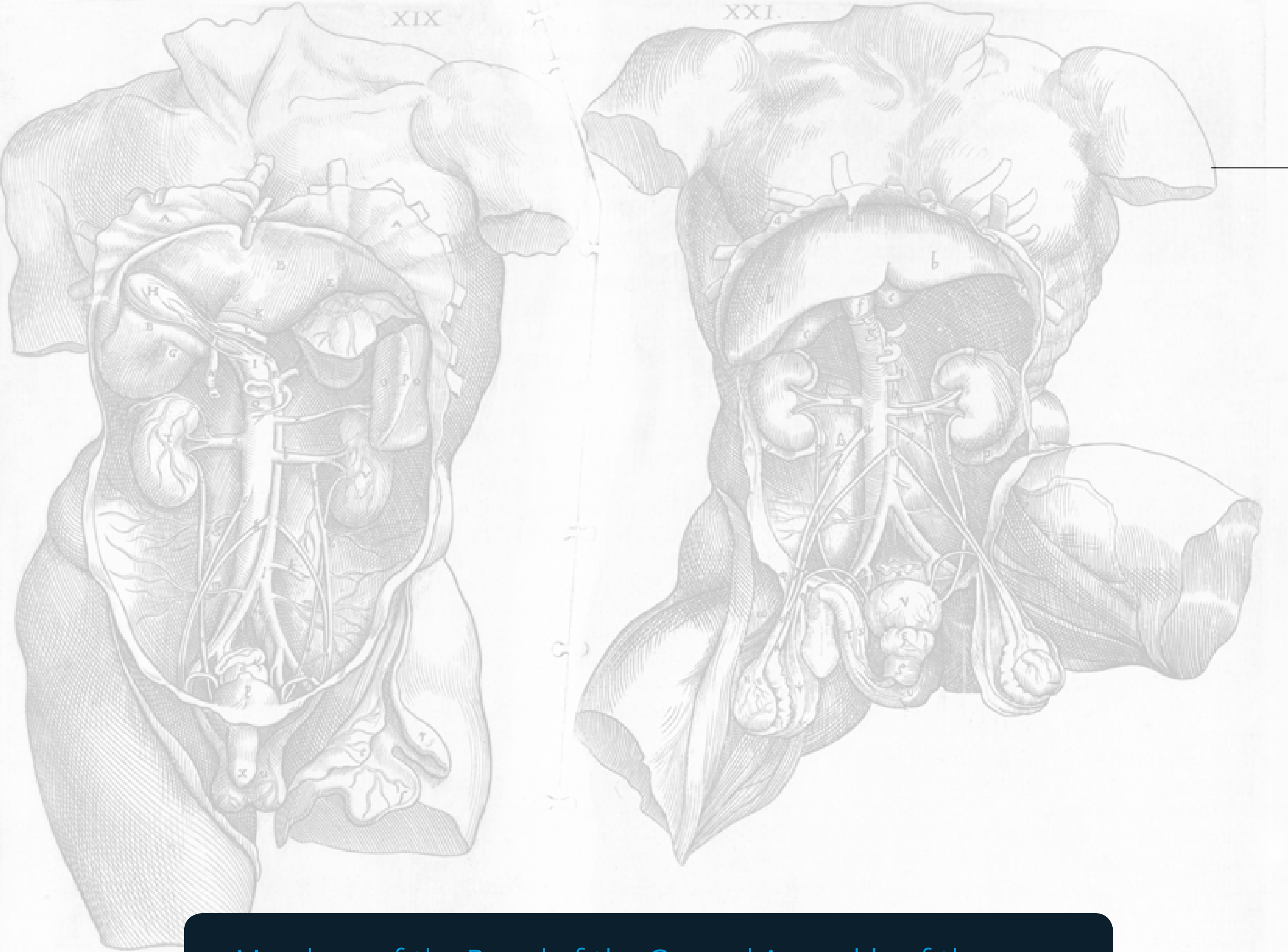
PHYSIOLOGY
Current Trends and Future Challenges

International Union of Physiological Sciences
in collaboration with
The Physiological Society



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Physiology – Current Trends and Future Challenges

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IUPS Foreword

This report has been produced at an opportune time. The physiological sciences were dominant in studying the mechanisms of living organisms during the first half of the 20th century, as the numerous major discoveries show. From the first discovery of hormones right through to the highly quantitative Hodgkin-Huxley model of nerve, physiology simply was the cutting edge of medical science.

During the second half of the twentieth century, the ball passed over to molecular biology, starting with the central dogma of molecular biology and culminating in the complete sequencing of the genomes of many species, including man.

It almost seems as though the study of biology has a fifty year cycle, because we are now witnessing a bounce back, through the growing understanding that from sequences alone we only get partial views of the complete picture. The physiology of cell networks, of tissue organisation, of organ function, and of complete systems is therefore returning to centre stage. Understanding those levels of organisation is totally necessary to interpret what genome sequencing has given us as basic data.

But this is not simply a return to the state of physiology half a century ago. Physiology may have become a back stage effort during those 50 years, but it certainly did not stagnate. On the contrary, the study of all these levels of organisation has become highly quantitative and far more detailed. The International Union of Physiological Sciences has played two important roles in these developments. The first is that, at the St Petersburg Congress 20 years ago, it launched the Physiome Project, with the mission to develop the quantitative, mathematical analysis of complex physiological systems. The second began at the last Congress in Birmingham, UK, in 2013 with the mission to 'return physiology to centre stage' and will continue at the Congress in Rio de Janeiro.

The question many people have asked is whether the physiological sciences is ready to deliver on what is its great challenge of the 21st Century. The leadership of the IUPS congratulates the Board of the General Assembly (BGA) of the IUPS for gathering, compiling, and analysing the information that is the basis of this report on the state of physiology around the globe. Remarkably, they have managed to achieve this in time for the Rio Congress. On behalf of IUPS, I would like to thank all those who have been involved in its production, notably members of the Executive Committee who offered valuable advice on the final document and The Physiological Society for partnering with the BGA in producing the report. This report is a landmark, and I look forward to the discussions of it in Rio de Janeiro.

But we need more than discussion. We now need a coherent plan for implementing the five major recommendations to strengthen the discipline of physiology, create and improve teaching, provide mentorship, promote the development of the means to support teaching and collaborative research, and to develop an outreach program. The reasons why physiology has to return to centre stage are now clear enough. Rising to the challenge of these five recommendations will require sustained work from all of us. IUPS looks forward to achieving that in collaboration with member societies worldwide.

Denis Noble
President, IUPS

The Physiological Society Foreword

The Physiological Society is the oldest learned society for the support of the discipline of physiology, and is delighted to have partnered with the Board of the General Assembly (BGA) of the IUPS in delivering this project to assess the worldwide situation in which the subject finds itself. Having published our report *Health of Physiology* in 2016, exploring physiology in the UK and Republic of Ireland, it is encouraging to see the concept expanded to a worldwide remit. The BGA has achieved excellent reach in its responses from societies new and old, large and small. These build a multifaceted picture of the strengths and weaknesses of research in various countries and continents; and of the challenges facing some of our colleagues, which we may forget in day-to-day activities. The future which emerges, however, is one of common goals and the wish to work towards them together.

Of course, every IUPS member organisation will do its part for the furtherance of physiology. Here in the UK and Ireland, it became apparent that efforts must be redoubled to keep physiology in the public consciousness and to protect the identity of the discipline to maintain a healthy pipeline of skilled students and researchers. To this end, The Society has tried to increase its outward-facing efforts and promote its work to political figures who have sway over the future of science.

Our Society has a long history of collaborations with others. In addition to holding joint meetings with other national societies, we hosted the 2013 IUPS Congress in Birmingham and have recently established the 'Europhysiology' initiative to hold biennial joint conferences with the German and Scandinavian physiological societies and the Federation of European Physiological Societies, starting in London in 2018.

While no organisation is yet in the optimum state for driving forward international physiology, I see hope in the future. This report is the first step in a unifying and momentum-raising process to bolster physiological research worldwide, and achieve its universal recognition as a vital and robust discipline. This will only happen if *Physiology - Current Trends and Future Challenges* does not languish on a shelf but is read and shared, and the recommendations followed through to full execution. This community must rise to the challenge set out here, and be diligent in driving it forward.

I look forward to the report's launch in Rio de Janeiro, and to hearing the suggestions put forward which will comprise the first steps in fulfilling the recommendations.

David Eisner
President, The Physiological Society

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Executive Summary

The Board of the General Assembly (BGA) of the International Union of Physiological Sciences (IUPS) commissioned this report to assess the global strength of physiology as a discipline. This exercise serves to shine a light on the similarities and differences within the international community of physiologists, and the realities of their work and lives.

Input was sought from the member organisations of the IUPS to fill in the picture of the field of physiology worldwide. The result is presented here at the General Assembly of the 38th IUPS-2017 Congress in Rio de Janeiro, Brazil. A companion piece to this report presents essays including The Progress of Physiological Sciences by the Chair of the BGA, and contributions from the respective Chairs of three Committees (Education, Ethics, and Physiome) and four Commissions (Locomotion, Circulation & Respiration, Secretion & Absorption, and Cellular & Molecular Physiology).

Member organisations gave details on the atmosphere around research, including funding, regulation, public perception, and links with government and industry. Most organisations expressed concern regarding the availability of funding, with financial support from government resources deteriorating in recent years. Several organisations noted that funds are more likely to be disbursed to researchers doing clinical rather than basic research. Most organisations reported technical expertise in physiological sciences, but several remarked on diminishing practical skills for *in vivo* techniques and animal-based experimentation. Several responding organisations noted that animal experimentation is being discouraged.

In all countries, research and training in physiology is conducted under the close surveillance of ethics committees for animal and human research, but in some countries, physiologists are challenged by regulations getting stricter, making both human and animal studies more complicated. The use of *in silico* models is on the rise and has been formalised in some countries via organised groups. The establishment of effective links for collaborative research with other national/international institutions and with industry is strongly encouraged in many regions. The social acceptance of basic research in the physiological sciences is variable across the world, ranging from strong support to the lack of a dialogue causing mutual misunderstanding. Public engagement with science could be improved around the world.

Physiology is taught in specific undergraduate and postgraduate degrees, as well as in medical, veterinary, dental, and nursing courses. Most respondents noted that physiology is taught to students in a broad range of academic programmes, though in some countries physiology as an undergraduate subject does not exist. Several respondents remarked that physiology is not always taught within a dedicated physiology course, although there is a growing emphasis that physiology is in fact clinically relevant as the foundation of scientific medical practice and has immediate bedside applicability.

Teaching in physiology utilises a mixture of traditional and innovative classroom and remote methods. Recently, there has been increased use of a flipped classroom model in which short video lectures are viewed by students at home before the class session, and in-class time is devoted to exercises, projects, or discussions. Examinations include a variety of question types. Practical teaching is variable around the world, especially as European regulations bar the use of animals in practical exercises. Human volunteers are common in medical educational settings in all countries.

The survey also considered the career prospects of new graduates. Globally, physiologists have good opportunities in academic positions as post-doctoral fellows, research associates in research laboratories, and as faculty members. Other professional opportunities are being sought by new PhDs as the struggle to obtain funding support is very onerous. Career opportunities for physiologists in non-academic institutions appear to be good in several countries. There are options in biopharmaceutical companies, biomedical - equipment related companies, government health programmes and in science journalism.

The achievements in the physiological sciences shared by the respondent societies are very encouraging. The American Physiological Society pointed to a global highlight of physiology in stating that 'Physiology can celebrate the fact that there is a Nobel Prize in Physiology or Medicine.' A common theme of achievements was establishing strong links between physiologists and other scientists in establishing national, international, and industrial collaborations. Many countries take pride in organising national and international meetings and workshops, and in the recognition of their members as recipients of major national and international awards. For example, over 30 members of The Physiological Society (UK) have been awarded a Nobel Prize, the most recent being to John O'Keefe in 2014.

This analysis has led to the development of recommendations to strengthen the global physiological community. With different countries experiencing very different situations, it is not envisaged that these will be universally and identically implemented, but it is hoped that the societies will work with the IUPS and its new Regional Representatives to bring about the recommendations and take physiology to 'Centre Stage'. Progress will be regularly updated to all member organisations, and fully evaluated at the next IUPS Congress in 2021.

Recommendations

1 Societies should advocate for continued funding of basic research and collect evidence to document its state in their country.

2 Networks and working groups should be created, domestically and internationally, by IUPS and member societies to facilitate the exchange of knowledge and best practice in teaching and research.

3 Societies should continue the efforts of the IUPS Outreach Programme to increase support among physiologists for IUPS initiatives and furthering of the World Health Organization's Health for All agenda.

4 Societies should implement outreach activities to raise awareness of and interest in physiology among the public, and encourage the uptake of physiology and related subjects by prospective undergraduate and postgraduate students.

5 Societies should develop resources to improve the teaching and learning of physiology, and to ensure graduates have a full appreciation of the complexities at all scales of physiological understanding.

6 IUPS must oversee a new Global Mentorship Building Platform to facilitate Mentor/Mentee relationships among physiologists at various career stages, and in academic and clinical settings, to promote dialogue and aid career development.

7 Societies should explore new means to leverage funding from government and private sources, to aid the development of new initiatives designed to strengthen the discipline.

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Introduction

The importance of physiology

Physiology is a core and fundamental scientific discipline that underpins the health and happiness of the world's inhabitants. The integrative attitude of physiology is the counterpart to the reductionist detail of chemical biology, and combining the two gives us vital full-system understanding of living organisms. This is necessary for advancements to be made in medical and veterinary sciences, which in turn underpin health, longevity, and economic productivity.

Purpose of this report

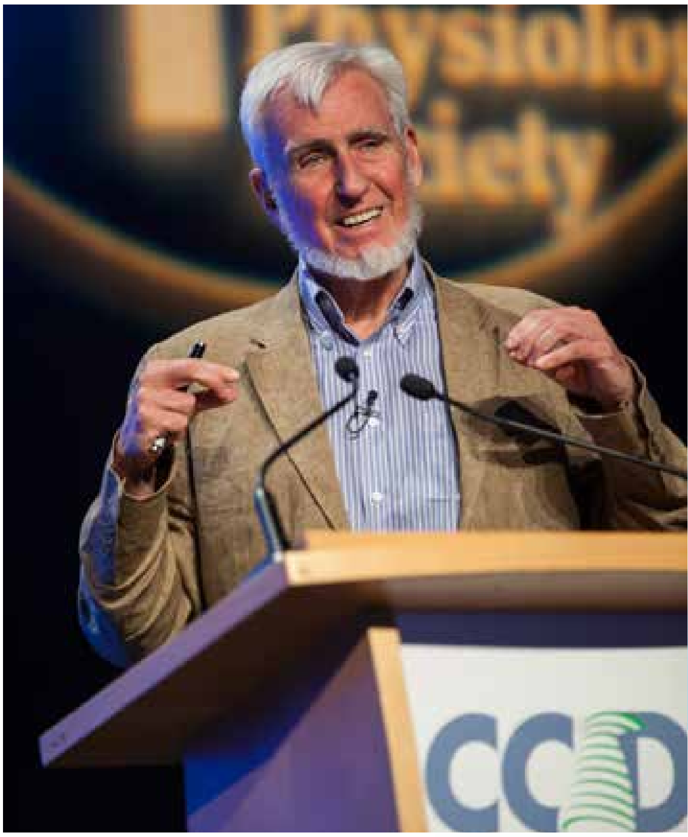
There is a perception that physiology is becoming less visible as it falls into the gap between the wider topic of biology and the specialisms of its subdivisions. Academics working on physiological topics may not refer to themselves as physiologists, and the word 'Physiology' is disappearing from the name of university departments. Despite this, there is a worldwide research community in physiology, represented by numerous national and regional societies. This report aims to emphasise the connections and common goals of the worldwide physiological community and steer the member bodies of the IUPS to collaboration, efficiency, and collegiality, becoming greater than the sum of their parts.

Per the International Union of Physiological Science (IUPS) Constitution, one of the duties of its Board of the General Assembly (BGA) is to provide 'a written assessment of the current status of the field of physiology worldwide, emphasising major challenges, opportunities, and problems' to be presented at the General Assembly of the IUPS-2017 Meeting in Rio de Janeiro, Brazil. This report will be presented at the IUPS Congress in 2017, and we hope it will enable physiological societies from around the world to discuss and plan concerted activities to shore up the status of physiology as a vital, vibrant research discipline.

Methodology behind the report

With 43 full Adhering Bodies and many other member organisations covering all six inhabited continents, the IUPS is ideally positioned to gather information on the state in which physiology finds itself across the world. This was achieved by sending a questionnaire (Appendix 1) to each member organisation, asking for details of physiology in their country or region. The questions covered three key areas: research, education, and career prospects. Information was received from 27 organisations. More details on the respondents can be found in Appendix 2.

The organisations comprising the IUPS were asked to comment on potential current challenges that impact the ability of their membership to do research, to educate undergraduate, graduate, and postgraduate trainees, to assess trainees in their mastery of physiology, and to gain employment as a physiologist. The responses gathered from the various societies for each of these topics are summarised below along with recommendations for moving forward as proposed by the BGA to the IUPS.



2014 Nobel Laureate in Physiology or Medicine John O'Keefe speaks at Physiology 2016, Dublin, Ireland

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Current challenges in research

In pushing the boundaries of human knowledge, it is inevitable that research is a complex and difficult endeavour. The physical, social, legislative, and economic environments in which research is pursued can have a significant effect in determining whether it is easy, or even possible, to make progress. Obviously, these vary greatly around the world. Ideally, a country would provide its research base strong support via competitive funding, easy collaboration to share knowledge and technical expertise, and support for academic and industrial efforts in tandem. Developed and developing nations could work together in a region-specific manner to promote development of research infrastructures and transfer of expertise. There is urgent need for innovative development of *in vivo* and *in vitro* experimental models, *in silico* models, and the training of young scientists in these fields, encouraging national and international research collaborations to create an effectively functioning research system that will also benefit the wider community.

The questions covering the broad area of research were intended to cover multiple aspects linked to the global conduct of research in physiological sciences across the physiological sciences that are linked to the IUPS. Societies from the following regions have provided specific relevant information for this report: Africa, Bangladesh, Brazil, Canada, Chile, Cuba, Estonia, Finland, Hungary, India, Italy, Japan, Korea, Nepal, New Zealand, Russia, South Africa, Sudan, Chinese Taipei, the UK, and the USA.

Funding situation

Most research in physiology is funded publically or philanthropically. The availability of funding varies widely around the world depending on economic strength and government priorities. Responding societies here describe the situation they experience in accessing funding to undertake research.

Most organisations have expressed some concern regarding the availability of funds to do physiological research. In Africa, research in physiological sciences is hampered by scant resources; often researchers rely on personal funds to support their research. The funding situation is reported to be challenging in Bangladesh, Brazil, Nepal, Sudan, and Russia. The availability of research funding in Brazil in the last 2 years has worsened. About 90% of funding comes from governmental sources (National and State Foundations). As the economic situation in Brazil has deteriorated, tax income for the whole country and to State governments decreased. The funding for science and universities was greatly compromised. This negatively impacts the access of scientists to products (e.g. imported chemicals and drugs) and equipment. In addition, the scientific exchange between national/international institutions was also adversely affected. The Association of Physiologists and Pharmacologists of India said that although funds are available, few apply since they are limited to targeted areas of research. The Physiological Society of Korea said that funding from government sources may be increased, especially to support basic research. In Italy, funding for basic research is reportedly amongst the lowest per head in Europe despite their large share of highly cited research papers. The Italian government considers basic research as an esoteric academic pursuit with no 'applied value' and is not supported by government funds. Funds for 'Research Projects of National Interest' are not disbursed in a timely manner, making it difficult to plan ahead and build a competitive research group. The Italian Society of Physiology has argued that a National Research Agency akin to the French National Research Agency or the National Science Foundation in the USA may be set up for more effective fund disbursal. The Hungarian Physiological Society has appropriate research funds at present, but this may cease at the end of the ongoing European Framework Programme, Horizon 2020 (2014–2020). State-funded research in Finland has decreased while funds from foundations and private organisations have not increased. Government-funded support through the Finnish Funding Agency for Innovation and the Academy of Finland is declining and needs to be increased as it helps with personnel and infrastructural costs; there is support to universities mainly through the Ministry of Education and Culture. In the UK, funding for research and innovation is likely to increase, though there is concern about the potential impact of Brexit on this plan due to a loss of European Union (EU) funding. Research funding has largely stagnated for basic research in Canada, with more emphasis on application, innovation, and patentable technologies. However, a recent change of government suggests there may be better recognition for basic biomedical research. In the USA, National Institutes of Health and National Science Foundation funding support has remained flat with minimal or non-existent growth in monies for investigator-initiated research grants. The outlook for improved funding is dim during the Trump administration.

Funding for physiological research in New Zealand is very competitive and comes from public sources, philanthropy, and commercial sources. In terms of government funding, the Health Research Council and the Marsden Fund have recently had a boost to their funding levels and this is expected to result in an increase in success rates. Physiological research in the medical devices field attracts funding through the MedTech Core, a Centre of Research Excellence set up by the Government to translate ideas about medical devices into commercial products.

Members of the Physiological Society of Japan obtain intramural funds, government-supported competitive grants, as well as grants from industry and pharmaceutical companies. The Japanese KAKENHI and Ministry of Education, Culture, Sports, Science and Technology provide competitive grants. These programmes are managed by the Japan Society for the Promotion of Science and experience a 20% success rate. Medical science related grants are supported by the Japan Agency for Medical Research and Development. Basic research is highly supported by the Ministry of Science and Technology in Taipei; more than 50% of its annual budget is allocated to support basic research. In addition, the government also encourages translational and multidisciplinary research projects.

The overall message presented here is that the global situation for research funding is, on the whole, becoming more challenging. This is especially the case for basic research, into which category physiology usually falls. This is happening despite growing recognition that research is necessary to address the challenges faced across the world by expanding populations and the accelerating pace of change. Government and economies are being stretched further, and those in charge may not be scientifically literate, meaning research funds are an easy casualty. It is clear that this trend will not be reversed without a solidly evidenced case for the benefits for health, wellbeing, and crucially wealth, accorded to countries by a solid research base in basic and applied science. Physiology must play a central role in this.

Recommendation

Societies should advocate for continued funding of basic research and collect evidence to document its state in their country.

Technical expertise

Conducting research at the forefront of the discipline requires access to and experience of the latest hands-on and computer-modelling techniques. This spreads around the world at varying paces due to resources and specialisations of existing research. Societies were asked to detail the accessibility of technical expertise in their countries.

Technical expertise is available only in the well-resourced institutions in South Africa and adequate in Bangladesh and Russia. Physiologists in India have expertise in many fields, but they have limited experience in cutting-edge technology. Some smaller countries, such as Estonia and Chile, have strong expertise but only in specific disciplines where there is a national specialism. Japan has a wide range of expertise covering the entire physiological sciences, employing traditional and cutting-edge tools for interdisciplinary scientific endeavors. Countries with more resources and established research infrastructures, such as Finland, Hungary, and Italy, take pride in expertise in wide ranges of physiological methodologies and techniques. In New Zealand, members have strong levels of expertise in the use of large animal models of disease. In the UK, expertise is very strong, but serious concern is being raised about the diminishing practical skills for *in vivo* techniques and animal-based experimentation that arises partly due to cost and difficulty of *in vivo* training. Thus, more fundamental training is required before specialisations can be developed for graduates and early career researchers. In the USA, efforts are underway to provide molecular biologists with specific expertise in physiological measurements; the American Physiological Society partnered with the American Society for Human Genetics to share knowledge on cardiovascular genomics.

Experimental models

Experimental models are fundamental to physiological research on humans and animals, and their complexity is growing rapidly with new advances in genetic technologies and experimental techniques. Resources and regulations mean the use of experimental models can be limited for some researchers, as described here.

Use of experimental models is nil in Nepal and inadequate in Bangladesh. In India, the use of experimental models is also limited and animal experimentation is discouraged. Physiologists in Japan have a wide range of models for research to focus upon mechanisms of life in invertebrates, higher vertebrates, and humans. Animal models include Zebrafish, *Caenorhabditis elegans*, birds, marmosets, and macaques in brain research; they also use cell culture models including cell lines. In Russia, Customs regulations prohibit the transport of animals across geographical borders; this hinders the development of experimental animal models there. A wide range of experimental models are in existence

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in Italy that cover cell culture techniques for primary cultures, immortalised cell lines, rodents for *in vivo* experimentation, and the use of non-human primates. The Italian government is set to introduce a bill that would cause drastic limitations on animal testing, which is likely to '...kill basic research...' according to the Chairman of the Committee on Animals for the Federation of European Neuroscience Societies. Rodent models, including genetically modified variants, are commonly used for research in the UK; large animal models are hard to use as some animal facilities do not handle them. Researchers in the USA use a wide range of animal models; however, the use of Chimpanzees is not permitted. Physiologists in New Zealand have significant expertise with large animal models of diseases such as the use of the sheep for heart and perinatal research. Transgenic animal models are used by most groups in New Zealand, but they do not have facilities to generate transgenic animals so animal models are often obtained from collaborators or are generated by commercial companies and imported into the country.

The use of *in silico* models is nil in Nepal and Bangladesh and is available only in well-resourced institutions in South Africa, while it is adequate in Russia and India. The Committee for Promotion of Physiome and Systems Biology allows researchers in Japan to work on *in silico* physiology. The Korean Physiome Research group is actively working under the Physiological Society of Korea in collaboration with the departments of bioinformatics, biochemistry, and biophysics. Though Hungarian software experts are recognised worldwide, expertise in *in silico* models is limited due to financial constraints. A large number of experts in this area are working in the UK; this field of research is well funded and includes support for collaborative research. Increases in computational modelling in the USA have resulted in a need to identify a repository for *in silico* models that will allow experimenters to further use and test them. The use of *in silico* models is a strength of physiological research in New Zealand, largely due to the close association of the Society with the Auckland Bioengineering Institute and its ongoing inputs into the Physiome project.

Regulation

Research in physiological sciences is being conducted globally, but within varying regulatory frameworks, which can be a burden when using animal models or esoteric compounds. Societies were asked to detail the effects of their country's regulatory framework.

