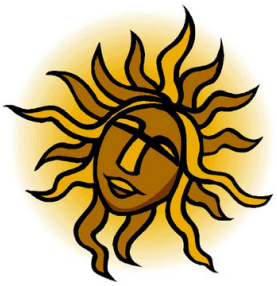
The Microcirculatory Society, Inc. Newsletter

Volume 32, Number 1 Summer 2004

Contents



Officers

President's Message

H. Glenn Bohlen

After a glorious 50-year celebration of the founding of the Microcirculatory Society in Washington, I can tell you that our Society is alive and well. It is on this theme of our Society as a living entity that strikes me as being very important to the future of our success.

Over the past 50 years, microcirculatory research has changed from beautiful descriptions of what the microcirculation does at a phenomenological level to how the regulatory processes control individual cells of the vessel wall and blood elements. Presentations at our meetings have evolved from visual descriptions of the microvessels to physical measurements of events in individual vessels to molecular and genomic regulation of cellular processes. The Society has done what all life forms do, evolve and adapt to new opportunities. However, one aspect of the Society that needs to remain constant and even be accentuated at every opportunity is the camaraderie between the members.

Over the past several years as a Council Member, President-Elect, and now President, I have been very pleased to see that one of the greatest concerns of members is maintaining the camaraderie of the Society. The change from a separate meeting before the Experimental Biology Meeting has eroded part of the opportunity for fellowship of the members at the national meeting. This year the celebration activities definitely helped with the fellowship aspect and interactions at posters had some of the flair of years when we met as a separate body. There have been a number of suggestions to attempt to improve the camaraderie aspects of the Society. One avenue with strong support and frankly, some strong opposition, is the testing of separate fall meetings each year or perhaps in alternate years. For the Fall of 2005, we will have a joint meeting with the British Microcirculatory Society and you will be hearing much more about the meeting from Ann Baldwin. Also, our Council is discussing a possible Fall Meeting in 2006 in Hawaii. To be sure that

...continued on page 2

...continued from page 1

the Membership supports this possibility, we have completed an on-line vote of the Membership. The vote "for" was highly favorable (77% in support of the proposed meeting). Like all living organisms, we have to try new opportunities. Some will be very successful, some will fail miserably. However, a few successes are more than worth the problems caused by failures. Council is very open to your suggestions to improve both the annual Spring Meeting and test new approaches to enrich the Society.

One of the reasons that our Society has flourished over the past 50 years is the dedication of both the Membership and elected leadership to serving the Society. If you have not been on a committee of the Society or an elected member, you have not seen the large amount of activity that goes on each year to nourish our Society. Over the past several months since becoming President, I have been replacing chairs for our various committees as needed and with the help of all of the chairs, replacing committee members. No one asked to be a chair of a committee has refused this commitment and only one person out of over a dozen had to decline being a committee member. In fact, most of the people contacted to serve say in one form or another how much the Society has helped their career and nourished their development as a scientist. They willingly wanted to actively repay a debt of gratitude. I do not see this level of Membership devotion in the several other societies where I have leadership roles. Our Society is quite unique in the devotion of the Membership to support and serve as needed. Committee Membership is a very important aspect of the Society because members provide the continuity of devotion and knowledge that keeps the Society growing and evolving. As both a member of the Society and President, I sincerely appreciate all the work of the former and current committee members over the past 50 years. They are the heart of our Society and that heart is strong.

If our Society is a living organism as I propose, one cannot help but wonder where it is in its life span. I would like to say the Society is a robust and young creature that weathers every storm, seeks new horizons, and strongly protects and nourishes its young. To a large extent, I think my description is substantially correct, but I realistically see some serious problems, as do many members of the Society. Most of the problems revolve around maintaining the identity of the Society at the Experimental Biology Meeting, increasing Membership payment of dues to support the financial responsibilities of the Society, enhancing the camaraderie of the Membership, and encouraging new members, particularly younger people, to join. A number of new approaches to highlight our Society at the Experimental Biology Meeting are being considered by various Committees and you will hear about them as they evolve. In recent years, payment of dues has frankly been poor: about half the membership pays dues. This has to change to maintain the Society's ability to support our journal Microcirculation, provide new awards and travel opportunities for young members, allow for another symposium at the spring meeting, and possibly separate meetings. I will be contacting all members who have not paid their dues by early Fall to personally find out if there is a problem they have with the Society that has caused them not to contribute. If you simply forgot or postponed paying your dues and do not want to hear from me, please pay your dues. If you have a problem with the Society that prevents you from paying your dues, let me know (gbohlen@iupui.edu or 317-274-8770). The Society exists for the benefit of the Membership and evolves based on the needs of the Membership. My image of the Society as a robust and young creature that weathers every storm, seeks new horizons, and strongly protects and nourishes its young is only true if the entire Membership supports the Society with their service and financial responsibility. We have prospered greatly for the past 50 years because of the service and financial support of the Membership. The health and well being of this great organism we call the Microcirculatory Society depends on your support today and over the years to come.

General Business Meeting
April 17, 2004

Convention Center Room 146C
Washington, D.C.

Geert Schmid-Schonbein, MCS President, called the meeting to order at 5:30 PM in Room 146C of the Washington D.C. Convention Center. There was verification of a quorum. The minutes of the 2003 General Business Meeting were accepted as written.

Report from the Secretary

None

Report from the Treasurer

Ann Baldwin provided a report on the financial status of the Society. She was much more optimistic about the state of the Society's assets, which have increased. More people have paid their dues (although the number of people not paying dues remains a problem for the Society).

Assets of the 2003 Spring Meeting: $192,072.72
Assets in 2004: $211,017.16

MCS income totaled $72,477.04 while MCS expenses in 2004 totaled $79,355.88

Membership Data: Only 203 members (out of 604 in the database) have paid their dues. Dues income has been falling each year.

COMMITTEE REPORTS

Publication Committee

Ginger Huxley presented a report for the Publication Committee. She reported that the transition to the new Editorial Office was successful. The Publication Committee discussed a Conflict of Interest form to be used for the Journal. The Committee decided to adopt a model of the form utilized by the American Physiological Society that deals with (1) access to data, (2) institutional conflicts and (3) monetary agreements. Bill Jackson made a motion to adopt this Conflict of Interest form for Microcirculation. Seconded by Julian Lombard. Motion carried by unanimous agreement.

Ginger also announced the two Journal award winners. Donald M. McDonald was awarded the Mary E. Gerritsen Award for the most cited review article published in Microcirculation 1999-2004. Allen Swei was awarded the Curt A. Wiederhielm Award for the most cited research article published in Microcirculation in the last five years. This article was entitled "A Mechanism of Oxygen Radical Production in the Dahl Hypertensive Rat" and appeared in Microcirculation 6(3): 179-187, 1999.

Journal Report

Bill Jackson presented a report on the Journal. The transition from Nature Publishing to Taylor and Francis is complete. Bill encouraged the membership to submit quality articles for publication in Microcirculation. Members may also submit ideas for the Hot Topic/Special Topic issues. Beginning in 2005 we will have ePublishing ahead of print to accelerate dissemination of information. All submissions and reviews are being done electronically which is speeding up the review process tremendously. The indexing format for MedLine has been corrected. Institutional subscriptions are way down so members were encouraged to approach their institutions to solicit subscription renewal. Microcirculation will publish abstracts from the Microcirculatory Society sessions at the spring meetings and will publish abstracts from the fall meetings when they begin.

Membership Committee

Molly Frame gave a report for the Membership Committee. The number of regular member applications has quadrupled with the use of the on-line form for membership. Sponsorship only requires email confirmation, no detailed letter. David Bates suggested changing the by-laws to allow individuals without a Ph.D. to be regular members. The Membership Committee will consider this proposal as well as the possibility of corporate memberships.

Historical Committee
There was no formal report from the Historical Committee. Geert Schmid-Schonbein reminded the membership that the historical posters displayed as part of the 50th Anniversary Celebration will be included on the MCS website. Members should suggest other posters that can be included in this display.

Liaison Committee/Long Range Planning Committee
Ingrid Sarelius reported that planning for the IUPS meeting is proceeding well. Programming was done earlier than usual. The Landis Award winner has already been selected and will be announced in conjunction with this meeting. The President's Symposium has already been selected. Members were cautioned that poster topics will be different for this meeting, but this may encourage new people to participate.

