The Physiological Society

Magazine

December 1992

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INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES 1953

Contents

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Department of Physiology, Queen Mary & Westfield College

In June 1990, after a 20-year gestation period, the departments of Physiology at The London Hospital Medical College and St Bartholomew's Hospital Medical School joined to form a single Department of Physiology in the Faculty of Basic Medical Sciences at Queen Mary & Westfield College. The present Head of Department is Bill Keatinge, who is also the Dean of Basic Medical Sciences and who took over the Chair of Physiology from Kenneth Cross in 1981 at The London. There are now ten full-time academic members of staff. The new department is housed in a generously equipped new building, largely built to our own design.

The teaching commitments of the department are undergoing expanding horizons in accordance with the new philosophy and requirements for lower staff-student ratios. The main body of the teaching is to a combined annual quota of 200 medical students and 55 dental students. In the third year some ten intercalated students take an Honours degree in Physiology, which remains among the most popular choices for the most able students. Teaching is now being expanded with a new intake of 20 BMedSci students, who take the same initial two-year course as the medical students and will join intercalated BScs in their final year. In addition, substantial co-operation with other faculties will commence over the next year with the introduction of two new ventures: Project 2000 teaching to nurses and teaching of course units in Physiology to Biomedical Science students in co-operation with the Department of Biology.

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A new initiative in medical education has been taken with the introduction of a new, module-based, inter-departmental course in Basic Medical Sciences, where the emphasis is on systems teaching, with considerable integration of clinical and basic physiological sciences. A major investment also has taken place in the design and equipping of a large multi-function teaching laboratory, where 150 students can be taught simultaneously for most practicals, and 290 for some. The design includes a mobile bench format and flexible arrangements of services. The laboratory was entirely designed in-house and is generously equipped with full video equipment and colour repeater screens and PC (386) computers with a facility for networking. Cambridge Electronic Design 1401 processors are installed for signal analysis, with the objective being to make all students "electronic-proficient". On-line teaching programmes are currently being developed in tandem with a research programme for assessment of student learning and teaching. All physiology teaching in laboratory classes, including neuroscience, is now based on human physiology, with the students making observations on each other.

The department is active in research in two major areas, Human Environment Physiology and Neuroscience.

In Human Environment Physiology, new research laboratories have been set up with climatic chambers and an immersion tank. Equipment in these includes ultrasonic Doppler imaging and flow measuring facilities, laser Doppler measurement of cutaneous blood flow, on-line systems for respiratory measurements, metabolic rate, and single breath cardiac output, and measurements of local and overall sweat rate. Current research is focused on studies of the physiological mechanisms underlying the exceptional ability of some individuals to stabilise body temperature in water near 0°C, and cold-related coronary and cerebral thrombosis which causes most of the large increase in mortality in Britain every winter. The work has involved co-operation with the Norwegian Underwater Technology Institute and contract work with the Department of Health. International co-operative studies with other laboratories within the EC on causes and prevention of winter mortality are being started. Other studies include analysis of gait in specific neuromuscular deficiencies, and physiological adjustments during high-level competitive synchro-swimming.

In Neuroscience, the major interests lie in somatosensory physiology of the spinal cord and neocortex, with all work concentrated in a new dedicated suite of Neuroscience laboratories. International co-operation for some years has been in place with laboratories in the United States and Switzerland with whom exchange fellowships and visiting professorships have been

undertaken. Principal support is from the NIH and Wellcome Trust. Most current research uses high speed cyclic voltammetry, iontophoretic studies on NMDA and quisqualate and monoaminergic receptor function in sensory processing, and modification of neural networks during learning.

A new patch-clamp laboratory is being set up for related studies *in vitro*. Co-operation with the Pharmacology Department continues, with which there is a history of joint grants. In addition, a fully equipped human hearing research laboratory has been installed.

Bill Keatinge

Enjoying Wine with a Hint of Physiology

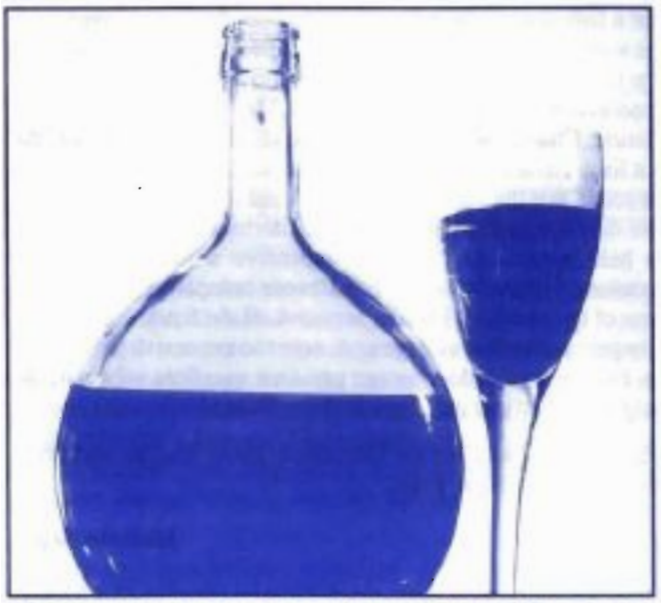
Wine is a delightfully complex mixture of some 2,500 compounds. It can exercise many of our special senses from taste and smell to vision, touch and even pain! To the layman, "taste" is just the flavour of food and drink in the mouth; yet, as physiologists, we know that the taste receptors in the mouth are only sensitive to four modalities (sweet, sour, bitter and salt), so that the majority of the sensations of flavour are in fact smell. The bouquet of a wine is the most exciting aspect of the "taste" of a wine, as the various organic compounds in the wine volatilise in the mouth, then pass by way of the nasopharynx to excite the olfactory epithelium.

A wine is composed of three of the key elements of taste - sweet, sour and bitter - which, although minor factors in the flavour, do reflect the major components in wine apart from the alcohol. A good wine should always have a reasonable degree of acidity: the pH of wine is in the range of 3-4; greater than 4 the wine tastes flabby. This acidity, mostly composed of tartrates, should be balanced by a degree of sweetness, even in a dry wine. On the other hand, if the sweetness of a wine is too high, without the balance of acidity, the wine tastes "cloying"; but when the balance is correct, a sweet wine with a good acid level tastes exquisite. The bitter component of wines, the tannins, are derived from the skin and the pulp of the grape. Red wines have a high level of these phenolics, whereas white wines, which are not usually fermented on the skins and the pulp, have much less. The relevance of the balance of these three groups of compounds relates to the stability and the keeping qualities of the wine and a knowledgeable wine maker can adjust these components in the crushed grapes prior to fermentation to produce a good quality wine from most grape crops.

The wine judge has, by experience, located the appreciation of sweetness in a wine to the tip of the tongue, sour (acid) to the sides and the bitter flavours of tannin to the back. Although a given taste receptor, the taste bud, can respond to all four modalities of taste, there does seem to be a degree of "regional tuning" which would broadly confirm the observations of the wine judge. We are extremely poor at judging the alcohol content of a wine, which can lead one into trouble. The alcohol content of Californian wines can be as high as 13% and home made wines, with their high starting sugar content, can easily run up to 16%, so be warned when drinking wines you do not know! The final aspect of wine detected in the mouth is the "body". This component is related to a complex interaction between the concentration of alcohol and glycerol in the wine which in turn reflects the quality and quantity of grapes used in the original fermentation. This component of the wine is most probably detected by touch receptors in the mouth, but as far as I know has not been subject to a physiological study!

With regard to the aroma or bouquet of a wine, this is derived from the variety of grape used and the fermentation process. The olfactory epithelium is found in the upper part of the nasal cavities and consists of specialised neurones with long microvilli buried in a layer of mucus which surprisingly always covers these olfactory receptors. The prime difficulty in interpretation of the sense of smell is our lack of vocabulary to explain the hundreds of similar but different odours. For example, there are at least 50 types of compounds which smell of camphor yet all smell slightly different. Molecules can be broadly divided into classes of rigid molecules with a "single" pure odour such as the floral smells, flexible molecules with two or more odours which can obviously "fit" into more than one receptor type and the less specific lipid soluble molecules such as the pungent and unpleasant smells or those with vague "hospital" aromatic odours. The olfactory receptors adapt extremely rapidly, so there is no point in repeatedly smelling a wine as the receptors will have adapted and the bouquet have "vanished". Nociceptors in the nose can detect molecules such as sulphur dioxide, often present in white wines as an anti-oxidant, which gives a prickly sensation in the nose.

To judge a wine, the wine should be poured into a narrow glass, a flute, and regarded in good light. A white wine, which is young, should be pale and bright; occasionally a few crystals of tartrate may be seen and in some wines a few bubbles of CO_2. Still wines which display this characteristic are termed "spritzy". Of course, this is the main feature of wines like Champagne, but this gas is a product of secondary fermentation. Old sweet wines are a rich yellow, as are the Chardonnays of Australia; but in most young white wines this colour usually is a reflection of oxidation. Red wines, depending on the grape variety, should range from a transparent red for the wines of Burgundy and Beaujolais to the intense deep reds of Bordeaux, the Riojas of Spain and the Barolos of Italy. With age, red wines show browning, which is a good sign in a mature wine. Some reds throw a deposit of tartrates and need careful decanting prior to being poured into the glass whereas others such as the Rhone wines have usually "dropped" their deposit prior to bottling. Decanting does, however, allow the wine to "breathe" and can improve many wines.



The next step is to pass the nose across the top of the glass and to inhale the bouquet. The aroma should be vinous, with a hint of other pleasant aromatic compounds in a good wine. **Do not be afraid to use any term to describe the aromas - anything from the hint of raspberry to sweaty socks is acceptable and possible!** Now, take a good mouthful of wine, keep it first in the front of the mouth and with the tip of the tongue determine its degree of sweetness; even the most "dry" of red wines should have an element of sweetness. With a red wine, it should be warm at a temperature of 25-28°C and this will improve the sweetness as it reduces hydrogen bonding in sugars. For white, it should be chilled but not too cold, 6-10°C or all flavour will be "lost". Next, run the wine around the sides of the tongue and a degree of sourness or acidity will be detected. If this is low or absent the wine is of poor quality. Finally, move the wine to the back of the tongue and detect the bitterness of the tannins. Females have a much lower threshold to bitterness than males. The threshold rises with age in both sexes, so allowing detection of other fine flavours of these complex phenolics and not just the bitterness. The last action is to swallow the wine and "examine" the farewell: a good wine should have a "length" of flavour as the aromatics are volatilised by the extra warmth in the throat and again pass up via the nasopharynx to stimulate the olfactory epithelium. All this "dissection" of course spoils the complexities of a good wine, so the next step is to drink it and enjoy it!

Not all wines will age and just because a wine is old does not mean it is excellent. Long keeping wines such as the Clarets of Bordeaux have a high acid content balanced with a degree of sweetness and tannins. The wines are full bodied and have the ability to improve over many years. These slow reactions are difficult to quantify but many of the forecast excellent vintages have failed to "open up". The usual advice is to keep them longer as they are still "closed" but often this is just an excuse for poor wine making and avoiding the financial consequences of replacing such wines!

Faults in wine do occur from poor wine making, so a good precaution is always to smell the cork after it is withdrawn. This should smell pleasant and vinous; if it has a musty smell the wine may be "corked". This term applies to bottles where the cork is too porous and a bacterial infection has entered the bottle. Wine should always be stored on its side to keep the cork wet. This improves the seal, but also permits a slow exchange of gas which aids the maturation of the wine. **Do not buy wines for keeping if they have been stored upright in the heat of a supermarket as this will dry the cork and the wine may have begun to deteriorate as the seal is lost.** White wines, when first opened and poured into the glass, can smell slightly of sulphides from the SO_2 used as an anti-oxidant. This preservative can be removed by a gentle swirling in the glass and the true bouquet will emerge.

However, there are some remarkable smells in bad wine, one called "mouse" and another "geranium", both of which are bacterial infections. A wine that is badly spoilt will degrade into vinegar (acetic acid). Another acid fault is too much succinic acid from poor fermentation, but it is interesting that even the finest wines contain small quantities of these two acids which, although they taste unpleasant, do enhance the fine flavour.

The quality of a wine must ultimately depend on the grape variety used, the latitude at which the grapes are grown and the soil. Obviously, old wine growing areas have varieties of grapes which are adapted to that area, whereas the new areas experiment with a wide variety of grape types, not all of which are successful. The climate of the region needs a frost-free spring to set the fruit, a warm moist summer with not too much heat and a reasonable level of humidity, followed by a long hot dry autumn. However, if the climate is too hot the grapes develop too much sugar with a low acidity so the flavour is poor; and conversely if it is too cold the grapes have too much acid with insufficient sugar. The soil is also fairly critical and should be low in nitrogen with a good range of trace elements which help to give an interesting flavour. Grapes grown on too rich a soil crop heavily, but are low in flavour. The exact balance of these factors is a matter of good husbandry, luck with the weather and choosing a good site. South facing slopes near a river or lake seem to be the most ideal at a latitude which is temperate.

Grapes do suffer from a variety of attacks by moulds and a mite - the dreaded *Phylloxera*. This beast destroyed the vineyards of France and Australia in the early part of this century. To replant grapes in these areas, American, *Phylloxera*-resistant root stocks have been used and the older varieties grafted on to these roots. However, just recently a new form of *Phylloxera* has evolved which is now attacking the Californian grapes, so many of these excellent vineyards have been decimated.

The grapes must be harvested at the correct moment, when the sugar and acids are adequate, then crushed to release their juice. Although there are natural wild yeasts on the skin, modern wine making techniques usually kill these yeasts with a dose of sulphite and then a specially cultivated specific yeast is added to the pulp and fermentation occurs. The pulp juice needs to have a pH of around 3-4 for a clean fermentation to alcohol or excess acetic or succinic acids will be produced. Many wine makers crush the grapes and run off the juice into tanks for the fermentation of white wines. Air is excluded during these processes, although in France open tanks and wild yeast are still used, which accounts for much of the variability in their wine making, so that both the very best and the worst wines are made in this country which is the birthplace of some of the world's finest wines.

In the New World, aging of the wine is carried out in small oak barrels which are used to give the special vanilla/oak flavour. A small amount of oak flavour from old barrels, and the leaking in of a little oxygen through the walls of the barrel, matures, gives an extra flavour to the wine; but the oak from new barrels can be too overpowering and can dominate the taste.

To choose a wine it is always vital to taste before buying in quantity, to ensure it has a good balance and a fine bouquet. The wine trade can be the most crooked in the world. The various marks of quality, such as *controlee*, *appelation*, DOCG etc, do give a guide to the intended quality of a wine but somehow the wine that ends up in the bottle often by-passes the "regulating authority"! It always amazes me that for a product which can be made well by modern techniques it is so often made so badly. The recent scandals of adding ethylene glycol instead of glycerol to give the wine "body" is but one of the tricks which could easily have been fatal. Always regard the label as only a guide and never buy just on the name and the price. The supermarkets often have excellent wines at a reasonable price as they can demand both these factors with their large buying power.

For Christmas, it is nice to start the proceedings with a fine "Champagne". Of course, if you are rich, real Champagne is wonderful, but grossly overpriced. The Australian wines from Great Western are excellent and I miss the opportunity of being able to buy a wide range of these fine sparkling wines available "down under".

For a fish course, there is nothing to beat the flinty flavours of the wines of the Loire, Muscadet for value, Sancerre for quality. For the turkey, the red wines of Beaujolais and the Rhone are excellent value and not too heavy. The Beaujolais Villages, Fleurie, Chateauneuf du Pape etc are all excellent value, but do not forget to serve them on the warm side to bring out their full flavours. For the Christmas "Pud", something rich is needed. I like the Muscats from Australia, wonderful sweet wines usually in half bottles. Another less expensive wine is the Italian "cooking" Marsala whose full flavour complements the richness of the pudding. Finally, to round off the feast, nothing can compare with a fine vintage port, now too expensive for most of us, but the late bottled vintage ports are excellent value and do help with the final indulgence of the Stilton!

May I wish you a Happy Christmas, good funding and great research in the New Year.

Malcolm Segal

New Affiliates

The Committee extends a warm welcome to the following newly approved Affiliates:

G L Ackland, Nicola Best, Gerald Connolly, John Connolly, Simon Dando, Suzanne Dickson, Henry Gibson, David Gallacher, J Antonio Lopez-Garcia, Dino Guissani, Carole Hackney, Noel Harris, Raheela Khan, Dimitri Kullman, Chris Louca, Dilwyn Marple-Horvat, Helen McKillen, Rubina Mian, Zolta'n Molna'r, Etienne Oliver, Gordon Reid, Marco Santello, Donal Skinner, Julie Ann Smith, Richard Stephens, Federico Villagra, Rachel Wilson, Anthony Woods

1993 Membership Subscriptions and Reductions

The increase in the full subscription rate for an Ordinary Member resident in the UK was increased to £110 at this year's AGM. The reductions and additional charges for 1993 under Domestic Rules D1 and D2 have now been agreed by the Committee. The full set of net subscription rates is set out in the Notice of Annual Subscriptions being circulated with this *Magazine*. The Notice also gives details of acceptable methods of payment.

Any Member who wishes to stop or resume receiving *The Journal of Physiology* and/or precirculated Abstracts and any Member who has retired during 1992 should inform the Administration Office immediately, so that mailing lists and subscription records can be amended in time. There is no need for cancellation of your direct debiting instruction if your subscription rate is about to change: the amount collected from your bank account will be amended automatically.

IUPS Congress, Glasgow, 1993 - Grants & Registration Deadlines

Apologies are due to readers for an error in the last issue of the *Magazine*. The latest date on which registrants will qualify for the lower registration fee of £250 is **17 April**, not 31 January, as previously stated.

However, **31 January** is the deadline both for submission of Congress abstracts and for grant applications to reach the Society's Administration Office in Oxford. There is a tear-out grant application form at the back of this *Magazine*.

Readers are reminded that they must register for the Congress (and pay the registration fee) before applying for a grant. To be eligible for a grant, all applicants (other than those qualifying for the reduced fee for students) should have submitted an abstract for the Congress.

Staff changes at the Oxford Office

We are sad to announce that Clare Haigh has left the Administration and Publications office in Oxford to move to another job. Although Clare joined the Society's employment only about two years ago, she played a major role in setting up the new office and revolutionising the Society's publications.

Since that time, from the "Special Issue" Newsletter for the 1990 AGM to the latest Annual Report and *Magazine*, Members will have been impressed by the increased professionalism she has brought to the design and layout of the Society's literature. Thanks to both Clare and Vic Howarth, the transition from the old method (whereby CUP typeset the Abstracts) to the new practice of accepting disks for desk-top publishing was accomplished with barely a hitch; and they have since succeeded in meeting all the deadlines, even for the largest Meetings.

Having started her career with a degree in Modern Languages, Clare has now moved to Berlitz as Reprints Manager for their travel guides. She will be missed; but we are glad to be able to reassure Members that training her successor in the Abstracts production is just one of the many other tasks she and Vic have performed so successfully. Diana Greenslade has therefore been promoted to the post of Publications and Administration Assistant and is now dealing with Abstracts and attending Scientific Meetings in her place.

Congratulations to ...

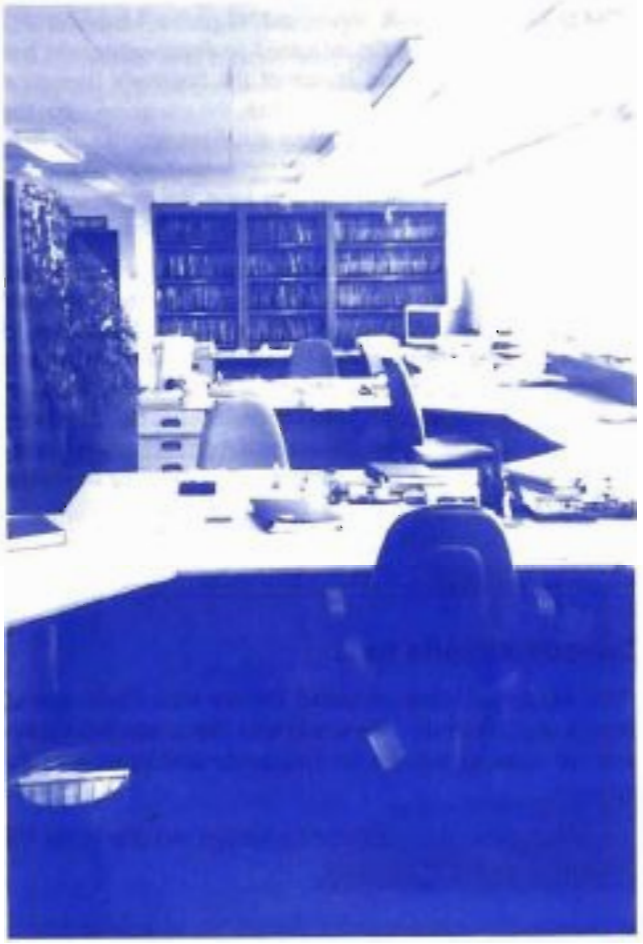
- Tim Biscoe on being appointed Deputy Vice Chancellor of Hong-Kong University. We would also like to take this opportunity of thanking him for his help in the development of the *Magazine*.

- John Waterlow on being elected a foreign member of the US National Academy of Sciences.

Journals Management Group

(members: Graham Dockray, David Cotterrell, Richard Dyball, Jim Gillespie, Dave Jordan, Cecil Kidd, Nick Standen, John Widdicombe, with Victoria Penrice in attendance)

The last few weeks have seen a flurry of activity in the Press Office in Cambridge. The decision of the Committee to invest in desk top publishing technology meant that additional staff were recruited which put pressure on the existing office space. Coupling the increased staff numbers with additional equipment made it clear that the *Journal's* copy editors had to move to a larger office.



Fortunately, CUP was able to offer the Society almost twice as much space on the same floor as the existing rooms so at the beginning of September, Mandy Kingsmill, the Senior Copy Editor, masterminded the transfer of the office. New furniture was ordered, to accommodate the computer equipment, and the entire move was carried out according to plan. The transfer of all manuscripts accepted over the past three years, current work, proofs and an almost complete set of *Journal* volumes were moved with great care to maintain their sequence. The move has had no effect on existing publication schedules.