Only nine respondents commented on regulation and ethics regimes. The Physiological Society of Japan has a Research Ethics Committee and Conflict of Interest Committee; many of the institutions in Japan also have their own regulations and committees for research ethics, animal research ethics, and recombinant DNA research ethics. In Finland, regulatory sanctions in human and experimental animal research follow common national requirements; also, national and/or local ethical committees approve all studies performed using animals or human subjects. In Russia, problems occur with borders and Customs, and regulations prohibit support for basic science from private sources. The Italian Physiological Society provides a portal for their members to be aware of policy areas, including limits on animal research. The regulatory landscape is mostly functional in the UK with dialogue between researchers and the regulatory bodies, especially in some areas such as registering animal trials. The process for obtaining a project licence is often slow as the regulatory framework is cumbersome with delays of several months. The UK BioScience Coalition and the government's Animals in Science Regulation Unit are focusing on ways to limit such delays. In Chinese Taipei, various accreditation bodies are responsible for monitoring health education outcomes, and the Institutional Animal Care and Use Committee is responsible for monitoring animal management in research; the Ministry of Science and Technology is responsible for research ethics, and the Ministry of Labor is responsible for occupational safety. The greatest challenge that physiologists encounter is the increasing strictness of regulations.

In India, ethical clearances are required for both animal and human experiments; regulatory bodies like the Medical Council of India are discouraging animal experimentation. The use of Animals and Human subjects in research in New Zealand is governed by local University Ethics Committees. All physiological researchers in New Zealand are aware of the regulatory frameworks that apply to their research; there is a consensus that the compliance required is increasing. This is only partially driven by the legislative framework but more so by the increase in the audit requirements necessary to show compliance with the legislation.

International collaboration

It has been shown that international collaboration leads to more successful and impactful science. Combining the knowledge and experience of the international community is a hallmark of modern science, but requires effective links, administration, and regulation.

The South Asia Association of Physiologists (SAAP) platform is helping to forge collaborative research links between Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka. Cuban Physiological Society members are also in the process of initiating international collaborative research programmes. The African Association of Physiological Sciences is in the process of identifying centres that have technical expertise as an initial step towards establishing a collaboration network for training and collaborative research. Several research centres in the continent have developed effective links with other research organisations outside of Africa through inter-university agreements and student exchange. Members of the Sudanese Physiological Society have established links with the German Academic Exchange Service and The World Academy of Sciences who sponsor international research collaborations. Chilean physiologists enjoy active collaborations with several international institutions, mainly from the USA and Europe. The Physiological Society of Japan promotes international collaboration through joint symposia/conferences at annual meetings, and joint research ties exist with Australia, China, Germany, Scandinavia, South Korea, Chinese Taipei, the UK, and the USA. Korea–Japan symposia are annual events.

As a member of the Federation of European Physiological Societies (FEPS) and the Italian Federation of Life Sciences, Italian physiologists conduct collaborative research with members of the Scandinavian Physiological Society, and the European Society of Comparative Physiology and Biochemistry. These collaborations are further strengthened through joint symposia at annual meetings and participation of guest scientists from other European Societies like the Croatian Physiological Society. Members of the Estonian Physiological Society in universities have several international links. International collaboration is at the forefront of research in Hungary. Strong links exist between physiologists at Finnish institutions and international institutions, study groups, and individual research scientists with national/international research programmes. Europe hosts several large-scale research infrastructures open for collaborative research. Such types of infrastructural facilities exist at more than one location in Finland and in principle are available to all researchers via a virtual platform. International research collaboration is adequate in Russia.

The UK is a hub of global science, leading and participating in international collaboration with an international workforce in its universities and research institutions. Concern is now being expressed that Brexit may affect its European collaboration if the UK does not maintain access to European Union Framework programmes and their funding for multinational projects. Complications due to a border situation with Northern Ireland could affect the ease of collaborations with Irish scientists as well as between Ireland and the UK, although research in the UK will not become entirely isolated. International collaborative research is well identified as a priority in the Canadian Physiological Society. The USA has a long history of effective collaboration in which US scientists partner with colleagues in international institutions. Physiologists in New Zealand have established effective links with other national/international research institutions for collaborative research. This has been traditionally done by investigator-driven collaborations but increasingly it has been driven and enhanced by government initiatives to sponsor national and international research collaborations. The introduction of the National Science Challenges has led to the development of national research teams to address a set of science challenges facing New Zealand. Three of these challenges involve the health of New Zealanders. Internationally, the government has developed funding streams to support international collaboration with a focus on neighbours in the Pacific Rim.

Societies' commitment to the benefits of international collaboration is commendable. However, it seems that these activities are sometimes arranged on an *ad hoc* basis dependent on lucky meetings or (relative) geographical proximity, rather than on the best partner for any particular project. An official network and meeting portal for members of various physiological societies seeking or offering collaboration could reduce reliance on serendipity and lead to powerful outputs.

Recommendation

Networks and working groups should be created, domestically and internationally, by IUPS and member societies to facilitate the exchange of knowledge and best practice in teaching and research.

Attendees view stalls at IUPS Congress 2013

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Industrial links

Science is not merely the preserve of academia; important research is carried out in the industrial sector. Collaboration and knowledge-sharing between industry and academia can lead to more effective research and commercialisation of intellectual property. Different countries have regulations and atmospheres which can promote or hinder links between academia and industry. Societies provided some details, which are given below.

There is no existing support for research collaboration with industry in Bangladesh, Brazil, Canada, Nepal, and South Africa. There is practically no such collaboration in Russia due to prohibitive regulations and cost factors in which each partner must pay twice to conduct such research; this deterrent has been in existence since the communist era. Links with industry are also a big challenge in Brazil; very few Brazilian industries perform, or support science in physiology or in correlated areas of research.

Japanese physiologists have joint research projects with industry in areas that also include translational research. Estonia has links with industry for research. Finland's government has launched several programmes aimed to develop and increase collaboration with industrial partners through the Finnish Funding Agency for Innovation and the Academy of Finland. Hungarian physiologists have limited opportunities for industrial research collaborations. Industries either do not provide financial support for research or they set up their own research and development laboratories to solve existing problems. Various industrial partners support researchers in Italy. Physiologists in Chinese Taipei have collaborative studies with industry that focus on the design and development of medical devices and pre-clinical tests of new drugs. Likewise, links with industry in the field of medical devices has been facilitated by the formation of the MedTech Core in New Zealand. The African Association of Physiological Sciences has recently established links with ADInstruments to support young researchers in selected research centers in Africa. Industry–academia partnerships are a recent phenomenon in government laboratories in India; earlier, there were restrictions on such collaborations. The UK government has initiatives that are aimed at improving innovation and linking academia with industry and allowing spin-outs to compete on their own (e.g. Precision Medicine Catapult, Innovate UK). In the USA, industry is seeking out competent physiologists to conduct animal experimentation, especially since many pharmaceutical company testing labs have been closed.

Public support for research

Scientific research is a world away from the daily experience of most people. This can be a problem if people are not made aware of the gains to be had in health, welfare and daily life, but merely associate research with scientists' pet projects, or, worse, dangerous and reckless experimentation. Research involving animals can be particularly vulnerable to public ire. Societies were asked to discuss the public support for research, and how that affects physiologists working around the world.

The Chinese Physiological Society in Taipei commented that the lack of dialogue between basic science researchers and the general population creates society's misconception of physiology, so fewer students are willing to study physiology. The challenge is to create more collaboration between social practice and physiological research through health education. Members of the Physiological Society of Japan also see a need for better understanding of the importance of basic research that is not directly linked with immediate benefit to society; they point to the fact that the breadth and depth of basic research remains critical for the promotion of science in the long run. In New Zealand, societal challenges around basic research tend to focus on the use of animals or human subjects in research or the introduction of genetically modified organisms rather that the specifics of the research. This may change as stem cell research becomes more prevalent in New Zealand. Animal activists in India are a major deterrent to basic research involving animals so not many opt for basic research; most of the students prefer clinical/patient-oriented studies.

The pressing nature of environmental problems of pollution, environmental disruptors, global warming, health concerns of the aged population, metabolic diseases, concerns around obesity, malnutrition, and other physical, social, and technological challenges have prompted Italian researchers to address such problems through scientific pursuits. However, the general perception of need for basic research remains low. The Finnish Science Barometer, a national survey conducted every 3 years, shows strong public support for scientific research in general. Though public support for basic research and its importance for future innovations exists in Finland, political approval is declining as seen through decreasing governmental funding support and the derogatory comments of politicians. There has been welcome decline in the last 5-10 years of hostility and resistance to experimental animal research. The general attitude towards basic research in Hungary is poor; the overall thought is that government resources should be spent on more pressing issues. While general trust for scientists remains high in the UK, public engagement with science and research is lacking. This may lead to resistance to basic research not considered as 'useful' if combined with aversion to animal research. That said, there is overall good support for basic research, and a healthy science communication sector aims to drive this message across. The 'Haldane Principle', first enunciated in the UK in 1918, led to the support of excellence in basic research through government funding, but this may now change with new provisions being suggested in which government may now be included in decision making of the research funding system.

Modest public support for basic research is evident in Korea, while in Russia the public perception of basic research is very negative as the press sends the message that it is for 'satisfying personal interest from taxpayers' money.' In the

USA, the general perception is that basic research is critical for the development of treatment and cures for disease. There is a strong belief that basic research is important in New Zealand, and this is generally supported by the Marsden Fund, which funds blue-skies research. Unfortunately, the success rate for this fund is only around 7%, which is lower than the success rate for the more translational funding agencies.

Public engagement with science is the 'holy grail' for increasing national and international support for research activities. A number of factors affect the level of public engagement in any country, including media representation of science and research, overall educational levels, proximity to centres of academic excellence, and the level of academic outreach. It is hard to build up scientific engagement from a standing start, but all efforts build on each other to reach a critical mass of public participation. This is especially difficult for physiology as the word has largely been eclipsed by 'biology', meaning there is not high public recognition. Outreach generating interest in physiology will have many positive outcomes including public support for research in the discipline and a greater pipeline of students choosing to study physiology.

Recommendation

Societies should continue the efforts of the IUPS Outreach Programme to increase support among physiologists for IUPS initiatives and furthering of the World Health Organization's Health for All agenda.

IUPS and the World Health Organization

IUPS is a member of the International Council of Scientific Unions (ICSU) and is therefore accredited by the World Health Organization (WHO) as a non-governmental organisation relevant to public health. IUPS supports the Health for All programme of the WHO, promoting health, human dignity, and enhanced quality of life. The WHO defined this programme in 1981 as, in part, 'a commitment to promote the advancement of all citizens on a broad front of development and a resolution to encourage the individual citizen to achieve a higher quality of life'. It demands continued progress in medical care and public health. Increasing the understanding of the physiological sciences will play a part in enabling this progress and facilitating its spread around the world.

6

Securing the global skills pipeline

Physiology in higher education

At the first Claude Bernard Distinguished Lecture of the American Physiological Society, eminent physiologist and teacher Arthur Vander eloquently presented the theme that '...the quality and breadth of our teaching, even more than our research, will decide the future of physiology'.[1] Physiology may be introduced early, at the school level, through structured visits and guided tours to research laboratories, institutions, and clinical physiology laboratories. This would aim to create an interest in physiological sciences amongst school and college students through educational and informed review of research projects. These enthusiastic students will then progress to higher education, where the real work of instilling the knowledge and skills for a physiology career takes place.

Study of physiology as a subject in its own right may be expanded to create a nexus between physiology, molecular biology, environmental biology, ecology, genetics, and systems biology. This may primarily be attained through well-designed undergraduate and postgraduate courses that medical students may also optionally attend. There is a need to emphasise the importance of understanding basic and integrative physiology in the underpinning of clinical practice.

This question addresses the policies in the various programmes through which physiology is being taught globally, at undergraduate and postgraduate levels, in basic science courses and in professional courses. Physiological societies from the following regions have provided specific relevant information for this section: Africa, Bangladesh, Brazil, Bulgaria, Canada, Chile, Cuba, Estonia, Finland, Hungary, India, Italy, Japan, Korea, Nepal, New Zealand, Pakistan, Slovakia, Sudan, Chinese Taipei, Russia, UK, and USA. Most of the physiological societies that responded to the questionnaire noted that physiology is taught to students in a broad range of academic programmes including undergraduate and graduate degrees at universities and in medical, dental, veterinary, and nursing courses. In a few countries, physiology as an undergraduate course in universities is either optional, as in Korea, or it does not exist, as is the case in Bangladesh, Bulgaria, Cuba, Estonia, Nepal, New Zealand, and Pakistan.

Some countries only provide named physiology courses for postgraduates: Sudanese programmes for MSc and PhD degrees in physiology are offered in the main universities, and in Bulgaria there are PhD programmes in Physiology in Medical Universities, Scientific Institutions of the Bulgarian Academy of Sciences, and the Academy of Agrarian Sciences.

In Japan, the education of physiological science is understood to be indispensable towards the understanding of mechanisms of life. In Canadian university programmes, there is competition from related areas, such as the comparative physiologists in Zoology, but many other health-related sciences require introductory courses in physiology, which places a high burden on teaching those courses. Although in decline in recent years, there has recently been an increase in the number of hours of physiology teaching in medical and dental school programmes. With problem-based learning, there is less emphasis on pathophysiology and more emphasis on social determinants of health. Both are important but the balance has not yet been established.

In Finland's five medical faculties, physiology is either an independent subject or an integrated part of a problem-based or hybrid curriculum. Integration may be lateral between the other basic sciences, vertical between the clinical sciences, or both. It is most common to teach physiology during the first two years of training. In general, neurosciences and neurophysiology are integral parts of the physiology curriculum. Pathophysiology is not an independent subject in Finnish universities, but integrated to general physiology. In most universities, clinical neurophysiology and clinical physiology and nuclear medicine are independent subjects in the later clinical years. Various clinical sciences are integrated to apply basic knowledge in a clinical context (gastroenterology, neurology, clinical physiology, general medicine, radiology, public health medicine, orthopedics, nephrology, surgery).

In Hungary, physiology is a major subject in medical, dental, and veterinary universities. The course includes weekly/ monthly written tests that motivate students to prepare for final examinations. Practical examinations and written tests are part of the interim and final exams. About 70% of the students pass the exam on their first attempt, with 20% receiving the highest grade; 10-15% have to repeat the course in the second year because of not showing mastery of physiology. This testifies to the need for a strong concept-based understanding of physiology to succeed in various professional courses. In Italy, physiology is a mandatory subject in both bachelors and master's degree courses in biology, medicine, and many related subjects. All Italian universities provide to the students of these disciplines at least 32 hours of general physiology and at least 48 hours of human, cell, molecular, or comparative physiology for bachelor's courses. Moreover, 48–200 hours of specialised physiology teaching is provided to master's students. Finally, physiology is a subject in several optional courses that undergraduate students can select. The Italian Society of Physiology has estimated that each member performs from 100 to 160 hours of classroom-taught lessons per year to students. Physiology is the subject of PhD courses and of several post-degree specialisation programmes (e.g., nutrition). In the UK, physiology graduate numbers have remained relatively steady from 2003–2013 in

[1] Vander AJ (1994). The Claude Bernard Distinguished Lecture. The excitement and challenge of teaching physiology: shaping ourselves and the future. *Am J Physiol*, 267 (6 Pt 3), S3–16.

absolute numbers but have fallen as a percentage of science, technology, engineering, and mathematics (STEM) graduates.

Several respondents remarked that physiology is not always taught within a dedicated physiology course. Due to degree diversification in UK universities, a lot of physiology teaching is now done in subjects not named as such. This is contributing to a lack of awareness of the term 'physiology' among students and the public. The numbers of physiology postgraduates have been increasing for some years; this may be due to the difficult labour market, encouraging some graduates to stay in a university. Challenges in physiology teaching include a shortage of teachers for whole-body, integrated physiology, as opposed to cellular, reductionist physiology. Increasing specialism means many may not consider themselves physiologists even though they work in a 'physiology' post.

In the USA, most medical schools have eliminated the traditional semester-long course in physiology and instead incorporate physiology into a problem-based teaching format, but a dedicated course in physiology is still common in veterinary medical colleges. Erica Wehrwein from the American Physiological Society provides some insights into undergraduate physiology programmes at US Universities in an article entitled 'Physiology Is Alive and Well. Just Ask an Undergraduate Student'.[2] Similarly, medical education in the UK is influenced by a growing emphasis on the need for all taught material in medical undergraduate degrees to be clinically relevant (and taught by clinicians). This is squeezing 'basic sciences' such as physiology into progressively smaller components of the medical degree program. Increasing use of problem-based learning decreases the identity of physiology and other biomedical subjects. The situation is particularly acute for medical undergraduate degrees in the UK as the General Medical Council (GMC) is moving the point of GMC registration to the point of graduation. This effectively means that all material must be taught in a four-year period with year five of the medical undergraduate degree programme becoming a 'medical apprenticeship'. Physiology is often also seen as being a 'difficult' and unduly 'mechanistic' subject with some clinicians claiming to have forgotten virtually all the physiology they were taught and yet still being able to be successful in their chosen field (e.g. surgery). The importance of understanding pathophysiology in carrying out differential diagnosis, in interpreting the results of many clinical tests, and in designing virtually all 'informed' therapeutic and other treatment regimens needs to be constantly emphasised in undergraduate medical teaching.

Recommendation

Societies should implement outreach activities to raise awareness of and interest in physiology among the public, and encourage the uptake of physiology and related subjects by prospective undergraduate and postgraduate students.

[2] www.the-aps.org/mm/Publications/Journals/Physiologist/Archive/2016-Issues/November-2016-Vol-59No-6/Physiology-Is-Alive-and-Well-Just-Ask-an-Undergraduate-Student

6

Learning and assessment

Understanding of physiology and physiological practice is the backbone of medical sciences. It is concept-based, and with the advent of newer biophysical, cellular, and molecular biology tools we are beginning to realise the complexity of multi-state, multi-level operations in the functioning of living cells and organisms. Since this understanding cannot be achieved through rote learning, the use of 'flipped classroom' modules, team-based learning, case-based learning tools, and problem-based learning modes are to be encouraged besides regular didactic lectures. The vertical model of physiology that starts at the basic level with upward integration in the clinical sciences should be promoted for creating healthy collaboration between physiologists and clinical faculty.

Societies from the following regions contributed to informing the Board of the General Assembly (BGA) with a global perspective of the methods and tools employed for teaching and learning assessment in physiological sciences: Africa, Bangladesh, Brazil, Bulgaria, Canada, Chile, Estonia, Finland, Hungary, India, Italy, Japan, Korea, Nepal, New Zealand, Russia, Slovakia, Sudan, South Africa, Chinese Taipei, UK, and USA.

Learning tools: The general pattern appears to be similar with didactic lectures, problem-based learning (PBL), and case-based learning (CBL) at the undergraduate level, with pursuance of Journal Clubs and Seminars for postgraduate-level students in Africa, Brazil, Bulgaria, China, Estonia, Finland, India, Japan, Italy, Nepal, Russia, and Sudan. Team-based learning (TBL) is also pursued in Korea and Africa along with PBL. Lectures form the backbone of teaching in physiological degree courses in the UK; PBL and CBL are common for medical, dental, and veterinary physiology courses. Flipped Classroom is a pedagogical model in which typical lecture and homework elements of a course are reversed. Short video lectures are viewed by students at home before the class session, while in-class time is devoted to exercises, projects, or discussions. This model is being practised in the UK and in Finland and challenges physiologists to improve upon quality for better understanding for all levels of students. The Life Sciences Teaching Resource Community[3] developed by the American Physiological Society offers information about the teaching resources available for students and teachers in the USA.

Computer-aided learning and educational films: Accessibility of computers in lecture halls limits their use in a few countries such as Brazil, South Africa, Sudan, and Chinese Taipei, but computer-aided learning tools are being commonly used in Bangladesh, Bulgaria, Estonia, Finland, India, Korea, Italy, Nepal, Russia, Slovakia, and the UK. In Japan, there is limited e-learning and computer-aided learning is uncommon. In Canada, the use of PBL and computer-aided learning tools are now being practised with the hiring of teaching-centred faculty members. In New Zealand, standard web-based systems are used by the students to access grades and submit assignments; specific computer exercises are used to support practical classes where appropriate. Chilean physiologists use LabTutor for educational purposes.

The Physiological Society (UK) has created educational films as multiple examples of video content for public or classroom use available on its YouTube Channel.[4] Educational films are rarely or only occasionally used to teach physiology in India, Italy, Japan, and Korea. Conversely, in Chinese Taipei, teachers and students commonly use educational films for various purposes. Physiologists in Estonia and Finland prepare some of their own educational videos; they also make use of a variety of educational films and materials commercially available or freely available on the internet. Physiologists in several other countries (Bangladesh, Canada, China, Russia, and Slovakia) also include educational films as a teaching resource.

Modules for learning assessment: In most of the responding countries (Bangladesh, Brazil, Bulgaria, Estonia, Finland, Hungary, Japan, India, Italy, Nepal, New Zealand, Slovakia, Sudan, UK), learning assessment for formative and summative assessments include a mixture of short- and long-answer questions, multiple-choice questions, and reasoning assertion, but the final examinations in the UK are essay-based. Some organisations did not respond to this question as learning assessment modules could vary considerably across the many educational institutions in their country.

Practical training: Animals are used for laboratory practical exercises in Bangladesh and in Brazil. Use of rabbits and frogs in laboratory exercises occurs in Nepal. Experiments on animals are rare in undergraduate teaching in the UK, but are performed in final year research projects. In Japan, mice, rats, and frogs are used for practical exercises but dogs and cats are no longer used. The responses from Bulgaria, Estonia, Italy, and Slovakia reported that European regulations bar the use of animals for practical exercise. In Finland, animals are used in research-oriented programmes in comparative physiology, medicine, and biomedical sciences. There is training in the handling of animals and their use in experimentation purposes. Due to ethical and financial constraints, practical experiments using animals are declining in Hungary. There are restrictions on the use of animals for practical exercises in Canada and New Zealand. Human volunteers are common for non-invasive laboratory practical exercises at both undergraduate and postgraduate level courses in all the respondent countries.

Practical assessment: Practical examinations (Objective structured practical examination, long and short practical, and *viva voce*) are common in Bangladesh, India, and Nepal. Objective structured clinical examinations (OSCE) are common in Japan. Practical skills are assessed through written or online tests and practical reports in the UK.

Continuing Medical Education (CME) programmes and the award of credit hours to presenting students and faculty members in meetings: CME is offered in several institutions and at scientific society meetings in Bangladesh, Brazil, Estonia, Hungary, Japan, India, Nepal, Chinese Taipei, and the UK.

[3] www.lifescitrc.org
[4] www.youtube.com/user/PhysocTV

There is great worldwide variety in educational systems, but a focus on pedagogy and teaching transferrable skills for graduate employability are priorities for many. Bodies with subject expertise (i.e. learned societies) are very well placed to lead initiatives in subject-specific pedagogy and disseminate them through members who specialise in teaching. These can include tangible resources such as videos, websites, and published material, and also teaching techniques and other career and skills development for teachers. Learned societies can also apply their expertise to ensuring the subject is taught with appropriate breadth and depth, with an up-to-date curriculum, producing the next generation of talented physiologists.

Recommendation

Societies should develop resources to improve the teaching and learning of physiology, and to ensure graduates have a full appreciation of the complexities at all scales of physiological understanding.

IUPS Education Workshop held in Bristol, UK, 2013

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Career options for physiologists

Academia today does not have the capacity for a professorship for every undergraduate. It is inevitable that a large proportion of every cohort of students will not pursue a career in academic research. Indeed, many will not have intended a research career even when choosing their degree.

It is important that all physiology courses have sufficient breadth to prepare students for research, but also equip them with useful transferrable skills to take to other walks of life. Physiology graduates can embark upon careers in academia or industry to apply their talent to the promotion of growth and development of physiological sciences in teaching and in applied fields of biotechnology, bioinformatics, biomedicine, pharmaceutical, and bio-industry. Additionally, for early career physiologists the field is now wide open to join science journalism, government and non-government healthcare programmes, and medical administration in which their critical problem solving and analytical skills would be well utilised. Such diverse job avenues should be given due attention at the entry stage of the education calendar in physiological sciences. Structured avenues of career opportunities for physiologists in assisted reproduction, bio-imaging, bio-feedback, bio-monitoring, imaging technology, psychology, and ophthalmology could also be explored.

A global perspective of the various career options available to physiologists is documented from the responses received from physiological societies in Africa, Bangladesh, Brazil, Bulgaria, Canada, Chile, China, Cuba, Estonia, Finland, Hungary, Japan, India, Italy, Korea, Nepal, New Zealand, Russia, South Africa, Sudan, Chinese Taipei, UK, and USA.

In all responding countries, there are good opportunities for academic positions for physiologists as post-doctoral fellows, research associates in research laboratories, and as university faculty members. An average university department in Finland comprises: mostly (75%) doctoral students, assistants, project researchers, graduate school students; 7% university instructors, post-doctoral researchers and grant holders; 10% senior lecturers/associate professors and research coordinators; and 8% academics at the highest career levels of professors, research professors and directors. The availability of academic positions is on the decline in Hungary with lower numbers of graduating students as the population of the country is declining. There are limited opportunities for physiology graduates to obtain jobs in the industrial sector, and virtually no availability of government or science writing positions in Hungary. As a result, physiologists leave the field or go abroad.

The career path for teaching and research in physiology in Italy comprises: a one-year contract as a post-doc; three-year contracts as Assistant researchers; associate professorship (a stable position of faculty member after national and local contest); and subsequently full professorship achieved in a similar manner. The opportunities in academic settings in Japan involve post-doctoral fellowships available only in research institutions and in research-oriented universities such as graduate schools of medicine. In the UK, around 30% of physiology undergraduates progress to postgraduate degrees or graduate-entry medicine courses.[5] There are limited numbers of positions at professor, associate, and assistant professor levels in each university, and professors generally conduct both teaching and research. At undergraduate campuses in the USA the growth of physiology programmes is promoting career opportunities but with intense competition, and in medical schools and large universities the new faculty members must arrive possessing research grants. Other professional opportunities are being sought by new PhDs as the struggle for obtaining funding support is very high and they take to this route only if they have a very strong passion for research.