Web Report
Bob Gore provided a report as the "Web Master." Major projects for 2003-2004 included (1) improving the on-line capability for credit card purchase of banquet tickets for the Annual Society Awards Dinner and the 50th Anniversary Banquet, (2) implementing an on-line membership application system to help streamline membership applications and recruitment, (3) implementing an on-line voting system for election of officers, and (4) completing the transfer of all on-line journals, volumes 5-10, of Microcirculation from The Nature Group Publishing Company to Taylor and Francis. Bob also provided the summary of the web server statistics and plans for 2004-2005.

Nominations Committee
Steve Segal presented a report from the Nominations Committee. Steve encouraged members to submit more nominations. The on-line voting system worked quite well for elections this year. However, only 20% of the membership voted, so Steve reminded members that they need to be more involved in Society activities.

Awards Committee
Leslie Ritter reported on activities of the Awards Committee. Awards are considered a high priority for the Society and take up a large portion of the meeting budget. Leslie reported that the Executive Council approved an increase in the Young Investigator Travel Award to $5000. The Crone Award will be temporarily disbanded due to loss of sponsorship.

Programming Committee
A total of 180 abstracts were submitted. Members were encouraged to submit to microcirculation categories rather than other categories. Suggestions for changes in the topic categories should be sent to Ingrid Sarelius, who will be the new Chair of the Programming Committee. The President's Symposium and the Landis Lecture will be held on Sunday. The Young Investigators' Symposium will be held on Monday.

Revisions to the By-Laws
Two proposed changes to the MCS bylaws were considered:

Article III, Section 9: Receipt of nominations and election to membership shall be carried out on a ~~rolling~~ continuing basis throughout the year.

Article IV, Section 7: Access to the directory information for individual members shall be made available on the Society's website.

A motion was made to accept these revisions. MOTION PASSED.

TRAVEL AWARD PRESENTATIONS

David Bates, 2003 recipient of the Crone Award, and Cuihua Zhang, 2003 recipient of the Young Investigator Travel Award, received their awards and made short presentations highlighting their travels.

OLD BUSINESS

Geert Schmid-Schonbein discussed the organization of the scientific meetings for the Society. The Society has seen some advantages from programming within Experimental Biology but has paid a price in losing new, young members. At the Executive Council Retreat in San Diego, the Council voted to set up

a Fall Meeting using the Gordon Conference style of morning and evening sessions with afternoons free. This will allow the Society to promote the work of young investigators and have full control of the programming. Geert asked the membership for acceptance of the Council's proposal to initiate a stand-alone meeting of the Society. There was discussion of the benefits of this atmosphere to re-establish camaraderie within the Society. A disadvantage of this meeting would be the risk of getting enough attendance to support the endeavor and getting attendance from investigators in areas outside of microcirculation. Ginger Huxley suggested a time limit for the "experiment" of fall meetings, to determine if the effort and cost will be successful. There were warnings from a number of individuals that coordination of this meeting with other society meetings was crucial so as not to compete for participants. MOTION to accept the Council proposal for fall meetings PASSES (22 in favor, 15 against, 4 abstentions). The Council has suggested that the 2005 meeting be in conjunction with the British Microcirculation Society and the 2006 meeting be in conjunction with the Japanese Microcirculation Society. Geert will suggest a revision of the by-laws to reflect this change in procedure.

NEW BUSINESS

Acknowledgment and thanks were given to past Council members as well as committee members/ chairs for their service. There was a transfer of the Presidency to Glenn Bohlen and an acknowledgment of the service of Robert Hester, President-Elect.

Ann Baldwin made a short presentation of the plans for the 2005 meeting.

The meeting was adjourned at 7:00 PM
[Respectfully submitted, Cynthia Meininger, Ph.D., MCS Secretary]

2004 Microcirculatory Society Treasurer's Report

Submitted by Ann L. Baldwin, MCS Treasurer

Assets as of 2003 Meeting		
Bank One Checking	2/28/03	33,010.54
Vanguard	3/27/03	74,834.19
Certificate of Deposit	3/26/03	$84,227.99
TOTAL		
MCS Assets 2004		
Bank One Checking	3/31/04	36,131.70
Vanguard	4/08/04	87,903.58
Certificate of Deposit	4/12/04	86,981.88
TOTAL		$211,017.16
MCS Income:		
APS Contribution to MCS		10,000.00
Nature/MacMillan Publishing		9,000.00
MCS Dues from 3/01/03 – 3/31/04		38,775.00
Banquet Tickets 2003		1,642.00
Banquet Tickets 2004		8,300.00
Donation for Crone Award, 2004		2,000.00
Donations for Young Investigator Travel Awards		690.00
Texas A & M Gerritsen Award 2002-03		2,070.00
TOTAL		$72,477.04
MCS Expenses 2004		
MCS Awards		14,000.00
Award Certificate Paperwork		311.70
MCS 2003 Banquet and Projector		9,030.33
MCS 2003 AV Equipment		125.75
MCS 2003 Speaker/Awardee Expenses		5,275.36
MCS 2003 Council Meeting		382.48
MacMillan Publishers		
250 copies Vol. 9 (4)		2,082.50
374 copies Vol. 9 (5)		3,115.42
286 copies Vol. 9 (6)		2,382.38
298 copies Vol. 10 (1)		2,771.40
376 copies Vol. 10 (2)		3,496.80
199 copies Vol. 10 (3/4)		1,783.04
Journal Editorial Operation Budget 2003		10,022.99
Compensation for Journal Manager		7,500.00
Holly Lopez, (Direct Operations)		2,180.52
Holly Lopez Conference Expenses 2003		497.76
Postage		1,031.38
Fed Tax Form Preparation		925.00
Computer Software, etc.		919.17
Conference Call Fees		584.47
Credit Card Fee		715.64

Bank Service Fee	96.79
Deposit for MCS 2004 Council Meeting	125.00
MCS/BMS Conference Deposit	10,000.00
TOTAL	$79,355.88

Membership Data

	2003	2004
Names in Database	569	604
Emeritus Members	55	58
Possible Dues Paying Members	514	546
Paid Members	274	203

Dues Income

2002	$24,760.00
2003	$23,710.00
2004 to date	$19,165.00

Welcome to New MCS Members

Regular Members

Daniel Goldman, Ph.D.
Department of Mathematical Sciences
Newark, New Jersey

Michele L. Barnard, Ph.D.
Review Branch
National Institutes of Diabetes & Digestive & Kidney Disorders
Bethesda, Maryland

Joseph Barnard, Ph.D.
Department of Pulmonary Critical Care Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland

Joseph Loscalzo, M.D., Ph.D.
Department of Medicine
Boston University School of Medicine
Boston, Massachusetts

Associate Members

Tamer Altay, M.D.
Department of Neurosurgery
College of Medicine
St. Louis, Missouri

Student Members

Feilim C. Mac Gabhann
Department of Biomedical Engineering
School of Medicine
Baltimore, Maryland

Melanie B. Elliott
Department of Physiology
School of Medicine
Philadelphia, Pennsylvania

Juliene Throop, D.V.M.
Department of Veterinary Medicine and Surgery
College of Veterinary Medicine
Columbia, Missouri

Derek D. Best
Department of Pharmacology and Physiology
University of Rochester School of Medicine
Rochester, New York

Emmanouil Karagiannis
Department of Biomedical Engineering
School of Medicine
Baltimore, Maryland

'News' Announcement

The International Union of Physiological Sciences (IUPS) and the American Physiological Society (APS) would like to inform those who subscribe to **News in Physiological Sciences (NIPS)** that when they receive their August issue in the next few weeks, the journal will have a new title and ISSN. The journal will be entitled *Physiology*, and the new ISSN is 1548-9213, but it is a continuation of NIPS, Volume 19.

IUPS Executive Secretary

INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES

3 May, 2004

Memorandum to: IUPS Member Societies

Subject: Young Investigators Awards

The IUPS is very pleased to be able to inform you that at the forthcoming 35th International Congress of Physiological Sciences (31 March - 5 April) in San Diego, a certain number of Young Investigator Awards will be offered.