At the same time as Mandy was organising the move, the Desktop Publishing Editor, Clive Semmens, was evaluating possible hardware and software. The Officers accepted his recommendation to use an Acorn system and the first machine has now arrived, with more equipment to follow soon. Once style and font sheets have been finalised, the office will be in a position to start preparing camera-ready copy (CRC) to be printed by CUP. The initial camera-ready pages should be in the March *Journal* and it is anticipated that the quantity of CRC pages will increase steadily. Some of the early pages of CRC may be scanned from clean manuscripts, rather than input by disk, as this will give staff the opportunity to explore the capabilities of the scanner. So far, it appears that the scanner more than lives up to expectations and can be used for some artwork - which should have a significant effect on the Society's publications bill.

The Press Office now accepts material on disk, and details about this have already been sent to contributors. The staff stress, however, that the medium in which a manuscript is submitted will not have any influence on the order in which papers are prepared for print. The Press Office would prefer to receive disks along with a clean hard copy of the paper which may be scanned if necessary, but hard copy alone will continue to be acceptable.

MRC Funding Policy - A Comment

In the May issue of the *Magazine* Dr Dai Rees, Secretary of the Medical Research Council, provided the Society's Members with an overview of the Council's plans for supporting UK medical research over the next five years. I have been asked by the Editor to comment, presumably because I was a member of the Council's Neurosciences and Mental Health Board from 1987 to 1991 and of its Training Awards Panel from 1989 to the present; also perhaps because the Bristol department has been more than averagely involved with the Council's current review of its Project Grants Scheme.

In the main Dr Rees's account is a straight forwardly descriptive one that tells us little that grant applicants and grant-supported staff would not already know. It could hardly perhaps be expected to be otherwise but some reference is made to the needs of the Council to make "difficult choices between competing programmes [of research] worthy of support" and also "to identify areas where investment can be reduced in order to release funding for new work as well as to create environments in which new ideas can emerge, be recognized and supported". That the MRC is confronted by such needs cannot be denied for in a sense it is a victim of its own past successes. Along with the charities, it has created an ever-growing pool of medical scientists, many highly gifted and all anxious for a sliver of cake - the cake being of course the Council's income, overwhelmingly provided by its Government grant-in-aid. Alas, growth in the cake has not kept pace with the appetites of the family it is meant to feed and how to cut it has indeed become a difficult and highly charged issue.

In this connection, Dr Rees's choice of focus and the qualitative nature of his account does leave out of the picture a strategic issue of vital importance to Society Members in Higher Educational Institutions (HEIs). To put things in perspective, it is evident from the Corporate Plan that, in the financial year 90/91, Project and Special Project grants accounted together for 19.7% of the MRC's expenditure with Programme (ie five year) grants accounting for a further 6.1% and Training Awards for 5.5%. Collectively, then, these aspects of MRC disbursement amounted to 31.3% of expenditure. In the same year support of Institutes and Units and the Capital Building and Equipment programme together constituted 57.5% of the expenditure. A query that might be raised here is whether this relative distribution is appropriate and desirable. This is of course an enormous issue. The distribution results from past policies of creating flagship Institutes (such as the Laboratory of Molecular Biology at Cambridge and the National Institute of Medical Research at Mill Hill) and centres of excellence and critical mass in the form of Units. The problem with such policies is of course that the Council inevitably inherits a legacy in the form of large numbers of directly supported staff to whose continued support it has both a moral duty and a legal commitment.

Can and should this balance be changed? I cannot pretend to have an answer and I hasten to say that I have no wish to renew the old line of argument that used sometimes to surface in HEIs - namely that MRC staff were somehow unduly privileged. These are after all scientists (and some of them Society Members) who have opted wholeheartedly for a full-time research career and moreover they also have been in recent years subject to many financial restrictions. I would, however, argue that this is a strategic issue that should be debated and that our Society and others like it should be active participants in the debate. As Dr Rees himself says "we recognize that it is members of the scientific community who are best placed to identify research needs and opportunities ..... MRC strategy is not a directory of prescribed routes: rather it is a commentary on the collective predictions of the most productive direction for research in the foreseeable future. The planning of research ..... rests with the researchers".

Were change in the balance to emerge as desirable there is no doubt that adjustments would inevitably be slow, but what does the Corporate Plan have to say about the balance during the period of the Plan? Comparison of the expenditure for 90/91 with that projected for 94/95 suggests that percentage allocations to Institutes and Units and to Capital will decline (respectively from 18.9 to 17.8%, from 30.5 to 29.3% and from 8.1 to 5.9% of total expenditure) though it is also stated that policy is "to ensure that the best programmes are properly resourced and as far as possible safeguarded from the general pressure of funds".

What of the HEIs in the same period? Here the news is mixed. Project grants are envisaged as declining from 11.0 to 10.3% of expenditure and Special (Topic) Projects from 9.7 to 9.6%. On the other hand, Training Awards and Programme Grants should increase, respectively from 5.5 to 8.3% and from 6.1 to 9.0% of total expenditure.

No one, least of all the Society's Members, could do other than applaud the projected increase in Training Award funding, though significant damage to future research has undoubtedly already been done over the last few years through Government niggardliness. The MRC has of course made real efforts to contain the damage through its policy of going it alone among the Research Councils and unilaterally increasing the value of its Studentships. Doubters might say that it had little choice given the forward-looking policies of the Wellcome Trust. This would, however, be churlish - the Trust is much freer than the Council to take such actions.

But what of the Grant schemes? The projected increase in Programme Grants will be good news to some but is unlikely to benefit more than 10 to 15% of those who apply from HEIs for MRC support. The decline in the expenditure fraction envisaged as available for Projects is a different matter and potentially a disaster for significant numbers of Members. Elsewhere in the Plan it is stated that "sufficient funds will be made available to hold the number of [project] awards at a level of approximately 320 (the level for year 90-91) for the award years 1991-92 and thereafter". This is better news than the original plan to decrease numbers to 250 in 91-92 and thereafter and may be possible provided the grant-in-aid does increase as envisaged. Nevertheless, even at the 320 level unacceptable numbers of excellent applications have failed to win funding so that in the matter of proportional expenditure more than a trace would seem to remain of the view that Project Grants are essentially 'seedcorn' to encourage new talent - with Programme support as the research career aim for HEI staff.

No doubt such a strategy would focus MRC support in HEIs increasingly on the most ambitious. But what of the rest? It is possible that the charities might be able to pick up the tab but they will have their own wishes to support large-scale efforts. And is the underlying assumption justified, namely that those content with Project support are necessarily less successful than Programme holders in carrying out exciting and innovative research? The assumption might be justified in some areas of medical research but in Physiology, with its emphasis on high level manipulative skills and personal bench-working by even the most senior researchers, I am personally convinced it is not: there are many who simply prefer the focus, the sense of urgency that comes from successive awards of three-year support.

Mine is a conviction, however, that Dr Rees may not at present share. In January of this year he visited the Bristol Department of Physiology as part of the current review of the Project Grant scheme, both to explain MRC policy and to solicit our views on future relations between the Council and the HEIs. This was a constructive initiative welcomed by the department but during its course Dr Rees did express the view that we appeared to have many small groups working in apparently disparate fields. This took us by surprise as we are, I believe, relatively tightly focused among Physiology departments - so much so as to be classed by the MRC for the purpose of Training Awards as a neuroscience department. I hope we did an adequate job of explaining that the experimental difficulties that characterise Physiology as a discipline make small group working almost mandatory but it would be well if this point were to be emphasised to the MRC by the Society as a whole.

This and other signals as to the vital importance of the scheme should be sent promptly because, as Dr Rees states and as already mentioned above, the Project scheme is currently the subject of a major review via visits to selected departments in HEIs, via a questionnaire recently sent to departmental heads and via a statistical survey of the productivity of the scheme.

As to the reasons for this review, Dr Rees mentions only that it has been prompted by the current funding climate and the changes in Dual Support funding arrangements but I have no doubt that another potent factor is a perception that the scheme has been insufficiently audited making it difficult to convince paymasters that it represents good value for money. One can after all see that, viewed from Whitehall, it might seem puzzling that an overall large sum has for long been given out in relatively small packets to support research programmes, often with esoteric titles that do not bring out their relevance to medicine. Moreover, those accustomed to notions of strategic direction might be tempted to label this a scattergun approach short on focus. Anything the Society can do to demonstrate that many projects do in fact fall into pretty coherent groups within areas of great importance would be highly useful. Individuals can also help: there is no doubt that (some) grantholders have in the past been remiss: in one recent period almost half failed to return the final report whose provision was supposedly an obligatory condition of accepting a grant. The loophole is now closed but it cannot have helped the case for that maintenance (indeed expansion) of the scheme which so many of us see as crucial.
So far I have concentrated on the Project scheme, but the issue of Training Awards is of equal importance - as is the related and thornier problem of a career structure for postdoctoral workers located in HEIs and employed on fixed term contracts. Dr Rees tells us that Training Awards will also be reviewed beginning later this year and notwithstanding the recent increase in Student stipends the Society must press vigorously the case for further increases. Schools are undoubtedly providing smaller numbers of science students to the HEIs and, although this ominous trend affects the physical more than the biological sciences, it more than ever emphasises the need to encourage the best new graduates to take up research careers. Too many have been lost already.

Finally, I come to the most difficult problem of all: the plight of fixed-tenure researchers for whom there are all too few permanent posts in prospect in the HEIs. A cynic might see this problem as self-limiting. The next decade will see a massive exodus of academic staff, as those recruited in the 1960s reach retirement, and opportunities may then abound. But by then, large numbers of gifted postdocs will have left the system and this is a drain I believe we cannot afford. It would be wholly unrealistic to expect the MRC alone to solve this problem but surely the case is strong for the creation as soon as practicable of a body briefed to seek solutions. It would need to involve at least the MRC and the charities plus representatives of the HEIs and of the researchers themselves. Measures worth considering might include the creation of a "lab manager" level of appointment which would at once provide a career grade for postdocs who do not aspire to head their own wholly independent research teams and high-grade support for academic staff faced with ever-growing administrative and teaching loads. Those HEIs conducting Campaigns for Resource might do worse than channel funds to such a scheme and they might also aim to finance fixed-term fellowships similar to those of the MRC and the charities.

David Armstrong

The Tomlinson Report and the Future of Medical Education in London.

The long awaited, and widely leaked, Tomlinson report was published on 23 October. Already the two main issues covered by Sir Bernard's report - health care provision in the capital and medical education and research - have become politically divorced. A detailed response concerning the Health Service will be delayed by the Secretary of State for Health, Virginia Bottomley, until the new year, while public debate takes place. As part of the discussion process, the Minister for Health, Brian Mawhinney, will carry out a programme of visits to the institutions potentially most affected by the Tomlinson recommendations. At the same time as welcoming the broad conclusions, Mrs Bottomley emphasised that the report was advisory and did not constitute government policy.

The situation for medical education and research is different. In a letter to Sir Ron Dearing, Chairman for the Higher Education Funding Council for England on 23 October, the Education Secretary, John Patten writes, "I believe that the broad principles underlying the report's proposals on medical education and research will remain valid whatever detailed pattern of NHS changes emerges after the statutory consultations". Later on he states, "Although the full implementation of any decisions is likely to take some time, it will be important to make an early start".

In summary, the Tomlinson report recommends the merger of all but one of the present nine undergraduate medical schools into four faculties of medicine within those multi-faculty

colleges of the University of London which teach medicine. Imperial College would merge with St Mary's and with Westminster-Charring Cross. Formal links with St Mary's have been established for some time. King's College would see the merger of King's College Hospital Medical School with Guy's and St Thomas's, who have, for some years, operated as the United Medical and Dental Schools (UMDS). University College would acquire the Royal Free in addition to the already established merger between UCH and Middlesex medical schools. Queen Mary and Westfield College (QMW) would merge with the Royal London and Bart's clinical schools, the preclinical schools having already merged and moved to the QMW site in 1990. At present, QMW, Bart's and the Royal London operate as the City and East London Confederation for Medical and Dental Education (CELC).

St George's alone is spared these sweeping mergers, because of the lack of a nearby multi-faculty institution with strong basic science. In expanding teaching in subjects allied to medicine, it is forming links with other higher education institutions in south London. St George's is expected to merge with one of these institutions if one of them develops sufficient strength in teaching and research in the life sciences.

The report insists that these mergers should be real, and not cosmetic, and that new institutions should have a single administrative and financial structure and no academic duplication, particularly of clinical posts.

Along with the mergers, there are likely to be changes in medical student numbers in London. An intake into each multi-faculty institution of more than 200-250 medical students is considered undesirable. This, taken together with difficulties in implementing greater emphasis on community based training (which both the Tomlinson report and a recent King's Fund report recommended), makes it likely that total medical student numbers in London will need to be reduced by around 150.

The report is less insistent on the recommendation that nine London postgraduate medical schools and institutions should form principal linkages with either Imperial College, King's College or University College. It is acknowledged that practical difficulties exist in both the pattern and timing of these proposals, but the report seeks to establish a development path which would lead to a multi-faculty framework for the operation of these organisations. The British Postgraduate Medical Federation, comprising eight independent research institutes, should build on its existing work in co-ordinating and assessing research until a multi-faculty framework is implemented.

For all the conjectures about what Tomlinson might eventually say, there is little here that is really new as far as medical education and research are concerned. For those of us who have worked in London University, Sir Bernard has done little more than rework a persistent policy theme, that of links with multi-faculty institutions, which can be traced back more than three decades through the Flowers' report to Lord Todd's Royal Commission on the organisation of medical education.

For those of us who teach medical, dental and medical science students in London, 1993 promises to be a more challenging year than most, not only as the implications of the Tomlinson report begin to take shape but also because of the imminent promulgation of the GMC's new recommendations on undergraduate medical education.

As the old saying goes, "may you live in interesting times"!

John Patterson

Special Interest Groups

CNS: Somatosensory Physiology

The group met in Oxford on the second day of the Society's Scientific Meeting. The major event was a plenary lecture by Dr Jurgen Sandkühler from the II Physiologisches Institut, Heidelberg, entitled "Volume transmission in the spinal cord; effects of neuropeptides on nociceptive dorsal horn neurones in the pentobarbital anaesthetised rat". There was standing room only for this excellent lecture that contained a fine, and appropriate, balance of observation and speculation. Discussion of the talk occupied the next 15 minutes fully. An account of this lecture is to published in a future edition of this *Magazine*.

A stampede for the exit immediately preceded the Business Meeting of the Group that was attended by only 20 or so stalwarts. It was decided by a show of hands that the present convenor should continue for a further year and that next year nomination forms should be circulated. The Group was formed in December 1988 following a symposium in Cardiff and has organised two Designated Sessions every year since then. Each session has attracted more speakers than the previous one and the audience has always been much larger than when talks are given in "non-designated" sessions. The Interest Group seems to serve a useful function. Please write to the convenor and get your name added to the mailing list if your interests are central or peripheral phenomena associated with high or low threshold afferents from skin or viscera. There was much discussion of the title of the group, which is perceived as inappropriate. It will be changed just as soon as a better title emerges. I would appreciate suggestions.

Drs Lovick and Lumb were thanked for joining Dr Huw Rees and me as an ad hoc committee. We welcomed the suggestion that Professor A Brown should join us to stress our interest in events that are not necessarily painful.

A symposium to be organised by the Group had been proposed a few months ago but the idea has been postponed beyond 1993 due to the IUPS in Glasgow, the BRA in St Andrews and the IASP in Paris. The idea is likely to be resurrected for the following year.

The Scientific Meeting continued with 15 communications (Nos. 86-100 inclusive) that were precirculated and to be published. It was a great pleasure to see members and visitors from overseas presenting their work including K I Baumann (Hong Kong), W D Willis (Galveston), G L Wilcox (Minneapolis) and R Donga (Baltimore). The longer the journey, the greater the value of the Special Interest Group.

Malcolm Roberts

Smooth Muscle

There have been two recent meetings of the Smooth Muscle Special Interest Group. The first was at the St Thomas's Hospital Meeting of the Society in November 1991. This was preceded by a research symposium on smooth muscle cell physiology and its relation to dysfunction. This was a very successful one day event organised by Drs Poston and Fry of St Thomas's. As well as distinguished speakers from the UK they also managed to attract Professor Murphy from Virginia (crossbridge regulation) and Professor von Breemen from Miami (activation

of vascular smooth muscle). The Designated Smooth Muscle Session was well supported and lively. Communications occupied most of the first day and several Posters were also displayed.

The second meeting of the Group was held at the Cambridge Meeting in September. On this occasion there was a plenary lecture from Professor Jean Mirroneau from Bordeaux. This was entitled "Ion channels and the control of smooth muscle contractility", and was very well attended, despite being at 9 am after a Society Dinner! Professor Keynes gave a vote of thanks on behalf of the audience. The Oral Communications followed Professor Mirroneau's lecture and these were all presented and led to a good level of debate afterwards; including the comment that one Committee member ought to get himself some glasses! One point of general interest which arose, was how much could an Abstract be changed at a Meeting? New or more results since the submission of an abstract had led to a definite change in flavour of one of the presentations. Can the audience accept new wording to replace around one-third of the original? Should it be rescission? (Most of us felt unclear about what a rescission actually is but it sounds faintly unpleasant? Perhaps via the *Magazine* columns somebody should explain the process?) The Meeting narrowly decided to accept the changed Abstract. Several posters had been presented earlier at the Meeting.

Future meetings of the Group will be at the Leicester and Kings College Meetings of the Society. There will be a short Business Meeting at the Leicester Meeting, at which a new Convenor will be appointed.

Susan Wray

Renal Physiology

Following an earlier meeting at Manchester in January the Renal Special Interest Group held its second meeting of the year at Cambridge in September. The meeting was well attended and included a programme of eighteen Communications, three Posters and a Business Meeting. Of the Communications and Posters eight were concerned directly with tubule cell transport mechanisms, seven covered different aspects of hormonal control, two related to the control of the vasculature and there was one each on diuretic action, the interstitium, water balance and hypoxia.

An unexpectedly heated discussion on whether frusemide could be referred to as "furosemide" in Society *Proceedings* (it cannot according to *J Physiol* recommendations) left one with the clear impression that life would be simpler if any one drug had one name only.

All Special Interest Groups had been asked by the Meetings Secretary to consider their future and at the Business Meeting strong confirmation emerged that the Group should continue to meet as a distinct group with the objective of strengthening activities in the broad field of renal physiology. It was noted that the Renal Special Interest Group had a longer history than most because it had existed informally for many years before the Society established these Groups. The possibility of holding a meeting jointly with another Group was considered positively and the common ground between the renal group and the recently amalgamated Membrane and Epithelial Transport Groups noted. It was decided that the next meeting would be held after the Glasgow Congress on a date still to be confirmed. Roger Green, Convenor of the group for many years, handed over this task to Dave Potts and David Shirley proposed a warmly supported vote of thanks to Roger for his time and effort in organising many memorable scientific occasions.

Dave Potts

Somatosensory & Motor Physiology

A Business Meeting of the Somatosensory & Motor Physiology Special Interest Group was held at the Scientific Meeting in Cambridge, at which the Group decided to change its name to **Sensorimotor Control** and elected Roger Lemon as Organiser.

The Group will hold its next Designated Session at the UCL Meeting (30 June - 2 July 1993), to which it hopes to invite a Designated Lecturer.

Anyone not yet associated with this Group who wishes to be in future should contact Roger Lemon.

Roger Lemon

Physiology in the USA: A View from New York

The Fall of 1992 is very much a season in America of questioning and concern. It may not be out of place to look at some of the problems of Physiology, with few easy fixes. The OED defines Physiology as the "Science of the normal functions and phenomena of living things", a definition so broad as to explain if not excuse the contemporary and past fission of our parent discipline. Ideally, when Physiology attempts to explain how organisms thrive despite environmental changes, the explanations extend through a series of structural levels from the whole organism to subcellular components. Nowadays, few physiologists cross many structural levels in explaining function, which is unfortunate because the wish and the ability to do so is what most clearly differentiates physiologists from other biologists. It is no accident that when physiologists restrict themselves to the study of control systems at a particular structural level, often cellular, others, usually clinicians have jumped into the vacuum, thereby furthering a competition, healthy or otherwise, between, for example, departments of Medicine and Physiology. This tendency has suffered in the last decade from the twin-impacts of the imperative in departments of Medicine to generate funds from private practice and to deal with AIDS and related problems in the inner city hospitals. Neonatologists have emerged as a new source of physiological research - they are especially good at cannulating small blood vessels.

An unfortunate paradox exists: when the physiologist is functioning uniquely as such (that is, across structural levels) research support by granting agencies becomes increasingly difficult to get because the project may be felt to "lack focus"; for example, the programme may combine whole body with organ and cell studies. Alternatively, the physiologist may pick one animal to answer part of a question and another to answer another part. By their nature, physiological questions are rarely answerable in a "yes" or "no" fashion. Their programmes do not usually resemble a train guided by an experienced driver at high speed on well laid tracks towards a clearly defined destination - an outsider's view of molecular biology. Physiological research, because it deals with complex interactions at a given level, let alone between levels, rarely solves a problem within a discrete period of support of, for example, three years, as compared with determining the amino acid or base sequence in a molecule. One only has to recall the elaborations on the theme, muscle spindle or motoneuron discharge, that have followed the original account of the stretch reflex.

Peer Review

To the specific problem of supporting physiological research must be added the general problem of evaluating research proposals. Traditionally, peer group evaluation by a panel of "experts" has been considered the best of bad solutions, recalling Winston Churchill's apology for democratic government. In the Gold Rush days of the late 50s through early 70s, an enormous expansion of biological research and training was fostered by the system. However, in recent years, far more research is approved than can be funded. Under stiff competition, physiological research of the type discussed above tends to invite criticism, which has a fatal effect on the priority score voted by the panel. Furthermore, the very diversity of physiology implies that in a federal panel of, for example, 14 members, with luck four and possibly as few as two are truly experts on the proposed project; the remaining members, who have equal voting power, evaluate as best they can the remarks of the few experts. Thus, much evaluation at the funding level is now at the noise level. Those not too far below the funding level feel encouraged to resubmit, after modifying their original proposal to meet the criticisms of the panel. At what point does the reshaping of a project interfere with the creative intent of the physiologist? More seriously, when does the system of evaluation completely break down? In the late 70s to early 80s, two projects failed to be funded by a major federal agency. One proposed to utilise whole body MRI to visualise tumours; the others to utilise a magnetic pulse to stimulate the nervous system. In the first instance, the scientist (at our medical school) subsequently founded his own company to manufacture a successful machine, later receiving a Presidential Medal of Science for his efforts. In the second, after the Sheffield group had proved it could be done, the group at MIT was funded. Both of these proposals had theoretical roots in Physics, whose extraordinary power to deduce particular consequences from universal laws was misapplied by the reviewers. Perhaps faced with a highly original project, an evaluating panel is particularly vulnerable to the minority expert opinion. How does one avoid turning down development of an MRI machine while still rejecting perpetual motion machines? One suspects the answer lies more in the personalities than in the narrow technical expertise of members of a panel examining "far out" projects; a Feynman vaulting the gap between theoretical physics and an experimental demonstration to a lay audience of the probable cause of the Challenger disaster might well have made the correct decisions.

