & Eire	Europe	Non-Europe
With Abstacts	£10	£30	£35
Without Absiracts	£ 5	£15	£20

Affiliates can attend Meetings in their own right but must be introduced by a Member of the Society when giving a Communication or Demonstration. Affiliates are not Members of the Society and do not have the right to vote at its General Meetings.

Field of Interest:

01	Anaesthesia
02	Anatomy & Embryology
03	Biochemistry
04	Biophysics
05	Biomedical Engineering
06	Blood
07	Cardiovascular
08	Cellular & Tissue
09	Comparative Physiology
10	Electrolyte & Water Balance
11	Endocrines
12	Energy Metabolism & Temperature Regulation
13	Environmental
14	Enzymes
15	Gastrointestinal
16	General Physiology
17	Immunology
18	Liver & Bile
19	Lipids & Steroids
20	Microbiology
21	Minerals, Bone & Teeth
22	Muscle & Exercise
23	Neuroscience
24	Nutrition & Food
25	Pathology
26	Pharmacology
27	Radiation
28	Renal
29	Reproduction
30	Respiration

You may specify up to three fields of interest.

Special Interest Groups

Current Codes

AF	Autonomic Function
BB	Blood-Brain Barrier
CC	Cardiovascular Control
CI	Comparative & Invertebrate Neuroscience
CN	Cellular Neurophysiology
CP	Comparative Physiology
DP	Developmental Physiology
EM	Epithelia & Membrane Transport
GI	Gastrointestinal Tract
HC	Heart Muscle
HI	History of Physiology
HP	Human Physiology
HS	Higher Sensory Functions
IC	Ionic Channels
ME	Microvascular & Endothelial Physiology
MC	Muscle Contraction
NB	Neurobiology
NE	Neuroendocrinology
PP	Placental & Perinatal Physiology
RP	Renal Physiology
RE	Respiratory Physiology
SC	Sensorimotor Control
SM	Smooth Muscle
SP	Somatosensory Physiology

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