The IUPS Congress Travel Award Program is designed to encourage the participation of students and physiologists who are within 15 years of receiving their doctoral degrees. Priority will be given to physiologists from developing countries and underrepresented minorities who have submitted abstracts to the Congress.

Please inform the members of your organization of this program. The deadline for receipt of six copies of the attached application by The American Physiological Society is 1 November 2004.

Sincerely yours,

Ole Petersen
Secretary General

IUPS Secretariat L.G.N., Bâtiment CERVI, Hôpital de la Pitié-Salpêtrière, 83 Boulevard de l'Hôpital

F-75013 Paris, France
Tel: (33) 1 4217 7537 fax: (33) 1 4217 7575 *suorsoni@infobiogen.fr*

Surname _____

XXXV IUPS CONGRESS TRAVEL GRANT PROGRAM

San Diego, California USA
March 31 – April 5, 2005

The IUPS Congress Travel Award Program is designed to encourage the participation of students and physiologists who are within 15 years of receiving their doctoral degree. Priority will be given to physiologists from developing countries and underrepresented minorities, who have submitted abstracts to the Congress.

1. Name and Degree: _____ Year of highest degree: _____
2. Position or employment title: _____ Year of Birth: _____
3. Address: _____
   _____
   _____
4. Phone Number: _____ Fax Number: _____
   Email Address: _____
5. Country of citizenship: _____
6. **Optional** Underrepresented Minority Applicants [For US applicants only]: Please circle ethnic group to which you belong: African American Hispanic Native American Pacific Islander
7. Male Female
8. Attending entire Congress? Yes ____ No ___
   If not, which days will you attend? _____
9. Do you plan to attend a satellite meeting? Yes _____ No ____
   If so, please indicate which satellite meeting you plan on attending _____
   _____
10. Do you intend to submit an abstract to the Congress? (If yes, please give title): _____
    _____
11. Please describe your area of specialty (e.g. cell physiology, neurophysiology, etc.): _____
    _____
    _____
12. List all physiological societies with which you are a member: _____
    _____
    _____
13. Are you employed by the U.S. federal government more than half-time? Yes _____ No _____
14. Travel: a. City of departure _____ b. Support requested _____
    c. Amount of other support available (excluding personal) _____

15. Recent publications (not more than 5 titles, giving full refs). If listing manuscripts in press or abstracts, please indicate.

16. Anticipated abstract (Not more than 250 words on paper or poster you plan to present at the Congress, including names of author and coauthors and indicate presenter. If none, abstract of current work.)

17. Give a brief resume of the scientific purposes and goals of your trip in addition to attending the Congress, including other meetings, satellite symposia, laboratories you plan to visit, work on collaborations, etc.

Microcirculatory Society Committees 2004-2005

Committee Members	*Term*	*Telephone No.*
Executive Council		
Joseph Unthank	(05)	317-630-7866
Ronald Korthuis	(05)	318-675-6028
Paul Kubes	(06)	403-220-8558
Mary (Molly) Frame	(06)	631-444-2320
Deborah Damon	(07)	802-656-2184
Sarah Yuan	(07)	254-742-7036-
Awards		
Leslie Ritter (C)	(05)	520-626-7434
Joseph Benoit	(05)	701-777-4388
Terrence Sweeney	(06)	570-941-7623
Russell Prewitt (VC)	(06)	757-446-5105
Roland Pittman	(07)	804-828-9545
Mark Clemens	(07)	704-687-2318
Finance		
David Sims	(05)	902-566-0812
Tim Secomb	(06)	520-626-4513
Roger Adamson	(06)	530-752-2180
Molly Frame (C)	(06)	631-444-2320
Development		
Michelle Mazzoni	(06)	858-410-5189
Mary Gerritsen (C)	(06)	650-244-6854
Jay Tuttle	(06)	760-510-1404
D. Neil Granger	(07)	318-675-6011
Donald Heistad	(07)	319-356-2706
Historical		
Paul Johnson	(05)	858-534-5686
Robert Gore	(05)	520-626-6569
Robert McCuskey (C)	(06)	520-626-6084
Herb Lipowsky	(06)	814-865-1407
Ronald Tuma	(06)	215-707-3248
Liaison		
H. Glenn Bohler	(05)	317-274-8770
Cynthia Meininger	(05)	254-742-7037
Makoto Suematsu	(06)	81-3-5363-3753
Paul Kubes	(06)	403-220-8558
Virginia Huxley (IUPS)	(06)	573-882-8069
Julian Lombard (C)	(07)	414-456-8530
Terry Sweeney	(07)	570-941-7623

Committee Members	*Term*	*Telephone No.*
Membership		
Travis Hein	(05)	254-742-
Chris Ellis	(05)	519-661-3100
David Zawieja (C)	(06)	979-845-7465
Dick Slaaf	(06)	31-43-3881657/59
J. Steven Alexander	(07)	318-675-4151
Anatoliy Gashev	(07)	979-845-7990
Nominating		
Steven Segal (C)	(05)	203-562-9901 ext. 253
Deborah Damon	(06)	802-656-2184
Thomas Skalak	(06)	434-924-0270
Tara Haas	(07)	416-736-2100 ext. 77313
Long-Range Planning		
Geert Schmid-Schonbein	(14)	858-534-3852
Paul McDonagh	(13)	520-626-2329
Ingrid Sarelius	(12)	575-275-7729
Walter Duran	(11)	973-972-4372
Ronald Tuma	(10)	215-707-3248
Bruce Klitzman	(09)	919-684-6686
Julian Lombard	(08)	414-456-8530
Virginia Huxley	(07)	573-882-8069
Gerald Meininger	(06)	979-845-7491
Fitz-Roy Curry	(05)	530-752-1973
Program		
Ingrid Sarelius (C)	(05)	575-275-7729
Donald Welsh	(05)	403-210-3819
Walter Duran	(06)	973-972-4372
David Bates	(06)	44-0117-9287283
Mike Flessner	(07)	601-984-5765
Judy Muller-Delp	(07)	979-458-3502
Publication		
D. Neil Granger	(06)	318-675-6011
Klaus Ley (VC)	(06)	434-924-1722
Fitz-Roy Curry	(06)	530-754-9380
Paul Kubes (C)	(07)	403-220-8558
Richard Price	(07)	434-492-0457
Samina Kanwar	(07)	732-594-2469

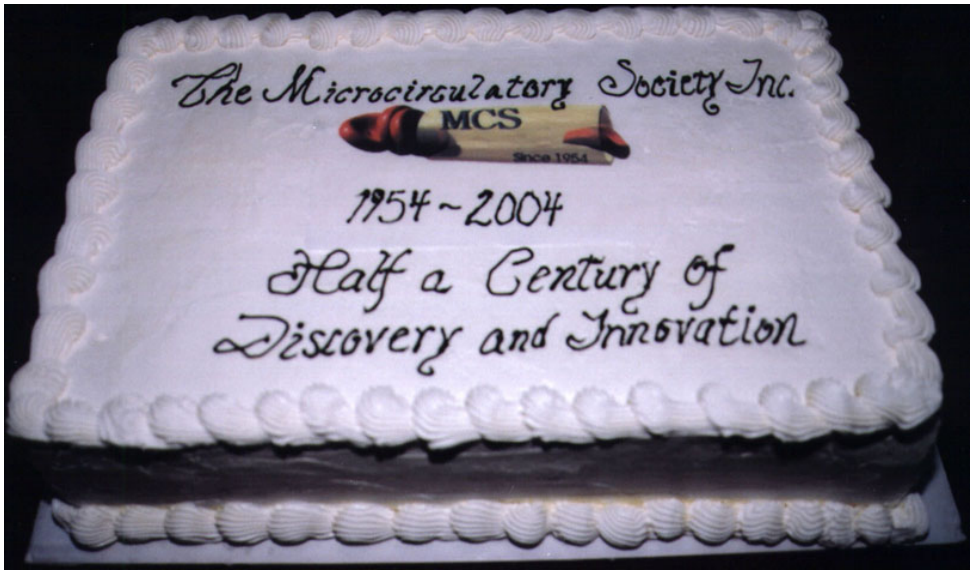
MCS 50th Anniversary Banquet

National Academies of Science Banquet Facilities

The Crowd Gathers

Past Presidents of the Microcirculatory Society

MCS 50th Anniversary Cake



Dr. Geert Schmid-Schonbein presents the Landis Award to Dr. Robert McCuskey

CAPILLARY PERMEATION THROUGH THE ENDOTHELIAL BARRIERS

James Baissingthwaite, Dept of Bioengineering, University of Washington, Seattle, WA