Animal Legislation

As a result of legislation, larger mammals, including cats and dogs, are now better cooled in hot summers than some of us. Much of this concern for animal comfort is for the good, but a parallel concern for increased funding to underwrite the better living conditions would have helped. Inexorably, a downscaling in species and numbers used per project has occurred, driven largely by the increased cost of the larger mammals and of maintaining them. To the good is an increased sensitivity to the possibility of animal distress. Few if any physiologists would now consider doing the type of experiment common in the USA and on the Continent in the 60s, where reticular or cerebral cortical studies were performed on locally anaesthetised, paralysed mammals. Significantly, the change occurred by consensus within the profession rather than by external pressure. Violent action by the animal rights movement has occurred at scattered sites across the USA, but the counter reaction has been impressive. The federal initiative to criminalise breaking into animal facilities reflects the majority public opinion, which is in favour of animal research. At last, the American Medical Association is also lending support to animal research. In the past, it seemed so inappropriate for physiologists to have to proclaim the utility of their work in the service of Medicine while the practising physician chose discretion.

Teaching

Graduate Programmes in Physiology have generally seen a profound drop in the number of American students entering. Market forces in the form of low stipends, anticipated difficulty to getting research funding and positions after graduation have driven many students from applying. By contrast, many from the Far East who are intellectually superbly gifted are happy to fill the vacant positions. In effect, the normal corrective action of market forces, that is, increasing stipends and career opportunities sufficiently to recruit USA students have been bypassed. The analogy with corporations moving manufacturing abroad because of reduced costs there is uncomfortably close. What will be the effect on future staffing and research in Physiology? The fraction of the many now being trained who will wish to settle in the USA is unknown. If a future shortage of faculty develops, the deficit over the broad range of Physiology, especially the integrative aspects, is unlikely to be corrected by faculty of other departments, as surgeons and radiologists have done for Gross Anatomy. This in not an exercise in xenophobia, talent for Physiology being internationally distributed. The plea is for a better mix of national with international intake, which can only occur by providing adequate financial and career incentives for a country's own young citizenry. Unfortunately, the size of the pie is rarely under faculty control. The necessary choice may have to be made to feed fewer mouths better from a given pie, requiring that we discard the notion of a "critical mass" of students in favour of treating the chosen few as junior colleagues.

Attacks on Medical Education

American medical education has recently had a bad press in two books for the laity, the first describing experiences in the first (preclinical) year at Harvard Medical School, and the second the training of residents in a university affiliated hospital in Boston. The take-home lessons were, respectively, only medically trained faculty should teach preclinical subjects and senior residents provide better teaching and patient care than the more experienced attending (consultant) physicians. The fallacies in these anti-intellectual conclusions are easily exposed. What is less comforting is the number of contemporary medical undergraduates and graduates who share these views. Students' complaints about preclinical teaching are hardly news. What has changed in recent years is that many faculty and senior administrators have come to agree that contemporary preclinical education is in trouble. The problems are both general and specific. Clearly, the growth of information has made the Flexnerian ideal of giving medical students a scientific underpinning to the many branches of Medicine impossible either now or in the near future. What has finally affronted many faculty is seeing students cramming a subject taught in a brief block of several months duration, followed by rapid erasure after the final exam and during the next block. At times, faculty curricular "reforms" resemble new ways of filling the bathtub, while students have to devise strategies to keep from drowning. (A common one is to study intensively collected, past local exams, or guides to the National Board exams.) The serious preclinical students cannot but resent being deprived of the intellectual enjoyment of the material. Two experiments to redress some of the above problems are in progress. Both emphasise small group teaching at the expense of large group lectures, which students have voted against with their feet. (The decline of the lecture was predictable once the student demand for a guide to the lecture material was met. The morecomprehensive the guide, the less point there seemed in attending the lecture.)

Experiments with new teaching formats for preclinical students

In the first experiment, the Patient-Oriented-Problem-Solving (POPS) system was introduced by Dr Parker Small (University of Florida, Gainesville) and extends throughout the first two years, that is, prior to clerking on the wards. The class is divided into groups of four students, who are required co-operatively to arrive at the correct basic explanation of a clinical problem presented to them. Co-operation is secured by providing each member of the group with only one quarter of the information needed to solve the problem. More specifically, each member receives a booklet providing: (a) the expected educational benefit from the exercise, that is, its objectives; (b) a series of pre-test questions with encouragement to consult available sources; (c) subsequently, a brief explanation of the correct answers is provided, each member receiving only one quarter of these; (d) a clinical problem is presented to the group with questions to be answered through interaction between its members; (e) a post-test examination is taken individually and self graded. The POPS exercises can be integrated into the rest of the preclinical curriculum. While preparing the booklet requires a major investment of time by the participating faculty, their subsequent involvement is surprisingly small, consistent with the belief that students learn best from mutual interchange. That many, more senior medical students are prepared to devote time to faculty collaboration in developing the POPS exercises for those following them evidences both a hunger for changing the curriculum and confidence in this particular method of teaching. What is not so clear is whether retention and application of the basic material to Medicine is improved over the long term. Furthermore, the level of explanation may not be as advanced as in a formally structured lecture sequence. Finally, some "good" students feel constrained by the enforced group interchange and prefer to have access to all four quarters of the information at the same time so they can study alone.

The second experiment, Problem Based Learning (PBL) is more radical. Although having its roots in the McMaster curriculum, the more recent expression of PBL by Harvard Medical School has excited interest across the USA. In a typical experiment, a segment of the class, for example, 10-15%, are tracked separately during the preclinical years. Subgroups of five to seven students are provided with carefully prepared case histories and the results of the clinical examination. A reading list is supplied, which is directed at the basic science (across disciplines) that is relevant to understanding the patient's disorder. Study questions are supplied, which guide the student's reading. The small group has access to the faculty at large, but meets formally with a faculty tutor, who does not need to be a Renaissance person, because the role played by the tutor is more to keep the student interchange productive than to supply scientific expertise. The tutor has a guide to assist in answering probable questions and can supply the answer to, for example, laboratory tests, which may be requested as a result of the group interchange. Again, student enthusiasm for this type of exercise is very high, but so are the stakes. Clearly, a curriculum based on a branching inquiry into the basic sciences, which stems from a "clinical stimulus" has to be very carefully designed to avoid major gaps if it is expected to supply the main diet in the preclinical years. (Lectures are still given, but at a much reduced rate.) Furthermore, are physiological interrelationships between systems

(cardiovascular, respiratory, renal, etc) more easily grasped by such teaching than by the more coherent, admittedly didactic traditional methods?

A clear advantage of both experiments is the major increase in student enthusiasm for the preclinical curriculum. Using explanation of human disease as an objective of preclinical teaching has always been well received by students. More importantly, focusing on a patient's disorder is a superb integrating device between disciplines in a preclinical curriculum that teaches by departments. However, the teaching of Physiology is more than transmitting a core of facts (where few agree on the size of the core) and the "rules" defining the interrelationships between facts, that is, the principles of Physiology and their application in understanding medicine. It is also about instilling a standard of what constitutes a valid explanation of a physiological problem. The physiologist may question whether the new curricula meet the level of scientific rigour that is the target of traditional teaching of their discipline. Perhaps the more compelling criterion in medical education is which method of teaching leaves the graduate best motivated to apply the basic sciences in the practice of Medicine?

Expansion of University Administration

A few words on the expansion of administration. It is estimated that a quarter of the total cost of health care in the USA is spent in its administration. Supposedly, during the Vietnam conflict, 14 soldiers stood on the shoulders of the one in the rice paddy. Medical schools are not quite at that ratio, but some of us can remember when they were presided over by a Dean, but run by a highly intelligent, well organised secretary. Her spiritual progeny have long since gone to senior positions in banking; the replacements, a hierarchy of associate and assistant deans, while arranged like Pacinian lamellae, unfortunately lack their transducing properties, serving splendidly as shields against the responsibilities of fast decision making. Clearly, a calculus is needed to establish the optimal ratio of administrators to faculty. How does one approach a solution? Traditionally, physiologists decide a structure is a necessary component of a system by seeing the effect of making a lesion there. A humane substitute, observing what goes wrong when personnel are away, leads to the wrong answer when a process has been artificially subdivided into components, with individuals exclusively assigned to each. It is ironical that a method of allocating human resources, so successful in the past industrial era, is multiplying in universities when, under challenge it is changing in industry. Perhaps we can learn from the brain, where neurones in the brainstem reticular formation, act in different combinations in subserving their various functions. The ability of these and other regions of the brain to continue functioning despite a reduction in number surely has lessons for how resources might be allocated in universities.

Vahe Amassian

Focus on Clinical Scientists

Clinicians and Basic Science Research

Clinicians become attracted to the basic sciences at different stages of their careers. For many, the attraction occurs early and these individuals take a year "out" of their undergraduate medical training to intercalate a basic science degree course. By the time they have graduated in medicine, many of these scientifically-inclined clinicians have already decided on an academic career, but are generally discouraged (and rightly so) from seeking a research post until they have completed general professional training and obtained a higher diploma from one of the Royal Colleges (eg MRCP, FRCS). For others, the realisation that biomedical science research can be both fascinating and directly relevant to clinical practice often dawns upon them when they work in junior clinical posts within a teaching hospital setting. Sad to say, there are also medical graduates who, in order to play the "promotion game", embark upon several years of quasi-scientific research supervised by senior clinicians who may be highly polished but not very bright. While these individuals usually fudge their way to an MD (or Heaven forbid, a PhD!), they can be ignored for the remainder of this article.

There are two main problems facing clinicians with serious inclinations towards basic science research: how to get started, and how to keep going.

How to get started

Despite the seemingly intractable problems facing the National Health Service, the universities, the Research Councils, and the medical charities, droves of bright, motivated, but blissfully ignorant clinicians continue to compete tooth-and-nail for the limited number of entrées to high quality biomedical research. At this stage, aspiring clinician-scientists (preferably equipped with a science degree, one or two publications, and a distinguished undergraduate career) should ideally have chosen their ultimate clinical speciality and the type of basic science research they intend to pursue. Obtaining a good research post in a stimulating clinical/scientific environment involves good luck, good timing, and a good deal of patronage. Outstanding candidates are usually snapped up by local heads of departments who will often have identified these talented individuals during their general professional training. However, a note of caution: UK medical schools may have oases of scientific excellence, but they also have oceans of scientific mediocrity (and worse). Strong candidates with good academic attainments should aim for the former, who will often be able to place them in one of the much sought-after research training fellowships funded by the Medical Research Council, the Wellcome Trust, or one of the speciality-based medical charities. Alternative funding for 2-3 years may be available in the form of Regional Health Authority project grants, but these resources seem destined to be used increasingly to support research into health care delivery. There are two additional types of research opportunity available to clinicians at this stage of their careers. One is the junior academic clinical post in a teaching hospital department, which is attractive because it is usually established on hard(ish) money and carries the title of Lecturer. However, holders of these posts frequently

replace NHS registrars and may have heavy clinical, teaching and administrative duties which prevent prime-time laboratory-based research. Young clinicians, no matter how highly motivated, are unlikely to be effective in basic science research if left to work alone in the laboratory during evenings and weekends. The other, which has a lower pedigree, is provided by funding from the pharmaceutical industry. These funds, allocated to a specific project, tend to be awarded to senior clinicians who may lack a strong science base but who nevertheless have established a rapport with a particular company. This type of opening provides a convenient way for a local clinician known to the fund-holder to begin a project that may lead to an MD. Unfortunately, these projects usually involve clinically-biased pharmacological studies in human subjects and/or laboratory animals, and rarely provide the opportunity to gain expertise in the basic sciences.

Sponsors and supervisors have important responsibilities towards these aspiring clinician-scientists, who are potentially the greatest asset available to academic clinical departments, and from whose ranks many of the future leaders of the biomedical community are drawn. Heads of academic clinical departments have a duty to ensure that young researchers at the most formative stage of their careers are properly trained in basic science techniques by non-clinical scientists, have the time and funding to visit other laboratories to gain additional experience, and have most of their time protected for research. Although most clinical departments have non-clinical scientists among their tenured staff they are often (for historical reasons) locked into laboratory methods appropriate for the study of clinically orientated problems. The most common techniques available in clinical departments are those related to biochemistry, immunology, cell biology and molecular biology. These disciplines exploded in the 1980s, scattering fragments that were grasped eagerly by academic clinical departments, including those that were (and some that remain) almost intellectually destitute. We now run the risk of producing clinicians well trained in "sexy", state-of-the-art techniques which enable them to pursue largely descriptive science. It is inevitable, however, that the time will come when these techniques have to be allied to functional studies at the cell, tissue and whole-organ level, which is when the expertise of physiologists, pharmacologists and clinical scientists (or should that be non-scientific clinicians?) will come to the fore. This should occur sooner rather than later. It is all too easy for clinicians and non-clinical scientists to plod on, following avenues of research using techniques with which they feel comfortable. In this era of over-specialisation, many researchers (both clinical and non-clinical) seem reluctant to take a less blinkered approach and take on board new techniques which would enhance the quality and impact of their work. Nearly every UK university possesses research staff who between them have the ideas and expertise to address a wide range of important problems in medicine and biology, yet our overall output at the international level (as judged by publications in top rank journals) is poor.

Young clinician-scientists must not be allowed to fall into this trap. Having identified a problem to study they should be strongly encouraged to use different but complementary experimental techniques. It is important that they become well-grounded in the theoretical aspects of their research, learn the necessary techniques (which may be physically and intellectually demanding), and acquire skills in scientific reasoning and criticism. This can usually be best achieved by having them spend much, if not most, of their time in a basic science department. This would have the additional advantage of allowing non-clinical scientists to see how their own technical skills and research plans might be applied to clinical problems. It is also time that heads of clinical and basic science departments realised that it is not enough to reach "critical mass". The cozy conglomerates that ensue are sometimes neither critical nor effective. Perhaps the time has come for those running our universities and medical schools to develop long-term corporate plans based on a consensus of the important growth areas in medicine and the biological sciences. Having done that (surely a miracle in itself), all barriers between departments should be removed, clinical-scientists and non-clinical scientists alike organised into multi-skilled groups with specific research targets to be achieved in a given period of time, and everyone told to get on with it. This or some similar sort of reorganisation is required urgently, should enhance the international standing of our biomedical research output, and may even be achieved without additional resources. It is this kind of environment which will produce the best clinician-scientists in terms of motivation, ability, and intellect. It is important to remember that, from the point of view of their future career advancement, some clinical exposure is essential during this period of basic science research, and clinician-scientists should be encouraged to continue some clinical activity (eg a weekly out-patient session), attend postgraduate clinical meetings, and remain aware of advances in their speciality. However, clinical-scientists should be supernumerary and not exploited by using them habitually to fill gaps in NHS on-call rotas.

How to keep going

We are at the point where clinical-scientists have completed their initial forays into the basic sciences, and emerged with an MD/PhD, a handful or more of good quality publications, experience of presentations at scientific meetings, and clear ideas of how they wish their research careers to develop. It is now that many of these talented individuals receive no, little, or bad advice about how to proceed, leading to their exit from the science arena with feelings of frustration and disappointment. Most clinician-scientists who wish to remain active in basic science are also aware of the need to develop their clinical skills, and indeed this is imperative if they are aiming for a senior appointment as a clinical senior lecturer or NHS teaching hospital consultant with an on-going programme of basic science research. The next stage of their training is therefore clinical, usually during a 2-3 year senior registrarship which is necessary for specialist accreditation from the Royal Colleges. To avoid a loss of research impetus, this period of higher clinical training should be arranged locally and ensure enough protected time to allow effective laboratory research. This is where problems may arise. Senior registrar posts within the NHS and university lectureships with honorary senior registrar status are excellent routes to specialist accreditation, but may entail heavy day-to-day and out-of-hours clinical commitments in addition to teaching and administrative responsibilities that prevent worthwhile basic science research. However, there are ways in which dedicated clinician-scientists can achieve a balanced clinical/scientific existence in the medium term which may have long-term benefits.

One approach is to compete for an MRC Clinician-Scientist Training Fellowship. These are an ideal way for clinicians with an MD or PhD to spend up to four years developing their research portfolios while pursuing the scientific aspects of one or more related clinical problems. Successful candidates are likely to have previously held a substantive research post (eg an

MRC Training Fellowship) and be working in an MRC unit or research group, or an academic department engaged in MRC-funded research. Competition for these posts is likely to be fierce. A second option, again involving intense competition, is for the clinician-scientist to apply for a project grant which would fund a research assistant, equipment and running costs. When successful, this approach releases the clinician-scientist from much of the routine laboratory work and demonstrates an ability to obtain independent funding. A third option which should be considered by any street-wise clinician-scientist is that of spending 1-2 years in a first-class research laboratory overseas, since it invariably leads to a widening of personal and professional horizons, opens up possibilities for future collaboration, and usually leads to the acquisition of new research techniques. Such opportunities are always to be found in the USA and Europe but rely very much on personal contacts. Obtaining funding for these visits is a constant problem. Each year the MRC invites applications from both clinical and non-clinical scientists for Travelling Fellowships, but these are limited to one year. The MRC also offers four French exchange fellowships. Other UK funding bodies seem extremely reluctant to fund clinician-scientists to pursue research overseas, even when the experience gained is likely to benefit the home department. It is difficult to understand this kind of short-sightedness when much of the best biomedical research involves international collaboration. Fortunately, established investigators in the USA appear to show more flexibility and initiative when it comes to funding, and a mixture of persistence and personal recommendation frequently leads to success.

Having completed their clinical training and shown that they can cope successfully with the basic sciences, highly skilled clinician-scientists in their early thirties often find themselves at a difficult cross-roads. Bearing in mind that they are supposed to be the future leaders of academic clinical medicine, these individuals tend to find that career opportunities dwindle, scratching around for research funds is a full-time occupation, and the Establishment (Government and its agencies) seems embarrassed by their existence. What's a clinician-scientist to do? Faced with these uncertainties, some will decide to abandon science and opt for a career as a clinical consultant (always assuming that appointment committees do not penalise them for being "too scientific"). Others will be appointed to clinical senior lectureships which usually carry substantial clinical responsibilities. While this provides a large university-funded subsidy to a strapped-for-cash NHS, it frequently compromises the type, depth and quality of basic science research pursued by these senior clinician-scientists. Senior Clinical Fellowships provide an alternative career path for an extremely limited number who wish to concentrate almost exclusively on research for a further five years or more. These highly prized posts are offered by the MRC, the Wellcome Trust, and speciality-based charities such as the British Heart Foundation and the Arthritis and Rheumatism Council. Those fortunate enough to obtain a Senior Clinical Fellowship almost always proceed to senior academic appointments. However, as these posts are scarce, a significant number of highly trained clinician-scientists are thwarted at a critical stage of their careers. The Wellcome Trust has already recognised the difficulties in providing stable funding to support highly rated researchers (hopefully clinical as well non-clinical) and is addressing this problem. It is less clear whether the MRC takes the same view; what is to become of outstanding clinician-scientists with interests outside the Corporate Plan? Should not universities take the initiative and identify resources within their existing budgets that could be used to fund similar posts for the benefit of high-flying clinical and non-clinical scientists? If substantial, such a scheme might also attract key researchers from overseas. Anyone who thinks they can't buy success doesn't know where to shop!

Geoff Sandle

Some practical problems faced by clinicians doing research in the basic sciences

In case this article about problems becomes too gloomy, let me start by saying that doing basic research as well as clinical practice is a marvellous combination with potential benefits in both areas. Clinical practice sharpens the questions asked of basic research and directs the benefits more accurately. In its turn, a good training in experimental science gives a critical approach to the application of diagnosis and treatment and the evaluation of studies in respect of patient care. The basic scientist in a clinical department is likely to have regular contact with a much wider range of research than non-clinical basic scientists outside the clinical environment. Research done by clinicians may be divided into four broad categories: epidemiology, whole-patient research, basic science and the evaluation of health care. The great expansion of experimental research in clinical departments has taken place in cellular and molecular biology research and it is these areas that I have particularly in mind in this article.

Many of the problems which clinicians face doing basic research are of course the same as those of non-clinicians, eg obtaining funding, difficulties in recruitment. I shall discuss these common and important problems when they have special features in the clinical environment. Also relevant to this article is the impact of the Health Service on basic research done by clinicians, and I shall make comparison between clinicians who do experimental research and those who do solely clinical research, or none at all.

The case for an increase in day length

On an individual level, the biggest problem that senior clinicians have in doing basic research is commonly that of correct allocation of time. Such individuals usually do several jobs, each competing for a share of his or her day: clinical practice, experimental research, clinical research, medical student teaching, supervision of junior doctors, administration and so on. Administration nowadays includes an increasing contribution towards management of the particular hospital service. Meetings feature much more in the clinicians' week than for the pre-clinical scientist and include a "staff round" (often an hour and a half, the staff meeting from all specialities with junior doctors and students); a departmental (speciality) research meeting; a clinical meeting; a clinical laboratory meeting (eg with a radiologist or a pathologist); and other sessions for management, policy, administration, audit etc. As to what out of this list gets done, fixed clinical sessions are indeed fixed (and may be combined with some clinical teaching), and clinical emergencies and on-call duties take up time in addition. Teaching commitments must be honoured, and numerous other duties pile into the day. It is therefore essential for the clinician scientist to have protected time available for experiments, and also to have collaborators who themselves have a full-time commitment to the laboratory.