The Italian Society of Physiology noted that the Human Genome Project has catapulted physiology to the 'centre-stage of science and innovation'.[6] Career opportunities for physiologists in non-academic institutions appear to be good in several countries. In South Africa and in Sudan, such openings are available in the pharmaceutical industry, complementary and natural medicine, government healthcare programmes, in non-government organisations for social and medical support, the bio-medical equipment industry, health-policy matters, related science journalism, bioinformatics, and patent law. In Cuba, opportunities exist in government bio-pharmaceutical enterprises and in hospitals. In Japan, though the choice for non-academic job opportunities exists, they are likely to under-utilise the knowledge and skills of a physiologist. Career options in Finland exist in medical, dental, veterinary doctor/surgeon, hospital administration, and marine biology pathways, as well as in various government institutions and ministries, or as entrepreneurs in wellness and medical technology. There are good career options in biopharmaceutical companies, biomedical - equipment related companies, government health programmes and in science journalism in Italy. In the UK, around 25-30% of physiology undergraduates opt to join related careers in physiotherapy and, science journalism/outreach, and the rest enter unrelated graduate jobs. In New Zealand, physiology graduates are informed of the diverse range of employment opportunities available, though these depend to some extent on the level of postgraduate qualification each student pursues. Hence, the undergraduate course provides the

[5] www.prospects.ac.uk/careers-advice/what-can-i-do-with-my-degree/physiology

[6] Stated based on Noble et al., (2014). *J Physiol* 592.11, 2237–2244.

platform to enter one of the professional medical courses, or a degree in physiology can gain you employment in virtually any industry or serve as a precursor for postgraduate research. In India, there are limited opportunities for careers in the biopharmaceutical industry, complementary medicine, natural medicine, government healthcare programmes, biomedical equipment, health policy work, and science journalism.

With the difficulties in heading down an academic or clinical career path for newly qualified physiologists, it is important that the international community can pass on its expertise in reaching these positions. Some societies, such as The Physiological Society, have previously used mentorship schemes to positive effect for junior physiologists. This helps the mentee identify opportunities for development and progression, and encourages confidence and autonomy in driving forward to their goals. With the interconnectedness of modern science, the IUPS is in a position to bring together potential mentors and mentees, who can share experience and the different perspectives of working in different countries.

Recommendation

IUPS must oversee a new Global Mentorship Building Platform to facilitate Mentor/Mentee relationships among physiologists at various career stages, and in academic and clinical settings, to promote dialogue and aid career development.

Denis Noble with IUPS Secretary General Walter Boron at IUPS Congress 2013

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Major global achievements

The physiological societies associated with the IUPS were asked to describe the major achievements and prospects for the future of their members. These can take many forms, though commonly were descriptions of conferences or prizes won by individual members. Scientific meetings organised by the various members of the IUPS are a wonderful opportunity to share new knowledge and for networking with other physiologists. These meetings can be the basis for developing research and teaching collaborations that will strengthen the impact of physiology amongst the biomedical sciences. These collaborations in turn will enhance the training of the next generation of physiologists and develoment of cures for disease. Physiological societies across the globe should promote their outstanding and successful members in an effort to gain recognition as potential recipients of prestigious national and international awards and membership in national academies.

Of the 26 responding societies, all except those representing physiologists in Bulgaria, Cuba, and Japan shared examples of achievements and all except Cuba described some of the prospects for the future of physiology. Below is a summary of the information shared by the responding organisations divided by geographical region.

The Americas

The American Physiological Society pointed to a global highlight of physiology in stating that 'Physiology still can celebrate the fact that there is a Nobel Prize in Physiology or Medicine.' Also, they noted that physiology is recognised when its members are elected to one of the National Academies (in the USA this includes the National Academy of Science, National Academy of Engineering, and National Academy of Medicine). Brazil has taken pride in successfully competing to host the 2017 IUPS meeting that will be held in Rio this summer. They are also looking forward to strengthening national and international collaborations among physiology research groups. In an effort to strengthen scientific research and to reduce regional asymmetry in terms of academic and scientific centres, the Brazilian Physiological Society has also received federal funding for the development of a Multicentre Postgraduate Program in Physiological Sciences. Students from institutions that have not been able to develop their own graduate programmes will be able to receive training and perform part of their thesis work at more established institutions. The exchange of knowledge and laboratories among professors of the participant institutions will create a rich environment for the development of young scientists in Institutions where previously this was not possible. The Canadian Physiological Society notes achievements including the attendance of its members at meetings, and the awarding of the Sarrazin Lecture to a senior scientist at a Canadian university. As a result of their recent strategic planning, in 2017 they are implementing two new events: a Chairs' Retreat for leaders in physiology in Canada, and a trainee workshop to assist with developing their best trainees for jobs in industry, academia, and other organisations. The Chilean Society of Physiological Sciences has generated a channel of communication between its members and Chilean scientists from other disciplines. Moreover, through the organisation of international meetings, they have generated instances of interaction between Chilean physiologists and physiologists from other countries. They plan to continue to organise an annual meeting and to increase the number of members by 20% over the next several years.

Brazilian Physiological Society meeting in progress

Writing and Reviewing Professional Skills Course sponsored by the American Physiological Society

Africa

The Physiological Society of Southern Africa takes pride in membership attendance at annual congresses, and they are optimistic about their future since they have built stronger links with the African Association of Physiological Sciences (AAPS). Members of the AAPS note that they have established collaborations with peer societies and industrial corporations, and they look forward to attracting more member societies and establishing a network of centres of excellence in physiology research and education in Africa. Members of the AAPS are very involved in teaching and research. They are active in curriculum development, healthcare programmes, and educational issues. Physiologists are also represented in national committees dealing with health or education. Members of the Sudanese Physiological Society also participate in the AAPS, including having its president serve as the president of the AAPS for two terms. The Sudanese Physiological Society is aiming to start a journal, to have scientific conferences and workshops, to participate in the international conferences, and to increase communication amongst its members.

IUPS Outreach event held in Lagos, Nigeria

Research at Stellenbosch University, South Africa

Asia

Despite being organised as recently as 2010, the Physiological Society of Nepal has had several notable achievements including organising a successful workshop on the Emerging role of Clinical Physiology in Medical Sciences in 2012, becoming an Associate Member of the IUPS in 2013 and the Federation of Asian and Oceanian Physiological Societies in 2015, and hosting its first national conference and an inter-medical school physiology quiz in 2013 and the 5th Biennial Conference of South Asian Association of Physiologists in 2016. They look forward to building on these achievements while they work for the advancement and dissemination of the knowledge base of the physiological sciences, unite Nepalese scientists involved in active research and teaching in physiological sciences in Nepal, and promote research in collaborations nationally and internationally.

The Association of Physiologists and Pharmacologists of India remarked on the fact that their members represent more than 450 medical colleges where physiology is taught for 1 year and have contributed significantly in academic teaching and research globally. They note that job opportunities for physiology postgraduates are bleak as MCI has cut down jobs. Techniques in animal experiments are vanishing. Biochemistry and pharmacology are offering more jobs opportunities. Physiology as a research career is the last option. There is growing demand for medical teachers in physiology in the country.

The theme of collaboration was also expressed by The Pakistan Physiological Society as its members strive to collaborate with other societies in the region to develop a culture of collaborative research and to contribute positively to IUPS activities. The Bangladesh Society of Physiologists notes that its members continue to strive to keep on par with the modern-day physiology by participating in international conferences, doing collaborative work, and publishing their results. They express optimism as they view physiology as an ever-expanding field in which more research scopes are being created daily. Members of the Physiological Society of Japan have been successful in publishing their research in high-profile journals such as *Nature*, *Science*, *PNAS USA*, *The Journal of Physiology*, *Journal of Neuroscience, Clinical Investigation*, and *Circulation Research*.

The members of the Chinese Association for Physiological Sciences have benefitted from the fact that the Chinese economy has experienced phenomenal growth over the past 20 years and the Chinese Government has been promoting a knowledge-based economy for sustainable growth. This remarkable phase of development has been associated with increases in the numbers of Chinese scientists returning to

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take up posts in top universities and research institutions, papers being published in highly visible international journals, and Chinese physiologists participating in international conferences and expanding their connections and collaborations with colleagues all over the world. In addition to the rapid development of the fields of neuroscience and cardiovascular systems, other disciplines such as digestive, kidney, endocrinology, respiratory, blood, and reproductive systems have flourished.

The Chinese Physiological Society in Taipei remarked on an initiative to promote interdisciplinary training in the life sciences. Application of basic physiology research to clinical studies has created new directions in translational medicine, regenerative medicine, and medical devices. More physiologists are expected to be recruited into departments of Biomedical Engineering in the College of Engineering. They see that regional collaboration promotes global mobility of physiologists in both teaching and research. Joint efforts in transforming physiological symposia from local to global settings will deepen understanding and identify future partnerships for further collaboration to enhance regional networking. This theme of interdisciplinary efforts was also expressed by The Korean Physiological Society, which sees a need to integrate physiology with other fields such as mathematics, engineering, information technology, social science, computation, and artificial intelligence to advance the life sciences. Likewise, the Physiological Society of India foresees a major role of physiologists in advancing research and teaching in different areas of Physiology and Allied Sciences.

Celebrating the 120th birthday of Robert KS Lim, founder of the Chinese Physiological Society, in Taipei

Europe

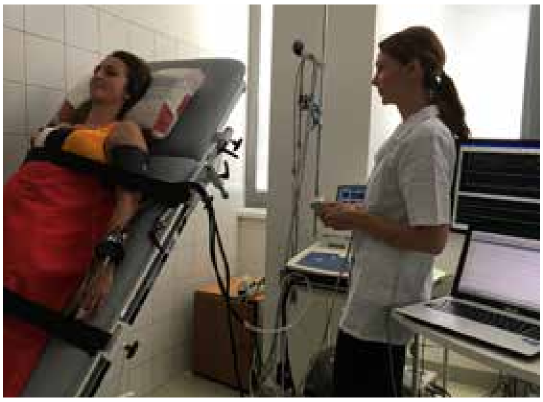
The Physiological Society (UK) takes pride in the fact that 20 of its members have been awarded a Nobel Prize, the most recent being to John O'Keefe in 2014. The Society represents the broad discipline of physiology in the UK and Republic of Ireland and hosts well-attended annual meetings. They recently completed an extensive report on the future of Physiology entitled *Health of Physiology*. The Society collaborated with the German and Scandinavian Societies in the creation of Europhysiology. The first meeting in this series will be held in 2018 and is designed to bring together European physiologists in a biennial meeting.

Members of the Estonian Physiological Society have been recognised by receipt of national research awards for excellence in research results. Members of the Finnish Physiological Society are well connected to the international scientific community, making it possible to apply also for international funding and carry out state-of-art research. Physiology, as a subject by its own right, is taught in all the relevant study programmes in Finnish universities and universities of applied sciences. Finnish physiologists are well educated and have considerably good career prospects in academic settings. In fact, there are indications that physiology is winning back some of its lost status as the central biomedical science in medical education. Nonetheless, in some universities, physiology is no longer a subject in natural science programmes. This unwanted development leads to reduced research funding for training the next generation of physiologists.

Despite the limited funds and resources for physiologists in Hungary, they still have an impact internationally in the field of physiology and on Medical/Life Sciences within the country. Their most important fields of expertise include cell physiology, cardiovascular physiology, endocrinology, and neuroscience. This being said, there is concern over the future of early career scientists with degrees in physiology, as positions in basic science are scarce and overall public attitude is not positive.

The principal achievement of members of the Italian Society of Physiology is the conclusion of an internationalisation process in which physiologists share interests, data, and grants worldwide. Other important achievements include the increased quality of research and the increased ability to attract young researchers in this fascinating field of study. The Russian Physiological Society is optimistic that there will be growth in all fields of physiology with a priority for the neurosciences. Members of the Bulgarian Society of Physiological Sciences are striving for better funding, international collaboration, and better representation in the field of Physiological Sciences.

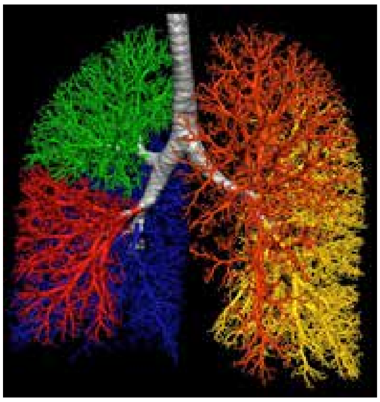
The Slovak Physiological Society notes achievements of its members who have been plenary speakers and symposia organisers at European and world conferences, the existence of scientific co-operation between Slovakia and other countries, and the ability to attract young physiologists to become members of the Society. They are hopeful that they will be able to host an IUPS meeting in the future.



Clinical experiment in the Laboratory of the Autonomous Nerve System, Martin Comenius University, Bratislava, Slovakia

Oceania

The Physiological Society of New Zealand has embraced the joint meeting concept embodied in MedSciNZ yet has maintained its prizes to recognise outstanding student achievement and emerging researchers. The Society's membership has stabilised and it is not expected to increase dramatically in the near future.



A computational model of the lungs used by Professor Merryn Tawhai at the Auckland Bioengineering Institute for studying spatially distributed respiratory diseases such as COPD and asthma

Analysis

Physiology is in a transitional period, currently facing declining recognition as it sits in the gap between growing subdisciplines and high-level biology and clinical sciences. It requires concerted efforts from all bodies worldwide that represent the discipline of physiology in order to help it adapt to modern circumstances. It is far from alone among research disciplines in this situation, but has to gather and marshal its resources to regain recognition and prominence. Populations in many countries are experiencing the paradoxical situation of benefitting greatly from scientific advances while growing sceptical of the promotion and funding of basic and blue-skies research. If physiology is to move with the times and be recognised as a key part of modern biological, pharmacological, and medical advances, it must be willing to promote itself within both the scientific community and the wider public. The tightening availability of research funding means little is left over to promote the discipline. In order to optimise work for the furtherance of physiology as an entity, new routes must be found to support this effort. Opportunities to do this will vary wildly across countries, manifesting perhaps in government programmes, charitable grants, or partnerships with private companies and citizens. The local expertise contained in the member organisations of IUPS must be applied to finding and exploiting these opportunities.

Recommendation

Societies should explore new means to leverage funding from government and private sources, to aid the development of new initiatives designed to strengthen the discipline.

Research Publications and Conferences

The questionnaire requested information on the numbers of peer-reviewed publications of society members over the past five years. Seven of the responding societies indicated that they do not survey their members to gather this information. Others indicated total publications from their membership during the past five years varying from fewer than 50 from small societies (Cuba, Nepal) to greater than 2000 publications.

The questionnaire also requested information on the numbers of national and international scientific conferences, symposia, and technical or educational workshops organised by their organisation in the past five years. Most societies hold a minimum of one national meeting each year, but a few noted that their national meetings are held every two to three years. Not surprisingly, these numbers varied widely. In each of the last five years, the Chinese Association for Physiological Sciences has held between three and five national conferences, up to two international meetings, and one to four educational workshops.

The questionnaire also requested information on the society-based publications. Fifteen of the responding organisations indicated that they do not publish a journal, but at least two of them (African Association of Physiological Sciences and Physiological Society of Nepal) have discussed the possibility of starting a society journal. Due to lack of financial resources, the Bulgarian Society of Physiological Sciences has had to cease publishing its journal. The Physiological Society of New Zealand also stopped publishing a journal, but the society makes abstracts submitted by its members to the annual MedSciNZ meeting available online via its website. The other eleven responding organisations publish one or more physiology journals. The longest-established publication is *The Journal of Physiology* by The Physiological Society, which was first published in 1878. The newest journal is *Physiological Reports*, an online open-access journal that is published jointly by the American Physiological Society and The Physiological Society, founded in 2013. The most extensive publication programme is that of the American Physiological Society, which includes 16 journals. One of these *(Physiology)* is published jointly with the IUPS. A complete list of Society publications is included in Appendix 4.

Attendees of the 2017 March for Science in Washington DC

Sir Paul Nurse, Past President of the Royal Society and now Director of the Francis Crick Institute, speaks at IUPS Congress 2013

9

Summary of Recommendations

1 Societies should advocate for continued funding of basic research and collect evidence to document its state in their country.

2 Networks and working groups should be created, domestically and internationally, by IUPS and member societies to facilitate the exchange of knowledge and best practice in teaching and research.

3 Societies should continue the efforts of the IUPS Outreach Programme to increase support among physiologists for IUPS initiatives and furthering of the World Health Organization's Health for All agenda.

4 Societies should implement outreach activities to raise awareness of and interest in physiology among the public, and encourage the uptake of physiology and related subjects by prospective undergraduate and postgraduate students.

5 Societies should develop resources to improve the teaching and learning of physiology, and to ensure graduates have a full appreciation of the complexities at all scales of physiological understanding.

6 IUPS must oversee a new Global Mentorship Building Platform to facilitate Mentor/Mentee relationships among physiologists at various career stages, and in academic and clinical settings, to promote dialogue and aid career development.

7 Societies should explore new means to leverage funding from government and private sources, to aid the development of new initiatives designed to strengthen the discipline.

Appendices

Appendix 1 – Data collection for this report

The questionnaire reproduced below was sent to all IUPS member organisations, with the collected responses forming the basis of this report:

IUPS-BGA Questionnaire for all IUPS Adhering Bodies, Supporting Societies, Regional Members, Associate Members, Affiliated Societies for inputs[1]

[Questionnaire to be sent to President/General Secretary/Finance Secretary, Executive Editor of journal, and any other responsible executive members of the Organisation]

1 Background Information:

(Please provide written information as requested and indicate as applicable)

1.1 Name of the organisation[2]:

1.2 Position of the signatory in the organisation:

1.3 Category of membership of your organisation in the IUPS (tick the most appropriate box):

- Adhering Body
- Supporting Society
- Regional Member
- Associate Member
- Affiliated Society

1.4 Geographical location[3] of your organisation (please select the correct one from the following list and mention the name of the country of its location):

Africa -	European Union -
The Americas -	Middle East -
Asia -	Oceania -
Europe -	

1.5 Total number of members in your organisation:

- Student
- Professional
- Supporting (e.g. Institutional, Industrial)

1.6 Specialisation[4] of your organisation as based on the overall genres of physiological sciences sub-speciality (tick appropriate boxes as applicable):

- Circulation and Respiration
- Comparative: Evolution, Adaptation, and Environment
- Education
- Endocrinology, Reproduction, and Development
- Ethics
- Genomics and Biodiversity
- Locomotion
- Molecular and Cellular Physiology
- Neurobiology
- Physiome
- Secretion and Absorption
- Any other (Please mention)

2 Current challenges in Physiological Sciences (please write briefly under each category)

2.1 Research in physiological sciences:

Funding situation
Technical expertise
Experimental models
Regulatory sanctions
Expertise in the use of *in silico* models
Effective links with other national/international research institutions for collaborative research
Effective links with industry for collaborative research
Social challenges in the pursuance of basic research
Governmental support
General perception of need for basic research

2.2 Policies in physiology teaching as a subject at undergraduate and postgraduate levels (please write briefly under each category):

Physiology as a subject in Universities
Physiology as a subject in Medical course programmes
Physiology as a subject in Veterinary course programmes
Physiology as a subject in Dentistry course programmes
Physiology as a subject in Nursing course programmes
Physiology as a subject in other course programmes (e.g. laboratory medicine, medical technician courses, etc.)

2.3 Methods in physiology learning-teaching and assessment at undergraduate and postgraduate levels (please write briefly under each category):

Learning tools (e.g. didactic lecture, problem-based learning, case-based learning, etc.)
Computer-aided learning
Educational films
Modules for learning assessment (e.g. formative and summative assessments; long/short answer questions, multiple choice questions, reasoning assertion, etc.)
Experimental modules for practical exercises using animals (e.g. frog, mouse, rat, rabbit, cat, dog, etc.)
Experimental modules for practical exercises using human volunteers
Modules for practical assessment (e.g. objective structured practical examination, long and short practical, *viva voce,* etc.)
Continuing Medical Education (CME) programmes and the award of credit hours to presenting students and faculty members in meetings

2.4 Career options for physiologists (please write briefly under each category):

In academic setting for teaching/research in university, medical, dental, nursing, and veterinary colleges/institutions
In other organisation (e.g. bio-pharmaceutical, complementary medicine, natural medicine, government health care programmes, non-government organisation for social and medical support, biomedical equipment related, health policy matter related, science journalism, bioinformatics, etc.)

3 Research Publication, Technical Workshop/Symposia/Conference in Physiological Sciences

3.1 Total number of peer-reviewed publications by members during the last five years (e.g. <50, >50, >100, etc.)

3.2 Categorise and enumerate the annual, semi-annual scientific conference/symposium/technical/educational workshop organisation by your organisation in the last five years at national and international levels.

3.3 International/national journal(s) in Physiology published by your organisation. Name of the journal(s) published and the year from which its publication started. Provide website link(s).

4 Highlights of Physiological Sciences in your geographical location (please write briefly under each category):

4.1 Achievements

4.2 Prospects

5 Any other issue(s) your organisation would like to address to the IUPS:

Signature:

Name:

Place:

Date:

IUPS, International Union of Physiological Sciences; BGA, Board of General Assembly; [1]For analysis and incorporation into the IUPS-BGA Document to be presented to the General Assembly in IUPS 2017 Congress; [2]Organisation means Physiological Association, Society, National Committee, any Affiliated group of Physiologists; [3]Based on the UN classification; [4]Based on IUPS Commissions and Committees.

Appendix 2 – Respondents

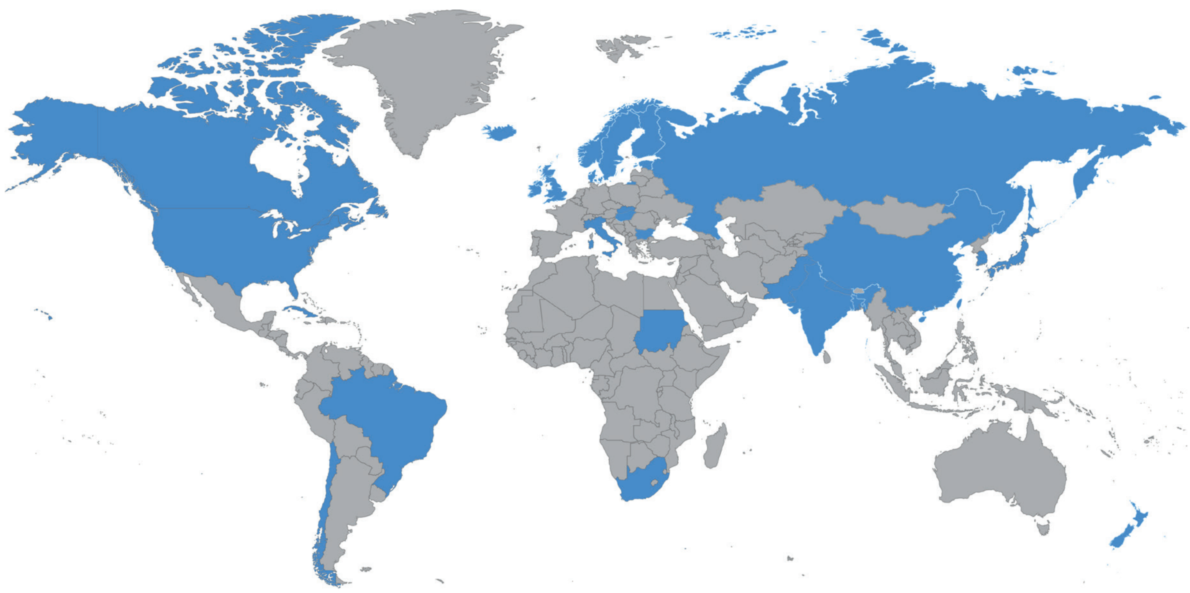
Per the International Union of Physiological Science (IUPS) Constitution, one of the duties of its Board of the General Assembly (BGA) is to provide 'a written assessment of the current status of the field of physiology world-wide, emphasizing major challenges, opportunities, and problems' to be presented at the General Assembly of the IUPS-2017 Meeting in Rio de Janeiro, Brazil. To gain relevant data for such an assessment, the BGA created a questionnaire that was sent to representatives of each of the Adhering Bodies, Supporting Societies, Regional Members, Associate Members, and Affiliated Societies. This report is based on a compilation of information received from 27 organisations that responded to our request to complete the questionnaire.

Characteristics of the 27 responding societies:

Responses were received from the following organisations: African Association of Physiological Sciences, American Physiological Society, Association of Physiologists and Pharmacologists of India, Bangladesh Society of Physiologists, Brazilian Physiological Society, Bulgarian Society of Physiological Sciences, Canadian Physiological Society, Chilean Physiological Society, Chinese Association for Physiological Sciences, Chinese Physiological Society in Taipei, Cuban Society of Physiological Sciences, Estonian Physiological Society, Finnish Physiological Society, Hungarian Physiological Society, Italian Society of Physiology, Korean Physiological Society, Pakistan Physiological Society, Physiological Society of India, Physiological Society of Japan, Physiological Society of Nepal, Physiological Society of New Zealand, Physiological Society of Southern Africa, Russian Physiological Society, Scandinavian Physiological Society, Slovak Physiological Society, and The Physiological Society.

These comprise 17 Adhering Bodies, four Affiliated Societies, two Supporting Societies, two Regional Members, and two Associate Members. The responding organisations were from Asia (n = 9), Europe/European Union (n = 10), The Americas (n = 5), Africa (n = 2), and Oceania (n = 1). The size of the membership of these societies varied from as few as 38 (Estonian Physiological Society) to as many as 9952 (American Physiological Society). The median size of the membership of the responding organisations was 300 individuals. At least 19 of the responding societies include both student and professional categories of membership. Only five societies indicated that their membership was comprised solely of professionals. Seven of the responding organisations noted that they include a supporting category of membership (e.g. Institutional, Industrial).