Modern developments in the understanding of the mechanisms for the passage of solutes between blood and tissue preceded clear visualization of capillary endothelium by electron microscopy, but were in fact greatly aided by the rapid advances in knowledge of the anatomy in the 1960's. Microcirculatory research was aided too by the use of quantitative approaches to analysis of data obtained on intact living systems. The pioneering works of Pappenheimer, Chinard and others was extended by developments of indicator dilutions techniques by Crone, Renkin, and Yudilevich following the mathematical analysis of Sheppard. Further novel approaches depended upon the systems analyses of Zierler and the analytical approaches of Goresky to indicator dilution experiments and of Johnson and Vargas to osmotic transient experiments. The systems approaches did not provide enough detail to interpret the mechanisms but there was a conflict in the interpretation of osmotic and tracer dilution studies, namely that the tracer technique suggested that reflection coefficients were close to zero for a wide range of small solute sizes, but osmotic transients suggested marked steric hindrance. This anomalous situation has been resolved by Agre's identification of aquaporin channels and subsequent mathematical analysis by Kellen accounting for the different paths taken by water, hydrophilic solutes and proteins across the capillary membrane.

DIABETES MELLITUS: FROM A HISTORICALLY RARE DISEASE TO AN EPIDEMIC OF METABOLIC AND VASCULAR COMPLICATIONS

H. Glenn Bohlen, Department of Cellular and Integrative Physiology, Indiana University Medical School, Indianapolis, IN

One of the strangest facets of diabetes mellitus is that the severe microvascular disease associated with both insulin dependent and independent diabetes was not realized until after the discovery of insulin. The role of obesity in adult onset diabetes was recognized centuries ago, but, prior to the advent of insulin treatment, diabetic humans seldom lived long enough to develop recognized microvascular disease. However, as insulin treatment increased the life span of diabetics from a few years to decades, it became apparent in the 1940-1950's that renal, neuronal, ocular, and cutaneous microvascular disease plus accelerated atherosclerosis would be major challenges in clinical care. For the past 60 years, the primary emphasis of vascular research in diabetes has been the causes, treatments, and prevention of microvascular complications. Two very clear issues have evolved, hyperglycemia is a key risk factor for microvascular disease and duration of the disease increases the probability of vascular impairment. The current understanding is that hyperglycemia leads to excess diacylglycerol in most cells that activate protein kinase C (PKC) and is associated with increased oxygen radical formation. The vascular smooth muscle cells generally overreact to excitation in endothelial cells, PKC activation among other problems suppresses endothelial nitric oxide synthase such that the local concentration of nitric oxide substantially declines. Fortunately, PKC inhibitors show great promise in early studies of both diabetic animals and humans to limit chronic abnormalities as well as quickly restore nitric oxide production during short term hyperglycemia. Despite the progress in diabetes research, the incidence of diabetes is increasing at an alarming rate due to obesity. Obesity is associated with most of the vascular regulatory problems associated with insulin resistant diabetes and is a leading contributor to moderate hypertension. Furthermore, obesity lowers the glucose concentration that causes vascular cell regulatory abnormalities. Therefore, what once was a rare disease has become an epidemic medical problem with 7-10% of the United States population known to have diabetes and twice that fraction at risk.

MICROELECTRODES IN THE MICROCIRCULATION

Donald G. Buerk, Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104

If you accept the time worn axiom (as I do) that you need the right tool to do the job right, and you really can't see what you are working on without a microscope, then you might agree that microelectrodes are the right tools for studying the microcirculation. This has certainly proven to be true for a number of distinguished members of the Microcirculatory Society, who perfected a variety of different microelectrode techniques. Practical uses for these tiny tools range from microneedles to mechanically compress individual capillaries as a way to study fluid exchange, to fluid filled open tip micropipettes to measure blood pressure in arterioles and venules, or to alter the local chemical environment or deliver drugs to individual blood vessels by microperfusion. Electrochemical sensors were also miniaturized, and early oxygen microelectrode measurements in the microcirculation were discussed as part of a methods workshop sponsored by the Microcirculatory Society at the University of Arizona in 1972. The desire to measure other physiologically relevant chemical species was also expressed in this workshop, and subsequently pursued over the years in many microcirculation laboratories. A history of these efforts will be reviewed.

THE MICROCIRCULATION OF THE HEART: A HISTORICAL PERSPECTIVE

In memory of Stephen H. Nellis, Ph.D. and Melvin L. Marcus, M.D.

William M. Chilian, Lih Kuo, Cuihua Zhang, Louisiana State University Health Sciences Center and Texas A&M University Health Science Center.

Over 100 years have elapsed since the classic work of Langendorff revealed phase differences between coronary inflow and outflow. Langendorff observed that during cardiac contraction coronary inflow was reduced, but outflow was augmented. During diastole, coronary inflow peaked, but outflow dropped to zero. He described the heart as a sponge that is wrung dry during systole, because of the squeezing action of the heart on the microcirculation, and the sponge refills during diastole when the sponge is no longer compressed. For the next 60–70 years, investigations into the microcirculation of the heart were at an impasse because of one major hindrance: the heart moves. Because of cardiac motion, microscopic analyses are difficult because not only is the desired image magnified, but motion is magnified. The first report of direct observations of coronary microvascular dynamics were accomplished without any attempts to compensate for cardiac motion. These investigators (Honig & colleagues) laboriously analyzed films of the epicardial surface of the heart and picked only those frames that were in focus. Richard J. Bing and his colleagues in the 1970's revitalized this area of research by using microscopic techniques, in conjunction with immobilization of the area that was being studied. Although this was traumatic, and such procedures likely influenced coronary tone, the series of contributions from Bing's laboratory set the stage for further advancements in ways to compensate for cardiac motion. In 1981 Nellis and coworkers published a study that showed the distribution of microvascular pressures in the beating right ventricle. These investigators developed a system that captured images from the beating heart using a stroboscopic illumination system that was synchronized to the heartbeat, which allowed captured images to remain in focus from beat to beat. These investigators also developed a three-dimensional micromanipulator that allowed measurement of microvascular pressures in the beating heart, and this micromanipulator could be programmed to mimic cardiac motion. Chilian, Marcus, and colleagues further refined the system developed by Nellis and reconfigured it to allow the system to acquire video images, and use epi-illumination to study the microcirculation of the left ventricle. At a similar point, Ashikawa and colleagues developed another preparation utilizing a floating objective to visualize the coronary microcirculation of the left ventricle. These investi-

gators reported the first measurements of microvascular flow velocities in the left ventricle and then reported the microvascular levels at which flow diverges during systole and diastole; thus dissecting the system further from what Langerdorff observed in the late 1800's. Since these studies in the 1980's, work on the coronary microcirculation has diverged with one path following the development and refinement of in vitro techniques for studying isolated coronary microvessels, and the other path is leading to the development of better and more non-invasive technologies to study the endocardial and intramural microcirculation. Studies of isolated coronary arterioles have been pioneered by the laboratories of Davis, Chilian and Kuo and have revealed a new understanding of regulatory systems within the coronary microcirculation, e.g., the myogenic response and flow-induced vasodilation. The development of more specialized imaging techniques to study the in situ beating heart, have lead to observations regarding the subendocardial coronary microcirculation and even the intramural coronary microcirculation using micro CT. What the future holds for the evolution of these technologies is still unknown, but perhaps in the next 100 years we will see further development of non-vasive imaging modalities which will allow us to study discrete segments of the intramural coronary microcirculation in the beating heart.