For practising clinicians there is an all-or-none law which operates to limit the extent to which they can reduce the clinical component of their work, for various reasons. To be safe and competent as a clinician it is necessary to do a certain amount of practice and for a specialist in hospital medicine the cut-off level is about one quarter to one third of the time. Unlike in the States, it is rarely possible in this country for the ward work to be concentrated in blocks, with weeks or months completely free of in-patient clinical duties when most of one's time can be spent in the lab. In addition, there may be difficulties in interacting with full-time NHS colleagues (who have a substantially different agenda for their week) when one wishes to do less clinical work than they do, for the rotas need to be drawn up and colleagues are unlikely to refer patients to someone who is rarely in the clinic or on the wards. Therefore there has to be a certain minimum commitment, for to do less means that the clinician becomes in effect a full-time basic scientist who then loses the benefits of spanning the two cultures.

Another powerful factor limiting the extent to which the fully-fledged clinician-basic scientist can avoid or shed some clinical responsibility is that many academic departments in this country are greatly overburdened with routine NHS service work. It could act as a tremendous boost for research in these units if NHS hospitals were to be provided with sufficient consultant staff and facilities to cope with routine patient care. In my own speciality (cardiology), it is said that there are more consultants in Boston (USA) than there are in the whole of the UK. The USA may be at the other extreme, but in respect of service work alone a firm case can be made for expanding the consultant staff in the UK in my speciality by between three and five-fold.

Research in the training grades

For young clinicians who want to enter basic research, problems arise from the very beginning. Junior doctors are best staying in full-time medicine until they have got their MRCP (or other diploma), even though the lack of intellectual stimulation during routine clinical work at that level can be exasperating. Once they have done two years or so as a registrar they are less likely to have to live in the hospital for their next medical job. More important, if they start research at mid-registrar level it should be possible to continue in basic research thereafter in combination with clinical practice, as having to break off after three years to do full-time clinical medicine makes it correspondingly more difficult to pick up research again at a later date. Having got the timing right, clinicians then need to decide if they really want to do experimental research for its own sake, because unless that is the case the absence of a proper career structure for academic clinicians makes the relatively more straight forward career paths of a full-time clinician so much more rewarding. Funding has to be sought and may not be available from grant-giving bodies for the full three years or more that are necessary for proper research training. The remainder has to be sought from industry, from NHS or university-based research trusts and funds or from a project grant.

There are a lot of very bright people at registrar level in hospital medicine and the fact that the majority of these are not being recruited into good experimental research, even for a three-year period, is one of the major problems for academic medicine. In order to progress up the NHS career ladder there is great pressure for these doctors to spend a short period of time on clinically-related "research". This is activity which their senior NHS colleagues can understand more easily than basic research and which they sense has more immediate clinical application. It can be devastating for an aspiring clinician scientist when a senior NHS consultant fails to understand why it is that they want to do experimental research which the consultant perceives as being of no use to clinical practice. The NHS medical ladder still operates as an old-fashioned hierarchy and it is just not possible for junior doctors to tell consultants that they are ignorant, blinkered, unimaginative and of no use to the progress of their speciality, for if a doctor wishes to continue in the speciality the consequences of such an action are likely to be detrimental to their career. Fortunately many consultants are not of this type and if they were not so overloaded with clinical work it would be possible to envisage the day in which all teaching hospital consultants made a significant contribution to research in the associated academic department. If aspiring basic researchers talk to clinicians slightly more senior than themself they may get the idea that their publication record from a period in experimental research will be less attractive than if they attach themselves to someone offering clinical research. It is unfortunately still the case that the number of publications a candidate has usually takes precedence over their quality at clinical interviews. Registrars who do clinical "research" may end up with three times as many (shorter) papers as their colleagues who have spent time in a laboratory and this will impress even though the latter candidate may have undergone a dismal research "training" and will serve in later years merely to perpetuate his species. In my experience it is rare for clinical interviewers to read candidates' published work to help in the selection procedure, and little attempt is made to assess their scientific content. Therefore only those clinicians who have fire in their belly for basic research are likely to take the risk of setting these considerations aside for the privilege of doing proper research in a good experimental laboratory, and although some change in the right direction is in the winds it will need to blow much more strongly if the majority of registrars are to be spared going the way of all flesh.

I hope that readers will forgive me for mentioning filthy lucre but another reason for the recruitment problem to experimental science among clinicians is that the financial rewards are potentially much higher in an NHS consultant post when this is combined with private practice than in an academic consultant job. In my speciality, which involves practical procedures such as cardiac catheterization, angioplasty and pacemaker insertion, the annual income of a hard-working consultant can be very high indeed and it is not surprising that registrars go all out to reach that position at the earliest possible moment. Non-clinical researchers may quibble that they earn substantially less than those with clinical responsibility but the issue is how to attract clinicians to research and, until they are valued properly and reimbursed accordingly, recruitment to experimental science among clinicians will be difficult.

Problems at the senior registrar grade

Once the first period in research is over and the individual is at senior registrar level, several new problems arise. Perhaps the majority of these people return to clinical practice for a few years' more training. It is a greater challenge to continue with experimental research as well, and some clinicians are daunted by having to set up what is usually more sophisticated equipment than they have used so far when they first apply for their own research funding, at a time of increased clinical commitment. It is highly desirable that those who wish to remain in experimental research can continue at the bench throughout what must now be a more intensive period of clinical training. It may, however, be necessary (and indeed beneficial for clinical training) to move to a job at another teaching hospital in a place

without facilities in their field of research, and clinical jobs at senior registrar and clinical lecturer level often carry a heavy service burden. I was very fortunate after I had spent three years in Denis Noble's lab (on an MRC training fellowship) to obtain an NHS senior registrar job in Leeds, where the posts at this level were (and may still be) to some extent supernumerary to service requirements. I was able to spend up to two days a week in research (not counting the nights spent struggling with Purkinje fibres!). I joined Mark Boyett in Brian Jewell's department where I was effectively a postdoc and I also did some clinical projects in Ron Linden's department.

The lack of a framework for people wanting to train to do both research and clinical practice is a very serious matter that has received some attention by the funding bodies, but the number of senior fellowships for clinical scientists is small and the competition severe. There are rather more clinical lecturer posts available but even these may be heavy clinical jobs and the recent move in many places to make a distinction between clinical lecturer and senior registrar job descriptions is essential and welcome. At senior registrar level, though, the clinical experience must usually be "accredited" by the Joint Committee on Higher Medical Training if the individual is to progress to hospital consultant status. Established senior registrar and clinical lecturer posts are inspected on a regular basis but if an individual raises his own funding from a fellowship, an application has to be made for ad hominem accreditation and these are limited by the extent of the local clinical experience and by the numbers allocated from above. Happily the whole question of accreditation is up for review in order to comply with EC law.

At present, senior registrars in the major specialities are often 35 or over before they are appointed to consultant or senior lecturer jobs and it would help greatly if this prolonged training period were reduced. Although the standard of clinical practice required in this country is very high, the training would be possible in substantially less time if it were better supervised and less dependent on years of service experience.

In the days when medicine was no more than giving out pills and the recording apparatus on the laboratory bench was a smoked drum, it used to be easier for clinicians to do basic research, though I don't know what some of today's cardiologists would say about Sidney Ringer using frog hearts! Given that both camps have become vastly more complicated, it is not surprising that the problems of trying to combine the two have multiplied, but to quote Sir David Weatherall, "it is from among people with this breadth of skills that many of our future leaders in academic medicine will be drawn. They are not, as is sometimes suggested, half trained scientists and half baked clinicians. If they have undergone rigorous clinical and scientific training, and if they set their sights on a limited clinical topic, they are equipped to function in both worlds."

George Hart

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Interactions with basic scientists: a neurologist's tale

A clinician doing basic research is like a monkey playing the piano: what is surprising is not that he plays it well, but that he plays it at all! This view is not as much of a caricature as one might think, particularly amongst basic scientists who collaborate with academic clinicians. In the week that the editor of this Magazine asked me to write a personal account about the interaction of clinicians with basic scientists, I was introduced by an eminent Member of The Physiological Society (who might well know better!) to a visiting scientist from the USA as a doctor who "dabbles with neuropeptides". This article charts the dabbler's progress in neurotrophism over 20 years, since a schoolboy, before the waves of fashionable interest in neuropeptides and trophic factors swept through physiological departments in the UK; it may help to read first the other more systematic accounts of clinicians and basic research in this Magazine, before this idiosyncratic view of the subject.

How does a neurologist start in research? And stay in it? The answer to the second question is often predicated to the first, as is the relationship with basic scientists.

The conventional way to get started is first to complete general medical training, including two years of clinical medicine and the MRCP examination, which are necessary before embarking on specialist neurological training. Some then do a year or two, as clinical neurology registrar before embarking on a research degree, while a few do their neurology registrarship after their research. The choice of research usually depends on the availability of posts, the safest being in a university department of clinical neurology, in an area thought to be of clinical interest in the next decade, and under the supervision of an academic clinician or scientist who is in a position to advance the neurological career of the protege. It is relatively unusual for researchers at this stage to follow their previous interests, such as those acquired during a BSc or a PhD prior to clinical training. The temptation to do basic science research which neurologists may regard as clever but obscure, or clinically irrelevant, is risky.

The conventional candidate therefore selects a laboratory which is headed by or linked to a neurologist who may be on the appointment committee of the researcher's next (registrar/senior registrar) post, or even the eventual academic neurology (senior lecturer/consultant) post. The research registrar in a neurology department keeps in close touch with clinical neurology, has a headstart when back in the clinical fold, and may continue to apply the fruits of research with ease during the senior registrarship within the same department. By this means, the start is linked to the staying on, with respect to ideas, techniques, clinical services, departments, meetings and sources of funding. The most "successful" initial career links are therefore with established academic neurologists and allied laboratories, not with basic scientists pursuing novel ideas away from the neurological mainstream. Little wonder that future interactions are few and difficult, and this limits progress in the field.

My own start and course were very different and show that alternative routes are not impossible. Two glorious Californian summers in Craig Heller's lab in the Department of Biological Sciences at Stanford turned me to neurobiology. Craig had just been appointed to the department which he now heads, and I was lucky to be able to participate in every stage of the project, from building the apparatus and trapping the animals (we worked on

CNS control of temperature in hibernators) to publishing the work in the American Journal of Physiology. It was a chance meeting at Stanford in the early 1970s with Jean Rivier, a friend and neighbour of Craig's from his La Jolla days, that set my interest in neuropeptides and trophism. Jean pulled out of his pocket a vial containing a substance he had just sequenced and called somatostatin. It was hardly a coincidence that my clinical student elective period in 1977 was spent just across the road from Addenbrooke's Hospital, Cambridge, in John Kelly's lab at the MRC Neurochemical Pharmacology Unit, iontophoresing somatostatin while recording from pyramidal cells in rat hippocampal slices.

When the time came to do a research degree in 1982, as a clinician with an interest in neuropeptides and trophism, I joined Steve Bloom's lab at the Hammersmith Hospital. This lab was able to measure the peptides, and was interested in their long-term (endocrine and gut) effects. The research subject - neuropeptides in primary afferents, and their role in pain states - was one that Tom Jessell and Leslie Iversen had made a contribution to at the MRC Unit in Cambridge, while I was doing my elective there. Pat Wall, at University College London, would supervise my work, alongside Steve Bloom. It would not be too far off the mark to say that we now know less about the significance of the changes in neuropeptides in primary afferent neurones after injury, at least centrally, than we thought we knew ten years ago! However, my discursive account aims to demonstrate that it is possible to persist with an early interest, even if it is considered obscure by neurologists and developed in a department of endocrinology, since this author continues to grapple with the same question as an academic neurologist a decade later. The imminent clinical trials with recombinant human neurotrophic factors should bring the subject out of the "obscure" category.

Clinicians usually get only one bite at the cherry of full-time research, and must therefore choose well. My own full-time research period, from 1982 to 1984 at the Hammersmith Hospital, was most productive and instructive, both in the science and politics of biomedical research. The academic culture of the Hammersmith Hospital was very different to my previous experiences in university departments, whether in Stanford, Oxford, or Cambridge. Some of the lessons derived then are not irrelevant to the subject of this article.

The academic clinician has to straddle the two different worlds of laboratory and clinic, and few have done so successfully. The reason for this is mainly to do with time and stamina, apart from ability, since it is like having two full-time jobs. Time is short and the art is long! Basic scientists sometimes fail to recognise that clinicians, rightly, must give absolute priority to their care of patients and clinical training: research must take second place, particularly in busy junior clinical jobs. As some of the best clinical training posts are so busy that it is difficult to get on with research other than at nights or weekends, when not on clinical duty, it is hardly surprising that only the very tough or the very interested clinicians manage to produce original research throughout their early careers. The system of moving from post to post as a junior doctor, often in different cities, makes it difficult to continue with research in a lab with a particular interest. At times research must take the place of a hobby. This does not look good to basic scientists. Lest it all sound too gloomy, let me say that the engine that drives on the clinical researcher is to make a scientific discovery of clinical relevance, or vice versa, and that the thrill of making a contribution that improves treatment of patients makes the effort well worthwhile.

Although this article is not entirely an apology for academic clinicians, there are other reasons, in defence of clinicians, why interactions with basic scientists often fail to mature. Basic scientists may be quite dismissive of clinicians with whom they collaborate as being superficial and flighty (usually voiced when the collaboration has ended, or in private!). Although this perception is true to an extent, and more self-discipline is clearly desirable, it is partly because of the structure and nature of the clinician's job. A clinician must have a much greater range of reliable knowledge; for example, a neurologist could, in the course of a morning, discuss the prognosis and modern treatment of a child suffering from a malignant astrocytoma with his parents, examine and manage an elderly patient brought into the intensive care unit with an undiagnosed coma, before setting up assays in the lab to measure VIP and nerve growth factor in injured rat sciatic nerve. Similarly, there is pressure not to put all the research eggs into one basket. By virtue of the limited access to patients and tissues studied, is often more difficult to control variables in clinically based research, or to study mechanisms in depth. This is sometimes mistaken as superficiality.

Having said all that, I have never had any personal difficulty in persuading basic scientists, however distinguished, to collaborate, if the idea was good and the methodology sound. That is as it should be! Furthermore, they continue to introduce fresh perspectives, and indeed new potential treatments. Basic scientists are key members of most successful clinical academic departments, and some of the best clinical neurology research in the UK has emerged from sustained collaboration between clinicians and basic scientists within the same department.

There is a niche for an academic clinician which is often overlooked: as a person who can conduct clinical trials of new treatments. Without being a scientific genius, such a person may be the first to identify both the need and the potential of new scientific discoveries, and apply them to selected patients in a safe and sound manner. Reducing the pool of academic clinicians, or their interaction with basic scientists, will inevitably lead to a loss of this essential function.

Finally, with regard to the question posed by the Editor, as to what advice would I give to someone starting out in clinical research, my best answer would probably be - where there is a will there is a way!

Praveen Anand

(Royal London Hospital)

Impact of Health Service Reforms on Clinical Medical Education

It makes sense for teachers of the basic medical sciences to take an interest in the problems of the medical school as a whole and in factors which affect the later stages of the careers of their students. The clinical academic departments are most obviously at risk from the effects of the Health Service reforms but departments cannot isolate themselves from the general financial or academic difficulties of their faculty if they occur.

There is a tide of change running through the universities and the currents are particularly strong in faculties of Medicine. Everything seems to be changing or under active review. The effects of the Health Service reforms will be compounded by the

disappearance of the binary divide with a dilution of the concern for the needs of Medicine in an expanded Higher Education Funding Council and Committee of Vice-Chancellors and Principals. Universities are competing with one another for students and for their research reputations.

Measures to protect clinical undergraduate education

To what extent are medical students safely isolated from the turmoil of these reforms and the changes which they have precipitated?

It has been suggested that the Deans of Medicine have never been in a better position to protect clinical undergraduate medical education. Those who say this have in mind the protection afforded by Sir Christopher France's ten key principles and the influence exerted by the Dean through a role in agreeing the distribution of the Service Increment For Teaching and Research (SIFTR). The principles, seen to be essential following the White Paper, are intended to serve as a code to guide the Universities and the NHS towards effective collaboration at national and local level. They emanated from the France Committee, a committee chaired by Sir Christopher France whilst he was the Permanent Secretary at the Department of Health. The code is intended to be binding, both Secretaries of State, those for Education and for Health, signed up to these principles in recognition that "undergraduate medical and dental education requires unity of purpose .....".

The first principle acknowledges that the aim of undergraduate medical and dental education is to produce doctors and dentists who are able to meet the present and future needs of the health services. It recognises that an educational environment which promotes high professional standards and a spirit of intellectual enquiry and innovation is important and that this environment must sustained by active research and development programmes.

The debate regarding the future educational needs of the Health Service has begun. We have received a consultation paper from the General Medical Council (GMC) containing revised recommendations for undergraduate medical education. These recommendations will be expensive to implement, taken together with the GMC's almost simultaneous recommendations for improving general medical training, the medical schools face a formidable challenge. General clinical training is carried out in hospitals and, more recently, in certain health centres under the aegis of the University. The Education Committee of the GMC wishes universities to "exercise greater control than hitherto over the clinical duties undertaken during general clinical training, over the educational content of posts, over the supervision of house officers, the general education provided and the monitoring of house officers' progress. The expectation is that the quality of the pre-registration year as an educational experience and its supervision will be improved.

Physiologists have themselves led with ideas on student-centred learning, with the introduction of problem-based and computer-assisted learning and with skills laboratories; these are ideas which require introducing into the undergraduate clinical curriculum. There are no signs that harm will come to the active research component of the educational environment; indeed Professor Michael Peckham, the Director of Research and Development at the Department of Health is increasing research activity rather than diminishing it; but priorities are changing. The implications of this for clinical research will be addressed later.

The second principle emphasises the sharing of responsibility for undergraduate medical and dental education between the universities and the NHS. This is where vigilance will be needed. Whereas teaching hospitals were constrained by their Health Authority and individual hospitals and units could be relied upon to follow local agreements, it is already clear that individual contracts will have to be negotiated with NHS Trusts and Units.

The third principle concerns the need for efficient and cost-effective provision of medical and dental education. Such a demand for efficiency and cost saving makes it difficult to envisage how the innovations mentioned above can be implemented.

It is stated that the "local provision of undergraduate medical and dental education should be guided by clearly defined and co-ordinated national policies". There is little support for the idea of a national curriculum in the medical schools but it could be on the agenda of some managers.

Several of the principles should lead to improvements in local practice. It is recommended that "local policies and plans relevant to undergraduate medical and dental education should be agreed and regularly reviewed by both parties; once established, local policies and plans should be disseminated". The need for academic clinical staff to agree, so far as their contribution to clinical service is concerned, either a collective departmental job plan or an individual plan with their Dean and Trust/Unit management is helpful. It serves as a basis for discussion which should provide the NHS with a reliable contribution to service but at the same time should establish a better balance between service and research and teaching which is sorely needed. At the same time, the contribution by NHS consultants to clinical teaching should be more secure. The monies received by teaching hospitals through the distribution of the Service Increment for Teaching and Research (SIFTR) are intended to take account of the extra costs of undergraduate teaching and of research and to enable the teaching hospital to price its clinical service competitively in the NHS 'market'. The identified sums are considerable (about £35,000 per clinical medical student, £14m for a Region or District Health Authority with a medical school accepting 145 medical students per annum). The contracts for undergraduate clinical education which the money underpins are intended to ensure that clinical teaching by consultants is not displaced by service and that the quality is maintained. SIFTR is the second measure which supposedly gives Deans added powers with which to protect the integrity of the clinical curriculum.

There is an admonition that plans and the outcome of reviews should be shared between universities and health service managers. This is a reasonable request and one which can only be met on the scale intended since the publication of Institutional Plans and Departmental profiles.

Research for Health (1991), a research and development strategy for the NHS, emphasises that good, relevant research findings should be made use of by the NHS clinicians and managers. It recommends that "universities and the NHS should take into account the implications of research for teaching and service provision and should foster both the application of current research and the development of high quality new projects". The same emphasis is found among the ten principles.

The ninth principle concerns consultation between universities and the NHS over the nature and special interest of senior medical appointments. It is too early to judge what will be the implications of this recommendation. The clinical service

provided by most academic departments is specialist and is not usually duplicated. The maintenance of this service and appointing for academic excellence will come into conflict.

Additional protection

Several other features of the purchaser-provider culture, the emphasis on contracting, on accountability and on the monitoring of effectiveness can also serve to protect the quality of clinical education. The principle of target setting can also be translated to education with advantage. The appraisal of academic staff, teaching quality assurance and general measures to improve teaching quality do not arise from the reforms but contribute to the protection of the integrity of the curriculum.

The morale of clinical medical students

There are possibly other more subtle effects of the reforms. Health and medicine have been the centre of media attention almost continuously for more than two years. Political feelings have run high on every side; problems and difficulties have been exaggerated and emotions aroused quite deliberately to win the political debate. There can have been no period when medical students felt themselves more in the midst of change. This atmosphere of uncertainty has bred some anxiety and it is more important than ever that clinical students receive support and have opportunities to unburden themselves of their concerns.

How serious are the threats to the clinical undergraduate course from the establishment of NHS Trusts?

It is premature to decide whether NHS Trusts and their competitive financial strategies represent threats to the quality and integrity of clinical curricula because contracting has only just begun. In Nottingham, at any rate, the application for NHS Trust status from each of the major teaching hospitals contained a clear commitment to undergraduate teaching and research and an expressed intention to sustain close integration with the University and the Medical School.

The facilities which teaching hospitals provide towards the clinical curriculum are indispensable. These are the items which, in effect, are purchased with the Service Increment For Teaching and Research (SIFTR). They can be listed as follows:

1 The clinical teaching of undergraduates by NHS consultants and other NHS staff

2 The provision of facilities on wards, in the out-patient clinics, operating theatres (including enhanced levels of nursing staff). An increased load on secretarial and other staff.

3 The provision of facilities for the clinical assessment/examination of undergraduates. NHS consultants are examiners, ward schedules are disrupted, levels of nursing staff must be enhanced.

4 The provision of research opportunities for doctors in training. There has often been some uncosted contribution to the expenses of maintaining adequate levels of suitably experienced staff in academic clinical departments and in relation too clinical teachers with active and successful research programmes. Some universities currently provide capital equipment and maintenance grants to clinical departments at a level less than the basic medical sciences but are now expecting the same research output.