The area of specialisation of the physiologists represented by these 27 responding societies included Circulation and Respiration (n = 24); Comparative: Evolution, Adaptation, and Environment (n = 12); Education (n = 21); Endocrinology, Reproduction, and Development (n = 23); Ethics (n = 8): Genomics (n = 12); Locomotion (16); Molecular and Cellular Physiology (n = 23); Neurobiology (n = 22); Physiome (n = 11); and Secretion and Absorption (n = 21). Other topics identified by one or more societies included Renal Physiology; Human and Exercise Physiology; Vascular and Smooth Muscle Physiology; Muscle Biology and Regeneration; Nutrition, Metabolism, and Systems Physiology; Perinatal Physiology; Chronic Diseases of Lifestyle; Physiological Psychology; and Yoga and Meditation.



Appendix 3 – Individual societies' priorities

Organisation	Priorities
African Association of Physiological Sciences	1. Attracting more members in the societies. 2. Development of research laboratories through provision of equipment and expertise for training of research personnel with inputs from the IUPS. 3. The establishment of a network of centres of excellence in physiology research and education.
American Physiological Society	1. Efforts are underway to provide molecular biologists and other reductionist scientists with expertise in physiological measurements. As an example, recently the Society partnered with the American Society for Human Genetics to contribute physiological knowledge and information in a session on cardiovascular genomics. 2. Basic research represents the building block for translational medicine and precision medicine. Without the knowledge of basic science, one cannot translate into clinical practice. 3. Many new PhDs see their advisors struggling to get funded. Since a PhD provides the individual with problem-solving ability and critical-thinking skills, they can tackle any job or opportunity. Many PhDs are finding this to be true as they search for professional opportunities.
Association of Physiologists and Pharmacologists of India	1. Creation of job opportunities for physiology in teaching and research. 2. Re-introduction of techniques in the use of animals in research.
Bangladesh Society of Physiologists	1. Improved funding for research. 2. Development of laboratory facilities with inputs from the IUPS. 3. Promotion of international collaborative research opportunities.
Brazilian Physiological Society	1. Improvement in research funding. 2. Strengthening of national and international collaborative research groups.
Bulgarian Society of Physiological Sciences	1. Better funding for research. 2. International research collaboration. 3. Better representation in the field of physiological sciences.
Canadian Physiological Society	1. Improved funding for basic science, which has stagnated with an increasing emphasis on application, innovation, and patentable technologies. 2. Effective links with other national/international research institutions for collaborative research. 3. Chairs Retreat, for leaders in physiology in Canada, and a trainee workshop to assist with developing our best trainees for jobs in industry, academia, and other organisations.

Organisation	Priorities
Chilean Physiological Society	1. To continue organising our annual meetings in Physiology. 2. To increase the number of members by 20%. 3. Inputs requested from the IUPS in organising international meetings/workshops of physiological sciences to motivate and train young scientists.
Chinese Association for Physiological Sciences	1. Greater opportunities for research in 'Omics' and Big data an opportunity for physiology. 2. Integrative biology as a challenge to physiology. 3. Translational medicine makes a demand on physiology. 4. Promote application of scientific achievements to improve people's livelihood, economic, and national defence development and industrialisation. 5. Organisation of IUPS-Workshops to improve teaching and research in developing countries.
Chinese Physiological Society in Taipei	1. Domain of Life Sciences re-structured to promote interdisciplinary training. 2. New directions in translational medicine, regenerative medicine, and medical devices by application of basic research to clinical medicine. 3. Recognition of physiology education and research by Engineering Institutions to permit recruitment of physiologists in Biomedical Engineering. 4. Regional collaboration in both research and teaching to promote global mobility of physiologists in both teaching and research.
Estonian Physiological Society	1. Develop strategies to draw young physiologists with medical background into teaching and research careers in physiology.
Finnish Physiological Society	1. The development of curricula and teaching of physiology in modern learning environments in order to promote its central status in biomedical science in medical education. 2. The development of curricula and teaching of physiology in modern learning environments in order to prevent physiology from fading away from natural science programmes.
Hungarian Physiological Society	1. Further improved funding for research to prevent talented young scientists from leaving the country. 2. Strengthen international collaborations. 3. Alternative career options outside of academia for those trained in physiology.
Italian Society of Physiology	1. Create career options for young physiologists in Italy and globally. 2. Improve connections among National Physiological Societies in the IUPS context.
Korean Physiological Society	1. Need greater support for basic research. 2. Integrate physiology with other fields such as mathematics, engineering, information, social science, computation, and artificial intelligence to develop physiological science and to understand the life system.
Pakistan Physiological Society	1. One of four founding members of the South Asian Association of Physiologists. 2. Promote culture of collaborative research with neighbouring societies. 3. Improve the participation of physiologists in international meetings that is hindered by financial and security concerns.

Organisation	Priorities
Physiological Society of Nepal	1. Work for advancement and dissemination of knowledge base in physiological sciences. 2. Organise regular national/ international conferences, training workshops, and the conduct of national/international collaborative research. 3. Promotion of research in high altitude physiology.
Physiological Society of New Zealand	1. Use of *in silico* models with close association with the Auckland Bioengineering Institute and its ongoing inputs into the IUPS-Physiome project. 2. Effective links with industry for collaborative research in the field of medical devices facilitated by the formation of MedTech Core www.cmdt.org.nz/. 3. Supporting the Society members to enhance their career development through organisation of local meetings and recognising achievement through awarding research excellence awards.
Physiological Society of Southern Africa	1. Improve ties with AAPS. 2. Conduct joint satellite meetings with members of the IUPS and the PSSA to foster collaborative research links.
Russian Physiological Society	1. Improve funding for basic research. 2. Research in neuroscience.
Scandinavian Physiological Society	1. Promote understanding of integrative physiology. 2. Promote application-oriented education in physiology.
Slovak Physiological Society	1. Continue scientific collaboration between Slovakia and other countries. 2. Organize IUPS Congress in future.
Sociedad Cubana de Ciencias Fisiológicas	1. Increase the support for basic research. 2. Perform international collaborative research.
The Physiological Society (UK)	1. Secure a favourable outcome for UK science in Brexit negotiations, including maintaining access to EU Framework Programmes; commitments to funding for multinational projects; and the continued ease of mobility for international researchers and students. 2. Continue to develop our scientific meetings, embracing the Europhysiology initiative, so that they become a focus for physiologists from all countries, and ensure that our journals continue to be an attractive place to publish the highest-quality physiological research. 3. Promote 'physiology' and, in particular, practical skills in university education, particularly training at a fundamental level of *in vivo* techniques prior to development of specialisations. 4. Promote science communication to increase public engagement and ensure continued support for basic research.
The Physiological Society of India	1. Promotion of physiological sciences for the improvement of societal problems. 2. Improvement of funding for research. 3. Greater collaboration with international organisations.
The Physiological Society of Japan	1. To continue the excellence in research in physiological sciences conducted in Japan and published in leading journals (http://int.physiology.jp/en/sciencetopics) 2. To promote the importance of research in physiology and pathophysiology whose width and depth are critical for the promotion of science and the breakthroughs in the next generation, as well as the benefits to the society.

Appendix 4 – Journals published by Physiological Societies

Organisation	Journal	Website
American Physiological Society	American Journal of Physiology – Cell Physiology	http://ajpcell.physiology.org/
	American Journal of Physiology – Endocrinology and Metabolism	http://ajpendo.physiology.org/
	American Journal of Physiology – Gastrointestinal and Liver Physiology	http://ajpgi.physiology.org/
	American Journal of Physiology – Heart and Circulatory Physiology	http://ajpheart.physiology.org/
	American Journal of Physiology – Lung Cellular and Molecular Physiology	http://ajplung.physiology.org/
	American Journal of Physiology – Regulatory	http://ajpregu.physiology.org/
	American Journal of Physiology – Renal Physiology	http://ajprenal.physiology.org/
	Journal of Applied Physiology	http://jap.physiology.org/
	Journal of Neurophysiology	http://jn.physiology.org/
	Physiological Genomics	http://physiolgenomics.physiology.org/
	Advances in Physiology Education	http://advan.physiology.org/
	Physiology (jointly with International Union of Physiological Sciences)	http://physiologyonline.physiology.org
	Physiological Reviews	http://physrev.physiology.org/
	Physiological Reports (jointly with The Physiological Society)	http://physreports.physiology.org
	Comprehensive Physiology	http://onlinelibrary.wiley.com/book/10.1002/cphy
Association of Physiologists And Pharmacologists of India	Indian Journal of Physiology and Pharmacology	http://www.ijpp.com
Bangladesh Society of Physiologists	Journal of Bangladesh Society of Physiologists	http://www.banglajol.info/index.php/JBSP
Chinese Association for Physiological Sciences	Acta Physiologica Sinica	www.actaps.com.cn/index.asp
	Progress in Physiological Sciences	http://118.145.16.229/jwk_slkxjz/CN/volumn/home.shtml E
The Chinese Physiological Society in Taipei	The Chinese Journal of Physiology	http://www.cps.org.tw

Organisation	Journal	Website
Korean Physiological Society	The Journal of Physiology and Pharmacology	http://www.kjpp.net
Pakistan Physiological Society	Pakistan Journal of Physiology	http://www.pps.org.pk/PJP/
Scandinavian Physiological Society	Acta Physiologica	http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291748-1716
Slovak Physiological Society	General Physiology and Biophysics Physiological Research	http://www.gpb.sav.sk http://www.biomed.cas.cz/physiolres
The Physiological Society	The Journal of Physiology Experimental Physiology Physiological Reports (jointly with the American Physiological Society)	http://physoc.onlinelibrary.wiley.com/hub/journal/10.1111/(ISSN)1469-7793 http://physoc.onlinelibrary.wiley.com/hub/journal/10.1111/(ISSN)1469-445X http://physreports.physiology.org
The Physiological Society of Japan	The Journal of Physiological Sciences	http://link.springer.com/journal/12576

Jayasree Sengupta is the Chair of the Board of the General Assembly of the International Union of Physiological Sciences.

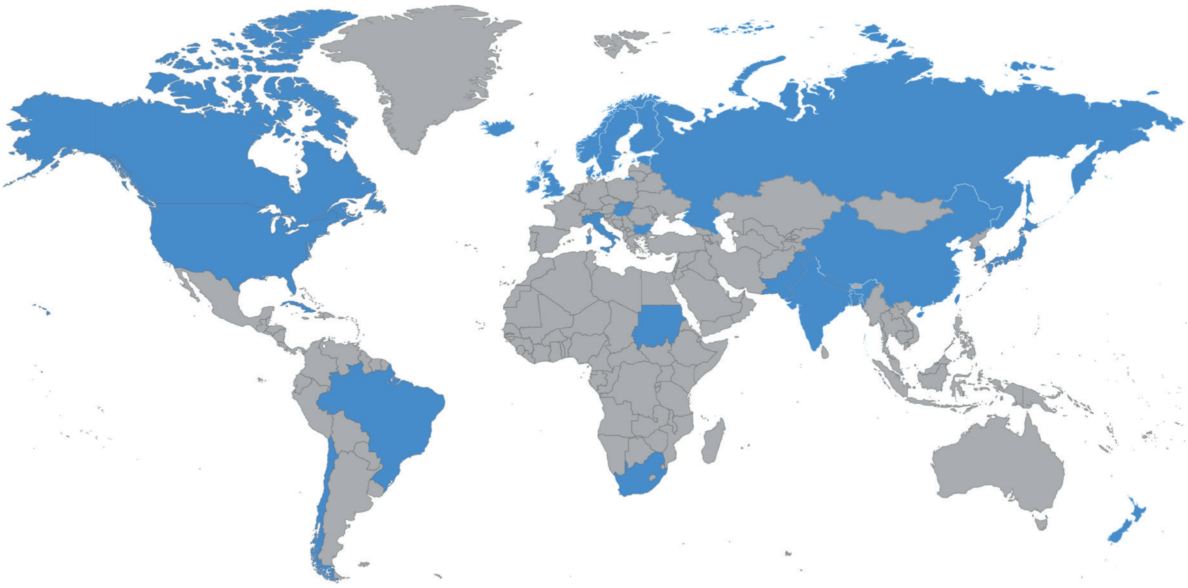
Jayasree Sengupta, PhD, is a former Professor and Chair, Physiology, at the All India Institute of Medical Sciences (AIIMS), New Delhi, India. Chaired annual courses on Assessment Methods for Learning Evaluation in Basic Medical Sciences for faculty members of physiology, anatomy, and biochemistry in a nationwide manner at AIIMS. Active in her leadership as Chair of an IUPS-supported and Indian Council of Medical Research (ICMR), Government of India funded Mentor-Mentee Programme for young scientists. With more than 130 research articles on embryo implantation, placentation, and endometriosis, she worked as the Co-Editor of the Journal of Reproductive Health and Medicine. She is now a member of the Governing Council of ICMR.

Susan M. Barman is the Co-Chair of the Board of the General Assembly of the International Union of Physiological Sciences.

Susan M. Barman, PhD, is a Professor, Department of Pharmacology and Toxicology, at Michigan State University. She has been very active in the leadership of the American Physiological Society, including serving as its 85th President. She has been a strong advocate of developing programs that promote the discipline of physiology and that encourage trainees to be actively engaged in the Society. In addition to being an author on nearly 100 research articles on neural control of the circulation, she is a co-author of Ganong's Review of Medical Physiology, which is read by medical students in many countries.

Henry Lovett is the Policy and Public Affairs Officer of The Physiological Society.

Henry Lovett, MChem MRes, holds degrees in chemistry from the University of Oxford and Imperial College London. He left the lab to pursue a career at the interface between science and politics, and has worked at key organisations in the science policy sector such as the Government Office for Science, and the Campaign for Science and Engineering. He now leads on policy development at The Physiological Society, specialising in the UK higher education and research landscape as well as physiology-specific topics.



The International Union of Physiological Sciences (IUPS) is the non-profit global umbrella organisation for physiology, representing and promoting the worldwide community of professional physiological scientists and educators. Since its founding in 1953, IUPS has aimed to facilitate initiatives that strengthen the discipline. IUPS is a scientific union member of the International Council for Science (ICSU) and is accredited with the World Health Organization (WHO). The Union is composed of 54 National Members, 10 Associate Members, 2 Affiliated Members, 5 Regional Members, and 5 Special Members.

The Physiological Society, founded in 1876, is the largest network of physiologists in Europe, bringing together over 3600 scientists from over 60 countries. Now a registered charity, The Society promotes physiology and supports those working in the field by organising world-class scientific meetings, offering grants for research, collaboration, and international travel, and by publishing the latest developments in its leading scientific journals. The Society also runs events for the general public on how physiology relates to everyday life, and for students who may be considering physiology as a career.

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PHYSIOLOGY
Current Trends and Future Challenges

Companion Essays

Physiology - Current Trends and Future Challenges

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The Progress of Physiological Sciences

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Running Head: Progress of physiological sciences

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Abstract

In the present paper, an attempt has been made to briefly describe how physiological sciences as a as a broad scientific discipline and a mother science with core and non-core sub-disciplines traversed through the path of integrative discourse since the European Renaissance till today's ventures at new higher levels of integration from 'gene to tissue to organism.'

Key words:

Integrative physiology, Logic of life, Quantitative biology

Introduction

Physiology is a branch of biology which studies all properties and functions of the living body, including mechanical, physical and biochemical. Physiology also intends to study how living body responds to external and internal stimuli, including exercise and stress, environmental conditions and disease in an integrated manner. Thus, physiology is essentially an integrative discourse towards understanding the life process in a given environment. The aim of this essay is to examine how physiological sciences progressed in time to the present state of Integrative Physiology taking up an interesting challenge of undertaking its movement from 'gene to tissue to organism.'

D'Arcy Thompson in the Introductory section of his *On Growth and Form* (37) writes:

> 'Of the chemistry of his day and generation, Kant declared that it was a science, but not Science - *eine Wissenschaft, aber nicht Wissenschaft* - for that the criterion of true science lay in its relation to mathematics...We need not wait for the full realisation of Kant's desire, to apply the natural sciences the principle which he laid down. Though chemistry fall short of its ultimate goal in mathematical mechanics, nevertheless physiology is vastly strengthened and enlarged by making use of the chemistry, and of the physics, of age. Little by little it draws nearer to our conception of a true science with each branch of physical science which it brings into relation with itself: with every physical law and mathematical theorem which it learns to take into its employ. Between the physiology of Haller, fine as it was, and that of Leibig, Helmholtz, Ludwig, Claude Bernard, there was all the difference in the world.'

Elsewhere he comments, '...the physiologists has long been eager, to invoke the aid of physical or mathematical sciences; and the reasons for this... lie deep, and are partly rooted in old tradition and partly in the diverse minds, and temperaments of men' (37). What 'old tradition' and which 'diverse minds' D'Arcy Thompson might have indicated in 1917, the year of the first publication of *On Growth and Form*? In the following sections, we shall discuss about the major coordinates in the journey of physiological sciences and physiologists, that gives shape to the present state of physiological sciences.

Kantian world view and Hegelian dialectics to analyse the history of progress

The idea that integrated gathering of knowledge and beliefs about material truth proceeds through the dialectics of 'abstraction - interrogation - investigation - concretisation' might have been perceived quite early by the human mind as indicated in many tales of ancient scripts from China and India. However, most historians believe that this was best expressed in form of the triad of 'thesis – antithesis – synthesis' in the deliberations by Immanuel Kant (1724-1804) and then it was expounded first by Johann Gottlieb Fichte (1762-1814) and later by Georg Wilhelm Friedrich Hegel (1770-1831). Hegelian dialectic movement from thesis to antithesis to synthesis is guided by three basic principles. First, anything and everything material is made out of opposing forces or sides, meaning there is always some element of contradiction – within or without or both – in a developing body. Second, quantitative changes lead to qualitative change, meaning gradual changes lead to leaps or jumps or turning points which may result in transformation. Thirdly, there is negation of the negation resulting in spiralling, not circular, movements in process. Thus, according to Hegelian dialectics, a thesis, because of the reaction from its action and process of development, falls into the negative of itself, and in the course gives rise to antithesis which contradicts or negates or challenges the thesis, and it is resolved by means of a synthesis (32). Thomas Kuhn, in his *The Structure of Scientific Revolutions*, has explained how such progressive process is associated with 'paradigm shift' in science (23). In fact, physiological sciences has experienced such paradigm shifts in its course of development over time by integrating first physics and chemistry, and then mathematics and systems analysis. In recent times, convergence of trajectories from ecological and evolutionary physiology, and more recently from molecular biology has resulted a new synthesis in approaching Integrative Physiology. In the following sections, brief stories of the major mile-stones in this journey path shall be discussed.

Jean Fernel - the first mover of comprehensive physiology

Jean François Fernel (1497?-1558) is probably the first Renaissance physiologist who attempted for the first time to effectively demonstrate how the elemental attributes of the body parts are woven into a whole that manifests all the temperaments, humours, powers and faculties of living organisms based on principles of deductive reasoning, causal analysis and physics (40). Fernel studied mathematics, philosophy, astronomy, anatomy and function of the human body with huge alacrity and made a serious attempt to give birth to the concept of comprehensive physiology in the womb of Hippocratic – Aristotelian – Galenic thesis and pushed hard to integrate the discourse of physiology with physical objective analysis, and to think physiology in integrative manner. Thus, he was the first to use the term 'physiology' in its modern scientific sense in 1542 which was the year of first publication of *Physiologia*, when 'physiologia' used to denote the study of nature or natural philosophy. Fernel was critical about illustrated anatomy based texts at the centre stage of contemporary medicine as he considered this shallow and lacked integrative principles of causation of bodily functions.

In his *Physiologia*, he reflected upon analytical approach, and settled on a 'top-down' method, which is recognized in today's physiological practice as well. He then described all the known anatomical parts and developed his idea of 'comprehensive physiology' of the human organism (33). Fernel's comment about five hundred years ago, 'Anatomy is to physiology as geography is to history; it describes the theatre of events' creates an awe in the mind even today (38).

Claude Bernard - the prime mover of modern Integrative Physiology

In the next century, Galileo Galilei (1564-1642) and his scientific methods using tools, observations and mathematics in one hand, and René Descartes (1596-1650) and his rationalism and anti-authority teachings on the other hand, played major role in the induction of scientific revolution of the 17th century which paved the path for new experimental integrative physiology best embodied in William Harvey (1578–1657) as discussed elsewhere (1). It took another one hundred and fifty years after Harvey, physiology being approached during this period in integrated manner involving quantitative mechanics, physics, chemistry and mathematics by Albrecht von Haller (1708-1777), Hermann von Helmholtz (1821-1894), and Carl Ludwig (1816-1895) towards the arrival of Claude Bernard (1813–1878) in the 19th century (17).

Claude Bernard propounded the concept that body systems function such manners as they do to maintain a constant internal environment, that is *milieu intérieur*. He emphasized that an organism is able to adjust itself to external physical and chemical variations by maintaining permanence of its *milieu intérieur* because of integrative control systems involving the cells, the organs and the organisms. Like Jean Fernel, Bernard was always attentive not to explain all his observations only by anatomy, since according to him, anatomy was to serve explanation of physiological complexity. Physiologists must start from studies of physiological phenomena to explain them in the whole organism and not try to explain a function from an organ (6).

In many ways, Bernard through his robust practice and theory paved the path of modern Integrative Physiology with emphasis on the physicochemical basis of various physiological phenomena. In this process, Bernard steadfastly fought against three basic antagonistic forces: (i) popular theory of vitalism, that is the whole living cell or organism is more than simple sum of its parts, and this holism of life is explained by action of a vital force which neutralizes the negative effects of physico-chemical forces in living organism, (ii) teleology (or teleonomy) based on attributions of 'providential destiny' on life processes making physiological processes mystic, and (iii) philosophy of pan-optimism. Thus, Claude Bernard had to fight against any philosophy and notion that had resulted in mystification of life. He believed that Science should always explain obscurity and complexity by clearer and simpler ideas and there is no place of vitalistic explanation in physiology (6). He insisted that physiologists must therefore seek the true foundation of animal physics and chemistry in the physical-chemical properties of the inner environment of the organisms. The life of an organism is simply the result of all its innermost workings (6).

Walter Cannon and Hans Seyle - Further movement of Integrative Physiology to form the basis of modern medicine

Bernardian notion of integrated physiology was closely followed by another great physiologist, Walter Bradford Cannon (1871–1945) in the 20th century. Bernard's theory addressed 'whys' of bodily processes by postulating that they help maintain a constant internal environment. Based on a series of magnificent experiments over almost three decades, Walter Cannon in fact examined the 'hows'. Cannon established the concept of 'homeostasis' in the theory of physiology, by which he referred to the stability of the inner sphere of the body. Both Bernard and Cannon postulated the actions of control systems operative at different levels and made the foundation of today's Integrative Physiology. Subsequently, physiological sciences expanded largely on Bernard-Cannon's kinetic model of negative feedback that explained regulation of monitored variables of the body at steady-state levels (16). In continuity of Cannon's model of 'Fight-or-Fright', Hans Selye (1907-1982) postulated around 1930s the modern concept of stress as a novel integrative physiological basis of medicine. According to Seyle's model, 'stress' reflects the difference between afferent information about conditions as sensed and the homeostatic set point for responding, and it may be conceptualized in terms of the error signal in a homeostatic negative feedback loop, with the integrated error signal as a measure of accumulated stress over time, resulting in what Seyle termed as 'heterostasis' (16,34). It is generally viewed that the efforts of Hans Seyle in the continuity of Walter Cannon's endeavour of theorizing physiological regulations was a serious historic attempt towards integrative scientific medicine involving multiple systems affecting the whole organism (16,34).

Emergence of ecological and evolutionary physiology

Around the same time, another tributary of physiological sciences began an interesting journey by blending of the traditions of comparative physiology and natural history. August Krogh's postulation, 'For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied' triggered a strong desire among the physiologists to undertake cross-disciplinary integration between animal physiology and the field of natural history (22). The former was progressing in physiological laboratories during the latter half of the 19th century and early 20th century. It has meanwhile developed a large and impressive body of data through rigorous protocol of experimental design and analysis on various physiological processes in different kinds of animals. The field of natural history, on the other hand, was already well-developed in the 19th century, and contributed a substantial knowledge base of animals, sometimes very unusual animals, and their habits under natural conditions in the field. The merger of these two areas resulted in experimental scientists undertaking research on non-traditional animals and referring the results of that research to the behaviour and functional responses of species under natural conditions. Animal ecological physiology began to assume a prominent place in modern Integrative Physiology since 1940's with the seminal contributions of George Bartholomew (1919-2006), Knut Schmidt-Nielsen (1915-2007) and many other investigators. Ecological physiology is concerned with the function and performance of organisms in their environment with a major objective to understand the underlying physiological, morphological, biochemical and molecular attributes of organisms with respect to the constraints imposed by the environment (5,12).

C.L. Prosser in his 1950 book on *Comparative Animal Physiology* delineated five broad objectives of ecological physiology (30):

> '(1) to describe the diverse ways which different kinds of animals meet their functional requirements; (2) to elucidate evolutionary relationships of animals by comparing physiological and biochemical characteristics; (3) to provide the physiological basis of ecology . . . ; (4) to call attention to animal preparations particularly suitable for demonstrating specific functions; and (5) to lead to broad biological generalizations arising from the use of kind of animal as one experimental variable.'

Garland and Carter (15) suggested that these broad objectives subsequently led to the notion of modern evolutionary physiology. Yet, attributing that thinking of evolution in physiology and vice versa only emerged with evolutionary physiology is factually not correct. A strong group of Russian physiologists, for example I. M. Sechenov (1829-1905), I.P. Pavlov (1849-1936), and N. E. Vvedenskii (1852-1922) reportedly contributed to this field long since. The term “evolutionary physiology” was probably coined by A. N. Severtsov in 1914, and the person most responsible for the creation of Russian evolutionary physiology was Leon Orbeli (1882-1958). In 1920s, Leon Orbeli devised the scientific method for studying evolutionary physiology, defined the main objectives, and outlined the direction in which it should develop. Many classical studies of comparative and environmental physiology interpreted patterns as the outcome of adaptive evolution. Moreover, physiologists have long exploited the results of evolution in choosing the most appropriate species for investigation of physiological problems, as well as, evolutionary analysis of the physiological impact of specific gene alleles. Evolutionary biologists such as Sewall Wright (1889-1988), Richard Goldschmidt (1878-1958), and Theodosius Dobzhansky (1900-1975) had major research foci on 'physiological genetics'. Physiology and Evolutionary Biology, nonetheless, remained separated from one another until 1970s (14).