ARTHUR C. GUYTON: THE MAN AND HIS SCIENCE

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The remarkable life and science of Arthur Clifton Guyton is reviewed with historical accounts of his many accomplishments. He graduated at the top of his class at the University of Mississippi, distinguished himself at Harvard Medical School, and began postgraduate surgical training at Massachusetts General Hospital. His medical training was interrupted twice - once to serve in the Navy during World War II and again in 1946 when he was stricken with polio during his final year of residency training. During his recovery, he built the first motorized wheelchair and many other devices to aid the handicapped for which he received a Presidential Citation. Dr. Guyton then returned to the University of Mississippi School of Medicine and was named chairman of the department of physiology in 1948. He rapidly developed one of the world's premier cardiovascular research programs. Dr. Guyton's research contributions, which include more than 600 papers and 40 books, place him among the greatest figures in the history of cardiovascular research. He developed the first large scale computer model of the cardiovascular system. His research covered virtually all areas of cardiovascular regulation and led to many seminal concepts that are now an integral part of our understanding cardiovascular physiology and disorders such as hypertension, heart failure, and edema. He trained over 150 scientists, at least 29 who became chairs of their own departments and 6 who became presidents of the American Physiological Society. He and his remarkable wife Ruth raised 10 children all of whom became outstanding physicians. Through his *Textbook of Medical Physiology*, which is translated in at least 15 languages, he has probably done more to teach physiology to the world than any other individual in history. He is honored each year by The American Physiological Society through the Arthur C. Guyton Teaching Award and has received more than 80 major honors from scientific societies around the world. Arthur Guyton was a giant in the fields of physiology and medicine, a leader among leaders, a master teacher, and an inspiring role model for people throughout the world.

DEVELOPMENT AND USE OF SYSTEMS FOR THE STUDY OF ISOLATED, PRESSURIZED MICROVESSELS

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The first system for studies of isolated, pressurized arterioles was adapted by Duling, Gore et al. (Am J Physiol 241:H108, 1981) from the Burg microperfusion system originally designed for the study of single renal tubules. The basic configuration consisted of dual micropipettes and pipette holders onto which single arterioles (~50 μm, ID) were mounted, pressurized and viewed using a compound microscope and video display system. The vessels exhibited vasoactive responses similar to those observed in vivo and remained viable for up to 12 hrs. Since that time, the system has been adapted for vessels of many sizes, from 20 to >200 μm ID, and for a variety of different vessel types, including small arteries, arterioles, venules and lymphatics. Several different methods have been devised for securing vessels to micropipettes, selective removal of the endothelium, and short-term introduction of peptides and proteins into cells of the vessel wall. Bioassay experiments involving donor and recipient vessels have been described. There are now many uses for the isolated microvessel system, including the study of pressure-induced responses, flow-induced responses, conducted responses, pharmacological experiments, permeability measurements, vascular mechanics, calcium imaging and electrophysiology. The system has recently been modified for longer-term (multi-day) experiments of vascular behavior under semi-sterile conditions in which vascular smooth muscle and/or endothelial cells can be transfected. Collectively, the isolated microvessel method has been and will continue to be extremely valuable in advancing our understanding of microvascular function.

OXYGEN TRANSPORT: STILL LIMITED IN OUR KNOWLEDGE OF WHAT'S LIMITING

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August Krogh, formulated the problem in early part of the 20th century. There are more capillaries in striated muscle than are needed to support oxidative metabolism. His simple anatomical analysis coupled with masterful mathematical insight led to the idea that capillaries can open and close and that the capillary design is based on the maximal needs of the working, not the resting muscle. Thews reconsidered the problem in the brain some years later and realized that the loss of oxygen along the vessel length meant that the venous end of the capillaries might be the foci of limiting PO_2's and thus of tissue function. The Microcirculatory Society has been home to many investigators who have used microelectrodes, optical, and computational approaches to develop a deeper understanding of the limits to tissue oxygenation. This work shows that total blood flow and total O_2 supply to an organ or an organism do not adequately describe the true state of tissue oxygenation. Heterogeneity of blood flow, local alterations in hematocrit, O_2 shunting from arteriole to venule, local barriers to diffusion within the tissues and biochemical limitations to utilization of available O_2 all leave many elements of our understanding of tissue O_2 utilization in doubt and suggest that new tools for research are needed and new paradigms for analysis are required.

SHEET FLOW IN PULMONARY CIRCULATION

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The understanding of pulmonary blood flow is the result of a long history of contributions by pioneers and contemporary researchers. We added the view that the pulmonary capillaries form a vast sheet whose geometry, mechanical properties, and functions are easier to understand if we do not treat them as millions of circular cylindrical tubes. Concomitantly, the mechanical properties of large and small arteries and veins do vary from generation to generation. We must obtain the whole set of data on the geometry, materials, and mechanical properties of the vessels. Then a systemic analysis of the lung can yield predictions that can be verified by experimental measurements.

MACROSCOPIC AND MICROSCOPIC FLOW PROPERTIES OF BLOOD

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We describe the advances in blood viscometry made since 1954 and the correlation of these macroscopic flow properties with the flow behavior of the individual corpuscles and their shear-induced interactions. We begin with the GDM Couette rotating cylinder viscometer and its use (i) at very low shear rates, G, to measure a yield stress ~0.005Pa, and the effect of red cell (rbc) aggregation on the measurements, (ii) to study the decrease in apparent viscosity with increasing G as a function of rbc aggregation and deformation. Study of the microscopic flow properties was made possible by visualizing blood flow in a Wells-Brookfield viscometer adapted with a transparent cone and plate mounted on an inverted microscope ("rheoscope"), and by tracking cells in a "traveling microtube" apparatus. Formation of a network of flexible rouleaux at low G, and their migration away from the walls of a viscometer or vertical microtube was observed; in the microtube this led to a decrease in hydrodynamic resistance and displacement of white cells (wbc) to the walls. In Dextran/saline, a transition from rotation of rbc as discs to fluid drop-like behavior occurred. The cells were aligned with the flow; their membrane rotated about the interior. In transparent ghost cell suspensions, deformation and erratic radial displacements of rbc were seen even at shear stress < 0.1 Pa. Use of the rheoscope and high speed video to study the kinetics of formation and rupture of bonds between red cells, platelets and wbc is also described.

LEUKOCYTE-ENDOTHELIAL CELL ADHESION

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Since the initial description of leukocyte migration across microvessels by Dutrochet in 1824, interactions between leukocytes and vascular endothelium have captured the imagination of many investigators with an interest in the area of inflammation. The concept that endothelial cells (Cohnheim, 1877) and leukocytes (Metchnikoff, 1893) are activated during inflammation was introduced in the latter part of the 19th century. The phenomenon of leukocyte-endothelial cell adhesion was not studied in a systematic, quantitative fashion until the 1970s, when Atherton and Born (1972) used the technique of intravital microscopy to describe the relationship between number and velocity of rolling leukocytes in mouse mesenteric venules. This decade also witnessed the successful culture of HUVEC (Jaffe, 1973), the development of in vitro assays for quantification of leukocyte-endothelial cell adhesion (Hoover, 1978), and the application of intravital microscopy to human tissue (Branemark, 1972). The 1980s ushered the discovery of adhesion molecules that mediate leukocyte adhesion, including the beta-2 integrins (Buchanan, 1982), ICAM-1

(Dustin, 1986), E-selectin (Bevilacqua, 1987) and P-selectin (Hsu-Lin, McEver, 1989). During this period, the parallel flow chamber was developed to study the influence of shear forces on leukocyte adhesion to monolayers of cultured endothelial cells (McIntire, 1984), and the introduction of multi-step model of leukocyte recruitment in venules (Arfors, 1987). This period also represented the beginning of a large number of studies that addressed the role of leukocyte-endothelial cell adhesion in different animal models of disease. The 1990s witnessed the development of adhesion molecule knock-out mice and the application of these mutants to studies focusing on the regulation of leukocyte-endothelial cell adhesion in vivo or on the role of adhesion molecules in different experimental pathological conditions. This vibrant area of research has yielded over 25,000 reports in the scientific literature and has resulted in a large number of clinical trials to test the effectiveness of anti-adhesion drugs in the treatment of different diseases. Trials of anti-adhesion therapy that targets lymphocyte trafficking show considerable promise in several immune diseases, including multiple sclerosis, Crohn's disease, and psoriasis.