5 The clinical laboratory service departments undertake additional investigations in support of undergraduate teaching and research.

Tertiary referrals to academic clinical departments will prove an attraction to Trusts. Whether the Trusts will in other circumstances seek to improve their cost-effectiveness remains to be seen.

The hope has been expressed that when major teaching hospitals are competing as Trusts the Health Authorities will use their influence to moderate any adverse effects of competition and will encourage the university to collaborate with the Authority in this role.

Trusts will have the option to develop policies for changing local pay and conditions. This may have implications for the staffing of academic departments. The financial help which most medical schools have received from Health Authorities towards the salaries of clinical academic staff is "protected" and will continue. The question remains whether the Trusts will "interfere" when the posts are refilled.

There is a need for continuing co-operation over the refinement of contracts for the teaching of our undergraduate medical students. The current review of the Nottingham undergraduate curriculum and the implementation of whatever changes are recommended by the General Medical Council, when consultation is complete, will lead to changes in the pattern of clinical teaching. We look forward to collaborating with the Trust in making these changes and monitoring their effectiveness.

The changes in general practice

The Trusts are offering to provide specialist services in GP practice. There is a move towards holding consultants' clinics off-site on general practitioners' premises. The Trusts usually say that they will have due regard for the effect on teaching, but it is not clear how this is going to be done. We have to await a much clearer statement about how the needs of undergraduate and postgraduate teaching are to be met and how junior staff in the hospital are to be supervised with consultants off-site. There will have to be some movement into the community but the problems must be addressed before problems arise.

The growth of day-case surgery and the discharge of patients earlier and earlier in their illness and following surgery mean that patients with common yet important conditions will be found in the community rather than the hospital. There will be a temptation to shift clinical teaching towards the community; that is, for general practice to provide students with basic learning of clinical method and skills. It is interesting to note that in the Second Report of the UFC Medical Committee on the NHS Reforms the Committee were encouraged by the number of innovative schemes for teaching in general practice and in the community, by the number of studies and experiments which were currently either in progress or being planned and by universities' expressed enthusiasm for an increased use of general practice for teaching. Such teaching will have to be appropriately financed.

Whereas the Trusts themselves are obliged to give some warning of their plans and intentions, the Fund-holding practices are not. It is far from clear whether the ambitions of senior general practitioners for a greater involvement in the delivery of the undergraduate curriculum is matched by the capacity of that branch of the profession to deliver change in the face of a the shift of the clinical work load into the community. The future role of fund-holding practices is a major imponderable. Whereas the Trust may agree to maintain a certain case-mix to

sustain clinical teaching, their ability to do so may easily be jeopardised by the freedom of choice that fund-holding practices enjoy, including the provision of specialist services within their health centres. There are signs that emergency admissions may be increasing; practices do not pay for these, with a resultant change in case-mix.

We face the possibility of an increased intake of medical students in some medical schools. The recommendations of the Standing Committee on Medical Manpower is awaited with interest. We shall need Trusts to be flexible about the number of undergraduate clinical medical students for which they will find facilities. The introduction of several of the innovations envisaged by the GMC will require a similar flexible response.

The changing research environment for academic clinical departments

There are forces which are likely to pull the research undertaken by clinical departments in two quite different directions. These departments feel under pressure to increase their involvement in molecular medicine. This is the natural inclination of many of the staff, and the Research Assessment Exercise has focused minds on generating research income and on increasing the value of the total of the grants received from the Research Councils. The "rewards" from obtaining MRC support have increased. This trend is important for those in the basic medical sciences; it means that the two halves of medical faculties have never "needed one another" so much as now.

On the other hand, the influence of the measures to promote Health Services Research, defined as "the identification of the health care needs of the community and the study of the provision, effectiveness and use of health services" and to provide research to underpin "the Health of the Nation" investment programmes will create new opportunities for applied (clinical) research. Those faculties which have maintained a reasonable balance between the three major categories of research, namely basic (bio-medical), applied (clinical) and pharmaceutical will be able to respond. There will be opportunities for those physiologists who have skills in human and clinical physiological measurement. The enhanced terms of reference of the MRC Health Services Research Board represents one of the supporting changes.

Allocation of resources for research and a regional research database

Besides the promotion of Health Services Research, there are two other initiatives arising from the policies contained in "Research for Health" which physiologists might note. Each Regional Health Authority has appointed a Regional Director of Research and Development and recruited to a Council for R & D. The Director is in most instances a senior clinical academic from either a clinical specialty or public health medicine. The second initiative concerns the assembly of comprehensive regional research databases to inform the Director and the Council where relevant research has been completed and where various research skills are to be found. These databases will be used to inform the distribution of the "R" component of SIFTR.

Conclusions

I am optimistic that the clinical course will survive and will flourish. I believe that the climate is ripe for the introduction of new ideas. The clinical teachers are of an instant keen to try new teaching methods. Some of the teaching initiatives pioneered by physiologists will be taken up in the revised clinical curricula. The clinical research environment will be managed and monitored; it will perhaps be less vulnerable to the results of the Research Assessment Exercise than in other subject areas. The most recent result will be known by the time this Magazine appears. Good opportunities for research in the physiological sciences by doctors in training will remain.

Peter Fentem

In the first of what will hopefully be an annual series of articles, eminent Members of the Society were asked to look forward over 1993 and discuss what they believe may be areas of breakthrough in their fields of interest.

Bernard Katz

Synaptic Function

I have been asked to forecast advances that may be expected in the field of my special interest, which is concerned with the function of synapses. Such predictions tend to be guesswork and, more often than not, are based on wishful thinking. All I can do here is to point out certain directions in which I hope successful research will be carried out in the near future.

During the past two decades, remarkable progress has been made in the elucidation of the chemical structure and physiological function of postsynaptic membrane receptors, the key macromolecules on which synaptic transmitter action depends. Before 1970, the identity of these molecules was unknown, whereas by now the amino acid composition of several of them has been determined and sequenced, their dynamic properties have been examined and altered experimentally by site-directed mutation and substitution of single amino acids, and one may anticipate that their three-dimensional structure and its agonist-induced changes will come under exploration before very long.

What I am hoping is that the powerful chemical and biophysical techniques, which have thrown so much new light on the postsynaptic macromolecules and their associated ion channels, will be successfully applied to the study of presynaptic transmitter release. The nerve terminals and the key molecules at their release sites are technically a more difficult proposition, but it looks as though they are now becoming amenable to experimentation, with the combined techniques of macromolecular biochemistry and further refinements of patch-clamping and its useful application to membrane capacity measurements.

It is almost 40 years since vesicular exocytosis was proposed as the basis of neurotransmitter release. Much supporting evidence has been produced during the last two decades; it is now widely regarded as the established mechanism and has entered into most of the textbooks. Nevertheless, direct proof for this hypothesis at neuronal synapses (where the evidence is not as clear-cut as in degranulating secretory cells) is very difficult to obtain and has not yet been achieved. For this, one still has to hope for further improvements in the sensitivity and time resolution of cytochemical and patch-clamp capacity measuring techniques. In the meantime, it is not surprising that alternative mechanisms to explain quantal transmitter release are put forward from time to time, and that the whole subject - even after 40 years - has to contend with a certain amount of controversy.

The development of patch-clamp recording has made it possible to explore quantal release in the central nervous system by more direct means than were previously available. Moreover, the method has been shown to be applicable to synapses on small central neurons which had been difficult or impossible to examine. Important results have already been obtained which throw interesting light on the kind of regulation that occurs at neurons of different sizes, and that is needed to limit the voltage amplitude of single quantal responses so as to maintain the integrative function of multiple converging synaptic inputs and, of course, to leave an ample safety margin between quantal response and firing threshold. This type of investigation has made a very promising start and is likely to lead to further important progress in the near future.

John Nicholls

Great Expectations

Over the years certain physiologists have been able to predict major new developments and concepts with uncanny accuracy. An example is provided by Helmholtz, who time and time again from psychophysical and physical measurements deduced how neurones could function for sight and hearing. Thus, in 1867 Helmholtz wrote:

"*There is in the retina a remarkable spot called the fovea. The cones are here packed most closely together and receive light... We may assume that a single ... nervous ... connection ... runs from each of these cones through the trunk of the optic nerve to the brain ... and there produces its special impression so that the excitation of each individual cone will produce a distinct and separate effect upon the senses.*"

It is worth remembering that Helmholtz formulated these concepts before the word "synapse" or even the cell doctrine existed. He thereby side-stepped issues that now seem trivial but were of burning importance at the time. Similarly, Langley and Clark invented the concept of mythical receptor molecules and were able to define their properties; and Hodgkin, Huxley and Katz defined channel mechanisms, again for structures that had never been seen. What, however, seems quite impossible for even the most brilliant scientist is to make guesses about revolutionary techniques. How could a neurobiologist in the 1930s have dreamed of PET or MRI scanning, optical recording, site-directed mutagenesis, in situ hybridisation or patch-clamp techniques, each of which has opened up new worlds?

As for imagining the future, my track record does not inspire confidence. What to me seems perhaps attainable in the not-so-distant future is to study and correlate the fine grain of what is happening in well-defined different brain areas as one picks up a pen, reads a poem or inspects a banana. It no longer seems unthinkable to go from measurement of signals to interpreting their meaning for perception or for the initiation of a voluntary movement.

It also seems to me that a fairly safe prediction is the even closer mutual benefit and stimulation that will be derived from collaboration between physiologists and clinical neurologists. The point here is not how the physiologist can help the clinician but vice versa. As in the early days of the study of the brain, the neurologist today can provide unique insights. Just as psychophysics and neurology were so powerful for understanding perceptual mechanisms, as well as localisation of function in the cortex, neurology today can once again provide the link between higher functions, chemistry, signalling and structure. From the beautiful work of Hubel and Wiesel with

microelectrodes, we have an idea of how neurones act as building blocks for perception in the visual system. Unlike EEG recordings, in which fine detail is obscured, newer imaging techniques now enable neurologists to measure the detailed patterns of activity of neurones in the living brain of a conscious, thinking human being. Nature's own experiments in the forms of aphasia, dyslexia, distortions of body image and disturbances of movement could perhaps provide key clues for understanding normal functions of the brain. Through non-invasive, high resolution techniques, one can hope to understand how the picture of the world that we see is put together and to attempt to tackle the type of problem that Adrian posed: how is it that once you have learned to write your name by holding a pencil in your fingers you can do so with your toes?

In fairness I must say that until now I have never predicted any major advances in physiology and often enough did not even understand the importance of those that did occur until they were explained to me much later. A fringe benefit has been that each new development was an unexpected source of wonder and pleasure.

Autar Paintal

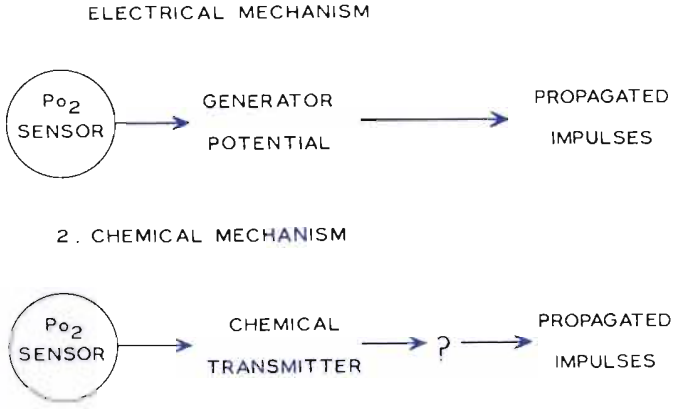
The Logic of Life: Two Small Questions

What do I look forward to in my field in 1993? Any breakthroughs? The short answer to the second question is "no". To the first, like many other physiologists, I can say that the main thing I look forward to in 1993 is the Congress in Glasgow, and to be part of the underlying spirit ie to explain the Logic of Life and to outline the challenge of Integrative Physiology. This is a much needed emphasis after almost two decades of a different approach, especially in some fields where much attention to events at the molecular level have overshadowed the main issues. This has not happened to a large extent yet in chemoreceptor physiology but I can see it coming slowly from the hints by certain agencies suggesting that they would fund project proposals on peripheral chemoreceptors preferably involving studies at the cellular and molecular level.

Mystery of Sensory Transduction

In a way, the above tendency suits my interests, partly because I very much look forward to the solution of the mystery of sensory transduction at chemoreceptors. Many others obviously have the same interest which is reflected in the forthcoming Congress symposium (number 45) being organised by McQueen, O'Regan and Patterson. This symposium will surely provide some interesting give and take, as the list of participants suggests. Here is an example where consideration of the Logic of Life and Integrative Physiology is needed because certain chemoreceptorologists molecularly inclined forget while patch clamping that the arterial Po_2 is definitely not the stimulus for the arterial chemoreceptors. The natural stimulus for them is the fall in the local tissue Po_2 which is itself determined by the oxygen availability (determined by the oxygen content of the blood and blood flow) and by the metabolism of the cells of the glomus. At present, no one knows what the transmitter at the chemoreceptors is. Some favourite transmitter candidates such as acetylcholine have lost the race and others such as dopamine are trying to make some headway but without much luck. I am not one of those who bets on races of this sort. As one who looks at things from the Logic of Life angle, I have been asking the question: is it necessary to have a transmitter at this sensory structure when other sensory receptors clearly work without one?

What is the Logic of Life here? Has nature made primary afferent fibre terminals of mammals such that some produce propagated impulses only to an electrical stimulus, ie the generator potential, while others are so made that they produce impulses only if their terminals are acted upon by a chemical substance - the sensory transmitter? This in my view is one of the main questions that needs to be answered - an issue that I have been raising since 1971 (Ann Rev Pharmacol (1971) 11: 231-240).



Should attempts not be made to falsify this proposition? - the proposition that all primary afferent fibres of mammals are so designed that their terminals respond only to electrical stimuli and not to a specific chemical stimulus.

The second thing I look forward to in 1993 (and further on) is finding the mechanism underlying visceral pain - for example, anginal pain. The pathways are now more or less known but what about the fundamental question: which are the receptors involved in this pain? Are there specific pain receptors in the myocardium that are stimulated only when myocardial ischaemia occurs? If the answer is "Yes" then these specific pain receptors must lie dormant for several decades before they get stimulated because they get stimulated in a small fraction of the population for the first time four to five decades after adulthood. This does not seem right to me (see Progress in Brain Research (1986) 67: 3-28). But maybe I am wrong. Maybe there are examples in the physiology of senescence where a structure becomes active only several decades after adulthood. So here is another proposition that needs to be falsified - the proposition that nature does not make sensory receptors that have to wait for long periods for their natural stimulus to arrive in order to get stimulated.

As you can see, teleology has been my companion from time to time and, unlike certain others (see H A Krebs (1954), Bull Johns Hopkins Hosp 95: 45-51), I have not been ashamed to be seen in public with her. But why should one be? After all, isn't teleology a key element in integrative physiology?

Peter Matthews

Physiology advances but most "breakthroughs" are for the media

When I was young, a scientific career offered the prospect of becoming a journeyman scientist and continuing to experiment throughout life. Adrian and Sherrington had both remained personally active to the very end. That world has now largely vanished, the scale of activity has increased and the ethos of business and the media are moving in; the scientist is becoming a manager, and in many areas there is no other way to advance. However, with all this has come the need for constant self-justification and the accompanying glorification of what one has done, with appropriate verbal hyperbole. Adrian can be said to have made a breakthrough in 1926 when he started recording from single afferent fibres and opened the way for the direct physiological study of sensory mechanisms; moreover, the importance of this technical achievement was easy to recognise at the time. But could Sherrington ever have looked back at the end of a year and claimed a breakthrough? We admire both men for the continued freshness of their experimentation and writings rather than for isolated "breakthroughs", that can be reported in a single screaming headline. The old analogy of scientist as bricklayer or stonemason, joined with his fellows in creating a noble building, is being replaced by the analogy of scientist as general, gloried simply for his breakthroughs. This denigrates the contributions of the many, without whom science would stop dead, and encourages steady progress to be dressed up as breakthrough upon breakthrough. Our colleagues in the humanities have a clearer view on the nature of intellectual progress.

Thus, as I warned our Editor at the outset, I refuse to attempt to predict "breakthroughs" for the coming year, but I will try to point out a few growing points that interest me, in the expectation that they will continue to flourish. Over the last decade the role of human experimentation in systems neurophysiology has been expanding ever more rapidly. In part this is for negative reasons, of which we are all too well aware. But the positive side is that technical advance has opened up a whole new range of experimental possibilities for the pursuit of "the proper study of mankind".

First, comes the microcomputer revolution which has touched everything in physiology. A particular application has been in the analysis of the firing patterns of single motor units, both individually and in pairs; much of this could in principle have been done earlier, but the labour would have been overwhelming. A prime target has been the extent to which a pair of units are synchronised during voluntary contraction, betokening a common input, and how this varies with the nature of the task, implying that motoneurones do not receive a single undifferentiated command simply specifying the level of muscle contraction. Computers have also enabled single units studies to supplement H wave studies in the analysis of the "spinal wiring" mediating human reflex action; once the existence of a particular connection has been established, work starts on the way transmission can be modulated by higher centres, as in the various stages of a voluntary movement.

A second major technical factor has been the introduction of the magnetic brain stimulator, cheaply available and painless in action. Indeed, it has become so fashionable that many motor physiologists seem simply to have stopped whatever else they were doing in order to play with it and stimulate the motor cortex for themselves. Much of what has been done has been largely groundwork, the inevitable description of what is to be found on charting new waters. Discussion continues as to what is being excited and where, and over the reasons for the slight differences from electrical stimulation; such understanding is essential for the routine use of a new tool. But, more and more, brain stimulation is being used to address wider questions of function, ones that needed answering anyhow and not just ones related to the introduction of a new technique. As ever, stimulation is better at demonstrating where things happen rather than in elucidating how they work. For example, certain long-latency "reflex" responses may be facilitated by stimulating the motor cortex, confirming (in conjunction with appropriate controls) that the reflex pathway involves the cortex. Stimulation may also interfere with an ongoing motor act, and the nature of the disturbance has the potential to throw light on the nature of the neural programming as well as on the location of the hardware involved. Localised electrical stimulation in animals has always suffered from the difficulty of restricting the stimulus to the desired group of neurones; the uncertainties are several orders of magnitude greater with transcranial magnetic stimulation in man, and efforts to improve the situation can be expected to continue.

The increasing political pressure for utility in science will encourage areas with a potential practical application. There is nothing bad about this, provided pure science is allowed to continue, since there need be no loss of intellectual challenge or scientific fascination. The attempt to understand disease and develop rational therapy has always been with us. The development of prostheses for those with permanent disability has gained a new impetus with the development of micro-electronics and the ability to create an interface between man and machine at a variety of levels. Collaboration with engineers can also be expected to grow in the area of robotics; they have come to realise that effective mechanical control requires massive feedback from the periphery, as in the body. Thus they have become ready to talk to us, rather than simply leaving us to model the workings of the body in terms of current technology.

I have not commented on animal work, since Anders Lundberg has more to say. But here also I would expect steady progress to continue. Taking everything together our view of the whole scene should be transformed in a few years time. Looking back to write history, it may then be appropriate to characterise a few rare findings as breakthroughs, though they would probably be better described as landmarks. Done for the present, taking stock too easily becomes self-aggrandisement. To attempt to foretell the future in any precise manner is to emulate the brashness of the economists. The "real" breakthroughs that one admires from the past arose from serendipity and new thinking, rather than from the massive concentration of resources upon a well-defined problem. The Manhattan project that produced the first atomic bomb gave the USA what it wanted in a magnificent breakthrough, but with the same material support the German scientists would probably have done as well. Our paymasters continue to need reminding that this is not the model for the development of science, and that any demand for a regular string of breakthroughs is to risk destroying the spirit of innovative scientific enquiry for which we have been famed.

Anders Lundberg

Do independent finger movements depend exclusively on the corticomotoneuronal connection?

Lawrence and Kuypers (1968) demonstrated that independent finger movements in monkeys were permanently lost after transection of the pyramids. They assumed that independent digit movements do not occur in cats and postulated that the existence of them in primates depends on the direct corticomotoneuronal connections which phylogenically appear in primates and do not exist in cats.

Evidence is now emerging that the control of the digits in cats may be more complex than previously assumed. It has recently been shown that there is a relatively high degree of independence in reflex control from the skin of the different digits (Hongo *et al*, 1990). If so, independent control of the digits from higher motor centres seems likely because the brain operates via interneurones of reflex pathways. Further information has been obtained from the study of food-taking, the movement by which cats grasp a morsel of food and carry it to the mouth. Some time ago we observed that atactic cats when trying to retrieve food from a tube could stabilise the paw by abducting one digit over the edge of the tube while the other digits were firmly adducted to allow entry into the narrow tube (Alstermark *et al*, 1981). However, the cat's forepaw is too compact to allow a systematic analysis of digit movement with standard kinematic methods. This obstacle has now been overcome by introduction of the technique of pulsed high frequency *x*-ray shots (Boczek-Funke *et al*, 1992). The results show unequivocally that grasping during food-taking occurs with independent digit movements (Illert, personal communication).

Food-taking was also investigated after transection of different descending pathways. It disappeared for several months after transection of the cortico- and rubrospinal tracts in C5; ultimately there was a recovery and the command was via reticulospinal pathways (Alstermark *et al*, 1981). Lesions were then made in series (Alstermark *et al*, 1987). After selective transection of the corticospinal tract in C5, food-taking did not disappear even temporarily; there was an effective rubrospinal take-over. Surprisingly, one month later after an additional transection of the rubrospinal tract there was an immediate reticulospinal take-over. Accordingly, the cortico-, rubro- and reticulospinal tracts are all of them potential carriers of the command for food-taking. On visual inspection the food-taking commanded via the reticulospinal tracts looks similar to that in the intact cat. Below I will assume that independent digit movement occurs in "reticulospinal food-taking" but this is one of the important issues for the further X-ray analysis now being carried out (Illert, personal communication).