Several seminal developments during 1960 to 1980 elicited a substantially increased constructive merger of evolutionary biology into the physiological sciences. In November 1961, Ernst Mayr in his paper “Cause and effect in biology" distinguished the notion of proximate causes from that of ultimate causes in biological effects (25). A proximate cause is an immediate, mechanical influence behind a trait, explaining how a trait in an organism is displayed. Ultimate causes are historically rooted explaining why an organism has one trait rather than another, often in terms of natural selection. Although the proximate-ultimate distinction had been mentioned as early as in 1938 by J. Baker (2), the provocative paper of Ernst Mayr (25) triggered an intent among a subset of functional physiologists and ecological physiologists to have a new look to the physiological explanation of function in the light of evolution. The expression 'in the light of evolution' although used by Julian Huxley in the 1950s (19), was later popularized by Theodosius Dobzhansky in his proverbial statement, "Nothing in biology makes sense except in the light of evolution" in his 1973 article bearing the same title (11).

One very significant step in the emergence of the field came from a workshop sponsored by the U.S. National Science Foundation, held in Washington, DC, in 1986, which resulted in an edited volume with the title, *New Directions in Ecological Physiology* (13). Pough then used the term "evolutionary physiology” to entitle a review in 1988 (29). Later, Diamond (10) and then Garland and Carter (15) codified the term - Evolutionary Physiology - to designate the emerging area of the integrative physiological sciences. In 1994, the U.S. National Science Foundation established a formal *Program in Ecological and Evolutionary Physiology*. There has been an impressive growth in this area of integrating physiological sciences since that time (14).

Present day status of physiology sciences

In a nutshell, the expansion of physiological sciences in the first half of the 20th century took place in the line of Bernard-Cannon’s approaches to integrative physiology based on physicochemical explanations and integrative modelling. August Krogh (22) had penned down the soul of this progress of physiological sciences succinctly in his paper, “The Progress of Physiology." Subsequently, in the second half of the 20th century the physiological sciences witnessed significant integrative confluences with ecology and evolutionary biology generating a promise of 'developing a quantitative understanding of biological design' (10). Further, two parallel lines of development, namely (i) physicochemical theories of self-organisation that arose from Lotka's theoretical and Bray-Belousov's experimental work on chemical oscillations and then Belousov-Zhabotinski's model of chemical oscillator on one side, and (ii) biological theories of self-organisation evolved in the womb of artificial intelligence and cybernetics on the other side, culminated in the 1970s giving rise to a paradigmatic development (31). The target of quantitative understanding of biological design and its pattern analysis became even more palpable by the emergence of application of systems analysis to biological and physiological problems. The credit of applicability of systems analysis to biological and physiological problems is generally attributed to Norbert Wiener (1894-1964).

Wiener writes in his *Cybernatics, or Control and Communication in the Animal and the Machine* published in 1948 (41):

> '...the present time is the age of communication and control...whether in the metal or in the flesh...and its cardinal notions are those of message, amount of disturbance or "noise" - a term taken over from the telephone engineer - quantity of information, coding technique, and so on.'

Wiener's biocybernetics plays a dominant role in today's theoretical biology by integrating different levels of information to explain how biological systems function. Wiener's theory of feedback regulation and its application for explanation of the mechanisms of homeostasis is considered as singularly most important contribution of cybernetics to integrative physiology and medicine and taken as a benchmark of the beginning of post-modern phase of physiological sciences (42). The entire scenario is well testified by John Brobeck when he writes in *Physiological Controls and Regulations* published in 1965 on the hundredth anniversary of Claude Barnard's *L'Introduction à l'étude de la Médecine Expérimentale* published in 1865 (9):

> 'One can now say that physiology has its foundations in three – not just two – fundamental sciences. The first is physics and the second is chemistry, both of which began to be applied to biological problems in the nineteenth century. The third is systems analysis based upon communications theory; its usefulness is only just beginning to be appreciated.'

The advent of molecular biology techniques and effective applications of control and communication engineering to molecular bioinformatics during the decades following 1980s, promptly resulted in a preoccupation with the problems and challenges inherent in these techniques, sometimes at the expense of the original perspectives and concepts. Many new mechanisms that have been discovered at the molecular level, as well as, their economical exploitation have contributed to a climate of reductionism. Among the scientific community, it created a dominating bias for molecular biology and a perception that the discipline of Physiology is in crisis (3,8,17). The root of such perception stemmed from the confusion between the biological questions to be solved and the methods/technologies to be applied. The study of control mechanisms, in fact, can be applied on functions at any level - subcellular, cellular, and organ, and reaches its highest level of complexity with the functioning of the body as a whole and its interaction with the external environment. This involves the determination of the interaction between genetic and environmental factors and the resulting integrated body adaptation. In the pursuit of these questions, it is apparent that any appropriate combination of techniques are to be used for examining biological information at any organizational level. Despite the undeniable and spectacular successes of molecular biology, the need for an integrative perspective has become increasingly evident. This is particularly true in many clinical cases of gene and drug therapies that failed despite promising results from defined animal models (39). In such a dominion of hiatus in understanding of physiology which would attempt to place the descriptive facts and proximate mechanisms of molecular and cellular biology into quantitative context, Integrative Physiology as a discipline comes with promises of providing significant inputs (28,39).

On the occasion of the 1993 Congress of the International Union of Physiological Sciences (IUPS) held in Glasgow, Charles Boyd and Denis Noble edited an anthology bearing a provocative title, *The Logic of Life - The Challenge of Integrative Physiology*. The Preface of the book starts with a reference to a statement given by Sir James Black, a 1988 Nobel laureate pharmacologist, about his views on the future of the health of science that it would be 'the progressive triumph of physiology over molecular biology' (26). Sir Black (7) writes in the Foreword Section of the same book:

> 'The repertoire of chemical messengers is already extensive - mind-boggling in fact - because we currently have no conceptual framework to integrate them. So the biochemical properties and components for physiological control by convergent amplification are known to exist. The point here is that trying to modify such systems pharmacologically will present us with great problems. Hopes of realizing the optimistic forecasts about the benefits that molecular biology will bring to pharmacology are likely, I believe, to be circumscribed by the state of physiological knowledge, models, and concepts.'

Meanwhile, with the completion of the Human Genome Project and with the advent of the '-omics' technologies, systems biology emerged with an aim to move beyond the traditional reductionist molecular approach towards a more holistic approach by studying networks and interactions between individual components of networks. However, to date systems biology has been applied to relatively simple systems, and has not been applied to studies of controls and communications in complex organisms, a field that has traditionally been the domain of physiological sciences. Clearly, physiology and systems biology share the goal of understanding the integrated function of complex systems from the level of genes to the whole organism. It appears imperative that physiologists embrace the cornerstones of researches in functional genomics, genetics, different animal model organisms, computational biology, and interdisciplinary research efforts and they must move away from naive reductionism and reemphasize the central importance of integration and synthesis in their research and teaching of physiological sciences. These issues have recently been discussed in several articles (18,21,24,35).

In today's physiological sciences, all of the sciences that include anatomy, biology, biochemistry, biomechanics, chemistry, mathematics, physics, physiology and statistics converge contributing to measure the response of biological systems. This issue has been succinctly summarized in a recent document titled, *Health of Physiology* (36) published by The Physiological Society, U.K. (Figure 1). Thus, present day physiology is multi-disciplinary in approach towards deciphering physiological processes differentiating at multiple levels throughout wide range of scales and their integration (4,18,21,24,35).This requires knowledge of interrelationship among macromolecules, cells, tissues, organs and systems in the body, and also the position and ability to utilize advanced technologies in numerical data development and their analysis. Physiology today - according to the IUPS - intends to encompass the study of the functions and integrative processes of life at all levels of structural complexity between the molecular level and that of the whole organism. It includes all organisms, and frames function in evolutionary, environmental, ecological and behavioural contexts. It embraces a cross-disciplinary approach to modern science, through which physiologists aim to achieve translation of this knowledge into the health of humans, animals and ecosystems (20). This constitutes the major mission of IUPS to be fulfilled with the help of eighty associated bodies all over the world (27).

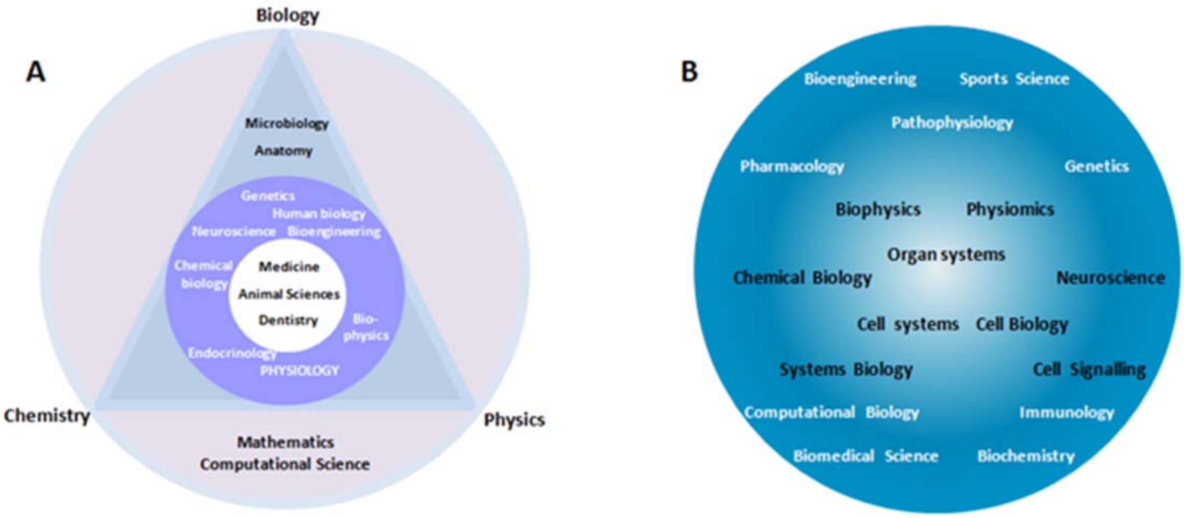

Figure 1. Defining physiology. Physiology as a broad scientific discipline spans from the molecular and cellular level to the organ, tissue and whole system levels, and provides a bridge between the basic sciences and the applied medical sciences (A). Physiology is a mother science with core and non-core sub-disciplines. Areas such as cell systems and systems physiology form the core of the discipline, while bioengineering and sports science are examples of related disciplines overlapping with physiology at its perimeter (B). Based on Health of Physiology (36).

Conclusion

Historically, physiological sciences traversed the path of integrative discourse since the European Renaissance with a mission to understand the life process in a given environment. With Bernard-Cannon's experimental legacy along with increasing knowledge in the domain of ecological and evolutionary physiology on one side, and newer genomic, cellular, molecular and computational tools on the other side, today's Physiology - as it appears now - can venture at new higher levels of integration and that a genuine, quantitative theory of biology may eventually be developed though future research in Integrative Physiology. Today's Physiologists cherish to realize their innate longing that physiology is to understand the logic of life.

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Physiology of the Musculoskeletal System and its Control: Topics of Current Interest and Trends in Publication

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Running Head: Publication trends in the physiology of movement

Abstract

In the terminology of the International Union of Physiological Sciences (IUPS), 'locomotion' is a shorthand for the physiology of the musculoskeletal system and its control. The tissues and systems included are the skeleton, the skeletal muscles and tendons, and the components of the nervous system that organize and control movements of parts of the body or the whole body. This essay on the current state of research into the physiology of 'locomotion' has two sections. First, there is a brief overview of topics that are of current interest in the area. These topics were identified through search of highly cited publications over the past 5 years. Second, some trends in publication of original research articles about the tissues and systems that subserve movement are reported. Overall, the rate of publication on these research subjects has increased by more than half over the last ten years. As the number of these publications designated as 'physiology' has stayed constant, the proportional contribution of 'physiology' has decreased. While there are exciting recent findings on the physiology of the musculoskeletal system and its control, and challenges in understanding remain, physiology research in these areas is holding steady rather than growing.

Keywords:

Locomotion, Physiology, Muscle, Bone, Motor System

Introduction

While locomotion, defined as 'movement from one place to another', may seem a relatively circumscribed area of physiology, the IUPS Commission title, Locomotion, can be thought of as shorthand for the musculoskeletal system and its control. Hence, the tissues and systems that should be considered include the skeleton (bones, cartilage and ligaments), the skeletal muscles and tendons, the neural elements that directly link to the muscles (motoneurons and muscle afferents), the spinal networks that subserve rhythmic movements plus all components of the nervous system that organize and control movements of parts of the body or the whole body. The parts of the nervous system that contribute to movement control include, but are not limited to, the motor areas of the cortex, basal ganglia, thalamus, brainstem, cerebellum and spinal cord. Moreover, most of the sensory systems, including proprioception, vestibular sensation, touch, pain, vision, and hearing link to motor output through various dedicated pathways, which do not require the sensory signals to reach conscious perception.

This essay will briefly consider the current topics of interest to researchers within the area of the musculoskeletal system and its control. This overview has been compiled based on highly cited articles that were published in the last 5 years. The essay will then examine the trajectory of publications that address the musculoskeletal system and its control and are designated to be in the research area of physiology.

Current topics of interest

The physiology of the musculoskeletal system and its control can be divided into several notional areas: 1) the peripheral substrate of the system and its maintenance, i.e. bone homeostasis and remodeling, and muscle mass maintenance, atrophy and hypertrophy; 2) musculoskeletal tissues as endocrine organs, i.e. secretion of factors that influence more distant organs; 3) the effects of exercise in health and disease; 4) the contractile function of muscle; 5) the control of muscle by the nervous system, i.e. spinal and brainstem networks, cerebellum, basal ganglia, cortical areas and the interactions between them; 6) activity-dependent plasticity of the nervous system related to the control of muscles, i.e. changes in the nervous system with motor learning or training. Examination of highly cited papers published over the past five years points out some areas that have been of particular interest (Fig. 1).

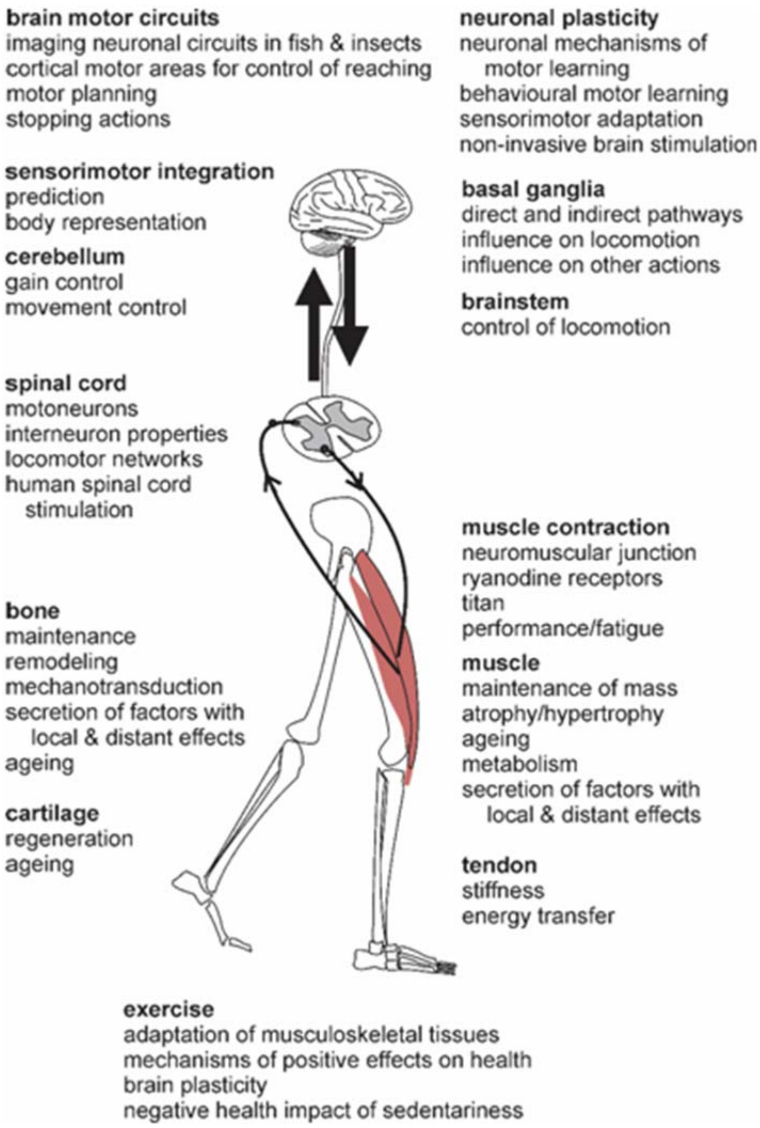

Figure 1. Current topics of interest in the musculoskeletal system and its control.

For bone, the osteocyte has come to the fore with interest in its mechanism for response to mechanical perturbations, the factors it releases and their local and more distant effects (8,15,27,47). These areas link to understanding bone homeostasis and remodeling with local signals from bone cells, interactions with muscle, and hormonal influences from more distant organs. Moreover, the influence of factors released from bone (e.g. FGF23 and osteocalcin, sclerostin) on skeletal muscle and cartilage, and other organs including the kidney and heart has begun to be recognised (15,49).

For muscle, the maintenance of muscle mass, atrophy with disuse and hypertrophy with exercise have proved of interest at levels from intra and extracellular signaling pathways through to the influence of specific nutrition and exercise regimens on protein metabolism and performance (4,9,12,22,39). Ageing muscle and why it becomes impaired has also drawn attention (31, 45). The possibility of reversing this decline by exposure to a young environment is particularly intriguing (13, 43). Similar to bone, the factors released by muscle and their effects on distant tissues are becoming better understood, including interactions with adipose tissue (34). However, there is controversy over the measurement of some secreted substances (e.g. irisin; 3, 25).

Exercise with its mechanical and metabolic effects on muscle and bone is paramount for the maintenance of both tissues (18, 22, 49). Moreover, the endocrine roles of the tissues, i.e. their secretion of osteokines and myokines, and the participation of muscle in glucose metabolism depend on exercise (33, 34). Hence, how exercise maintains health and ameliorates disease is of major interest at levels from the signaling of released factors and their specific actions through to what specific exercise is best for human health (e.g. 22, 35).

Of particular current interest is how much or what kind of exercise can counter the negative health impacts of prolonged sitting (5, 16).

While aspects of muscle contraction are well understood, new imaging techniques have allowed the ryanodine receptor, and hence its molecular mechanisms and interactions, to be described in more detail (e.g. 17, 48). A new role for titin has also been proposed and this may start to fill some of the holes in our understanding of the mechanisms of eccentric (lengthening) muscle contraction (41).

There have been new findings and advances in understanding of the control of movement at all levels of the nervous system. The use of rabies virus to trace pathways antidromically, gene manipulation, optogenetic activation of specific cell types and calcium imaging in vivo has given unprecedented opportunities to identify motor networks and examine the contributions of different cells. In the spinal cord, the networks that underlie rhythm generation are being identified (e.g. 26). Amongst other findings, for which the functional consequences are not yet clear, is the identification of gap junctions in mixed synapses associated with afferent input to the motoneurons in adult rats , while in zebrafish, locomotor rhythm is influenced by retrograde control of some premotoneurons via gap junctions from motoneurons (7,44).

One example of the use of optogenetics comes from the demonstration of the effects of specific cell types in the mesencephalic locomotor region (MLR) in the brainstem on locomotion; glutamatergic neurons start and drive locomotion, cholinergic neurons modulate locomotion and GABAergic neurons stop it. The optogenetic investigation was combined with electrophysiology to tease out the influence of the basal ganglia on the MLR neurones

(38). More widely, the way in which the direct and indirect basal ganglia pathways control movements other than locomotion is a topic of current interest, as is the role of the cerebellum in movement control and the interaction of the cerebellum and basal ganglia (10,11,14,21). Similar techniques can be used in cortical areas to perturb specific areas to identify their contribution to motor planning and movement (28), or to investigate how motor activity alters responses to sensory stimuli (20,29).

The capacity for integration of knowledge from neurons through to behavior is increasing. It is now possible to examine the integrated working of motor circuits of the whole brain of larval zebrafish through optical calcium imaging of neural activity (2). Similar techniques are being extended to mice and non-human primates where optical imaging will not allow a view of the whole brain but will allow the activity of populations of neurons to be measured simultaneously (32). Optical imaging has also allowed longitudinal studies that were not possible with electrophysiological recordings. Imaging of specific neurons over weeks has given new insights into the changes of dendritic structure and neuronal activity that occur during the process of motor learning (19, 24).

Motor learning in humans is also a topic of strong interest, with functional magnetic resonance imaging used to identify changes in functional connectivity between brain circuits over time. In particular, integration between visual and motor areas decreased, and other areas disengaged, as a visually-guided learned motor sequence became more automatic (6). Other areas of recent interest range from how movements are stopped to how prediction of sensations produced by movements allows better perception and better performance. Functional imaging, tractography, EEG analysis and cortical recording have all been employed to examine the interactions between inferior frontal gyrus, pre-supplementary motor area and subcortical nuclei to delineate inhibitory circuits (36, 46). However, measures of performance also continue to provide insight into physiological processes (e.g. planned movements can be stopped up to ~200 ms prior to the movement initiation; 40).

The goal of understanding the selection, production and adaptation of motor behaviours is coming closer, but the challenge remains to link insights at a neuronal level to changes at the level of human performance. For human physiology, measurement of brain activity is limited to non-invasive techniques and restricted recordings in patient populations. Therefore, neuronal models are needed to make predictions that can then be tested through non-invasive recording or stimulation techniques, or through performance of perceptual or motor tasks (42). Currently, modeling of human cortical activity is making progress with the practical aim to translate brain activity into machine commands that can control robotic prostheses or bypass the spinal cord to produce muscle contraction through electrical stimulation (1, 23).

Overall, there are interesting new findings on the homeostasis of the musculoskeletal system, its links to the endocrine system and the role of exercise in health and disease. Progress is also being made in understanding the neural and muscular mechanisms underpinning the primary function of the musculoskeletal system, i.e. to move the body or parts of the body.

Publications related to the musculoskeletal system and its control over the past 3 decades

One way to describe the state of physiological research into the musculoskeletal system and its control is through the number of research articles published in the area. Table 1 shows publication numbers from searches through the Web of Science performed with simple search terms relevant to musculoskeletal control and confined to research articles. While the search terms will by no means capture all publications in the area, they should give a reasonable sample. Publication numbers listed for 'all terms' were derived through a combined search and count each publication once. As search terms were not mutually exclusive, publications may be represented under more than one topic. Of ~1.26 million articles published since 1900 and relevant to the selected topics, ~63 thousand (5%) are identified to be in the research area of physiology. These 63 thousand 'locomotion' physiology papers make up ~14.5% of the total 430 thousand papers with the subject area physiology.

Table 1: Total number of publications indexed in Web of Science for the listed 'locomotion' topics and those identified by the research area 'physiology'

	Total Pubs (thousands)	Physiology Total Pubs (thousands)	Physiology (% total)
bone	527.4	6.0	1.1%
cartilage	67.8	0.8	1.2%
ligament	53.5	0.7	1.3%
skeletal muscle	142.0	24.2	17.0%
tendon	45.4	1.4	3.2%
motor unit	4.7	1.3	27.1%
motoneuron	28.6	3.6	12.7%
motor nervous system	18.0	1.2	6.9%
locomotion	33.7	2.5	7.4%
walking/gait	129.3	3.3	2.6%
voluntary movement	8.8	1.2	13.6%
exercise	250.4	28.1	11.2%
motor control	94.6	5.2	5.5%
all terms	***1262***	***63.1***	***5.0%***

The total number of publications for each topic can be compared with those identified as physiology. Table 1 emphasizes that a large proportion of physiology publications in 'locomotion' address the topics of bone, skeletal muscle and/or exercise. Also of note is that the 6000 publications on bone in the area of physiology account for a small proportion of the total publications on this topic. That is, papers on bone contribute >9% of the physiology papers but physiology contributes only 1.1% of the bone papers. By contrast, physiology contributes ~17% of skeletal muscle papers and ~11% of exercise papers.

Trajectory of publication over the past three decades

Overall, the numbers of 'locomotion' publications identified as physiology have risen across the past three decades. Of the 63 thousand publications, some 25 thousand have been published in the last ten years (2007-2016) compared with 19.5 thousand in the previous decade (1997-2006) and ~19 thousand prior to 1997. Table 2 breaks down the total by topic and shows that 28-49% of all papers in each 'locomotion' topic were published in the most recent decade. Papers on exercise (48%), skeletal muscle (35%) and bone (12%) continue to

Table 2: Number of 'physiology' publications indexed in Web of Science for the listed 'locomotion' topics from 1987-2016. Percentages are of the total number of 'physiology' publications in each topic (see Table 1).

	Physiology Publications (hundreds)			% Total Physiology Publications		
	1987-1996	1997-2006	2007-2016	1987-1996	1997-2006	2007-2016
bone	7.3	14.1	29.6	12.1%	23.3%	49.0%
cartilage	1.2	2.3	3.8	14.0%	27.0%	45.4%
ligament	0.7	1.9	3.9	10.3%	28.4%	57.2%
skeletal muscle	47.6	85.0	88.0	19.7%	35.1%	36.4%
tendon	1.7	4.6	6.9	11.6%	32.1%	47.8%
motor unit	2.2	4.3	5.4	17.5%	34.1%	42.6%
motoneuron	8.8	13.0	10.3	24.1%	35.7%	28.4%
motor nervous system	2.0	4.8	5.5	15.8%	38.2%	44.4%
locomotion	4.7	9.3	9.9	18.7%	36.8%	39.2%
walking /gait	3.7	9.1	18.7	11.0%	27.2%	55.8%
voluntary movement	2.0	4.4	5.2	16.8%	36.7%	43.5%
exercise	49.1	84.4	120.1	17.4%	30.0%	42.7%
motor control	7.9	18.2	25.5	15.1%	34.8%	48.5%

provide high proportions of the physiology papers. Together, locomotion, walking and gait provide 11% of publications.