ANGIOGENESIS AND MICROCIRCULATION

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Angiogenesis, or growth of capillaries, occurs during development, in female reproductive organs, in skeletal and cardiac muscle exposed to long-term activity, and in pathological conditions such as healing wounds, tumors, psoriasis, arthritis or retino-pathies. Although originally described as capillary growth by sprouting, angiogenesis can also occur by intussusceptive growth, longitudinal splitting or endothelial cell elongation. In vivo observations have been made in tissues such as tadpole tails, rabbit ear, hamster cheek pouch or dorsal skin chambers, trans- or epi-illuminated skeletal muscles, chicken chorioallantoic membrane or corneas of various species. Two main causes for initiation and development of angiogenesis have been considered: mechanical (increased capillary blood flow and hence shear stress, elevated capillary pressure leading to increased filtration and permeability, and stretch of capillaries due to growth or malformation of surrounding tissues) or metabolic (hypoxia, metabolites, cytokines and assorted growth factors and their receptors). Recent work on angiogenesis from our and other laboratories shows how mechanical factors in the microcirculation act directly to activate various genes or indirectly, e.g. via nitric oxide, to modulate signals involved in its initiation. Inhibition of angiogenesis (mainly in tumors) and its initiation together with larger vessel growth in ischemic tissues particularly heart and skeletal muscle has enabled promising therapeutic developments. Future research should aim at finding better ways to assess angiogenesis non-invasively and to modulate relevant mechanical/growth factors and signal transduction in the in vivo context by physiological means.

THE LANDIS TECHNIQUE: EXPERIMENTAL VERIFICATION OF STARLING'S PRINCIPLE OF FLUID FILTRATION

V.H. Huxley, C.C. Michel and F.E. Curry

Following the observations of Carl Ludwig in 1861 that blood pressure in capillaries (P_c) could drive fluid out of the vascular space into the tissue, in 1896 Ernest Starling found that saline injected into tissue could be absorbed into the blood and that the osmotic pressure of large plasma proteins (plasma 'colloids) provided the counteracting force to draw fluids into the vascular space. It was E.M. Landis in 1926 while a medical student at Harvard, who provided the experimental evidence verifying the Starling Principle. In individual capillaries of autoperfused frog mesenteric microvasculature Landis measured net filtration of fluid from occluded capillaries when capillary pressure (P_c) exceeded the measured colloid osmotic pressure (COP, π) of plasma and absorption of fluid from those vessels with P_c below COP. In this population of capillaries, he found that volume flux per unit area (Jv/S) to be a linear function of the capillary pressure with a slope equal to the conductance of the wall (L_p). By the 1960's the Starling Principle was commonly

expressed as a flux equation describing fluid movement (J_v) between plasma (p) and interstitium (i): $J_v = L_pS [(P_c – P_i) – \sigma(\pi_p – \pi_i)]$. The effective osmotic pressure is less than (Πp-Πi) by the factor σ, the osmotic reflection coefficient In the 1970's interest in the mechanisms controlling capillary volume flux J_v in individual exchange microvessels was invigorated by modification of the original Landis method to enable measurements of multiple filtration rates in single microvessels as P or Π were changed. The introduction of glass micropipettes for the control of perfusate composition enabled direct measurement of Lp and σ in individual capillaries extending Landis' observations. (Michel CC, Mason JC, Curry FE and Tooke JE, J Physiol, 1974). Starling (1896) recognized that increased J_v would dilute proteins in the interstitium and reduce Pi providing a feedback mechanism to regulate filtration. Recent experiments in single capillaries demonstrate that filtration maintains the plasma protein concentration in a protected region beneath the endothelial surface glycocalyx lower that mean interstitial protein concentration, and the effective osmotic pressure difference opposing filtration is larger than σ(Πp-Πi), and closer to σΠp as originally proposed by Starling (Adamson et al. J. Physiol, 2004). As of today the Landis technique has been modified and applied to in situ and excised arterioles, capillaries and venules from humans, pigs, and rodents from organs ranging from heart, to brain, gut, kidney, bone, and skeletal muscle examining acute and chronic alterations in volume flux under steady state and transient conditions in a variety of normal and pathophysiological conditions.

BLOOD SUBSTITUTES

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Initial efforts to develop blood substitutes focused on producing fluids whose oxygen carrying capacity was similar to blood. This approach identified hemoglobin as the oxygen carrier of choice, where the human variety soon became the only realistic source of this material. Consequently if the aim in producing blood substitutes is that addressing shortages in the transfusional blood availability a multiplication factor between supply of natural blood and blood substitute must be introduced, while maintaining efficacy. Thus a unit of blood should be the source of several units of equivalent blood substitute. This is now possible with the development of technology that has allowed to obtain a more complete understanding of how blood delivers oxygen in the microcirculation and during hemorrhage. This information was used to design improved resuscitation modalities that tailor the properties of a blood substitute to the task of maintaining microvascular function, rather than oxygen delivery capacity. Central to this approach is the concept in rescuing a hemorrhaging organism it is critical to maintain perfusion, a process directly linked to mechano transduction in the endothelium via shear stress, induced by either increased blood/plasma viscosity or increased blood flow velocity in the microcirculation. This process must also insure that no portion of the tissue is anoxic, and that central pressure does not became elevated to the point that hemorrhage is further enhanced. These conflicting requirements are satisfied using low concentration, high viscosity hemoglobin solutions that have high affinity for oxygen, a combination of properties that causes the microcirculation to remain functional during shock resuscitation.

BAYLISS AND THE MYOGENIC RESPONSE: THE DEATH AND REBIRTH OF A SCIENTIFIC CONCEPT

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The concept of the myogenic response of arterial vessels first came to general attention in 1902 with the publication by W.M. Bayliss of his classic study on the local reaction of the blood vessel wall to changes of internal pressure (J. Physiol. London, 2:220-231,1902). Bayliss had observed a biphasic change in volume of the dog hind limb following a brief period of arterial pressure reduction. He also observed that an isolated artery segment "began to writhe like a worm" when the internal pressure was elevated. Based on

this indirect evidence, Bayliss proposed that normal intravascular pressure levels stimulated smooth muscle in arteries and arterioles to contract. The suggestion was not entirely new; in 1852 Jones reported that veins in the bat wing contracted with pressure elevation. Remarkably, Bayliss also proposed that this mechanism would tend to maintain blood flow constant despite changes in arterial pressure (autoregulation) a phenomenon which was not observed experimentally until over 30 years later. In 1912 Anrep repeated Bayliss' experiments on the dog hindlimb but disputed his interpretation and suggested instead that buildup of lactic acid could explain the transient dilation. Furthermore, Anrep and other investigators were unable to repeat Bayliss' findings on isolated vessels. As a consequence, support for the myogenic theory waned. In fact in his monograph entitled *The vasomotor system* published in 1923 Bayliss stated "on the whole, I am afraid we must regard the question as undecided." In the 1930's several investigators reported that large vessels contracted transiently with pressure elevation but no evidence was found for a sustained constriction as Bayliss had proposed. The first strong evidence in support of the myogenic concept was presented by Bjorn Folkow in 1949. He showed in studies on the hind limb that blood flow increased only transiently with a step increase in arterial pressure, as had been demonstrated in the kidney by Kramer in 1936 and Selkurt in 1946 but was thought to be unique to the kidney. In the 1950's and 60's evidence accumulated from whole organ studies on arterial and venous pressure elevation that was consistent with a myogenic mechanism although in many cases the results could also be explained by a metabolic mechanism, which is more intuitively obvious. Subsequent microcirculatory and isolated vessel studies have provided convincing evidence for Bayliss' suggestion.