I believe that the findings in cats have bearing on the understanding of finger movements in primates. It seems likely that the interneuronal system for independent digit control in cats has survived phylogenetically and that the fingers in primates are controlled in parallel via direct corticomotoneuronal and interneuronal routes. Transection of the pyramid interrupts both pathways and the permanent loss of independent digit control after pyramidotomy in monkeys suggests that the interneuronal system for digit control is more dependent on the corticospinal tract in monkeys that in cats. However, there is evidence from human stroke patients indicating that independent digit movements may not depend exclusively on the corticospinal tract. A particularly interesting case has been described by Bach-y-Rita (1980). A 66-year-old patient (his father) survived for six years a stroke which initially gave right hemiplegia. The subsequent autopsy with neuropathological examination revealed a large cyst in the rostral basal part of the left pons and a virtually complete degeneration of the fibres in the left pyramid with only "sparsely scattered intact fibres remaining" (Aguilar, 1969); 3 % is given as the approximate number of surviving fibres (Bach-y-Rita, 1980), but the count was made in the region of the corticospinal tract in the spinal cord, where other fibres may be interspersed, so the real percentage is likely to be lower. An extraordinary intense rehabilitation programme in the highly motivated patient gave remarkable results: he recovered all motor functions on the right side including independent finger movements; he performed fast typewriting using all fingers independently and could tie his shoestrings and his necktie (Bach-y-Rita, 1980 and personal communication). Since the pyramidal lesion in this case was unilateral, it might be argued that the recovery was due to the uncrossed right corticospinal tract. However, this explanation is unlikely since the role of this pathway is to control axial muscles (Kuypers & Brinkman, 1970). The rubrospinal tract is lacking in humans and on the basis of the findings in cats it is suggested that the recovered command is via cortico-reticulospinal pathways.

The difference between monkeys and humans may be due to motivation based on the insight that a well informed person has into the function of the brain. Even if the assumed reticulospinal control of the interneuronal system for independent control of fingers normally plays a subordinate role to the corticospinal control, the very knowledge of the existence of the former may mean all the difference for the stroke patient and the physiotherapist.

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Andrew Huxley

Prospects in research on muscle contraction

As I suppose is true of most fields of research, advances in the understanding of muscular contraction have come in bursts. A tremendous number of accurate observations were made by light microscopy in the second half of the nineteenth century, though nearly all of this was lost as interest switched after 1900 to the underlying chemical and physical processes. The first quarter of the 20th century was relatively unproductive, largely because of the dominance of the lactic acid theory, which survived an accumulation of difficulties until it was demolished by Lundsgaard in 1930, when he showed that a muscle poisoned with iodoacetic acid could give many normal contractions without producing lactic acid. The period from 1930 until research was stopped by World War II was the great period of classical biochemistry of muscle: the roles of phosphocreatine and adenosine triphosphate were established; "myosin" was shown to be an ATPase; and in the early years of the war "myosin" was shown to be a complex of what is now known as myosin with a distinct protein, actin. The same period included A V Hill's classic paper of 1938 on the heat production of muscle.

The 12-year lull that followed included the earliest useful electron micrographs of muscle; unfortunately these were interpreted as supporting the then current view that the contractile protein - actomyosin - existed as continuous filaments that shortened either by specific folding or by random coiling. The lull was ended by the evidence for sliding filaments, coming from X-ray diffraction, electron microscopy, and interference and phase light microscopy. The subsequent 20 years saw progress of many kinds: elucidation of intermediate steps in the ATPase activity of myosin and actomyosin; cross-bridges between myosin and actin filaments as independent force generators; investigation of the "working stroke" by recording tension changes following a sudden length change imposed during isometric contraction; the rediscovery of the transverse tubule system and the demonstration of its function in conducting excitation inwards from the surface membrane; and the discovery that calcium is the intracellular activator of contraction and that it acts by combining with troponin, a newly-discovered protein component of the thin (actin) filament.

These numerous advances were summarised at the Cold Spring Harbor Symposium of 1972. Despite the progress that clearly had been made, I remember disagreeing strongly with a number of the participants at that meeting who were saying that "the problem of muscle contraction is solved in principle". In a Review Lecture to The Physiological Society 18 months later I listed eight major unanswered questions about the mechanism of contraction; none of them has been satisfactorily answered even now.

There followed another lull, until about a decade ago when several new approaches began to give exciting results: exploitation of "skinned" muscle fibres in which the composition of the fluid surrounding the filaments can be altered at the will of the experimenter; the use of "caged compounds", ie substances that can be decomposed by a flash of light yielding as one of the products a substance such as ATP, ADP, inorganic phosphate or calcium that interacts with the contractile material; time-resolved X-ray diffraction; and "*in vitro* methods". This last phrase covers a number of different methods in which the experimental material consists of separate actin filaments interacting with myosin or myosin fragments which may be present either as single filaments or as a layer adhering to a surface, and either movement or force generation is measured. Finally, the structure of the actin monomer and of the myosin head (subfragment 1) have been determined by X-ray diffraction from crystals of the two proteins during the past two years.

Up to now, these new approaches have raised more questions than they have answered. It is clear, however, that they will be exploited by increasing numbers of workers in the coming years, and everyone concerned will be very much disappointed if they do not soon give a number of decisive answers.

Yet another approach which is certain to be of major importance in the coming years is through molecular genetics, by investigating the mechanical and biochemical characteristics of actin-myosin systems containing mutant forms of the proteins. A start has been made but so far no important conclusion concerning the contractile process has been reached.

Now that complete (actin) or almost complete (myosin head) structures have been obtained for the two proteins whose interaction is the cause of force generation and shortening, there will be a huge opportunity for theorists to work out ways in which those proteins can attach to one another and how the binding of nucleotide to the myosin head reduces the strength of the attachment. There is already much experimental information about the attachment (eg from cross-linking studies, and estimates of the distances between particular amino acid residues in the two proteins obtained by fluorescent resonance energy transfer) that needs to be incorporated into theoretical work, and no doubt further experimental work of these kinds will be stimulated by the possibility of interpreting the results in relation to the protein structures.

Perhaps the three questions about the contraction process that are most actively discussed at present are: (1) whether both heads of a single myosin molecule can function simultaneously in generating force, (2) over what distance the utilisation of one ATP molecule can cause myosin to move relative to actin, and (3) what is the "conformational change" that actually gives rise to the relative motion of thick and thin filaments?

(1) *Relationship between the two heads of myosin*

There is strong evidence that in the rigor state both heads of each myosin molecule are bound to actin. The longitudinal stiffness of a muscle fibre is found to be about equal in isometric contraction and in rigor. It is often argued from these two points that both heads are active simultaneously in contraction. However, there are no grounds for supposing that in a rigor fibre both heads contribute fully to stiffness; it seems at least equally likely that only one head may be rigidly bound and the other, although attached, is prevented by steric factors from making a rigid bond to actin. This is a crucial question since estimates of the force generated, and the work done, by each myosin-actin interaction differ by a factor of two in the two cases, making major uncertainties both in attempts to relate work to the free energy of hydrolysis of ATP and in calculating the influence of force on rate constants in the transitions which generate movement.

A technique which has a prospect of answering this question in the near future is cryo-electronmicroscopy, which is in use by several groups both on intact muscle and on separated actin filaments with bound myosin. The degree of steric hindrance

between the two heads may also become clear from the understanding of bonds between myosin and actin that is likely to follow from knowledge of their respective structures.

(2) *Length of "working stroke"*

After a quick release of a muscle fibre during isometric contraction, the fibre is capable of redeveloping tension over a range of about 12 nm per half-sarcomere in a time of the order of 1 ms, and in some sense this is the "working stroke" of a myosin head. It was widely assumed until recently that this amount of shortening would need to be accompanied by the hydrolysis of one ATP molecule per active myosin head, but it has now been found that the fibre is "reprimed" (ie regains its ability to perform this amount of rapid force redevelopment) in 10 ms or so (frog muscles near 0 °C), much less than the time for one ATP to be split per myosin head. Is the energy from ATP being partitioned between two "working strokes", or is the second head of each myosin molecule coming into play with a 10 ms time delay, or both, or something different?

Much the same question has been raised by some of the *in vitro* experiments with actin filaments moving over a surface coated with myosin (or one of its fragments). Different groups have, however, reached different conclusions from rather similar experiments; no doubt these disagreements will be resolved by the large amount of work with preparations of this type that is now under way or planned. The discrepancies are large: some experiments seem to show that the distance over which a myosin head can propel itself along an actin filament for the expenditure of one molecule of ATP is at least an order of magnitude larger than the 12 nm "working stroke" indicated by mechanical transients in intact muscle fibres.

(3) *Nature of the "conformational change"*

I put this phrase in inverted commas since it is not clear whether it is a correct description of the event which generates the sliding movement of thick relative to thin filaments. For example, the phrase is usually used for switches between two conformational states of a single protein whereas (a) the longest-standing idea about the elementary event in muscle contraction is that the myosin head rotates bodily relative to the thin filament and (b) another idea that is widely current at present ("slippage") is that the myosin head may detach from its original point of attachment and re-attach further along the thin filament with a very high rate constant, and neither of these hypothetical processes come within the normal definition of "conformational change". On the other hand, two other processes currently under active discussion do come within such a definition: (a) the "head rotation" may involve only a part of the myosin head which may have a hinge within itself, the attachment of the tip of the head to actin being rigid, and (b) the elementary event may be shortening (by folding or random coiling) of the S-2 fragment of the myosin molecule which connects the heads to the shaft of the thick filament. We must also keep our minds open to the possibility that more than one of these propositions (or indeed others) may be involved at different stages of the working of one myosin molecule using one ATP for each of its two heads; indeed the "repriming" experiment mentioned in the previous section strongly suggests that at least two different processes are involved.

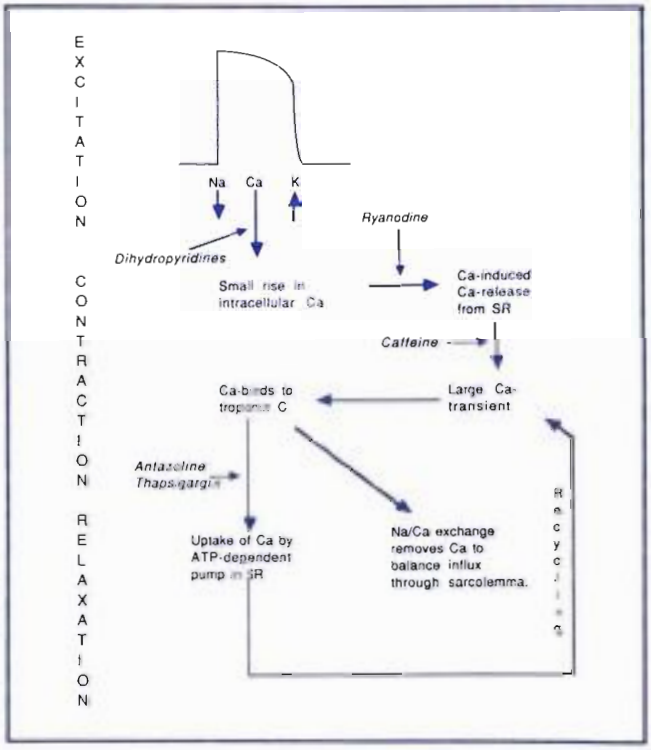
Information relevant to these questions is coming from many directions - time-resolved X-ray diffraction; birefringence changes; cryo-electron-microscopy; orientation-sensitive probes attached to the myosin head or to actin; and changes in the state of myosin head in solution when it binds nucleotide, detected by X-ray scattering or other methods.

This review of the prospects for research on muscle contraction naturally emphasises the aspects with which my own work has been concerned in recent years: the steps by which force or shortening is actually generated. We can expect equally far-reaching advance on other aspects such as intramolecular events during the ATPase cycle, and the processes by which a rise in free Ca^{2+} concentration turns on the contractile events, as well as the huge range of events that must be involved in the development and differentiation of muscle, already being heavily influenced by molecular genetics.

Reg Chapman

Our hoard is little, but our hearts are great

Undergraduates who have attended my lectures and colleagues who have read my reviews are familiar with my addiction to flow charts. Over the years, the chart which describes the initiation of the heart beat and the influence of chemical scalpels upon it has become progressively simpler. The current version is shown in the figure. This level of understanding, which is sadly seen in few textbooks of physiology, is ample evidence of the recent progress made in the study of cardiac muscle. Once the heart was very much a Cinderella but now it has taken its rightful place in the mainstream of research on excitable tissues. The impressive progress has been achieved as a result of the conjunction of a number of separate events which have enabled the questions that faced us to be open to experiment. It was the successful preparation of isolated myocytes by enzymatic means, the development of patchclamp techniques and intracellular dialysis, various means of measuring intracellular events, better isolation of organelles and proteins, the development of more specific inhibitors of a whole range of biological reactions and the personal computer that have made it all possible. Looking backwards is easier than looking into the future but in many ways the latter is much more challenging. One can be sure that the techniques that have served us well will be refined and developed further and we are all aware that the techniques of molecular biology are already having an impact.



Let me select some topics from the chart and suggest where I believe research on the heart is going.

The heart is very well endowed with ion channels and several have been isolated, sequenced and cloned. The differences from similar channels from other tissues, site-directed mutagenesis allied with functional studies is going to enable us to ascribe function to different parts of the channel protein. Already, the different sensitivity of the cardiac Na channel to TTX and Cd^{2+} has been associated with a cysteine at position 346 rather than a tyrosine or phenylanaline as in skeletal muscle or neuronal channel and argues that this region of the protein is close to the outer mouth of the channel. We can expect the organisation of ion channel proteins within the membrane and those parts involved in activation and inactivation, ionic selectivty and regulation (by such things as phosphorylation) to be worked out. This will be followed by the recognition of differences that are associated with inherited disease (much as for malignant hyperthermia and the Ca channel in skeletal muscle SR.

What channels are likely to set the pace? My vote goes to the K-channels that are chemically activated from their sarcoplasmic side. The ATP-dependent, the Na-dependent and Ca-dependent K-channels, although having a high incidence, would seem to be inactive in healthy heart (they resemble a racing car on the starting grid). Currently, an activation during hypoxia and ischaemia is favoured because intracellular ATP falls while $[Ca^{2+}]_i$ and $[Na^+]_i$ rise and an activation of the K currents would account for the shortening of the action potential. This would reduce contraction and metabolic demand and thereby place them in the business of salvaging as much of the heart as possible after an ischaemic insult, something upon which Natural Selection could certainly work. However, the data derived from excised patches do not fit with the changes in ATP, $[Na]_i$ and action potential duration seen in during hypoxia, etc in intact systems. There is a clear case for a second intracellular regulator (omitted from the artificial intracellular solution) which will act to shift the sensitivity of the channel into a more realistic range, to reveal another elegant dual regulation. The newer fluorescent methods to measure changes within the sarcoplasm of isolated myocytes will have an impact when combined with electrophysiology, particularly the technique for ATP.

The metabolism of the heart subtly interdigitates with many other functions as would be expected in a muscle that cannot rest and has to vary its output at the cellular level. There is still a lot to be done in this field. The range of effects produced by sympathetic stimulation is suitable example. The whole sequence from β-receptor binding to the final phosphorylation is reasonably well understood but how dephosphorylation is regulated has still to be addressed. The time course of the change in phosphorylation of target proteins are often very different, yet there is little evidence of variation in protein kinase A, suggesting a variation in the endogenous phosphatases (which themselves might be regulated by phosphorylation) is responsible for the diversity. Already differences in the action of endogenous phosphatases on neuronal and cardiac L-type Ca channels are suggested by the effect of chemical phosphatases like oximes. The action of parasympathetic stimulation on the heart was once thought to be simple will have to be re-addressed. Not only are there atropine-insensitive effects but the events down stream of the muscarinic receptors are also diverse and vary with the part of the heart and the species. The muscarinic receptor and the Gi-type GTP binding protein would seem to be the same but can either activate a K channel, inhibit adenylyl cyclase or activate phospholipase C to generate IP3 and diacylglycerol. The actions of calmodulin will become clearer; already there is evidence of kinase-dependent and independent effect on Ca uptake by the SR and a calmodulin binding site is suggested on an intracellular region of the Na/Ca exchange protein.

New exciting data on the possibility of two types of sodium pump in cardiac muscle will set us off again on the foxglove trail (or is it trial?).

Work on the behaviour of intracellular structures, the contractile proteins, mitochondria and sarcoplasmic reticulum has been continuing relentlessly. Years ago I urged those who work on skinned muscle to use experimental solutions that more closely resembled the intracellular milieu. Now at last both effects of and changes in endogenous substances like amino acids and imidazoles are being discovered: more will follow. Some of these compounds have structures similar to the contraction potentiators being developed by pharmaceutical companies in the hope of treating the failing heart.

Progress with the Na/Ca exchange has quickened with the development of the giant patch technique and the cloning of the protein. We can expect similar progress with other sarcolemmal transport processes associated with pH regulation, and the movement of sugars, amino acids and other metabolites. Evidence that these sarcolemmal processes are affected by intracellular second messengers is already appearing and this must be an area where progress will be made.

So how will my flow chart be in several years time? I suppose it will be replaced by several separate charts (if not several lectures) as information becomes more detailed. Each will then be concerned with one of the component processes of the present chart together with the endogenous regulators coupled to new extracellular or even intracellular receptors. These will show how the normal excitation-contraction coupling of the heart is modified and how it may be altered by threatening conditions like ischaemia.

There is still lots to do and our hoard is growing greater.

John Vane

New Therapies for Cardiovascular Diseases and Inflammation in the 1990s

The Fruits of Fatty Acids

The metabolism of arachidonic acid to prostaglandins, thromboxane A_2 (TXA_2) and leukotrienes is now well defined. An even more unsaturated precursor is eicosapentanoic acid which is metabolised to prostaglandins of the 3 series, thromboxane A_3 (which is much less potent than TXA_2) and leukotrienes of the 5 series (also less potent). Many therapeutic benefits are emerging from our knowledge of the arachidonic acid cascade.

(a) Development of Orally Active Prostacyclin Analogues

In a number of clinical trials conducted during the past twelve years, intravenous infusions of prostacyclin or its stable analogue, iloprost, have successfully relieved the symptoms of peripheral vascular disease (PVD). Similarly, prostacyclin or the stable analogue OP-41483 improved the circulation of patients suffering from severe congestive heart failure (CHF). So far, two orally active prostacyclin analogues, cicaprost and beraprost, have been tested in the treatment of PVD and the development of others will provide important new therapies for cardiovascular diseases as well as for tumour metastases and diabetes.

(b) Thromboxane Inhibitors as Anti-Thrombotic Agents

Prostacyclin formed in the endothelial cells is the physiological antagonist of thromboxane A_2 which is made by platelets and which causes vasoconstriction and platelet aggregation. Both compounds are made by the enzyme cyclo-oxygenase and so the anti-thrombotic activities of aspirin are clouded by the possibility of reductions in prostacyclin formation. Thromboxane synthetase inhibitors and thromboxane antagonists have been developed but are unlikely to be marketed because their cost is so much higher than that of aspirin, unless new indications are suggested from the discovery of other functions for TXA_2.

(c) Inhibitors of Lipoxygenase or Leukotriene Antagonists

The first clinical trials of 5-lipoxygenase inhibitors and leukotriene antagonists clearly show that leukotrienes contribute importantly to the bronchoconstriction of asthmatic patients. Some of the present potent compounds will reach the prescription market and even more potent ones will follow. Leukotriene antagonists or inhibitors will also be of benefit in irritable bowel syndrome.

(d) The Role of the Second Cyclo-Oxygenase in Inflammation

The anti-inflammatory activities of aspirin and similar drugs depend on inhibition of cyclo-oxygenase (COX). They are always accompanied by side-effects including gastric irritation. The recent discovery that inflammation, through the release of cytokines, induces a second cyclo-oxygenase (COX2) which is structurally distinct from COX1, the constitutive enzyme, means that selective inhibitors of prostaglandin biosynthesis in inflammation will be discovered which do not affect the constitutive enzyme in the stomach, kidney etc.

(e) Eating More Fish to Protect Against Cardiovascular Disease

The trend towards eating fish and away from eating meat will continue in order to supply eicosapentanoic acid as a precursor for prostaglandins of the 3 series.

Other Mediators from the Endothelial Cell

(a) Nitric Oxide Synthase Inhibitors for Endotoxic Shock

The explosion of work on nitric oxide (NO) showing that it is as important a chemical messenger as acetylcholine or noradrenaline will surely lead to new therapies. A continuous formation of NO by endothelial cells (EC) keeps our blood vessels in a dilated state; remove it and you see hypertension. An excessive secretion of nitric oxide from an enzyme induced by bacterial lipopolysaccharide or cytokines in EC and smooth muscle cells contributes to the cardiovascular collapse in endotoxic shock. Selective inhibitors of the induced nitric oxide synthase based upon simple analogues of the precursor L-arginine should be beneficial in endotoxic shock.

Improved Nitric Oxide Release for Cardiovascular Disease

In all of its transmitter functions, nitric oxide works through the second messenger cGMP and the nitrovasodilators used for 100 years in medicine also work through the formation of nitric oxide and stimulation of guanylyl-cyclase. They can be regarded as a replacement therapy for deficiencies in nitric oxide formation by EC. The next 10-20 years will see therapies based upon improving the endogenous formation of nitric oxide by endothelial cells.

(b) Endothelin Converting Enzyme Antagonists for Hypertension

Some forms of hypertension will be linked with nitric oxide deficiency and others with excess endothelin-1 formation. Inhibitors of endothelin converting enzyme or endothelin-1 antagonists will form the basis of new treatments for hypertension.

Development of New Therapies for Atherosclerosis

Prostacyclin, nitric oxide and anti-oxidants are all likely to protect against atherosclerosis and within 20 years, the scourge of atherosclerosis should be eliminated by new therapies based upon these activities, as well as by changes in diet. Thus, atherosclerosis will become a disease preventable or reversible by drug therapy, eliminating the present vogue in by-pass surgery.

Stanley Peart

The Future of Physiology

The past 50 years have seen research in Physiology subject to a reductionist approach, in which studies of the whole animal and man have gradually given way to studies of cell physiology, encompassing principally biochemical events and the electrical activity secondary to these processes. Pharmacology has contributed enormously and the merging of scientific disciplines has led to a much wider utilisation of different techniques. This is seen perhaps at its most dramatic in immunology, where the importance of receptors and the influence of different substances on cell behaviour with liberation of ions, internally and externally, of hormones, cytokines and immunoglobulin, with local and general effects, is of paramount importance. Cell behaviour and interaction is nowhere better illustrated than in studies of developmental physiology in the embryo. The techniques developed in one area are rapidly put to the service of others, so that DNA "fingerprinting" arising from studies in biochemical genetics finds its place in, for example, taxonomy.