Remarkably, total publications in many of these topics have increased at an even faster rate, so that the last ten years have seen the publication of 40-60% of total research articles. Therefore, despite the increase in physiology publications in 'locomotion', the greater rise overall has produced a slow decline in the percentage of publications attributed to physiology from 6.7% (1987-1996) to 5.3% (1997-2006) to 3.9% (2007-2016; see Fig. 2). Physiology has held reasonably steady for some 'locomotion' topics (bone, ligament, motor unit) but has fallen for skeletal muscle and exercise, which comprise the bulk of physiology papers.

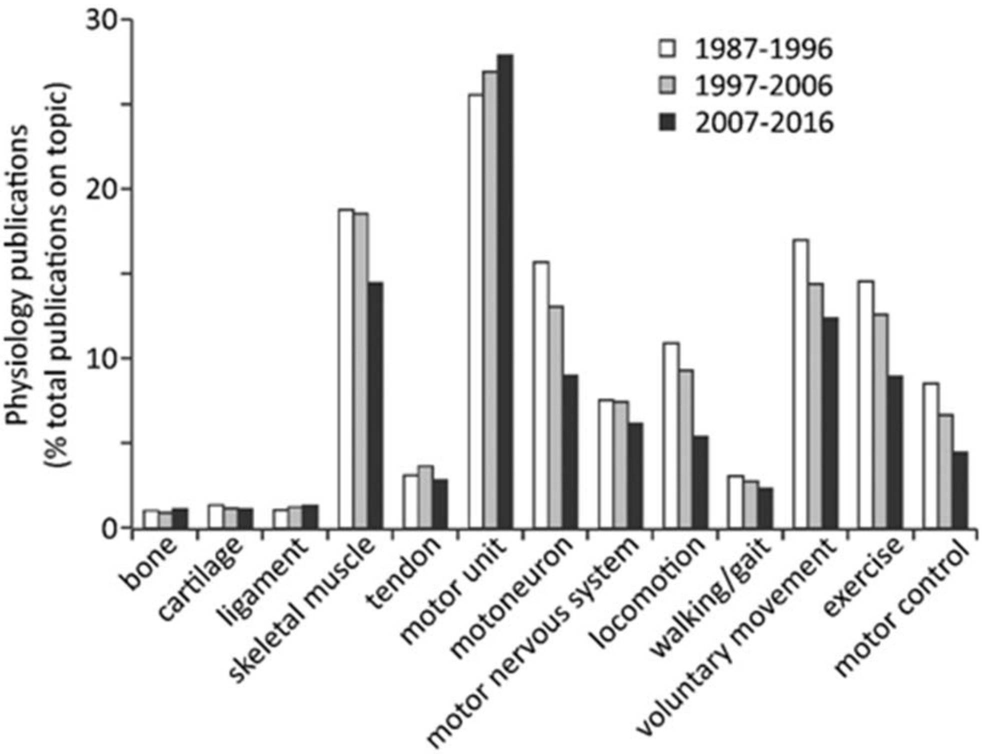

Figure 2. Web of Science publications designated to be in the research area 'physiology' for the searched 'locomotion' topics. Number of publications per decade is displayed as a percentage of all publications on the topics. This has decreased for most topic areas.

Surprisingly, other physiology papers are increasing less quickly than those on 'locomotion' topics with only 23% published in the last 10 years. Hence, the proportion of physiology papers identified as 'locomotion' topics has steadily increased from ~14% (1987-1996) to ~22% (1997-2006) to ~25% (2007-2016).

With the apparent relative decline in physiological research, what areas dominate in research into the musculoskeletal system and its control? For the last ten years, neurosciences/ neurology is the research area with the highest representation (10.8%) in the chosen 'locomotion' topics. However, this area has not risen substantially over the past 3 decades. Areas in engineering and technology (Engineering, Science technology other topics, Material science) all show large increases. Summed together, these technology areas have increased from 6% to 9% to 16% across the decades. The human oriented fields of Sport Sciences and Orthopedics show small increases (<1% per decade), as does Cell Biology.

Trajectory of publication over the past ten years

Within the past decade the number of publications per year on 'locomotion' topics has risen by >50%. The numbers of physiology publications has remained steady whereas other research areas have increasing numbers of publications (Fig. 3). Therefore, physiology has declined in its representation from 4.8% to 3.2% of 'locomotion' topic papers from 2007-08 to 2015-16. The most dramatic increases in papers are in Science Technology Other (1.6% to 6.0%) and Research Experimental Medicine (2.8% to 4.1%). For areas such as Neuroscience, Orthopedics and Sport Sciences increases in publication numbers of 26-44% were not sufficient to maintain a steady percentage of the total publications in 'locomotion' topics.

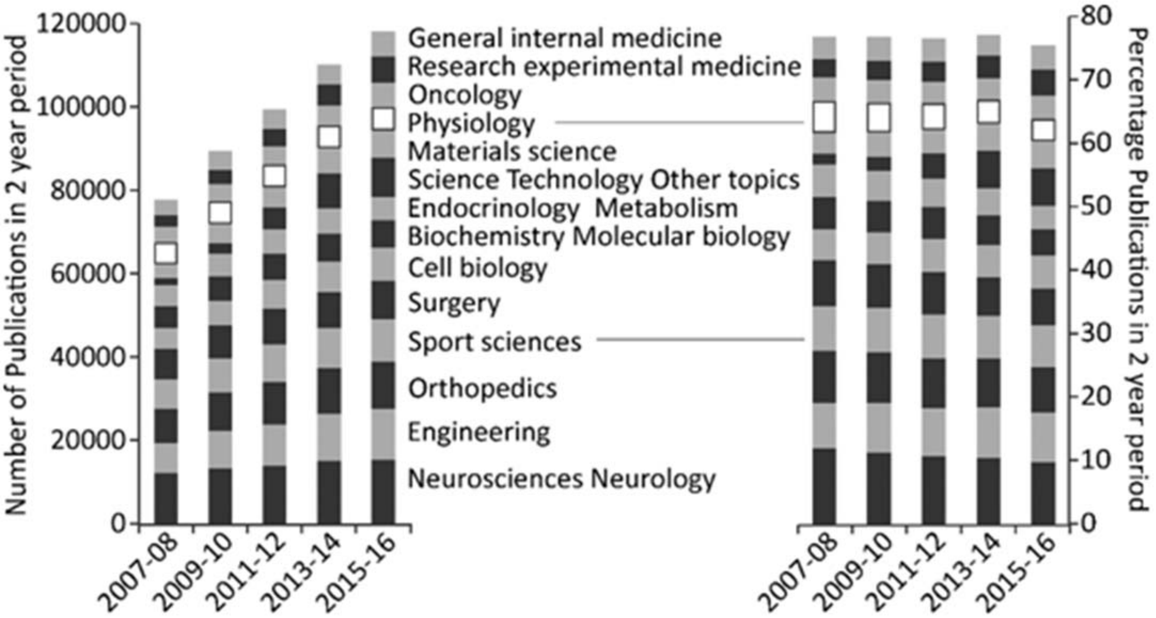

Figure 3. Number of publications on 'locomotion' topics from different research areas (Web of Science) in 2 year periods from 2007-2016. The top 14 research areas are included. The graph on the left shows the number of publications in each research area. The graph on the right shows the same data as percentages. Note that 'physiology' publications (white) remain steady in number but decrease as percentage of the total.

Skeletal muscle and exercise are two topics where physiology accounts for a relatively high percentage of publications. For the skeletal muscle topic, physiology publications per year declined over the past decade from 990 in 2007 to 838 in 2016. In contrast, total publications in the area increased by ~30%. Hence, the percentage of physiology publications fell from ~18% in 2007-08 to ~12% in 2015-16. For exercise, physiology publications rose by 21% but total publications rose by 83%. Thus, this topic also shows a drop in the percentage of physiology publications across the decade from ~11% to ~7.5%. Indeed, a relative reduction in the prominence of physiology across the past decade is a common feature across all the topics searched.

What does the decrease in the percentage of published papers identified as physiology mean?

For Web of Science, the research areas of articles are derived from the journals in which the articles are published. That is, each journal is designated to belong to one or more research areas. For physiology, 87 journals are currently designated as 'physiology'. Surprisingly, 'locomotion' articles in the subject area of physiology have been published in 163 sources in the past decade. It is not clear whether this reflects changes in journal categorization over the decade or whether articles from sources other than journals (e.g. books/ book series) are included. Nevertheless, for 2-year periods over the decade, the number of relevant sources varied between 83 and 111 with no consistent trend over time. However, closer examination of article numbers in each journal shows decreasing publication numbers in some established journals such as the Journal of Physiology, the Journal of Applied Physiology, and the American Journals of Physiology with increasing numbers in other journals, such as Frontiers in Physiology, Cellular Physiology and Biochemistry, and International Journal of Sports Physiology and Performance. The European Journal of Applied Physiology, Applied Physiology Nutrition and Metabolism (previously the Canadian Journal of Applied Physiology) and the Journal of Neurophysiology have held relatively steady. For the journals that are publishing fewer 'locomotion' articles, this decrease appears to be an overall decrease in articles published rather than a specific decline in the topic areas.

The mix of journals in which the top 25 authors (by number of publications in the area) publish has broadened between 2007-08 and 2015-16. In each period, the top 25 authors published 265 articles. In 2007-08 >90% of the publications were in 11 journals and in 2015-16 in 17 journals. The most obvious change echoes the trends for all authors. There is a drop in the share of publications in the Journal of Applied Physiology (26 to 12%) and Journal of

Physiology (18 to 11%) with the Journal of Biological Regulators and Homeostatic Agents (established 2006) rising from 0 to 9% and Cellular Physiology and Biochemistry (est. 1991) from 0 to 4%. The open access general physiology journals, Frontiers in Physiology (est. 2007) and Physiological Reports (est. 2013), have also each increased from 0 to 3%.

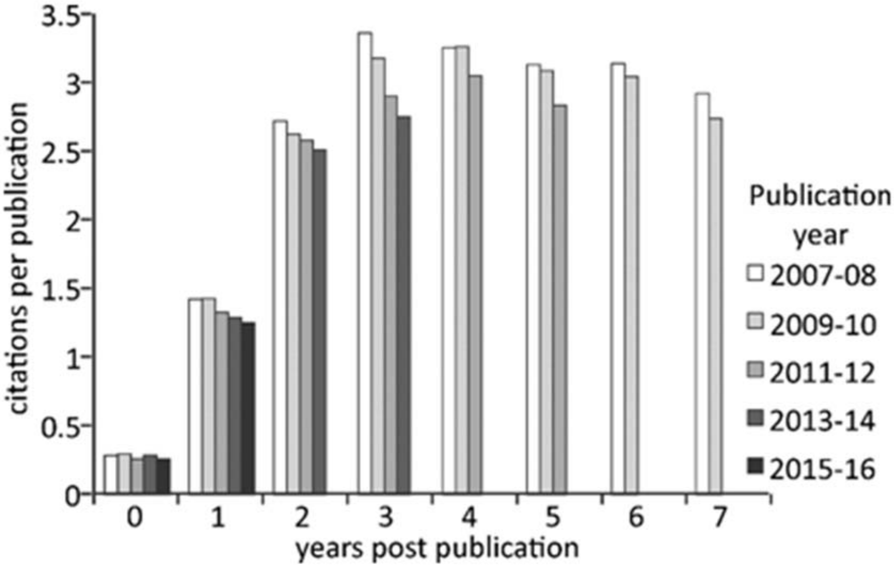

Figure 4. Citations per year per publications for 'physiology' publications published in 2-year periods from 2007-2016. Each 2-year period is represented by a shaded column. Note that year 0 goes from 2007 for 2007-08 publications (white columns) through to 2015 for 2015-16 publications (black columns). Of note is that for the same number of years post-publication, citations are gradually decreasing for more recent publications.

A particularly worrying trend is that more recent 'locomotion' physiology publications also appear to be gathering fewer citations. For example, articles published in 2007-2008 were cited an average of 2.7 times in 2009 and 3.3 times in 2010. By contrast, articles published in 2013-2014 were cited 2.5 times in 2015 and 2.7 times in 2016. Moreover, this decrease seems to be consistent across publication years (see Fig. 4). When 'locomotion' publications identified as sport sciences are analyzed in the same way, there is not a similar consistent fall in citations. Articles published in 2007-2008 were cited 2.0 and 2.8 times in 2009 and 2010, respectively, and articles published in 2013-2014 were cited 2.1 and 2.5 times in 2015 and 2016.

It is difficult to identify what underlies the plateau in publications in the physiology of the musculoskeletal system over the last decade, and the apparent drop in citation rates is even more difficult to explain. The number of physiology journals is stable and this could underlie the stable number of publications attributed to physiology. However, other areas have seen increases in publications without increases in journal numbers.

Data from the National Institutes of Health (NIH; 30) show two trends in funding over the past decade for physiology research (identified by the medical school department from which applications originate). First, the number of applications decreased by ~10% from 2007 to subsequent years and second, the percentage of applications funded also decreased. Together, this means that ~20% fewer physiology grants were funded in 2015-16 compared to 2007-08. That is, ~200 per year compared to ~250 per year (Fig. 5). By comparison, neurosciences

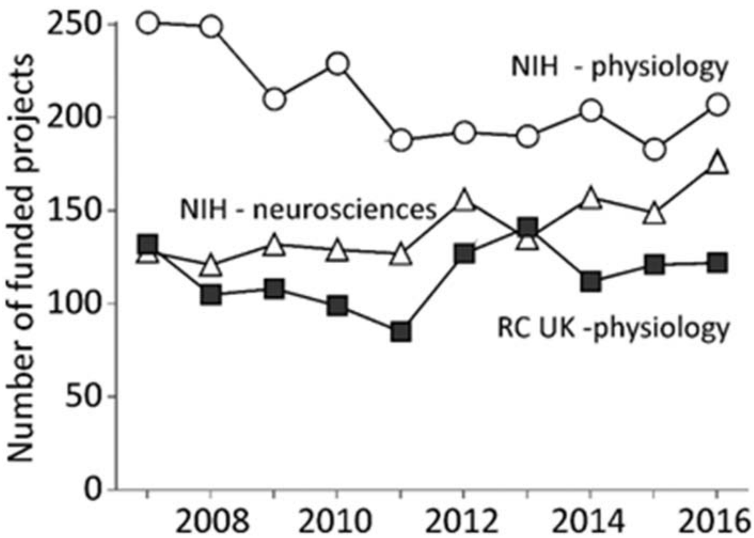

Figure 5. Number of research grants funded each year (2007-2016) by National Institutes of Health (NIH) and Research Councils UK (RC UK). NIH grants were identified by the medical school department from which applications originated. Physiology (white circles) and neurosciences (white triangles) are graphed. RC UK grants were identified by the search term 'physiology'.

applications have increased by ~50% across the decade with funded grants increasing by ~38%, although the number funded in 2016 (176) remains lower than for physiology (207).

For the UK, data from Research Councils UK (37) show that research grants identified by the search term "physiology" decreased from 132 in 2007 to 85 in 2011 but then recovered over the past 5 years to 122 in 2016. Over the same time, total research grant numbers also fell from 2007-11 and then partially recovered, so that physiology grants have become a slightly higher percentage of the total (2.9% in 2007-08 to 3.8% in 2015-16). Thus, based on the number of funded research grants, the U.S. and U.K. data suggest that physiology funding started at a high ~ten years ago, went through a particularly bad period and has started to recover over the last 2-4 years.

Finally, what of falling citations? This essay began with a brief overview of the field based on highly cited papers from the past 5 years. These papers were identified by Web of Science as "highly cited" or "hot", but were not selected on their automatic identification as physiology papers. Rather, they were selected based on my personal opinion that they were "physiology" with subject matter relevant to the musculoskeletal system and its control. From this idiosyncratic selection of ~120 papers only 10% would be identified as physiology from their publication source. Some 20% of the publications came from generalist journals, while the others were from specialist journals. This suggests that many well-cited papers that could be classified as physiology are missed in the wholesale assignment of journals to research areas.

Difficulty in identifying research as physiology is not necessarily a problem for progress in understanding 'locomotion' or the musculoskeletal system and its control, as it is the substance of research that is of interest to scientists rather than the way it is categorized. However, it may mean that the discipline of physiology may be undervalued.

Conclusion

It is an exciting time for the musculoskeletal system. We are starting to understand how factors released by the musculoskeletal tissues underlie the benefits of exercise across many organs and also how these molecules are linked to ageing and disease both of musculoskeletal tissues and throughout the body. Advances in neuronal imaging and optogenetic techniques are putting together the neuronal circuitry for movements from locomotion to reach and grasp. While many details remain unknown in each area, large challenges also remain in translation of findings from cell and animal models to human health and finally prevention or amelioration of human disease.

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The Post-Genomic Cardiovascular/Respiratory Physiology Will Go More Diverse but Necessitate Multi-levels of Integration based on New Technological Innovations

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Running Head: Post-genomic cardiovascular/respiratory physiology.

Abbreviations: ASC: apoptosis-associated speck-like protein containing a CARD

NLPR3: NOD-like receptor family, pyrin domain-containing-3

Abstract

After the complete sequencing of whole human genome, vigorous efforts have been devoted to deciphering the enigma of life and disease from a viewpoint of gene- or molecule-based functionalities. As the consequence, new and diverse knowledge is being deposited at an unprecedently rapid pace, culminating in formation of intractably huge databases. The cardiovascular/respiratory physiology is not an exception of this trend as seen in the major strategic visions for bioscience of many leading research institutions in front-runner countries. However, such flood of information simultaneously necessitates, in addition to enormous power of super-computation, new optimal concepts/logics and methodologies/technologies whereby to integrate the data accumulated at multiple functional levels from molecules to whole body. In particular, the tissue/organ-level theory and methodology seem most seriously lacking. This short essay attempts to overview what has been achieved so far in our field in last one and half decades, and to provide possible future directions to go, which will probably rely on innovations in intravital imaging modalities, development of new tissue/organ engineering techniques or bio-fabrications, and active utilization of systems biology approaches.

Key words:

Genome-based Medicine, Tissue/Organ Logics, Intravital Imaging, Bio-fabrication, Systems Biology

Current Research Status

Post-genomic study prevails in cardiovascular/respiratory physiology and medicine

The basic research of cardiovascular (CV) and respiratory (RS) medicine in the post-genomic era, like in the other fields of bioscience, has focused on elucidating how genomic information is translated into organismal functions, individual behaviors and diseases, by combing the molecular biological methods with the phenotyping or functional analyses of transgenic animals and animal disease models. Consequently, huge databases cataloging the linkage of genes to cellular-to-whole body functions and vulnerabilities to diseases have been created and are now available for contemporary and future research uses (e.g. Mouse Genome Informatics; 43). At the time of writing, there are more than 11,000 and 8,000 entries by quick key word search with ‘CV’ and ‘RS’ respectively. Along with this is active identification of causative genes or chromosomal loci for human Mendelian-type or rare diseases by gene-linkage analyses, whole- genome screen and exome-sequencing, and their vast information are deposited in the OMIM-catalog (e.g. long QT syndromes: 75 entries, familial cardiomyopathies: 744 entries; 44). More recently, efforts have been devoted to elucidating the complex genetic background for common CV diseases (CVDs) and RS diseases (RSVs) such as hypertension, atherosclerosis, coronary artery disease, myocardial infarction, heart failure, asthma, chronic obstructive pulmonary disease (COPD), by means of large cohort surveys of human genome polymorphisms (SNPs) and concomitant functional analyses (GWAS-catalog[45]) in conjunction with studies on epi-transcriptional and post-translational modifications as well as various levels of ‘omics’ studies (e.g. TOPMed program; 46), with the aid of powerful bioinformatics and computational tools.

Chronic inflammation is critical for the pathogenesis of CVDs and RSVs

From quite a different viewpoint against this enthusiasm for the ‘genotype-phenotype’ paradigm, however, more complex and intricate mechanisms have gained attention as for the pathogenesis of common diseases. It is well recognized that common diseases such as diabetes mellitus, heart failure (34), atherosclerosis (36) and COPD (2) follow long progressive time courses over the whole life span. These highly prevalent diseases involve a series of pathological events evoked/promoted by environmental factors comprised of the onset and sustainment of inflammation and subsequent tissue remodeling processes manifested as hypertrophy, degeneration, fibrosis or calcification, thus being classified as ‘inflammatory diseases’. There are numerous factors/mediators identified to initiate/promote/modify the transition from inflammation to pathological remodeling, including a variety of cellular stresses [oxidative stress or reactive oxygen species (ROS), carbonyl stress or reactive carbonyl compounds (RCOs), nitrosative stress, reactive cysteine persulfide, mechanical stresses, etc.], migrating immune cells, pro-/anti-inflammatory cytokines and the other bioactive mediators. For example, sustained hyperglycemia (e.g. in diabetes mellitus) has been shown to increase both oxidative and carbonyl stresses inducing various cardiac and vascular dysfunctions and remodeling. This occurs through very complex and interwoven signaling pathways involving non-enzymatic formation of advanced glycation end-products (AGEs) [and lipooxidation end-products (ALEs)] and activation of their specific receptors (RAGEs) present on all cells relevant to the atherosclerotic process (macrophages, endothelial cells, and smooth muscle cells), which results in the induction of oxidative stress and proinflammatory responses, and activation of other biochemical cascades involving PKC, p38MAPK, fetuin-A, TGF-β, NF-κB, ERK1/2 (1, 22).

Emerging concepts and subdisciplines for CV/RS physiology/pathophysiology

Further complexities are added to the pathogenesis of inflammatory diseases by the discovery of newly-emerging mechanisms that modulate inflammation/remodeling responses in various ways:

(1) ‘Inflammasomes’ play active roles in both pathogen-initiated and sterile inflammations which are caused by damage- or danger-associated molecule pattern (DAMPs) derived from damaged tissues or exobiotic agents (e.g. silica, cholesterol crystals). The canonical signaling pathway downstream of inflammasomes includes the NLPR3/ASC/caspase-1 complex, activation of which facilitates the production of IL-1β to cause cell death contributing to atherosclerogenesis, myocardial infarction and other CVDs and RSVs (>400 Medline hits for 2 years and 3 months;30)

(2) Perivascular adipose tissues (PVAT) actively release numerous bioprotective/biotoxic factors (adipokines, adiponectin, leptin, prostanoids, NO, hydrogen sulphide, palmitic acid, miRNAs, etc.) and contribute to the pathogenesis for CVDs (e.g. coronary artery disease via increase oxidative stress, angiogenesis, vascular remodeling etc.), but also to beneficial vasodilative actions to maintain the patency of vein grafts, in part via NO release and adipocyte-derived relaxing factor (ADRF)-mediated K channel activation (>100 Medline hits for 2 years and 3 months; 9)

(3) Mitochondrial dysfunction is known to impair intracellular energy metabolism and increase oxidative stress via ROS production via uncoupling of electron transfer chain, and associated with numerous CV and RS dysfunctions. However, recent studies provide different lines of evidence that impaired mitochondrial dynamics, which occurs through defective mitochondrial fusion, fission, biogenesis or mitophagy, causes a broad spectrum of CVDs and RSVs (>5000 Medline hits for 2 years and 3 months; 29,41).

(4) Autophagy plays essential roles for cell/tissue homeostasis maintenance by removing damaged organelles. Many of age- and oxidative stress-related CVDs and RSVs (myocardial infarction, cardiac hypertrophy, diabetic cardiomyopathy, atherosclerosis, hypertension, asthma, COPD etc.) are tightly associated with the defective autophagy, and often involve the

impairment of mitochondrial dynamics (>1500 Medline hits for 2 years and 3 months; 29,31).
(5) Non-coding RNAs (miRNAs, long non-coding RNAs, circular RNAs) critically contribute to cardiovascular function via epigenetic control and serve, when abnormally increased and released to the circulation, as biomarkers for risk stratification, diagnosis and prognosis of many CVDs and RVSs (>2000 Medline hits for 2 years and 3 months;35).
(6) Exosomes are secreted from almost all types of cells and serve as a cargo safely delivering proteins, enzymes, lipids and miRNAs to distant recipient cells to regulate a variety of physiological functions. Under pathological conditions, abnormally released exosomes cause CVDs as well as RVDs exemplified by the progression/metastasis of lung cancer, hypersensitivity of airways (via exosomes of microbacterial origin), and myofibroblast trans-differentiation in COPD (>200 Medline hits for 2 years and 3 months;4).
(7) The gut harbors trillions of bacteria which interact with adjacent cells in a symbiotic relationship called 'microbiome'. Gut microbiomes modify the intestinal immunity and metabolism and affect a wide range of physiological and metabolic processes of the body, and their imbalance ('dysbiosis'; induced by foods, drugs and diseases) can produce various CVDs and RSDs. A noteworthy pathogenic mechanism associated with microbiomes is the production of a toxic metabolite trimethylamine-N-oxide (TMAO) from dietary phosphatidylcholine and L-carnitine, the elevated serum level of which correlates well with the aggravation of atherosclerotic lesion via suppression of reverse cholesterol transport in macrophage, liver and intestinal cells, thus increasing the risk of coronary artery disease. The microbiota dysbiosis in the lung, which can influence its host defense and immunity, may also be causally related to the pathogenesis and exacerbations of chronic lung diseases, i.e. asthma, COPD, cystic fibrosis, and idiopathic pulmonary fibrosis. A new notion of 'vascular' microbiome in diseased blood vessels is emerging as another potential pathomechanism for atherosclerosis, aneurysms and vasculitis (>1200 Medline hits for 2 years and 3 months;

7,18,27,31).

The above list is continuously expanding to generate further enormous complexities for the pathogenesis of inflammation. Needless to say, this flood of information is beyond our intuitive understanding and handling, necessitating the systems approaches whereby to incorporate all key players of signaling into relevant dynamical models and integrate their intricate interactions to simulate the whole system's functionality (e.g. Cell Designer, Pathway Commons; 48,49).

Innovations strongly promote physiological studies

There are many innovative advances made in microscopic research which have enabled to observe atomic-, nano- and meso-scale subcellular and intercellular structures in association to function. Several notable examples include:

(1) the atomic structures of cAMP-bound human hyperpolarization-activated cation channel and open/closed conformations of ryanodine receptor which are essential for cardiac pace-making and contraction have been resolved by the cryo-electron microscopy; 8,25).