One of the stumbling blocks to general acceptance of the myogenic response has been that it is not intuitively obvious since the smooth muscle cell must remain shortened in the steady state when intravascular pressure increases. Klaus Thurau in 1964 suggested a way out of this dilemma by proposing that circumferential wall tension, a function of both pressure and vessel radius, was the controlled variable. Another criticism is that elevation of arterial pressure would lead to arteriolar constriction which would increase pressure further and a vicious cycle would develop. It can be shown, however, that this would occur only if the arteriolar constriction were sufficient to actually reduce flow with pressure elevation, which rarely occurs in any organ and certainly not in the systemic circulation overall; not to mention the buffering effect of pressor reflexes. It is a lesson in the ways of science that this concept, once dismissed by others and even doubted by its originator, is now well accepted as one of the key regulatory mechanisms in the circulation

HISTORY OF THE DISCOVERY AND SIGNIFICANCE OF SHEAR STRESS DEPENDENT REGULATION OF VASCULAR RESISTANCE

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For a long time, locally released metabolic factors from parenchymal cells and the myogenic response were considered to be the two main peripheral regulatory mechanisms to control microvascular resistance. However, many responses, such as reactive and functional hyperemia could not be satisfactorily explained by these two mechanisms. The idea that an increase in blood flow may itself cause vessel dilation evolved at the beginning of the last century, although earlier observations have been documented. For example, the renowned surgeon William Hunter (1761), already recognized the importance of changes in distal resistance causing dilation of the proximal portion of large vessels. In 1893, Thoma summarized, with great insight, his own and other investigators' ideas about blood flow and vascular dimensions. He posited that growth of the "cross-diameter" of vessels was dependent on the velocity of blood flow. Recklinghausen (1883) and Nothnagel (1889) drew similar conclusions, namely, that it is not an increase in pressure but rather an increase in flow velocity which brings about the development of widened or new collateral blood vessels.

Perhaps the first experimental demonstration of an acute "flow sensitive" vascular response was published by Schretzenmayr (1933) who showed an increase in the diameter of an upstream segment of cat femoral artery during activity of the calf muscle. Fleisch (1935) observed proximal dilation of dog femoral artery following ACh-induced downstream dilation. Others ((Hilton (1959), Duling and Berne (1970) Segal and Duling (1986)) observed proximal vasodilation to a variety of stimuli, which they attributed not to flow but a conducted process, hence the idea of reflex or conducted dilation.

Flow induced vasodilation was observed in conduit vessels by Ingebrigtsen and Leraand (1970), Smiesko et al. (1980), Bassange et al (1981), Holtz et al. (1983) Hintze and Vatner (1984), Khayutin et al. (1986), Gerova et al. and Sinoway et al. (1989). Yet the nature and importance of this phenomenon in blood flow regulation was delineated only in recent decades. In vivo in the microcirculation "flow dependent" dilation of arterioles (~20mm) was observed by Koller and Kaley, (1989) and Smiesko et al. (1989), a response which was absent after the endothelial cell layer of arterioles was impaired (Koller and Kaley (1990). In vitro studies by Kuo et al. (1990, 1991) confirmed these findings and revealed further the underlying endothelial mechanisms. It is known that WSS= η WSR (wall shear stress = WSS, η=viscosity, WSR=wall shear rate) and that WSR=dv/dr (v = velocity, r = radius).l Thus, given a constant viscosity (of the perfusion solution or blood) and diameter, an increase in blood flow or an increase in the velocity of flow, will cause a linear increase in WSS; this results in dilation of the vessel which will reduce WSS. Further evidence for these relationships was provided when an increase in viscosity was used to increase WSS, resulting in vasodilation ((Melkumyants et al (1989) Pohl et al. (1991) and Koller et al. 1993)).

More recently, several endothelial mechanisms have been recognized to be involved in transduction of the shear stress signal. Also, the role of shear stress mechanisms in the regulation of basal vascular tone, collateral development, blood flow during reactive and functional hyperemia and in a variety of physiologic and pathologic condition, such as angiogenesis, exercise and diverse vascular diseases has been established. NIH HL-43023 and HL-46813.

IN VIVO RHEOLOGY OF MICROVASCULAR BLOOD FLOW

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The pioneering studies of Poiseuille (1864) led to active investigations on the rheology (science of the flow and deformation of materials) of blood, including studies of its flow properties within the microvasculature. In 1929, Fahraeus recognized that the particulate nature of blood resulted in unique flow characteristics that could affect flow resistance and microvessel perfusion. With the advent of intravital microscopy and specialized instrumentation, a methodical delineation of the rheological determinants of microvascular blood flow has developed by members in the Microcirculatory Society. In concert with *in vitro* experimentation using bulk viscometry and microscale simulations, as well as theoretical analyses of blood cell mechanics, a comprehensive description of the biophysical basis of microcirculatory blood flow has evolved over the past five decades. It is now clearly recognized that red cell deformability and aggregation affect flow resistance and the "apparent viscosity" of blood, with their effects being modulated by shear rates and microvessel hematocrit. The adhesive interactions of erythrocytes and leukocytes to the endothelium have been elucidated in blood cell disorders and inflammation, in light of receptor-ligand interactions and the hemodynamic forces that oppose them. The effects of cell properties and cell-cell interactions on physiological transport and function have been characterized in terms of red cell distribution, transit times, branching patterns, lumen geometry and the molecular composition of the endothelial surface layer. These studies have served to establish a framework for the development of new therapeutic strategies to treat

blood cell disorders, inflammation, low flow states, and many other pathological conditions, and to provide a firm foundation for elucidating the physiological basis of microvascular function.

IN VIVO MICROSCOPY OF LIVING ORGANS

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During the past 50+ years, *in vivo* microscopic studies of living tissues and organs have expanded knowledge of dynamic structure-function relationships during health and disease since the methods permit the rate, duration, magnitude and direction of dynamic events to be directly visualized, evaluated, quantified and recorded continuously in life at the light microscopic level. Much of this work has focused on the mechanisms that regulate blood flow through small blood vessels in vital organs and how these are affected by drugs, toxins, toxicants, and various diseases. More recently, the use some of the fluorescence and spectrophotometric methods developed for studying molecular events in cultured individual cells isolated from organs are now being applied to studies of cells in their native environment within intact organs using *in vivo* microscopic techniques. While the vast majority of *in vivo* microscopic studies have been conducted on thin tissues which are relatively easy to image, e.g., mesentery, hamster cheek pouch, selected skeletal muscle preparations, most internal organs, e.g., liver, pancreas, spleen, intestine, kidney, lung, and bone marrow also have been studied, frequently using unique and innovative techniques and instrumentation. This poster reviews some of the techniques and instrumentation used for such studies during the past 50+ years. The basic methods used include: (a) examination of surgically exposed organs *in situ* or as isolated, perfused preparations; (b) examination of organs *in situ* through windows implanted in the body wall; and (c) examination of grafts of organs contained within chambers implanted in ectopic sites. Each method has advantages as well as limitations. Most organs can be studied by light microscopy in a variety of small laboratory animals including rats, mice, hamsters, rabbits, guinea pigs, etc. by transillumination of relatively thin (3-5mm) areas of the organ. Two basic methods of transillumination have been used for light microscopy of organs. These include the use of quartz, glass or plastic light rods or fiber optic light guides which generally are not focusable; alternatively, a focusable condenser contained on a modified compound microscope is used. Thicker areas of the organs in these species as well as the thicker organs of larger animals such as cats, dogs and monkeys can be examined only by epi-illumination. The resolution obtainable using epi-illumination usually is inferior to that realized with transillumination. However, it does permit visualization of fluorescent vascular tracers and cellular events monitored with fluorescent probes. A number of chambers have been devised for chronic implantation in various sites. Examples are the mouse and rat back chamber, the hamster cheek pouch chamber, the rabbit ear chamber. Such chambers permit the study of their contained tissue or grafts of organs for considerable periods of time. In addition, chambers or windows have been implanted for the chronic study of some organs in their normal anatomical sites, e.g., brain, bone and bone marrow, pancreas, and lung. Examples of all of these methods will be presented.