Cellular physiology of this type will obviously continue to yield exciting results, but there are limitations in these approaches since cells in isolation are necessarily in a foreign environment and may sometimes give misleading results.

Transposition of findings in isolated cell systems to the whole animal, tissue or organ will become essential once more, even though there are fewer physiologists engaged in this type of study, as shown by perusal of the main journals.

What is clear from these considerations is that the terms used in the past to describe departments labelled Physiology, Anatomy or Biochemistry are now recognised as inappropriate and this has led to the creation in many of our universities of broader based groupings such as Life or Biological Sciences. Opportunities to translate the advances of cellular physiology to the whole animal will, however, grow necessarily, and in this area the needs of medicine in the investigation of patients have already led to repayment of some of the debts it owes to Physiology. The refinement of non- or semi-invasive techniques which have revolutionised medical investigation is bringing back whole animal physiology, especially in man. Some major areas will serve as examples.

In the cardiovascular system, ultrasound has enabled the functioning of the heart, its valves, the fluid movements in its chambers and its output to be studied from beat to beat; fluid movements of complex pattern may be analysed by ultrasound and the use of magnetic resonance can give similar information about the heart and blood vessels, as well as changing oxygenation states of the haemoglobin within the vessels. An excellent example of the way in which transfer from cellular physiology to the whole animal is essential has come recently from the acceptance of the importance of the vascular endothelium in local hormonal control of the circulation, and much more will arise in this area.

Lasers can follow changes in the circulation in varying depths of the skin and other surfaces and infra-red spectroscopy is being used to follow states of oxygenation of haemoglobin in the foetal and adult brain.

In the nervous system, the first functional analyses were made by PET, which exploited the new pharmacological knowledge on receptors and the development of radioactive ligands, as well as following changes in blood flow and metabolism related to function. The rise of magnetic resonance, with its ability to relate precisely the functional changes of blood flow and energy metabolism to anatomical images, transformed in their precision by the revelations of the tissue water distribution, will be further developed, so that the animal best equipped to collaborate in more subtle physiological studies will yield information about brain function hitherto subject only to conjecture. The additional strength of magnetic resonance spectroscopy, which has revealed the state of energy metabolism through phosphorous detection in many tissues and organs, including the brain, has been increased by the acquisition of the much wider range of compounds involved in proton detection, thus giving much greater depth to these studies.

Physics is joining with Chemistry to provide the tools for the new era, in which the findings of cellular physiology will be explored in the whole animal and man.

James Black & Nigel Shankley

Pharmacological Precepts for Future Drug Research

Pharmacology, like every other specialism, has its in-house jargon. Two favourites are *selectivity* and specificity. As far as we can see, these words are used almost interchangeably by pharmacologists. We think our technical vocabulary will be debased if we allow these powerfully descriptive words to become confused. Pharmacologists recognise two kinds of partiality or singularity in drug actions. Firstly, there are the actions (which are the basis of therapeutics) which can be described in terms of physiological changes, such as hypoglycaemic or antihypertensive, without specifying how these selective actions are achieved; then there are the rapidly growing number of selective drug actions which we believe can be specified in terms of explicit sites of molecular interactions, such as $5HT_{1A}$-receptor antagonism or H^+/K^+ ATPase inhibition. Specifications like these are the basis of attempts to use drugs to analyse physiological/biochemical systems.

Experimentally, we try to achieve specification of drug actions in complex biosystems by allowing a foreign ligand to interact with the site of action of a native ligand. The success of this procedure is becoming so great that we can begin to contemplate a First "*Law*" *of Pharmacology* - that foreign ligands produce selective interactions in biosystems by acting at those molecular sites used by native ligands to subserve physiological activity; thus, substrate/enzyme, hormone/receptor, solute/transporter, ion/channel and so on.

There is a necessary corollary to this "*law*". Biologically, there is a finite number of cognitive biochemical sites; chemically, there is an infinite number of potential organic molecules. Apparently, one biochemical site can recognise many structurally distinct ligands. Biochemical site specification can, therefore, be used to gather ligands into groups or classes. Classification, orderliness, is at the heart of every branch of science. If all phenomena are unique and mutually exclusive, thoughtful pattern-seeking is impossible. On the other hand, rigorous classification challenges the imagination; for example, chemically speaking, what do the members of the class have in common? All new drug research, all new studies of structure-activity relationships, are based on the premise of class membership which can be identified by minimal criteria. Studies of the structure-activity relations of synthetic hormone analogues have been a particularly fruitful approach to new-drug research. The native hormone not only specifies the chemical template for medicinal chemistry but also specifies the classifying bioassay and the pharmacological expectations from new receptor-specific ligands.

Hormone receptor research has dramatically changed in recent years, providing new opportunities for medicinal chemists. Hormone receptors, once considered solely as logical necessities in model building, mere mathematical operators, have now developed to become manipulable chemical entities. Receptors can now be isolated, and sequenced, leading to isolation of corresponding cDNAs and mRNAs and hence to gene cloning and expression in naive cells. Catalogues of specific hormone receptor assays are now available as tools for new drug research. Indeed, receptors as gene products are now being identified faster than physiologists can identify their function.

Great progress is also being made in characterising the business end of hormone receptors. *Active sites* are being identified by determining the highly conserved sequences across species and in using site-directed mutagenesis to identify essential amino acid residues. We are about to see a great change in hormone-related medicinal chemistry. Until now, hormone-based structure-activity studies has been a game of blind man's buff. Discovering the molecular constraints at the receptor site has, until now, been a slow and painful process of blind head-butting. We can now begin to see a future where the cognitive features of the receptor site become, quite literally, visible on the molecular modeller's screen. A whole new era of *rational* drug design is promised.

Paradoxically, the design and discovery of specific ligands using the new chemical assays will not make the traditional functional bioassays redundant; on the contrary, the development of functional assays is now more important than ever. At the very least, the classification of a new ligand using a chemical bioassay will need to be validated in a physiological assay. Functional assays can only be interpreted in a chemical sense by reference to an explanatory model involving the exploring ligand. We still prefer the approach which systematically explores the widest possible concentration/effect relations and then uses all of the experimental data to try to derive an appropriate minimally parameterised model. These models yield solutions which are often counterintuitive and provide drug parameter estimates which could not be got any other way.

Isolated tissues, including tissue culture, have been developed to provide *low noise* bioassays. We are now beginning to realise that, in seeking simplicity and feasibility in this way, we have traded signal strength. Thus, for example, the gastrointestinal hormones, gastrin and cholecystokinin, are known to be about 100 times less potent *in vitro* than *in vivo*. The worrying aspect is that this loss of potency is apparently due to a failure in the expression of agonist efficacy. We are now recognising that molecules classified *in vitro* as silent competitive antagonists can exhibit powerful agonism *in vivo*. Examples include analogues of vasopressin and angiotensin-II. The practical problems involved are obvious. The explanation for these efficacy changes is far from obvious. We believe that the problem is not due to a general metabolic attenuation. A feature of these gastrointestinal hormones is that they are potentiated by, for example, cholinergic activity. A rash generalisation suggests a principle of physiological control in which the efficacy of one hormone is controlled by the convergent action of another one making effective transmission more information-rich. We believe that the development and analysis of convergently controlled bioassys is now urgently needed to allow us to exploit the terrific advances in molecular biology.

IUPS Congress, Glasgow, 1993

Congress Update

During recent Scientific Meetings of the Society, some of my colleagues have commented on the fact that the satellite symposia which used to be held the week before and the week after the Main Congress are now no longer taking place and the whole Congress might therefore become a very large meeting, which I know does not appeal to a number of our Members. It will, therefore, come as a reassurance to know that, except in one or two extremely popular areas, this is not going to happen.

Taking as an example 5,000 participants and an average of 100 symposia over the five day period and 25 simultaneous sessions per day, this gives an average of 200 per session, which is similar to the attendance at some of the very best Physiological Society Meetings. It provides the critical mass of expert discussion and fits into the kind of lecture theatre which we are all used to. Of course, the distribution between the different subjects will vary widely. We do anticipate that one or two extremely popular areas will be large; there is no way of avoiding this but those who attend the meetings of the Society of Neuroscience, for example, also know that these can be well organised, and we are seeking to benefit from their experience. At the other extreme, no doubt some of the sessions, such as the smaller workshops and the like, may have an attendance of less than 50 people.

In fact, it could be said that the old-style Main Congress is now taking a background seat for it is only the Plenary Lecture (one held each morning at the SECC between 8.30 and 9.915) and Named IUPS Lectures (each evening, 17.45-18.45) which are not held concurrently with other sessions and could therefore attract larger audiences. For those who may not wish to be present at the Lectures, the Exhibition will be open and the Posters on display, as they will be during the whole meeting.

IUPS Congress, Glasgow, 1993

Glasgow Parks

Glasgow offers a wide range of social activities and from now until the Congress we will be publishing an article and "What to see and do in Glasgow" both during the day and in the evenings. The articles will provide general information on pubs, clubs, theatres, restaurants, art galleries and museums, tours etc. The first of these contributions is on Glasgow parks and I hope it will give you a taste of what is to come.

Glasgow means "Dear Green Place" in Gaelic and a more apt description of a city could not exist. Glasgow has over 100 parks and gardens and has more parks per head of population than any other city in Europe. These parks hold many of Glasgow's famous and not so famous attractions.

The Burrell Collection sits in Glasgow's biggest park, Pollok Country Park, which covers 361 acres in the city's southside. This world famous museum is the result of one man's passion, Sir William Burrell, who amassed a collection of over 8,000 items and presented it to the City of Glasgow in 1944. It includes objects from all eras and all parts of the world. Best known, perhaps, are the collections of French 19th Century paintings, tapestries and stained glass. The present building was opened by the Queen in 1983 and complements the beautiful objects it contains.

Also set in Pollok Country Park is Pollok House. Presented to the City in 1969 by the Maxwell family, who had been associated with Glasgow for over 700 years, the house (circa 1752) sits in well tended formal gardens. The ground and first floor rooms are open to the public and contain one of Britain's most famous collection of Spanish paintings. These paintings, from the Collection of Sir William Stirling Maxwell, include works by El Greco and Goya.

In the City's West End, Kelvingrove Park contains Art Galleries and Museum. This purpose-built red sandstone building was constructed in 1902 on the site of the 1888 British Empire exhibition. Its many galleries hold fascinating displays such as European arms and armour, and the permanent fine art collection on the first floor holds work from all the major European art schools. One of the most impressive paintings is Salvador Dali's 20th Century "Christ of St John on the Cross". It was purchased for £8,200 in 1952 by the then Director of the Art Galleries and at the time he was heavily critised for spending so much money. Other famous artists presented include Monet, Rembrandt and Van Gogh.

Natural art is well represented in the City's Botanic Gardens. The Kibble Palace, the main glasshouse, was built in 1873 and houses the National Tree Ferns Collection. Kibble Palace was originally built in Helensburgh, a town on the Firth of Clyde, it was sold to the City of Glasgow, moved and used for meetings and concerts - both Gladstone and Disraeli spoke there. The Botanic Gardens grow the second largest collection of orchids in the world, the reason why perhaps the World Orchid Conference is to held in Glasgow at the Scottish Exhibition and Conference Centre in April 1993.

Botanical treasures of a different type abound in the West End's Victoria Park. In 1887 fossilised tree stumps and roots, which date back 330 million years, were uncovered and can be viewed today in the Fossil Grove.

Glasgow's other treasure, its history, is celebrated in the oldest public park in Europe. Glasgow Green was granted to the people by a 14th Century charter, which stated it was to be used only as a place of leisure. The People's Palace of Glasgow Green tells Glasgow's story from its foundation in 1175 to the present day and incorporates the many political and industrial events that typify Glasgow's history.

There are another 94 parks and gardens in Glasgow to explore, all of which can be enjoyed (as can those mentioned above) for nothing. All that Glasgow asks for are voluntary contributions to the upkeep of these collections.

IUPS Congress, Glasgow, 1993

Getting There

From left to right: T Graham Brown (standing; Professor of Physiology, Cardiff); E P Cathcart (Regius Professor of Physiology, Glasgow); E H Starling; Sir Charles Lovatt Evans (almost obscured); Sir Henry H Dale (wearing cap); on the way to Sweden for International Physiological Congress, 1926. Photograph by Dr John Pryde.

The best things in life are free, the expression goes, but unfortunately the same cannot be said of Physiology. Attending the 1993 IUPS Congress is likely to amount to a significant item in most people's budgets, but there are ways of controlling the costs. Participating at the Congress may be done relatively cheaply, but there is also scope for making the event an excuse for the trip of a lifetime.

Accommodation has already been block-booked through the Greater Glasgow Tourist Board. This ranges from student rooms with shared facilities through to luxury hotels, and the prices reflect this range. If you wish to take advantage of this accommodation, you should complete the form in the Final Announcement and submit it to CEP when you register for the Congress.

Glasgow is well linked to the rest of the United Kingdom by road and rail, and the mode of transport chosen will depend as much on convenience as cost, especially as there is some blurring in the price differentials among coaches, trains and planes. Using London as a starting point, the cheapest form of public transport is coach, with returns to Glasgow currently being offered by Scottish Citylink and National Express from London Victoria from £25. The most expensive fare coach fare is £36. Taking the budget approach, you could attend the Congress for around £440, including seven nights' hostel accommodation (£23 per night), registration fee (£250) and travel (£25), or £320 if eligible for the student registration fee. [*Editor's Note: The total cost can be even lower if you are eligible for a grant from the Society - see the Committee News section and the application form at the back of this issue.*]

However, it is possible to travel by train, and not pay a significantly different figure. British Rail currently offers a Super Apex fare of £29 return from London Euston and an Apex fare of £44 return. Apex and Super Apex fares are available, at similar low costs, from most cities. The Super Apex must be booked two clear weeks in advance of travelling, and the Apex seven days before departure. Any train on any day may be booked, but the number of tickets available is limited. Alternatively, a Supersaver ticket, costing £57, may be used on any day except Friday, and so is ideal for those who wish to travel to the Congress on the Saturday before it starts. The standard British Rail fare to Glasgow is £114, so it does make sense to plan the journey in advance, or to wield any railcards you may possess. A middle range cost for participating in the Congress might be £730, including seven nights in a three star hotel (say £60 per night), registration fee (£250) and a Supersaver rail fare (£57).

For those wishing to travel in style, British Airways can transport you to Glasgow airport for £212 return. This is the Club Class ticket and, of course, many cheaper seats are also available. For those who can confirm their return travel date, there is a £130 fare which can be booked at the last minute, subject to availability. The Physiological Society has also negotiated a special fare of £94, which must be booked in advance through British Airways, quoting the reference number RXJS3Y. The availability of this fare is strictly limited, but from time to time British Airways also offers other low fares and may even be able to undercut this if you book at an opportune moment. Couple a flight (£130) with a week in a top hotel (£140 per night), add the registration fee and the total will approach the £1400 mark.

Although these are all current ticket prices and will naturally be subject to alteration between now and August 1993, they should give some idea of the range of fares available. The best advice is to start planning early and take advantage of any special offers that may be around.

Victoria Penrice

IUPS Congress, Glasgow, 1993

Named Lectures

A feature of every Congress are Named Lectures given by distinguished physiologists.

The Fenn Lecture, awarded by the IUPS Council to Sir Bernard Katz

Wallace Osgood Fenn (1893-1971) who, in 1968, presided over the XXIV International Congress of Physiological Sciences in Washington DC, made lasting contributions to our understanding of a broad range of physiology as well as being a major force

for the development of our subject in the United States. Born in Lanesboro, Mass, he spent his early adult life at Harvard, apart from a year during the First World War when he was Nutrition Officer in the US Army. In 1922 he came to London as a Rockefeller Travelling Fellow and, working in A V Hill's laboratory at UCL, he showed that the heat released from muscle when it contracted is always greater when external work is performed (the Fenn effect). In 1924 he returned to the USA as Professor of Physiology at the then new School of Medicine & Dentistry at Rochester, NY, where he stayed for the rest of his life. While continuing work on muscle contraction (he described the force-velocity curves in 1935), he developed techniques for investigating gas exchange in muscle and nerve, made the first estimates of intracellular pH of muscle and began to study the mechanisms responsible for the uptake and retention of K+ by muscle cells. Using tedious chemical methods, Fenn demonstrated that, during contraction, K^+ was lost from muscle in exchange for Na^+ and later, with the advent of radioactive isotopes, he showed that all the K^+ within muscle is exchangeable.

With the onset of the Second World War, Fenn turned to the practical problems arising from pressure breathing devices for flying crew in non-pressurised aircraft. This led him into respiratory physiology, which occupied him for much of the rest of his life. Classic papers on the mechanics and work of breathing and steady-state gas exchange were followed by studies on the effects of high barometric pressures, on oxygen toxicity and on the regulation of breathing in exercise. Still an active experimentalist in his late seventies, his obituary notice in *Respiration Physiology* was published alongside a paper (of which he was sole author) describing measurements suggesting that the partial molal volume of haemoglobin was reduced on oxygenation.

A clear and stimulating lecturer, Fenn held office in many learned societies and chaired innumerable committees. A man of great integrity and sound judgement, he inspired much loyalty and affection in those who worked with him.

The Robert Pitts Lecture, awarded by the Renal Commission and Chairman of the Cornell Physiology Department to Walter F Boron

Robert Franklin Pitts (1908-77) was bron in Indianapolis. He graduated from Butler University in 1929 and earned a PhD in Zoology from Johns Hopkins in 1932. Thereafter he went to New York Unitveristy, taught and did some physiological research until he was awarded his MD in 1938. Between 1938 and 1942 Pitts was a neurophysiologist working in Ransom and Mageun's laboratory in Chicago, where he gained an international reputation for his studies on the brain's control of breathing. From Chicago he moved back to New York to join Homer Smith's laboratory as Assistant Professor and he developed the renal interest which stayed with him for the rest of his life. He headed distinguished departments of Physiology first at Syracuse (1946-50) and then at Cornell (1950-75). At the time of his death he was Research Professor at the University of Florida.

His first and abiding passion in the kidney was acidification of urine and he was the first to postulate that sodium reabsorption was linked to hydrion excretion. Later he developed interests in diuretic agents and ammonia metabolism in the kidney. Pitts loved to work at the bench, do his own experiments and in virtually all his human experiments was the first "guinea pig".

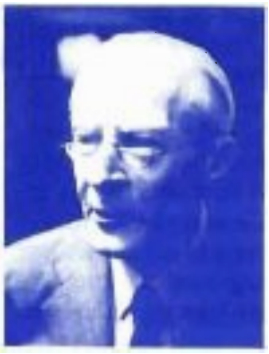
He was very concerned about teaching, particularly medical students, attended all the lectures on the course and every year ran a student laboratory. He was particularly proud to be the first recipient of the Distinguished Teachers award of the Association of Chairmen of Physiology in 1972.

As a person, Pitts was highly admired and respected. He was a quiet reflective man who, nevertheless, could exhibit great warmth and sympathy. He was extremely loyal to his associates, encouraged the gifted and fostered a strong esprit de corps in his department.

The August Krogh Lecture, awarded by the Danish Physiological Society to Axel Michelson

August Krogh (1874-49) worked at the Zoophysiological Institute at the University of Copenhagen which was built for him by the University. He combined remarkable physical insight with a wide interest in zoology and human physiology to be one of the greatest experimental physiologists of all time. Awarded the Nobel Prize in 1922 for his work on the capillary circulation, he also demonstrated that diffusion alone could account for O_2 uptake in the lung and conducted important studies in human respiratory and cardiovascular physiology. His ingenuity in developing new methods was essential for this work but is most apparent in his books and papers on comparative physiology. For problems as different as flotation mechanisms in fresh water larvae, osmoregulation and insect flight, Krogh devised elegant experimental methods which provided clear answers to well directed questions. It is appropriate that his name should be associated with one of the IUPS Lectures.

The Adrian Zotterman Lecture, awarded by the Somatosensory Physiology Commission to Robert F Schmidt



E D Adrian (1889-1977) was successively Professor of Physiology, Master of Trinity College and Chancellor of the University of Cambridge. His demonstrations before and after his appointment as Professor were long remembered by undergraduates. In his early research he wished to establish the nature of the messages from afferent endings to the central nervous system and for this he needed active single units. One of the first to be isolated was from a single muscle spindle in a thin muscle in the frog, isolated by cutting down the muscle till only one active unit remained. This dissection was done by his research pupil Yngve Zotterman from Sweden, who reported the work at the Stockholm Congress in 1926. Adrian went on to record from cutaneous fibres in the frog, from the vagus in the cat, from the vestibular and from the optic systems. Later he moved into the central nervous system, defining the somatosensory areas in a variety of animals and describing activity in the motor area and motor tracts with Moruzzi. His last major work was an analysis of the electroencephalogram with BHC Matthews.

Y Zotterman (1899-1982) was the first to record from afferent C fibres in the cat, so starting the modern study of pain. He observed the small chemoreceptor fibres in the nerve from the carotid body and with von Euler and Liljestrand established their sensitivity to oxygen and carbon dioxide partial pressures. After becoming Professor of Veterinary Physiology in Stockholm he had a large number of research pupils, one of whom (Bengt Anderson) produced spectacular observations on the control of drinking by the hypothalamus in the goat.

The Eric Neil Memorial Lecture awarded by the IUPS Council to Bjorn Folkow

Eric Neil (1918-90) was the John Astor Professor of Physiology at the Middlesex Hospital Medical School from 1956 until his retirement. A gifted man of great vigour, he made significant contributions to Physiology in many fields. He had a distinguished career in research, primarily by his investigation on the carotid bodies and sinus, in which he showed a great manual dexterity and experimental skills. He used his experience in this field to write several monographs on the circulation and related subjects with collaborators such as Heymans and Folkow.

As a teacher Neil inspired many pupils and spent much of his time and energy as the author of Applied Physiology, used by many students during their physiology course. As an administrator, he will be remembered primarily by the physiological community at large as Secretary (1968-74) and President (1974-80) of the IUPS during the Congresses at Paris and at Budapest.