(2) super-resolution fluorescence microscopy revealed that microdomain-targeted remodeling of L-type Ca^{++} channel properties may contribute to ventricular arrhythmogenesis in heart failure models and that cholesterol-enriched domains in the cell membrane may mediate high density lipoprotein-induced eNOS activity; two-photon microscopy-based intravital imaging is used to track the extravasation and movement of immune cells in small blood vessels; 37,39).

(3) 3D-scanning electron microscopy (e.g. FIB-SEM) has started to be applied to uncover the functional connection of otherwise unrecognizable fine 3D structures. In addition, optical

mapping with voltage-sensitive dyes and optogenetic approaches are becoming indispensable tools to investigate the multi-dimensional mechanisms for cardiac action potential propagation and (reentrant) arrhythmias in the heart and neurovascular coupling and control of heart and blood vessels; 40).

For the whole animals or human subjects/patients, several important imaging modalities have been widely used to monitor the intact organ function in situ (e.g. cardiac motion and myocardial flow), by echography, CT, MRI and PET/SPECT. However, novel technologies (high resolution MRI, Diffusion tensor MR etc.) are emerging that can probe the mesoscale structure and local functional dynamics, quantifying the anatomical-functional variability in health and pathology (e.g. myocardial infraction), many of which are evolving toward the personalized clinical use (24). It is important to emphasize again that all these functional data will be ultimately utilized to construct comprehensive computer models based on realistic anatomy to better understand and explain how central and local (hemo-)dynamics work to regulate respective organ functions. Of particular note, recent computational modelling of cardiac electrophysiology is evolving successfully toward integrating these functional imaging data with other experimental findings from expression systems and animal models and developing novel testable hypotheses.

Regenerative medicine will require more physiological research

The advent of inducible pluripotent stem cell (iPSC) technology is one of most epoch-making advances in CV (and perhaps RS) regenerative medicines. It is becoming increasingly realistic that dysfunction of damaged tissues and organs can adequately be replaced or compensated by regenerated tissues/organs, or those engineered on artificial scaffolds/devices. Although no such clinically useful applications yet exist for the heart, blood vessels and the lung, transplantation of iPSC-derived cardiac tissue sheets consisting of cardiomyocytes and vascular cells has paved a new avenue to the unprecedented regenerative therapy of infarcted hearts (28). iPSC-derived cells also allow benchtop investigation of complex patho-mechanisms underlying human cardiovascular diseases such as arrhythmias (16) and facilitate the effective screening of cardiotoxic or new anti-arrhythmic compounds by automated analyses, the information of which can further be used to construct *in silico* models to select and validate drug candidates (6,11,32,42).

Beside their use as regenerative resources, iPSCs overexpressing miRNAs with anti-inflammatory and/or immunomodulatory actions can be applied in the proximity of damaged cells/tissues, or iPSC-derived exosomes containing bioactive proteins and lipids can be delivered to recipient cells to alleviate local inflammatory/immune reactions sustaining in diseased tissues such as infarcted myocardium and atherosclerotic lesions (19). Despite these enormous therapeutic potentials in clinical practice, our physiological and pathophysiological understanding about how iPSCs exert such beneficial effects on damaged cells/tissues is still premature. In this regard, this emerging field should become one of the major targets of future physiological research.

Another stream of modern physiology – holistic approach

Entirely opposite to the large-scale, cutting-edge research trends described above, another stream of physiological research holistically views health and disease as the continuum. This type of physiology aims to investigate the practical aspects of or apply the basic principles of physiology to health promotion and disease prevention rather than direct treatment of diseases, and is becoming a non-trivial subspecialty of cardiovascular and respiratory physiology in the post-industrial era. In particular, the notion of 'Mibyo' ('not yet ill' in

Japanese), which originally came from the eastern traditional medicine, has received growing attention as an unprecedented clue to understanding the pathogenesis, preventing the onset or even reversing the course of diseases. In the modern definition, 'Mibyo' represents a pre-symptomatic or preclinical state without any subjective complaints but with objective abnormalities associated with e.g. obesity, hypertension, borderline diabetes mellitus, gout, non-symptomatic cerebral infarction, non-ruptured arterial aneurysm, latent heart failure, and fatty liver (47). For example, oxidative stress, the major cause of CVDs, is thought to increase depending on sex, high-calorie, high carbohydrate diet, short sleep, smoking, alcohol and stress, and improving these risk factors is believed to reduce the oxidative stress. There are numerous such physiological studies, and it is an important issue of intense investigation how transition from pre-symptomatic to symptomatic states can be prevented or decelerated by health-promoting regimens such as aerobics, yoga, calorie restriction, and regular dietary intake of polyphenols, anti-oxidant herbs and phytochemicals. The proposed mechanisms so far suggest the common involvement of anti-oxidant, anti-inflammatory and anti-ageing reactions such as activation of eNOS and induction of sirtuins (47). Importantly, the pathophysiological research on pre-symptomatic state is now getting correlated with the comprehensive study of genetic variability (SNPs) annotated with phenotypic traits, which are being profiled in large public databases ('big data') and could be used in future to detect the pre-symptomatic state to prevent the onset of illness by active medical interventions. And early warning signals for critical transitions from pre-symptomatic to diseased states could be predicted by combining both appropriate biomarkers and theoretical approach (23).

Finally, as the globalization and diversification of life style and other activities proceed, the new frontiers are emerging for the CV/RS physiology. This is related to the ethnicity, environment (climate, altitude, temperature, humidity, air pollution, etc.), culture, profession, sports, travelling, individual habits and preferences etc., creating many interesting subspecialties of physiology which meet the needs of the times. Note that the 'extreme' CV/RS physiology at the Himalaya mountain (high-altitude physiology) is an interesting topic of plenary lectures in the 2017 Rio meeting!

Interestingly, some of these emerging new physiological sub-disciplines appear to be intimately associated with various innate rhythms of whole body, organ or cellular activities such as circadian rhythm, and may reflect, to considerable extent, the periodic changes of nerve activities (autonomic tones), as found in the condensed incidence of myocardial infarction, asthmatic attack, and some arrhythmia in specific time zones of the day (12). This new category of biology, called 'chronobiology', will provide a new investigational framework for normal physiology and human disease (38).

Future perspectives

Although there is little doubt that physiologists-initiated research will continue to underpin the whole bioscience by discovering the new basic principles of life, social requests and the funding status will prompt the physiology of next post-genomic decade to go with governmental strategic visions known as the 'precision medicine'(50) or 'personalized medicine'. As recently announced in the strategic initiatives of major research institutions in several frontrunner countries (NHLB, MRC, ERC and AMED; 51-54) clear timelines and goals have been set to accomplish the selected research priorities represented by the key words, innovation, resilience, repair and replacement. The essence of resilience would lie in the reversible continuum between health and disease, and one of the missions of future medicine will be to understand how resilience to disease develops and breaks down and to discover the way to prevents it by appropriate medical interventions. The mechanisms for

Mibyo, ageing and frailty could be interpreted in similar contexts. Thus, the future direction of physiological research will be not simply to discover the new logics and principles governing normal biological function across all hierarchical levels of the body (from molecules through organ functions to behaviors/environmental adaptations), but to re-integrate them in such a way of reconstructing a realistic multi-scale, multi-physics system that can reproduce the continuum of health and disease, thereby contributing to the personalized medicine and health promotion. This difficult mission will be exactly the ultimate goal of 'physiome' projects (33,55-58) running in several international collaborations. To promote this 'mission impossible', we probably have to: (1) accumulate multi-dimensional functional data using innovative technologies; (2) develop the recording modalities enabling detailed functional monitoring/profiling of both healthy subjects and patients on daily basis (e.g. via mobile or wearable devices) and garner the data with them; (3) evolve the advanced bioinformatics and systems physiology and improve the high-performance computing power so as to pertinently interpret the various levels of physiological data and organically integrate them with the fruits of genomic medicine such as the 'big data' obtained from 'trans-omics' studies as well as new findings from regenerative medicine (33). This will be further accelerated by constructing international networks of bioscience platforms freely accessible by researchers for active use (e.g. Garuda Alliance; 59), and by exploiting mobile medical devices/applications that connect healthy subjects/patients with remote medical services via the IoT technology (e.g. smart phones) and allow real-time sampling and diagnosis of personalized functional data (e.g. Pathway OME; 60).

As such innovative tools, a remarkable progress is being made in the quality and application of intravital recording modalities, exemplified by; motion vector prediction method for a high-speed, high-resolution tracking of cardiac motion (MVP); super-resolution optical fluctuation imaging for flow dynamics monitoring in microcirculation (SOFI); photo-acoustic imaging for small blood vessel diameter measurement; deep-tissue imaging or stimulation modalities using near-infrared (NIR) light such as diffusive optical tomography (DOT) and nano-particle activation technique based on photon upconversion; ultra-thin, deformable, high-resolution multiple-electrode array for minimally-invasive electrophysiological recording (NeuroGrid; 3,10,13,15,18,21). All these new modalities will enable to monitor or elicit dynamic functional changes in small localized regions of various visceral organs, thereby providing unprecedented new information about the complex reactions occurring *in vivo*.

In my personal view, the physiological research in coming years will bifurcate into two directions, i.e. 'generalized' approach covering the full spectrum of 'average human' life which is tightly combined with large-scale biologic databases, and 'personalized' or 'individualized' approach which does not aim at the 'one-size-fits-all' principle and is tightly linked with individual variability in all aspects that determine each self. These two opposite approaches would not be exclusive but rather complementary helping each other to foster more exact understanding about the life. There is however a huge gap of knowledge left between molecular/cellular and whole body levels. One promising approach to fill in this gap may be a 'reverse' or 'synthetic' physiology in which cells are used to re-build functioning tissues and organs by means of bio-fabrication technologies. In fact, 3D-bioprining has been successfully applied to create visceral organ-mimetics of blood vessel, trachea and heart or to construct heart tissue on a chip device (14,26,33). These artificially constructed tissues/organs could be, in addition to their ultimate use for replacement therapy, extremely instrumental to pursue the tissue/organ-level logics and principles governing their functions. In either case, physiologists will have many different thrilling options for their future research, which should be navigated by their own genuine scientific curiosities and motivations.

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Future Perspectives of Secretion and Absorption Processes in Health and Disease

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Running Head: Future perspectives of secretion and absorption processes

Physiological relevance of secretion and absorption processes

Secretion and absorption are physiological processes carried out by epithelial cells present in for instance the kidney and gastro-intestinal tract. In general, secretion encompasses the cellular release of ions and molecules to the external environment of the cell. This can be achieved by exocytosis, by transport of the substances across the plasma membrane or by simple diffusion through the lipid bilayer of the plasma membrane. For example, endocrine cells secrete hormones that subsequently enter the bloodstream or epithelial cells in the pancreas secrete digestive enzymes into the digestive tract to facilitate the digestion. Thus, secretion moves material from the extracellular space to the lumen of the kidney or gastro-intestinal tract. Conversely, absorption is the transfer of substances from the lumen of the kidney or gastro-intestinal tract to the extracellular fluid. In the gastro-intestinal tract absorption follows the digestive process of nutrients. This can be achieved by endocytosis, by transport of the substances across the plasma membrane or by simple diffusion across the tight junctions. In the last decades, the underlying molecular mechanisms of the secretion and absorption process have been studied in great detail. The following arbitrary subdivision can be appreciated:

Gastro-intestinal tract

Our digestion starts by eating food and ends in general a day later by removal of the remaining waste via the stool. The digestion is facilitated by the many digestive enzymes that are secreted along the way. Nutrients from the diet are absorbed into blood across the polarized epithelial cell layers forming the small and large intestinal mucosa via both passive and active mechanisms. The mechanisms of intestinal absorption of nutrients involve sodium, anions (chloride, sulphate, oxalate), carbohydrates, amino acids and peptides, lipids, vitamins, as well as the major minerals and micronutrients. In recent years, the molecular identity, specificity, and coordinated activities of key transport proteins and genes involved, has been resolved and can often explain the pathophysiology of acquired and congenital intestinal malabsorption, and form the basis of clinical tools to treat malabsorptive symptoms.

The kidneys

Renal physiology encompasses all functions of the kidney, including maintenance of fluid and acid-base balance; regulation of sodium, potassium, and other electrolytes; clearance of toxins; absorption of glucose, amino acids, and other small molecules; control of blood pressure; production of various hormones, such as erythropoietin; and activation of vitamin D. On a daily basis ~180 L of blood is filtered by the glomeruli and passes into the lumen of the nephrons. Here, the glomerular filtrate is eventually concentrated to ~1.5 L of urine as a consequence of the reabsorption and secretion processes. Through a delicate series of long-standing studies involving, micropuncture, *in vitro* tubule perfusion, genetic, cell biological and animal studies, the various reabsorption and secretion processes along the nephron have been unravelled. These seminal studies have greatly contributed to our current physiological understanding of electrolyte and acid-base disturbances. Above all they have shown the integrative function of the kidney in achieving homeostasis in our bodies.

Exocrine glands

Exocrine glands secrete various products including hormones, enzymes, metabolites, and other molecules which via the duct of the gland flow towards the surface to which the duct is in contact. For instance, a mammary gland produces milk to feed young offspring. In the breasts, during pregnancy when levels of prolactin, estrogen, and progesterone rise secretory alveoli develop. Milk secretion (lactation) begins a few days after birth, caused by reduction in circulating progesterone and the presence of prolactin, which mediates further alveologenesis and milk protein production and regulates osmotic balance and tight junction function.

Future perspectives

In the last decade, a wealth of information has been obtained about the molecular mechanisms regulating the various secretion and absorption process in the body. This has been fueled by the genomic area disclosing ample new genes and by their subsequent physiological characterization. Most transporters have been identified which are instrumental in the individual secretion and absorption processes, their tissue distribution has been unraveled and importantly the molecular players of the signaling pathways controlling their activity have been disclosed.

In the coming area, several scientific avenues based on new technical developments will be pursued to further broaden our physiological knowledge. For instance, single cell omics will be a new frontier in physiology which could have important implications for further unraveling the molecular mechanisms regulating secretion and absorption processes. Single cell omics methods will shed new light on these processes by recognizing the heterogeneous nature of the cell populations composing the various epithelia involved. In addition, the recently established technique of growing organoids from stem cells will revolutionize our knowledge of human physiology. Organoids are clusters of cells that organize themselves into mini versions of their respective organs. They can be grown from stem cells when the precise conditions to keep them alive outside the body are applied. Organoids were first made from intestines but have since been made for many other tissues, including liver, brain and kidney. Organoids will allow scientists to better study the development and diseases of organs. Organoids have several advantages over existing approaches. They can be maintained for months and provide an unlimited supply of material for study, meaning fewer animal studies are required. Making organoids from patients also raises intriguing possibilities for personalized medicine. All this makes organoids an exciting new tool for researchers. Organoids will transform the way we conduct medical research, from basic understanding to drug development and personalized therapies.

In the field of absorption and secretion a major development is the recognition of the gut microbiome as a new vital organ. The human microbiome is composed of bacteria, archaea, viruses and eukaryotic microbes that reside in and on our bodies. These microbes have tremendous potential to impact our physiology, both in health and in disease. They contribute to our metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions. The study of the human microbiome will be furthered by technological advancements on the functional interactions between the microbiota and the host. Still a lot can be learned about the interaction of the gut with for instance the brain or the kidney. Physiology and physiologists are therefore crucial to our understanding of these systems, and the best hope for discovering novel treatments.

Related, epithelial function plays a central role in physiology for transport of substrates, salts, and water. Basically, two pathways are available: a trans- and paracellular route. The transcellular pathways have been extensively studies. Recent studies have identified claudins as critical molecular components of the tight junction forming the paracellular pathway. They determine the selectivity, permeability, and tightness. Several disease mechanisms can now be explained by the dysfunction of claudins within the tight junction. Novel insights from claudin research in the coming decade will provide tools for diagnostics and treatment and a better understanding of the pathophysiology and clinics of diseases related to malabsorption or secretion.

For exocrine physiology future areas of research will include exocrine gland development, regenerative approaches, functional relevance of salivary proteins, membrane functions in exocrine glands, understanding the aetiology of autoimmune disease, and targeting inflammation to retard disease pathogenesis. Likewise, details of exocytotic and endocytotic process in beta cells of the pancreas can now be studied at the single vesicle level through a variety of new approaches including combined electrophysiological and imaging techniques. These are exciting future possibility that may contribute to our knowledge of the pathophysiology of type 2 diabetes in humans.

Thus, the newly developed technical approaches will revolutionize both fundamental physiology as well as our understanding of disease, and technologies involved in translation to medicine. A better health outcome for humanity will benefit from translational physiology. This will, however, require an increased interaction between physiology and other disciplines to promote basic findings to the clinic and *vice versa*, and will make physiology an even more exciting and important area of research.

Molecular and Cellular Physiology Meets Big Data: Current Status and Future Directions

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Running Head: Essay on molecular and cellular physiology

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Molecular physiology, cellular physiology, bioinformatics, genome, RNA editing

Physiology aims to understand and explain the function of entire organisms like humans and their individual organs. While in early times functional investigations were mostly restricted to more descriptive terms, the introduction of molecular biology and the availability of cellular model systems in the middle of the last century allowed physiologists to precisely determine the contribution of individual proteins and molecules to cellular function. Subsequently, transgenic animal models were generated to transfer this knowledge into organisms to elucidate the contribution to organ function and organism behaviour. For physiology, this revolutionary approach led to the development and growth of sub-disciplines like molecular biology, cell biology and neuroscience.

Currently, another revolution in physiological research is taking place. The revolution started with the sequencing of the human genome that was completed more than a decade after its initiation in 1990 (1). We began to understand that although there is a surprisingly low number of coding information within our genome, many genes exist in many different variations, thus also generating a large complexity on the protein level. Thanks to the evolution of technological developments the entire genome of human cells is now sequenced within a few hours and allows physicians to examine patient material for potential genetic defects. In addition, new disciplines like bioinformatics and epigenetics generate a huge amount of data about the modification of genetic information of organs, cells and even subcellular compartments on the DNA as well as on the RNA level (2). As a consequence, physiologists have access to a plethora of data about the current status of functional units. The resulting challenges for physiologists in the future are manifold. This may best be illustrated by an example: RNA editing of CAPS, a protein involved in neurotransmitter and hormone release (3), results in an amino acid exchange that alters its binding affinity to another protein. Editing is tissue-specific, occuring at a frequency of 70% in chromaffin cells of the adrenal gland and only at a frequency of 15% in the brain. The physiological consequence of this selective amino acid exchange is a 50% increase of adrenaline, a hormone that increases heart rate and regulates blood pressure (4). Mutant mice carrying this edited CAPS protein are leaner than their wild-type counterparts and show an increased physical activity. Thus, a single point mutation in a single protein expressed in a single organ leads to entirely different behaviour and appearance of the entire organism. Therefore, physiologists in the future have to consider the source, physiological condition, age and many more parameters under which genomic, bioinformatic and epigenetic data were obtained.

The balancing act between having an enormous amount of data available and bringing them into a physiological context of organ and organism function will certainly shape the field of molecular and cellular physiology for the next decades. It should be an exciting journey.

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Professionalization of Physiology Education Activities

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Abstract

Changes in physiology education are being driven by outcomes-based evidence documanting the benefits to learner-centered instructional methods. The learning environment no longer consists of a lecture hall, and the goal is no longer the transmission of information. Physiologists are at the leading edge of developing and disseminating pertinent educaitonal research, using both regional workshops with a facuclty development theme and using the journal *Advances in Physiology Educaiton.* The International Union of Physiological Sceinces plays an active role in promoting educaitonal activities at national and regional physiology workshops, facilitating the movement toward a learner-centered teaching model by developing the understanding and skills of the participants.

Key Words:

Faculty development, regional workshops, IUPS, learner-centered education

This is an exciting time for **physiology education and physiology educators** - embracing both the most promising and most threatening meanings of the word “exciting”. The opportunities and challenges come from advances in both “physiology” and “education”, as research findings into both fields continues to shape the teaching environment.

Physiology educators, particularly those in the health professional programs benefit from the integrative and foundational nature of the science of physiology. An understanding of physiology is key to understanding our health and the world around us, and is essential to the intelligent practice of medicine (3). Physiology research continues to shape our understanding of body function and consequently impacts clinical practice.

The largest expansion of interest in physiology training (at least in the USA) is driven by an interest at the undergraduate level in the benefits of health and fitness (2,8). Research in sports physiology continues to shape both the general population approaches to fitness as well as the performance of competitive athletes. The physical benefits of fitness are being complimented by research into Mind-Body Medicine (6), drawing on millennia of international expertise and practice.

Physiology is at its core a research science. Physiology is not what physiologists know, it is what physiologists do. Physiology as a core life science is ideally suited to guide the development of a scientifically literate public, particularly in the pre-college learning setting. In this era of explosive information availability, understanding the science of physiology can help individuals navigate through competing claims and data in order to make informed decisions about topics shaping the future of the individual and the world.

Physiology **educators** draw on a separate robust experimental literature – that of the science of education. The convergence of new pedagogical understanding and technological innovations has changed physiology instruction more in the past 30 years than in the century preceding that. The impact of educational technology is massive and needs to be a topic for another discussion. This essay will focus on one of the major pedagogical shifts – the move from instructor-centered to learner centered instructional approaches.

For physiologists, learner-centered instructional approaches are both familiar and challenging. Familiarity comes from our experiences in graduate and postgraduate training. Once we finished with the 'classroom' component of our instruction, we entered the ultimate learner centered environment, the research laboratory. The supervisor's role was that of a guide, a coach, and we appropriately refer to them as our 'mentor'. Responsibility for learning and mastery of knowledge, skills and attitudes resided with the student, along with the responsibility of meeting performance expectations (1).

This learner-centered experience is in stark contrast to our (40 years ago for me) learning in the lecture hall. Lectures were generally passive events, centered on transmission of information. In 1927, E.E. Slossan (7) was credited with the observation

"Lecturing is that mysterious process by means of which the contents of the note-book of the professor are transferred through the instrument of the fountain pen to the note-book of the student without passing through the mind of either."

That description unfortunately captures the lecture hall experience of many students 90 years later.

There is compelling evidence proving the benefits of active learning approaches (4). Engaging students in the lecture hall setting can be stimulated by using active learning approaches, such as think-pair-share-share activities and audience response systems. There is clear experimental evidence that active learning approaches improve both learning and retention. Some learner-centered approaches, such as problem-based learning (PBL) require significant physical and faculty resources, but specifically foster the development of self-directed, independent learners. Other approaches, such as team-based learning (TBL) and flipped classrooms, evolved specifically to address the resource limitation characteristic of student-centered learning activities.

One major challenge in the implementation of learner-centered instructional approaches lies in the lack of familiarity to both students and instructors. Changing from a familiar educational approach to a novel approach requires preparation of both the instructors and the students for their new roles. This requires both familiarity with the approaches and their limitations, as well as a commitment to change.

The real promise of **physiology education** comes from the professionalization of physiology educators. Professionalization requires more than just a commitment to expert practice. Professionalization requires physiology educators to shape and refine their activity through reflective, data-driven approaches that to contribute to the experimental literature in order to advance the field. The physiology classroom is an ideal setting for educational scholarship, as physiology instructors apply their training in experimental design to address important issues in teaching and learning.

One essential component of scholarship is the dissemination of findings. Physiology educators have significantly shaped the educational literature, particularly as reflected in the growth and impact factor of the journal "*Advances in Physiology Education*". National and international physiology conferences now include venues for poster and oral communication of educational projects, including outcomes of research in the classroom.

The program of the November 2016 regional meeting of the SAAP (South Asian Association of Physiologists) is an excellent example of the professionalization of physiology educators. As part of the conference, Dr. Rita Khadka and her colleagues organized a 1 day pre-conference teaching workshop with the theme "LEARNING OF PHYSIOLOGY IN 21ST CENTURY (WITH FOCUS ON FACULTY DEVELOPMENT). In addition, education-themed oral and poster presentations were interwoven throughout the conference. The recommendations from this conference were developed and delivered by the recently deceased Prof. Shyamal Roy Choudhury, who is greatly missed. This slate of recommendations provides a clear indication of the state of physiology education and the areas of need and growth. They are reproduced below with the permission of Prof. Choudhury.

RECOMMENDATIONS

1. The workshop recognizes the urgent need for student-centered and team - based learning opportunities for undergraduate students of Physiology.
2. The workshop recommends inquiry-based laboratories, case and problem based activities, human physiology experiments and special projects to enhance student learning and to build confidence in physiology students.
3. The Workshop recommends introduction of e-learning in physiology. The workshop

believes that curricula and course materials including teaching-learning activities, assignments and quizzes can be presented during e-learning. The workshop recommends that a set of interactive CDs to be prepared to supplement e-learning at Physiology practical.

4. The workshop recognizes the issues related to teaching of attitudes, ethical issues on biomedical research and an approach on ethical teaching for physiology educators. The workshop recommends proper orientation and training of the faculty members towards the use of various teaching-learning methodologies like (i) introducing scenario as a stimulus at the beginning of lecture, (ii) introducing Flip classroom for active learning, (iii) Real case presentation and clinical examination in lecture, (iv) development of critical thinking in lecture, (v) introducing evidence-based learning, (vi) concept mapping, (vii) Learning by Role-Play, Reflection, E-Summarization.
5. The workshop recommends the introduction of objective-structured Practical Examination (OSPE) and objective-structured Clinical Examination (OSCE) for the assessment of student's practical skills in pre-clinical and para-clinical subjects.
6. The workshop recognizes the need of developing a lesson plan which will facilitate the learning of students, stimulate higher cognitive skills of students promoting critical thinking and highlighting clinical relevance.
7. The workshop suggests that it is an integral part of faculty development to equip them with a skill of emotional intelligence through hands on workshops. This skill will help them to control and understand the emotions of themselves and the students, other faculty members, administrators, patients and attendants to be able to place themselves under adverse circumstances.

8. The workshop recommends introduction of Flipped classroom to facilitate student engagement and active learning. The workshop urges that integrated Flipped classroom to be planned if the curriculum is of integrated type.
9. The workshop urges upon the Professional Associations, such as **IUPS, APS, PS, UK, SAAP** to take steps in organizing Training Programmers/Workshops, Seminars etc. at regular intervals for promoting Faculty development in Physiology and Medical Education.