With this background it is fitting that Eric Neil's name should be given to a lecture at the first Congress in this country for nearly half a century and that the lecturer should be Bjorn Folkow, his great friend and collaborator.

The Society of General Physiologists Lecture awarded to Ernest Wright

In 1975 The Society of General Physiologists decided to sponsor a Distinguished Lecture to be presented annually on a three year cycle in consecutive years, first at the International Congress of Physiology, then at the International Congress of Biophysics and subsequently at the International Congress of Biochemistry. The International Congresses were chosen because these three disciplines comprise the major interests of the members of the Society of General Physiologists. Thus, an outstanding scientist working in the field of General Physiology would be named Distinguished Lecturer of the Society who, in addition to presenting a general lecture concerning his/her area of expertise, would expand the lecture into a monograph that would be of interest to these Societies' membership and to a scientist wanting a broad survey on an important field. The first Distinguished Lecturer was auspiciously inaugurated by the selection of Dr Paul Greengard who presented at the 27th International Union of Physiological Scientists which was held in Paris in 1977.

New Directions for Biochemistry and Physiology Teaching

Abstracts

The Requirement for Change

David Shaw

Chairman, Education Committee, General Medical Council, London

Two main aims underlie the proposals set out in the recent GMC discussion document on the future of undergraduate education:

(i) to reduce the load of factual information now imposed by most curricula; and,

(ii) to enhance the educational merits of the course through curiosity-led enquiry and self-directed learning.

The undergraduate course must ensure that the new graduate is adequately prepared for the responsibilities appropriate to a properly supervised pre-registration year and for subsequent professional training and development, but it is argued that the traditional demand for comprehensive coverage of medical theory and practice, often at a superficial level, should be re-examined. It is proposed that there should be a mandatory core course and that enhanced learning opportunities should be provided by special studies or options depending on student interest and aptitude. There are historical reasons for the conventional split between preclinical and clinical studies and it is often perpetuated by institutional organisation. The interface between basic medical science and clinical teaching will be examined and the merits of a greater degree of integration discussed. The aims set out in the discussion document are not new. Most were embodied in the 1980 GMC recommendations on Basic Medical Education. Reasons for reluctance to change will be examined and possible means to encourage implementation of the proposals will be considered.

The contribution of basic medical science to a new medical curriculum

P McRorie

Curriculum Co-ordinator, Basic Medical Sciences, Queen Mary & Westfield College, London

The role of Anatomy, Biochemistry, Pharmacology and Physiology in the medical course of today is changing. There is a strong move away from subject-based courses towards systems-based courses. This is causing a headache for many staff who have little or no expertise outside their own discipline (indeed outside their own microcosm of research interest). It is continually pointed out that the purpose of medical education is to train doctors, not biochemists or physiologists. Students endlessly complain about the irrelevance of much of the basic science course. Excessive factual overload must be eliminated; tedious irrelevant practicals must go! Furthermore, we are having to adopt new approaches to learning and are ourselves soon to come under the microscope for our teaching ability. We at Queen Mary & Westfield College have successfully adapted to the new rules. The result? -a tremendously exciting and stimulating period of co-operation; and infection of vitality into an old curriculum; a student body that is greatly appreciative of staff who try to adapt; a promise of basic medical science teaching in the clinical years. We live in exciting times!

Teaching Versus Learning

John Patterson

Dept of Physiology, Queen Mary & Westfield College, London

Traditional, lecture-based curricula rely heavily on formal instruction in which students are the passive recipients of knowledge. Such courses can produce a superficial approach to learning, leading to poor retention of facts and concepts, and a reduction in student motivation to learn independently. Most professions demand life-long and active learning of their members and undergraduate training should reflect this general principle. Active learning, in which students exert control over their study, produces a deeper approach and results in longer lasting learning. Active learning techniques also improve communication skills and team work. Within medical education, active learning is most fully developed in the problem-based curriculum, where formal instruction is kept to a minimum and students learn by solving problems, based mainly on patient histories. In other areas of higher education, students may take even greater responsibility for defining and negotiating their own studies. Many advocated of active learning claim that, to be effective, the entire curriculum should be based on this approach. The recognition by teachers of the importance of active learning can, however, enhance the delivery of any curriculum. This session will provide a general background and introduce participants to some easily applied active learning techniques.

Two Revolutions and the Scientific Culture

Gordon Moore

Teaching Center, Harvard Community Health Plan, Boston, USA

Two major changes are occurring in basic science teaching: an increasing dysfunction between the skills and knowledge needed to teach medical students and do research, and a shift from the teacher as expert to the student as active learner. In earlier times, methods and knowledge used for research were often those of use in teaching systems physiology, gross and microscopic anatomy, and classic biochemistry. Thus, it was easy for departments to meet research goals with individuals easily able to teach medical students. Today's "hot" research is molecular but medical students need to learn the "old" disciplines. The traditional disciplines will be replaced by functionally defined departments oriented to be competitive in research. Fewer faculties will find it easy to teach medical students. The second revolution is the shift towards student-directed, active learning, where the teacher's role is less as a lecturer than tutor. The implications of these changes will be discussed.

Designated Sessions at the Queen Mary and Westfield College Meeting

Cardiovascular/Respiratory Control Group

Designated Session and Plenary Lecture

There will be a Cardiovascular/Respiratory Control Designated Session at Queen Mary & Westfield College London Meeting in December. This is the second of the year and once again there is a substantial programme consisting of 17 Oral and four Poster Communications, a Designated Lecture and a Business Meeting.

As cardiovascular and respiratory systems have evolved together to ensure a suitable exchange of O_2 and CO_2 between air and tissues, the philosophy behind the Group is that their physiology should be considered together. Prof Diethelm W Richter of the Georg-August-Universitat Gottingen will give a Designated Lecture on the thesis that there is a direct coupling

between the central neuronal structures dedicated to their control. His lecture is entitled "A Common Cardiorespiratory Network Within the CNS."

The Business Meeting to be held at the end of the Session will consider the future direction of the Group. I hope all interested persons will attend. The Cardiovascular/Respiratory Control Special Interest Group has been in existence for a number of years and I have been its convenor for the last two. I am willing and would like to continue as convenor for another year. Any ideas on how we can further develop our Special Interest Group would be greatly appreciated. Please attend and let us know your thoughts.

Michael Gilbey

Human Physiology Group

Symposium and Designated Session

The Queen Mary College Meeting of the Society promises to be an important meeting for the Group. Besides the Designated Session in the scientific programme, Dr Ron Maughan and Dr David Jones have organised a Symposium entitled "Physiological Limitations to Human Exercise Performance", and there will be a plenary meeting of the Group. At this meeting the Interest Group needs to prepare a plan for the next three years. The executive group needs to be re-structured and new officers appointed. The programme for 1993 has still to be decided and there are issues concerning the IUPS Congress which should be considered. I hope that members will write to me or to Dr Ron Maughan about new ideas for the running of the Group and for its activities; some agenda papers can then be available ahead of the day. Alternatively, please come to the meeting with new ideas for the running of the Group.

Peter Fentem

Microvascular & Endothelial Physiology

Designated Session and Plenary Lecture

The Special Interest Group for Microvascular and Endothelial Physiology will be holding a full day Designated Session at the forthcoming Scientific Meeting of the Society at Queen Mary & Westfield College, 16-18 December 1992. The Designated Session begins at 9.00 am on Friday, 18 December with a Plenary Lecture given by Dr Dorian Haskard entitled "Leukocyte-endothelial cell interactions in vitro and their relevance to inflammation".

Dr Haskard completed his pre-clinical studies at Oxford and clinical training at the Middlesex Hospital Medical School. He was a Wellcome Trust Senior Research Fellow at UMDS and Guy's Hospital (1987-1990) and is currently a Senior Lecturer/ Hon Consultant in Medicine in the Department of Rheumatology, Royal Postgraduate Medical School. Dr Haskard aims to focus his lecture on the advances that have been made to understanding the molecular mechanisms of leukocyte-endothelial cell interactions. He will give an overview of leukocyte and endothelial cell adhesion molecules that have been characterised in vitro and then cite examples of how these molecules are expressed in experimental and clinical inflammatory tissues ex vivo. He will end his lecture showing recent data on quantifying the expression of endothelial cell surface antigens using radiolabelled monoclonal antibodies in vivo.

Eighteen Oral Communications and nine Poster Communications are scheduled for this Designated Session. Abstracts in the morning session include research on constitutive and inducible nitric oxide synthases in vascular endothelium, neutrophil adhesion to human endothelium, arteriolar vasodilation mediated by sensory nerve fibres, effects of cooling on the hamster cheek pouch microcirculation, and increases in human nailfold capillary pressure following injury. Topics covered by abstracts in the afternoon session include transcellular openings in mesenteric microvessels induced by A23187 and transmural pressure, histamine-induced changes in the permeability of cerebral venules, transarterial fibrinogen fluxes, role of abhiogenesis of pericytes in chronically stimulted skeletal muscle, excitation of pulmonary blood vessels by 4-aminopyridine and hypoxia, responses of ATP-activated potassium channels in pulmonary artery smooth muscle, and inhibition of ADP-evoked Ca^{2+} entry in human platelets by a tyrosine kinase inhibitor.

All those interested are encouraged to attend the Designated Session and should you wish your name to be included on our mailing list please contact Dr Giovanni Mann by telephone (071) 333 4450 or fax (071) 937 7783.

Giovanni Mann

Physiological Society Symposium for Final Year Students University of Leeds

Friday 11 December 1992

This symposium will consist of three sessions, chaired by Malcolm Hunter, Roger Hainsworth and John Morrison. The first session will begin at 11.00 am with talks by Richard Boyd, Bernard Rossier and Roger Thomas on: transport proteins, membrane vesicles, isolated cells and epithelial function; Na, K-ATPase: structure, function and regulation in sodium transporting epithelia; ionic mechanisms for intracellular pH regulation in nerve and glia cells. The second session consists of talks by Charles Michel and John Widdicombe on how studies on single capillaries can help us to understand the circulation and the physiology of the airway mucosa and its relevance to asthma. During the final session, Patrick Wall and Richard Morris will discuss the questions "Why do some pains resist treatment?" and "Does hippocampal LTP have anything to do with learning or memory?" Discussions will then continue less formally until 6.00 pm, with beer and wine available free of charge.

The symposium is to be attended by students from the Universities of Newcastle, Leeds, Sheffield, Birmingham, Manchester, Liverpool, Nottingham and Bristol. From the replies received so far, nearly 300 students and staff will be present. However, there is still space for more students: any other departments wishing to send students should contact Kwabena Appenteng. Merck, Sharp & Dohme have contributed towards the cost of staging the symposium and representatives from this company will be present throughout the day and available for consultation by students.

Notices

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 April (Leicester) edition should reach the Editor or the Administration Office by 5 February 1993.

8th Annual Symposium on Biotechnology
CYTOKINES IN HEALTH AND DISEASE
10-11 December 1992

This symposium aims to offer a view of the cytokine network in general and the principles of its action and then to focus on individual cytokine/receptor systems of particular interest and future advances in cytokine biology and clinical applications. Further information from: Mrs B Cavilla, Institute of Biology, 20 Queensberry Place, London SW7 2DZ ★★★

Physiological Society Symposium
for Final Year BSc Students
11 December 1992
University of Leeds

Invited speakers include Bernard Rossier, Richard Boyd, Roger Thomas, Charles Michel, John Widdicombe, Pat Wall and Richard Morris. Further details from: Kwabena Appenteng (address and tel on page 1). *See also Events section of this issue.* ★★★

The Physiological Society
and The Biochemical Society
NEW DIRECTIONS FOR
BIOCHEMISTRY AND PHYSIOLOGY TEACHING
A Teaching Forum on
the Future of Basic Medical Science
16 December 1992

Further information from: Dr J A Patterson, Dept of Physiology, Basic Medical Sciences, Queen Mary & Westfield College, Mile End Road, London E1 4NS, tel (071) 982 6378, fax (071) 975 5500 or Dr M D Yudkin, Biochemistry Dept, South Parks Road, Oxford OX1 3QU, tel (0865) 275302, fax (0865) 275297. *See the Events section of this Magazine for session Abstracts* ★★★

A Physiological Society Teaching Symposium
PHYSIOLOGICAL LIMITATIONS TO HUMAN HIGH INTENSITY EXERCISE PERFORMANCE
16 December 1992

The symposium is open (and free) to all Physiological Society Members. Full details of this symposium will appear in the Programme for the Queen Mary & Westfield College Meeting. Non-Members who are interested in attending should contact Dr D L Turner or Dr D A Jones, Dept of Physiology, University College London, Gower Street, London WC1E 6BT, tel (071) 387 7050 ext 3218, fax (071) 373 7005 ★★★

The Anatomical Society of Great Britain & Ireland - Symposium
***IN SITU* HYBRIDISATION**
7 January 1993
Royal Veterinary College, London

Further information from: Dr Neil Stickland, Dept of Veterinary Basic Sciences, The Royal Veterinary College, Royal College Street, London NW1 0TU, tel (071) 387 2898 ★

The Pain Society and the Scandinavian Society for the Study of Pain
COMBINED SCIENTIFIC MEETING
1-3 April 1993
University of Edinburgh

Submission of abstracts for free paper or poster is invited. Further information from: Dr G L M Carmichael, Western General Hospital, Edinburgh EH4 2XU, Scotland, tel (031) 332 2525, fax (031) 332 5150 ★★

Society for the Social History of Medicine
THE HISTORY OF NUTRITION SCIENCE
2-3 April 1993
Strathclyde University, Glasgow

Provisional list of speakers includes Mark Weatherall, Sally Horrocks, Susan Williams, Tim Boon, David Smith, Tim Laing, Nancy Blakestad, George Davey-Smith, Robert Bud. Further information from: David Smith, Wellcome Unit for the History of Medicine, Glasgow University, University Gardens, Glasgow G12 8QQ, tel (041) 339 8855 ext 6071, fax (041) 307 8011 ★

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 ★

European Tissue Culture Society
UK Branch Workshop
VECTORIAL TRANSPORT IN CULTURED EPITHELIAL & ENDOTHELIAL CELLS
16 April 1993
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 ★

New York Academy of Sciences
SLOW INFECTIONS OF THE CENTRAL NERVOUS SYSTEM: THE LEGACY OF DR BJORN SIGURDSSON
2-5 June 1993
Haskolabio Conference Centre, Reykjavik, Iceland

Deadline for submission of poster abstracts: 15 February 1993. Further information from: Conference Dept, New York Academy of Sciences, 2 East 63rd St, New York, NY 10021, USA, tel (010 1 212) 838 0230, fax (010 1 212) 888 2894 ★★

New York Academy of Sciences
3RD INTERNATIONAL MEETING ON PLATELETS AND VASCULAR OCCLUSION
6-9 June 1993
Santa Fe, New Mexico
Deadline for submission of poster abstracts: 30 March 1993. Further information from: Conference Dept, New York Academy of Sciences, 2 East 63rd St, New York, NY 10021, USA, tel (010 1) 212 838 0230, fax (010 1) 212 888 2894 ★★

New York Academy of Sciences
HUMAN GENE THERAPY
26-30 June 1993
Washington DC, USA
Deadline for submission of poster abstracts: 15 March 1993. Further information from: Conference Dept, New York Academy of Sciences, 2 East 63rd St, New York, NY 10021, USA, tel (010 1) 212 838 0230, fax (010 1) 212 888 2894 ★★

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. ★

International Research Group for Colour Vision Deficiencies
XII SYMPOSIUM
18-22 July 1993
Tübingen, Germany
Functional, morphological and pathophysiological processes of colour vision will be dealt with. Deadline for abstracts: 15 January 1993. Further information from: Prof E Zrenner, IRGCVD, Dept of Pathophysiology of Vision and Neuro-ophthalmology, Schleichstrasse 12 - 7400 Tübingen Germany ★

International Union of Pure and Applied Biophysics
11TH INTERNATIONAL CONGRESS OF BIOPHYSICS
25-30 July 1993
Budapest, Hungary
Further information from: L I Hovath, Institute of Biophysics, Biological Research Centre, H-6701 Szeged, P O Box 521, Hungary, tel (36-62) 23-022, fax (36-62) 13-726 ★★★

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
For further information, see the Events section of this Newsletter ★★

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. ★

7TH WORLD CONGRESS ON PAIN
22-27 August 1993
Paris, France
Further information from: International Association for the Study of Pain, 909 NE 43rd St, Suite 306, Seattle, WA 98105, USA, tel (010 1) 206 547 6409, fax (010 1) 206 547 1703 ★★★

3RD INTERNATIONAL CONGRESS ON AMINO ACIDS, PEPTIDES AND ANALOGUES
23-27 August 1993
Crete, Greece
Further information from: Prof Dr G Lubec, University of Vienna, Dept of Paediatrics, Whringer Gurtel 18, A1090 Vienna, Austria, fax (43) 1 40400 3238 ★★★

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
8-11 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 ★

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 ★

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 ★

PHARMACOLOGY OF THERMOREGULATION
9th International Symposium
8-12 August 1994
Giessen, Germany

Preliminary registration deadline: 31 December 1992. Further information from Prof Dr E Zeisberger, Physiologisches Institut, Klinikum der Justus Liebig Universitat, Aulweg 129, D-6300 Giessen, Germany, tel (010 641) 702 4550/4553, fax (010 641) 702 4575 ★★

2ND INTERNATIONAL CONGRESS FOR PATHOPHYSIOLOGY
20-25 November 1994
Kyoto International Conference Hall, Kyoto, Japan

Further information from: Dr Toshiie Sakata, First Department of Internal Medicine, Ooita Medical University, 1-1 Idaigaoka Hazamacho, Ooita-gun, Ooita, 879-55, Japan, tel (81) 975 49 4411, fax (81) 975 49 4217 or Dr Vladimir Shinkarenko, International Society for Pathophysiology, Baltiyskaya str 8, Moscow 125315, Russia, fax +7 (095) 151 9540, E-mail: ISP@BIOMED.MSK.SU ★★★

Wellcome Trust Toxicology Initiative

The Wellcome Trust wishes to promote research in molecular and cellular aspects of Toxicology. Therefore, in addition to funding project grants, the Trust will support individuals wishing to develop careers in this area in two ways:

Post-doctoral Research Fellowships, tenable for up to three years in an appropriate academic institution in the UK or Republic of Ireland. Candidates who have experience in a relevant scientific discipline and now wish to develop a career in toxicology are particularly encouraged to apply; such applications should include details of the training which will be provided during the Fellowship. Proposals from post-doctoral toxicologists who wish to develop an independent research programme are also welcome.

PhD Research Studentships, tenable for three years in an appropriate institution in the UK or Republic of Ireland. Applicants should have, or expect to attain, at least a Class II(i) degree in an appropriate subject.

Requests for application forms should be sent to Dr P M Goodwin, The Wellcome Trust, 183 Euston Road, London NW1 2BE, tel (071) 611 8888, fax (071) 611 8545. All requests should include a letter of support from the head of the department in which the candidate wishes to work.

For the Fellowship Scheme, a brief CV and an outline (500 words) of the proposed research should also be included.

The closing date for applications is 1 February 1993.

Personal Accident Insurance

The Society has negotiated a group Personal Accident Insurance scheme, through Windrush Insurance Brokers, which can be taken out on an individual basis by UK residents.

Although this scheme has been negotiated by The Physiological Society, it is not restricted to Society Members. Therefore this scheme may be appropriate for providing cover to your family, colleagues, or even your entire department.

Two separate levels of cover are available costing £30 or £55 per annum, the level of benefit to be chosen by the proposer. The premium is payable annually by the insured, or by a department on behalf of its staff.

The rates and benefits are highly competitive and we are sure they will be of interest to you. The cover is on a 24-hour basis, worldwide, and includes accidents of occupation.

If you require further details about the scheme, please contact Nigel Cox or Maggie Foster at Windrush Insurance Brokers:

Windrush Insurance Brokers
272 Cowley Road
Oxford
OX4 1UH
Tel (0865) 722852

Application forms are available from the Administration and Publications Office.

Missing Member

The Administration Office is trying to locate Dr J A Hodgson, who was elected to Membership of the Society in 1983, at which time he was working in the Dept of Physiology in the Medical School at Bristol. His last known address was the Faculty of Medicine at Southampton General Hospital and it is believed that he may have moved to the USA. Please could anyone who knows his current (or recent) whereabouts contact the Administration Office.

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 210 (1970) to 334 (1983), please write to Prof J C Waterlow, 15 Hillgate Street, London W8 7SP.

Educational Physiological Films

A Russian physiologist, recently retired, has organised an association which produces educational physiological films and would like to make contact with other similar groups. If you have a similar interest or experience (or, possibly, redundant equipment!) and would be interested in establishing contact with him, please contact the Administration Office. ★★

Mathematical Modelling of Muscle Mechanics
SERC Research Studentship
University of Birmingham

This Studentship is available immediately for a period of three years. Graduates in mathematical sciences, physics, engineering or biology with a strong mathematical background should seek further information from: Prof John Blake (Mathematics & Statistics), tel (021) 414 6581 or Dr Martin McDonagh (Sports & Exercise Science), tel (021) 414 4107.

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.

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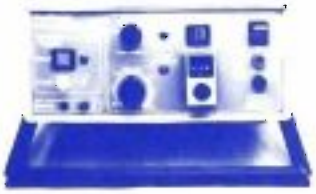

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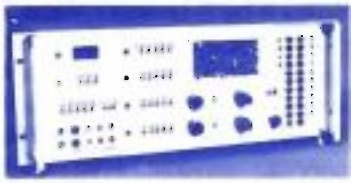

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32nd International Congress of Physiological Sciences

GLASGOW, 1-6 AUGUST 1993

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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 fee is determined from time to time by the Treasurer; it is currently £5 for receipt of Notices and Programmes of Scientific Meetings and Newsletters OR £10 for precirculated Abstracts as well as the above.

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 a 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
CP Comparative Physiology
CS CNS: Somatosensory Physiology
DP Developmental Physiology
EM Epithelia & Membrane Transport
GI Gastrointestinal Tract
HC Heart and Cardiac Muscle
HI History of Physiology
HP Human Physiology
IC Ionic Channels
MI Microvascular & Endothelial Physiology
MC Muscle Contraction
NB Neurobiology
NE Neuroendocrinology
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