Moving forward – The Role of IUPS

The IUPS has provided active leadership in the professionalization of physiology educators. These activities began in 1983, and a teaching workshop has been held as a satellite conference of the main IUPS Congress ever since. In subsequent years, IUPS education committee has cooperated with local, national and regional groups to help organize workshops that had education themes, allowing a community of educators to flourish.

The programs of these workshops reflect the characteristics needed for the development of professionals.

1. Provide the broader physiology education community with context for educational changes rooted in research-based literature. Most of us were introduced to the classroom with little if any formal training in teaching. Our teaching approaches were mostly shaped by our positive and negative experiences as a student. One early and continuing aim of the teaching workshops is to better educate physiologists about the new approaches to teaching, including providing outcomes-based evidence of effectiveness (4).

2. Provide workshop experiences that will enhance the teaching and facilitation skills of physiologists. One major barrier to implementing pedagogical change is the lack of opportunities to experiment with novel pedagogical approaches. The teaching satellite conferences incorporate small group activities allowing physiologists to role-play both the instructor and the learner as they gain insights into novel teaching approaches.

3. Develop communities of practice. One unfortunate reality of any workshops is that implementing lasting change is difficult. As instructors return to their home institutions, competing pressures in the environment lead faculty to return to the familiar and comfortable. One way to solidify a commitment to change is to develop communities of practice (5), where shared experiences, continuing interactions and commitment to the community facilitate lasting change.

4. Identify, develop and share effective educational resources. The creation of instructional resources is expensive and most commonly occurs in the developed world. In contrast, student centered learning approaches indicate that learning resources need to be those with which the students can easily identify. Regional collaborations can identify unique educational needs, and allow the in the development and refinement of items and objects to be used in the classroom.

IUPS education Committee has a modest grant program to support these goals. The largest impact in the past 4-year cycle has been to help support regional and trans-national meetings.

Conclusion

There is a threat implied in the phrase "May you live in exciting times". The physiology learning environment is changing. In order to remain relevant, physiology educators must understand and embrace the emerging opportunities. The educational literature is guiding many of the dramatic changes that are occurring at the University. Physiology educators must consume this literature, and apply it as possible to their educational setting.

My wish for all in physiology educators is that we flourish in 'exciting' times. This requires the ability to embrace change. Educators who rely on the pedagogy of 1960 will find themselves rapidly isolated and consequently lose their effectiveness as instructors. In contrast, educators who understand and embrace change will emerge as leaders their institutional setting, and continuing to shape the experiences of our learners.

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How do Ethical Considerations Impact Physiological Sciences?

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Running Head: Ethical considerations in physiological sciences

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Abstract

As physiologists we rely on careful and rigorous research methods to understand the complexities of living organisms and correct and accurate documentation in the scientific literature in order to advance science. It is understood that the research will be conducted in the most ethical fashion, maintaining the highest levels of integrity. This brief report describes the role that the International Union of Physiological Sciences (IUPS) Ethics Committee plays in providing guidance to the members of the IUPS, and a description of four topics that are often of concern in physiology and can impact physiological sciences and the credibility of the scientific record. The essay begins with an introduction by the Chair of the Committee, Dr. Penny Moody-Corbett, followed by four ethics topics: Ethical Issues in Experimental Animal Physiology, Professor Andrea Calkovska; Authorship Issues, Dr. Ashima Anand; Reproducibility and Reliability of Research, Professor Pat Buckley; and Publication Ethics and Impacts on Physiology, Dr. Bill Yates.

Keywords:

Ethics, Integrity, Animal research, Research reproducibility, Authorship, Publication

Introduction

August 21, 2001 the International Union of Physiological Sciences (IUPS), at its Council meeting in Christchurch NZ, established the IUPS Ethics Committee under the Chair of Professor Ewald Weibel, noted biologist and physiologist, University of Berne SUI. The committee at that time had 16 members, representing 15 countries. Although we are a leaner committee now of only 7 members from 7 countries, we continue to be active and engaged with Physiology and Ethics.

As you will learn in this essay, which contributes to the Compendium for the Board of the IUPS General Assembly, issues of ethics are always a concern in conducting physiology research and the best research is that which adheres to the highest ethical standards. Our essay includes three topics of on-going concern to our committee: ethical handling and care of animals in physiological experimentation, understanding the responsibilities that come with being an author and current ethical issues in physiology publications.

We begin with a brief outline of the mandate of the Ethics Committee and the highlights of the Ethics Symposia that have been part of the IUPS Congresses since 2001.

The mandate of the Ethics Committee is to provide expertise and guidance to Council in the areas of human and animal ethics as they relate to physiological sciences. The Committee is called upon to contribute to the Council for International Organizations of Medical Sciences (CIOMS) and the International Council for Laboratory Animal Science (ICLAS), to review guidelines for these and other organizations and to contribute to the quadrennial IUPS Congress. In addition, committee members contribute within their Societies on topics of ethics and physiological sciences.

A major role of the committee is to contribute to the dissemination of knowledge on topics of ethics to members of the physiological community worldwide. It is in this context that the Committee has played a major role by contributing to the IUPS Congresses. Since 2001 there have been four Congresses, including the Congress to be held in Rio de Janeiro. Each Congress has provided an amazing opportunity to connect with students, post-docs and junior and senior physiologists.

In San Diego, USA, 2005 the Congress title was “From Genomes to Functions” and fitting with the theme of the Congress the Walter C. Randall lecture given by Professor Robert Williamson was titled “The Future of Physiology in the Era of the Human Genome: Medical Miracles or Ethical Dilemmas?” The lecture was immediately followed by a panel discussion with a number of notable ethicists and physiologists: E. R. Weibel, B. M. Knoppers, A. W. Cowley, D. A. Prentice and P. Corvol

In Kyoto Japan 2009, “Functions of Life: Elements of Integration” was the theme of the Congress and the Ethics Committee sponsored an ethics symposium on “Best Practices in Physiological Research: Ethics and Integrity. The symposium focused on talks highlighting both the importance of animal research, the attention to the humane and ethical treatment of animals in physiological research and the importance of integrity in physiology research and the consequences of research misconduct. The speakers included C. Blakemore, N. Kagiyama, K. Barrett and P. Moody-Corbett.

In 2013, the 37th Congress was co-hosted with The Physiological Society meeting in Birmingham UK. The Ethics Committee sponsored a symposium highlighting a topic of community concern “Synthetic Biology: Scientific progress or ethical dilemma”. The presenters provided both physiological and ethical perspectives on this topic and included: F. Kepes, T. Baldwin, D. Milius, C. Rhodes and D. Benoit-Browaeyes.

In 2017 we are celebrating the "Rhythms of Life" at the 38th IUPS Congress and for this Congress the Ethics Committee is pleased to sponsor a symposium which will highlight the members of the Ethics Committee: "Promoting Ethical Practices in Physiological Research". The focus of the presentations will be on "Knowing what is right and Doing what is right". The scientific rationale for this symposium is to promote ethical research practices, from planning to publishing, for all of our research community, particularly early career scientists, to support the best physiological research possible. In addition to three members of the Ethics Committee, P. Moody-Corbett, A. Anand and B. Yates, we are happy to be joined by S. Vasconcelos, an early career researcher from Brazil.

The IUPS Congresses continue to be the best opportunity for dissemination of the topics of research ethics and integrity to a wide selection of international physiologists at all career levels.

Ethical issues in Experimental Animal Physiology

Experiment (in Latin *experiri* – to try, to attempt) signifies the repeated observation under simplified and standardized conditions. An *in vivo* experiment is an important part of Physiology. It indicates an experiment with/on living organism and requires utilization of laboratory animals. Over the years, the use of animals in research has become morally justifiable in the light of the potential health "benefits" in relation to the experiments. Most often mice, rats, rabbits and guinea pigs are used. Especially mice and rats are highly popular among researchers as they are small and have short reproduction cycles. The special kinds of experiments are those in activity Physiology ("Actophysiology"), which are in many aspects more complicated than research on restrained and anesthetized animal. Because these experiments are usually long-term, the adaptation of animals is necessary. Moreover, surgical interventions are very specific in order to make both registration and application of stimuli possible. However, research in the field of activity Physiology affords results that are specific and representative for living organisms during locomotion and exercise (15).

Legislation and ethics in animal research is one of the main parts of laboratory animal science. As long as animals have been used in experiments there has been a deep concern about it. This has led to development of guidelines and restrictions of different kinds. The first law to be adopted was the "Cruelty to Animals Act" in Great Britain in 1876. This Act did require the use of anaesthetics for many types of animal experimentation and it was in force for more than 100 years.

Council for International Organizations of Medical Sciences (CIOMS) and International Council for Laboratory Animal Science (ICLAS) prepared revised International Guiding Principles for Biomedical Research Involving Animals (20). This document reflects current best practices and standards of care in laboratory animal medicine and science and provides the framework of responsibility and oversight to ensure the appropriate use of animals. This document has been the framework for the development of laws, policies, and guidelines for over 30 years. When Guiding Principles were written in 1985, the profession of laboratory animal medicine and science was still establishing best practices and standards of care. Since the publication of the original Guiding Principles, the scope of animal research has expanded significantly, numerous technological advancements have occurred, and societal attention to the welfare of research animals has increased. This evolution has prompted an update and expansion of the focus of the Guiding Principles is to address contemporary issues facing scientists when animals are used for research and education.

The International Guiding Principles for Biomedical Research Involving Animals were adopted by international organizations and governmental agencies and are used by scientific community worldwide. Today most developed countries have adopted their own laws for animal protection. However, laws and decrees are always too remote to give full protection to the animals (12). At the end it is the attitude of the people that handle the animals that is the most important thing. Promotion and development of such attitudes is one of laboratory animal science most important duties. In many countries, Ethical committees have been set up to stimulate ethical discussions and improve ethical consciousness.

Future challenges

Still there is the discussion regarding the use of animals in medical research. Among all topics, several subjects seem to be of special interest (30). First, although detailed regulations governing the use of animals in research have been in place for several decades, there is a problem with upholding these regulations. The question also is if scientists pay enough attention to the justification of the increasing numbers of experimental animals required to conduct biomedical studies. Second, the formation of radical animal-rights organizations that do not see the potential health benefits and consider all animal research unethical. Finally, it is important to mention that several decades' worth of experience with current regulations regarding the use of animals in biomedical research has produced a strong moral consensus for these practices. Probably the importance of increased regulatory vigilance should be pointed out.

Authorship issues

Most scientific research these days is a collaborative activity. It is being carried out not only interdepartmentally but also inter-institutionally and increasingly across the globe. The requirement of funding agencies that support most research work is to have the outcomes communicated and this is done by writing of scientific papers. Thus beyond conducting ethically approved research projects and obtaining informed consent wherever required, there exist important issues of communicating the scientific outcome with fairness and integrity. Of these, 'appropriate authorship' is one of the most important ones. Being an 'author' accrues great benefit to the researcher as it provides academic and professional standing, credibility in the chosen field and a means for career enhancement. Some of the benefits that a long list of published work can provide include enabling authors to apply to or be nominated for academic awards and eventually to academic-empire building. An example of the latter is to get recognition for what they project as their exclusive contribution in their field so as to have new research centers or even institutes setup around these.

Inappropriate Authorship

However complaints of younger researchers who have contributed substantially to a study, of having being denied first authorship or authorship at all are being seen increasingly. Instances of insertion of names of non-participants in the study, but who were either involved in acquiring funds for it or of a head or a senior member of their laboratory or head of the Institution, are becoming ever more obvious. This situation is further complicated by the fact that some organizations have also started to include the names of 'ghost writers' i.e., those who have only written up but not participated in the study.

The way forward

All persons designated as authors should have made substantial contributions to the conception and design of the study, its supervision and or acquisition of data, its analysis, interpretation and writing of substantial parts of the paper. But as far as listing of authors is concerned generally (this is not the case in all disciplines) the first author by definition or practice is one who has done most of the experimental work and writes substantial parts or all of the paper and thus is *able to reply to reviewers' queries and stand up to their criticism.*

Given the above criteria one can then differentiate between those who have contributed to the conduct of the study, yet cannot be considered as qualifying as authors. These would be individuals who have provided technical assistance, who have run the necessary equipment, provided the manual labor of data gathering for large studies, assisted with patients if they were part of the study or carried out the statistical analyses. In addition they would be those who were involved in acquiring funding for the project or the study or editing the manuscript after it has been written up. This category of contributors does not have the intellectual ownership or responsibility for the final product or findings. However they would be made preeminent in the list of contributors to be acknowledged at the end of the publication.

Finally it is to be emphasized that with having claimed credit and acknowledged responsibility of their findings the task of the authors is not over. The new scientific knowledge that has been created and put into print has now to be disseminated by presenting it at scientific meeting, symposia and congresses. Appropriate authorship requires that each of those who have been listed as authors and irrespective of whether their contribution amounted to 10%, 20%, or more should be able to present it to an audience, to answer questions and be able to provide future directions of the work in order to qualify as authors of that piece of work. Otherwise they should only be acknowledged for whatever they have contributed to the study. (source reference, 2)

Reproducibility and Reliability of Research

The reproducibility and reliability of biomedical research is firmly in the spotlight these days. The Oxford English Dictionary defines (scientific) reproducibility as *the extent to which consistent results are obtained when an experiment is repeated.* Reproducibility is a fundamental principle of scientific research and published science is expected to be reproducible.

However, reproducibility has come under intense scrutiny in recent years. A recent UK symposium co-hosted by the Academy of Medical Sciences, the Biotechnology & Biological Sciences Research Council, the Medical Research Council and Wellcome generated a formal call to action to improve reproducibility and reliability of biomedical research in the UK from the host organizations (27). In late 2016, the InterAcademy Partnership for Health published a similarly-intentioned statement, endorsed by 46 national Academies (1). The Reproducibility Project aims to repeat 100 published experimental and correlational psychological studies: the work is being led by the Centre for Open Science (8), whose goal is to increase the openness, integrity and reproducibility of scientific research. Nature published a special edition recently – *Challenges in Reproducible Research* – to promote awareness of the issue within the scientific community and to promote their mission to improve the transparency and robustness of what they publish (24). The list could continue.

The reasons for (ir)reproducible science are varied. It may be poorly conducted science. A recent survey of researchers found that 87% of more than 1,576 researchers (which included over 700 biologists) named poor experimental design as a cause of irreproducibility, and 89% named flaws in statistical analysis (5). The exact magnitude of the issue can be difficult to establish, given studies may not be replicated exactly, and statistically one expects failure in replication. The oft-cited publication bias to publish positive results can generate compounding challenges to reproducibility: the implication that researchers seek to find positive – and therefore publishable – results, and the career and reputation disincentives that travel with a lesser publication track record.

There are many reasons to argue for the principle and practice of reproducibility, and important amongst those is the imperative for excellent research training of Masters and PhD candidates. These are, after all, the people who will continue the scientific endeavor on our behalf.

A powerful anecdote is provided by Alyssa Ward, reported in Nature (4). In the course of her PhD, Alyssa was citing a meta-analysis of studies on reproducibility, which identified that scientists routinely fail to explain how they choose the number of samples to use in their studies. What startled Alyssa was her realization that she had no idea 'how, or when, to calculate sample size'. She knew not to forge data. But what she *needed* to know was how to achieve valid findings through excellent research design. 'Mistakes are more important than misconduct', she is quoted as saying in the article. 'I wanted a course on mistakes.'

Reassuringly, and although the literature is arguably focused on the factors that contribute to the irreproducibility of scientific findings, there are significant practical steps being taken to foreground this issue and to optimize the validity of research findings.

A good example is the UK symposium referred to previously (27). The symposium sponsors – who include major funders of research – have since collaborated on a range of measures focused on improving: the openness and transparency of methods, data and results; research design and the completeness of reporting; funding decisions; and education & training. Some of these measures are mirrored in initiatives elsewhere, and it is clear that there is a concerted effort being staged world-wide to ensure that research is as valid, efficient and productive as possible.

Publication Ethics and Impacts on Physiology

A variety of problems in the publication of physiological data have recently been described, which diminish the quality of the scientific literature, and may eventually erode public confidence in the scientific enterprise. These problems include:

- Inadequate description of the methodology used in experiments, and "cherry-picking" of data, such that findings cannot be reproduced between laboratories (11, 22, 23, 31, 33).
- Faulty statistical analysis of data, resulting in reporting of false positive or negative results (9, 10, 25).
- Unreliability of the peer review process, allowing flawed manuscripts to be published and meritorious manuscripts to be rejected (34).

These problems will be discussed below, along with efforts of scientific publishers to address the concerns.

A number of recent articles (11, 22, 23, 31, 33) including those in the popular press (19, 32) have discussed an increasing unreliability of published scientific findings. A number of factors have been attributed as contributing to the diminished quality of published scientific data, particularly the competitiveness of the academic environment (29). Scientists often rush to get their data into print, without adequate replication of the findings. They also may not have sufficient resources to repeat experiments that were potentially contaminated. In addition, scientists may not be aware of the effects on experimental results of extraneous factors such as the bedding and diet of research animals. Moreover, it has become uncommon to publish negative data or to replicate studies conducted in other labs, so investigators are unsure whether their conclusions are valid.

Another issue of concern is the use of inappropriate statistical methods when analyzing data (9, 10, 25). Such flawed data analysis can result from an inadequate background in statistics, or intentional use of inappropriate practices such as p-hacking (repeating an experiment only until statistically significant findings are obtained). Conducting a study with too few research subjects (or too few samples), or use of a statistical method that is not sufficiently rigorous, can result in flawed conclusions.

As discussed in a recent editorial (34), it is also becoming increasingly difficult to secure qualified reviewers to provide editorial feedback on papers. As a result, peer review is often left to less qualified experts, who can provide misleading advice to editors, who in turn make a poor editorial decision. One trend is for senior investigators to defer peer review to their trainees (29). Although it is highly encouraged for investigators to involve their students and postdoctoral associates in peer review to provide critical training, the exercise is only effective if mentors offer oversight for the process. Unless senior investigators consider peer review to be a critical component of their professional lives, the primary gatekeeper for the scientific literature will be lost.

Even more troubling is the emergence of new "predatory" scientific journals that claim to conduct peer review, but really don't (6, 7, 13, 17). It is possible to publish a paper in such a journal that has not been rigorously scrutinized. If a study is funded by government agencies like the National Institutes of Health (NIH), then a related publication in a predatory journal will be indexed in search engines such as PubMed, leading many readers to falsely believe that it has been subjected to a thorough editorial process (16).

In response to these troubling developments, a number of publishers have taken some steps to improve the quality of the manuscripts that they publish. They include checklists for authors and reviewers to assure that all salient methodological details are included in articles (3, 18), and the addition of a statistical reviewer for submissions (9, 25, 28). Some journals are also requiring the inclusion of a power analysis in manuscripts to demonstrate that the sample size for the study was adequate (31). New legitimate open-access journals have emerged to provide outlets for publication of negative data (26). Organizations like scholarly open access are providing information to authors about predatory journals (6), and there are actions in courts to suppress predatory publishers (14). Journals are increasingly offering venues for authors to provide feedback about the articles they read (21).

However, scientists and scientific administrators must do a better job of self- policing to assure the validity of the scientific literature. Pressure to publish in high impact factor journals must subside; investigators should be rewarded for the quality of the work that they publish, and not the name of the journal it is published in. Granting agencies should appreciate the importance of replicating data, and provide funding to do so. Senior scientists must understand that performing thorough and timely peer review of articles is their responsibility, and their supervisors must value these peer review activities. Failure to take these steps will result in wasted scientific efforts, diminished confidence of the public in the research enterprise, and ultimately the loss of monetary investment in research.

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The Future of Computational Physiology and Medicine

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Running Head: The Physiome

Abstract

The IUPS has been at the forefront of promoting collaborative international research on multi-scale computational modeling and systems biology physiology. Recent progress in this field is paving the way for fundamental advances in computer-aided physiology and personalized medicine.

Key words:

Physiome, Systems Biology, Multi-Scale Modeling

The sequencing of the human genome and the advent of the big data era of biomedical science have driven the vision of a new personalized medicine enabled by the new universe of personal health data that technologies like DNA sequencing, transcriptomics, proteomics, metabolomics and microbiome profiling promise to deliver to physicians. But standing in the way of this new era of medicine are the weak correlations found in most GWAS studies and the realization that personalized diagnosis can only be translated to personalized therapy with a much larger pharmacy of individualized combination therapies. Hence, the more immediate, if less ambitious, goal has turned to "precision medicine", which aims to refine the taxonomy of disease to better reflect the specific molecular etiology and thus inform the optimal choice of targeted therapeutics. Already this approach is allowing clinical trials of new cancer therapeutics to be tested in better selected patient cohorts and is leading to promising outcomes. But how readily this strategy will translate to many other diseases will depend on how well biomedical science can reliably integrate from genome to physiome so that the natural history of disease and responses to therapy can be predicted in individual patients. Fortunately, the international physiology community in general - and the IUPS in particular - has been at the forefront of mapping the path to this goal for the past quarter of a century.

Predictive, mechanistic mathematical models have informed experiments and enhanced understanding of physiology since Poiseuille and Hagen, Krogh and Huxley. In the 21st century, building on the success of reductionist biological science, modern computational physiology has provided powerful tools to integrate this new information into physiological knowledge. Indeed, computational approaches facilitate the goal of integration in three separate yet highly complementary ways: *Information* or *data integration* is the goal of bioinformatics, which annotates, archives, searches, compares and mines the troves of genome-scale biological data; With the list of components in hand, it becomes possible to reconstruct and model the cellular networks involved in signaling and gene expression, protein synthesis and degradation, metabolism and other cell functions. This *functional integration* is the goal of systems biology, which attempts to build computational models that predict the emergent functions of these cellular networks from the functional interactions of their components. But neither a complete parts list nor large, comprehensive network models of cellular subsystems and their dynamics are sufficient alone to explain normal organ, system and whole body physiology, much less the phenotypes of disease and aging. This missing link, of course, is *structure*. The third way in which computation can be integrative is structurally across physical scales of biological organization from molecular to population scales. In contrast to data-driven systems biology, multi-scale biological modeling is physics-driven and limited in large part by available computational power. But rapid advances in algorithms and computer hardware performance are beginning to push atomic-resolution molecular models to physiologically relevant spatial and temporal scales, and also advancing multi-scale cell-to-organ models towards clinical feasibility.

Integrated multi-scale models of physiological structure-function relations and pathophysiological dysfunction actually require the synthesis of all three computational approaches to integration: bioinformatics to organize molecular, structural and functional data; molecular modeling to predict the proximal effects of drugs, mutations, polymorphisms, or post-translational modifications; systems biology to integrate those molecular functions into network models of cellular dynamics, and anatomically explicit multi-scale "physiome" models of cell to organism scale biophysics and physiology. This ambitious vision of a new computational physiology was first articulated nearly three decades ago by Denis Noble at Oxford and James Bassingthwaighte in Seattle. They gave us the Physiome moniker and, along with Peter Hunter (New Zealand), Aleksander Popel (USA), Yung Earm (South Korea), Akinori Noma (Japan), Adriano Henney (UK) and many others established the IUPS as it's leading international flag-bearer.

I have not yet seen a fully executed example of a multi-scale physiome model that has integrated from atomic molecular dynamics to whole body systems physiology, but in some areas such as cardiac, liver and microvascular physiology just about every bridge between scales has been built, and in some cases many of the scales of biological organization have already been spanned - from atoms to molecules, molecules to complexes, complexes to networks, networks to cells, single cells to multi-cellular tissue niches, tissues to organ, organs to system, systems to whole organism, and organisms to populations. I would not be surprised to see the first complete example by the time of the 2021 congress. Needless to say, the approach is not to model every atom in the body. The challenge is in identifying, for the problem at hand, the variables that must be exchanged between one scale and the next, and the answer will invariably depend on the problem that the model is addressing. In some cases, cellular noise and stochasticity, or multi-cellular heterogeneity are critical to understanding emergent tissue functions, while in others mean field approximations can be sufficient. In some problems the paracrine interactions between different cell types are paramount, whereas in others a single cell type may be sufficient to predict the organ-scale phenotype.

As new paradigms for genome to physiome modeling are developed, shared and validated with properly designed physiological experiments, the way that physiologists design and conduct experiments will change. Increasingly, we will turn first to computational models to generate and test hypotheses *in silico*, to understand sources of variability better, to identify physiological responses that are most sensitive to upstream perturbations, and to better understand homeostasis and physiological robustness and how they are changed by aging and disease. Failure of model prediction will become as valuable as success, by pointing to areas where new mechanisms are needed and in turn leading to better models.

While multi-scale physiome modeling is already experiencing success in bridging wide ranges of spatial scale, the ranges of *temporal* scale in physiology are even greater, from the picosecond scale of atomic motions to the decades of human life-span and the generations of evolutionary time. Among the most pressing immediate challenges in modern multi-scale modeling is extending models of cell, tissue and organ physiology to the time-scales of development, the natural history of disease and aging. But as models of gene regulatory networks, transcription and translation in mammalian cells continue to improve, it is now realistic to anticipate a new generation of physiome model that remodel themselves over periods of days, weeks, months and perhaps even longer. Today's engineers use computational simulations for "accelerated wear testing" of their designs so that lifetime performance can be predicted in a fraction of real time. We are starting to see the first examples of this new class of model in simulations of chronic pathophysiological processes and therapeutic responses.

So how does all of this progress advance the vision of personalized, precision computational medicine? Already in musculoskeletal, cardiac, lung, blood, liver, metabolic and infectious diseases, modeling is being tested to plan surgical procedures, provide clinical decision support for device therapies and medical management of individual patients, to optimize pharmacotherapies, design better clinical trials, provide training simulators, and predict the spread of infectious outbreaks. As these clinical and patient-specific models become less empirical and more mechanistic by spanning more scales of biological organization, they will become a natural foundation for fusing biomedical “big data” in a rationale, disease-centric and patient-specific way. The notion that machine learning will improve health by mining everything from our genomes to our Facebook profiles is largely a fantasy to most physiologists who know that the foundations of medical science are much more than a large stack of data but the culmination of centuries of carefully designed models and experiments, hypothesis testing, quantitative analysis and theoretical analysis. Only with carefully validated, mechanistic functionally and structurally integrated multi-scale models can the opportunities for biomedical big data fusion and computational medicine be realized. Fortunately, the IUPS is leading the way.