THE ROLE OF THE MICROCIRCULATION IN ISCHEMIA-REPERFUSION INJURY

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It has long been understood that an adequate blood supply is necessary for proper organ function and survival. Insufficient blood flow (ischemia) to critical organs remains the number one killer in the developed world. However, the notion that reperfusion of ischemic tissue causes an additional injury is not intuitive and for many years ischemia-reperfusion (I/R) injury was not readily accepted. In the past thirty-plus years, as the mechanisms underlying I/R injury became clearer and as effective treatments were dem-

onstrated, at least in the laboratory, I/R injury gained broader acceptance. Yet, no standard clinical treatment for I/R injury has emerged. Alterations in microvascular structure, perfusion and permeability are associated with I/R injury. One theory suggests that microvascular dysfunction causes I/R injury. Others suggest that parenchymal cell damage occurs concurrently with microvascular injury. The Cell Swelling Hypothesis was initially proposed to explain microvascular failure due to reperfusion. Tissue cell swelling, contracture (for organs such as the heart) and edema were suspected to cause microvascular compression, limiting perfusion. Endothelial cell (EC) swelling, was linked to the No-reflow phenomenon, a reduction in perfused capillarity during reperfusion. Hypertonic reperfusates, such as mannitol, were actively investigated to limit swelling and improve reperfusion. A major step forward in our understanding of the etiology of I/R injury occurred when it was appreciated that the resupply of oxygen to an ischemic organ led to the production of toxic reactive oxygen species (ROS). Injured endothelial cells are capable of producing significant amounts of ROS inducing further cell injury. In addition, inflammatory blood cells (neutrophils, monocytes and platelets) sequester in the microcirculation during reperfusion. These blood cells can occlude capillaries and serve as another potent source of ROS. Exactly where these cells accumulate (i.e., in capillaries, venules or both) and the time course of accumulation varies among organ vasculatures. Regardless of where and when these blood cells sequester, they are major players in I/R injury. Studies of exactly how white cells sequester during reperfusion revealed that, in addition to ROS, injured ECs express adhesion proteins and cytokines. Firm binding of phagocytes occurs via CD11b. Studies of leukocyte depletion or CD11b blockade demonstrated improved recovery from ischemia. Further investigations found that injured ECs lose their ability to produce nitric oxide (NO). An acute reduction of available NO enhances leukocyte adhesion, reduces effective scavenging of the superoxide radical, alters normal vascular tone and enhances platelet aggregation. When microvascular NO is chronically reduced, such as occurs in diabetes, the severity of microvascular I/R injury is increased. I/R injury is a type of inflammatory response and the roles of other components of inflammation, e.g., cytokines and complement, are under active investigation. New approaches to limit inflammation will likely lead to effective prophylaxis and treatment of I/R injury.

MICROVASCULAR RAREFACTION IN HYPERTENSION

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Members of the Microcirculatory Society have performed several investigations to document the reduction in the number of arterioles and capillaries in human and animal subjects with hypertension. Although observations in patients were reported as early as the 1930's, David Short published quantitative data on a reduction in the number of small arterioles in the intestine of subjects with long-standing essential hypertension in 1958. Systematic study of rarefaction began with the availability of the spontaneously hypertensive rat which was used by Phillip Hutchins to show the reduction in arteriolar number in the cremaster muscle. Studying the gracilis muscle in SHR from 4 to 12 weeks of age, Prewitt et al. showed that rarefaction develops from a functional state, where arterioles are present but unperfused, to a structural state where the arterioles are physically absent. Greene et al. found that angiotensin II modulates the number of arterioles stimulating growth through the AT1 receptor and promoting degeneration via apoptosis mediated through the AT2 receptor. A high sodium diet induced rarefaction without a change in blood pressure. Hansen et al. showed that the degeneration of arterioles occurred through proteolysis of their basement membranes, leading to dissociation of critical endothelial-smooth muscle interactions. Thus microvascular density is the result of multiple factors, some of which change during the development of hypertension, tilting the balance toward rarefaction.

THE "CLASSICAL PORE THEORY" OF CAPILLARY PERMEABILITY, A HISTORICAL PERSPECTIVE

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Publication by John Pappenheimer, Luis Borrero and myself of the paper "Filtration, diffusion and molecular sieving through peripheral capillary membranes. A contribution to the pore theory of capillary permeability," Am. J. of Physiol. 167: 13-46, 1951 inaugurated a new and powerful approach to the experimental study of capillary permeability and transcapillary exchange. In this paper, we proposed that the transport of water and small lipid-insoluble solutes across capillary walls could be accounted for by the interaction of ultrafiltration and diffusion through molecular-size openings through the endothelium ("pores" or "slits").

The "Classical Pore Theory" provided a simple, geometrical model that could be used 1) to interpret observed permeability properties of capillaries in different tissues and organs, 2) to correlate microvascular permeability with microvascular morphology and 3) to relate microscopic studies of capillary circulation with macroscopic studies of blood-tissue exchange in whole organs and intact animals. Though too simple to be definitive, the theory has been a fruitful stimulus to subsequent research.

This poster outlines the background of our investigation, and reviews the experimental procedures and analysis that led to our conclusions. Later revisions and extensions of the original proposal are described briefly, and a perspective of its present role in endothelial transport research is offered.

BRAIN MICROCIRCULATION LAST FIFTY YEARS - A SAMPLING OF IMPORTANT PAPERS

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Ten papers have been selected of particular importance to the field of cerebral microcirculation over the past 50 years. Sometimes a given laboratory produced many papers that qualified for inclusion. In such cases we have selected only one or two, in order to keep the total number to ten major citations listed under REFERENCES. In addition, the text refers to other papers and laboratories selected from the many that provided important data over that period. The ten selected papers include: [a] one that reintroduced direct observation of brain microcirculation following a hiatus of over 20 years; [b] two papers presenting important technological advances in the on-line microscopy of brain microcirculation; [c] papers that implicated the importance of reactive oxygen species in the mediation of pathophysiological and physiological alterations of tone; [d]the paper that proved the existence of endothelium dependent responses in the microcirculation; [e] the paper that established changes in local hydrogen ion concentration as the factor determining changes of tone in response to changes in ambient $CO_{2;}$ [f] papers introducing knockout mice and direct gene transfer to the study of microvascular control in the brain-one of these papers implicating neuronal NO as a link coupling neuronal demand to local blood flow; [g] a paper using electron microscopy to show that occlusion of brain microvessels by neutrophils occurs in ischemia-reperfusion and may provide one explanation for the no-reflow phenomenon; [h] a paper implicating dysfunctional microcirculation in the pathophysiology of Alzheimer's disease.

FREE RADICAL BIOIMAGING IN MICROCIRCULATION

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Superoxide and nitric oxide (NO) are short-lived compounds that are generated in and around microvascular endothelium. Because of difficulties to collect spatial and temporal information on their generation, pathophysiologic roles of these species in microcirculation had not fully been examined. In 1987, we first reported real-time visualization of oxidative burst from activated neutrophils through a microscope equipped with a photon-counting image intensifier that allowed us to visualize luminal-dependent chemiluminescence (1). This technique was applied to demonstrate photonic burst from leukocytes adhering on venular endothelium stimulated with pro-inflammatory stimuli such as platelet-activating factor (2) or lipopolysaccharide (LPS). The LPS administration in rats stimulated interactions between venular endothelium and leukocytes and triggered photonic burst right on the site of adhesion. Since then, several different bioprobes became available to demonstrate other radical species and helped further understanding of radical-mediated regulation of microvascular functions; in-vivo NO detection using diaminofluorescein diacetate is such an example that shed light on mechanisms for the gas delivery and signaling in microcirculation (3). The early data of the chemiluminescence study in microcirculation from our group and its extension to modern knowledge of "Gas Biology" will be presented in the poster.

(1) Suematsu M, et al. Biochem. Biophys Res Commun 1987, 149, 1106-1110.

(2) Suematsu M, et al. J. Biochem. 1989, 106, 355-360.

(3) Kashiwagi S, et al. Circ Res 2002, 91, e55-e64.

PERMEABILITY OF THE ALVEOLAR-CAPILLARY BARRIER

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Early isotopic flux and osmotic transient studies clearly show that the pulmonary microvascular membrane is highly permeable to small molecules but the alveolar membrane had permeability characteristics similar to cell membranes. Norman Staub modified Strang's lung lymphatic model and greatly accelerated the number and quality of permeability studies in lungs which measured plasma protein permeability in normal and diseased lungs. Lymphatic protein flux analyses using radioactive and native plasma proteins indicated that the reflection coefficient of the microvascular walls for total plasma proteins and albumin ranged from 0.60-0.92 and 0.50-0.81, respectively. But, it is not known how plasma proteins actually cross the microvascular membrane. Some studies clearly indicate that caveolae (vesicles) on endothelial cells may transport plasma proteins across the microvascular barrier. Many studies in lungs and other organs indicate that microvascular protein transport is described by physical processes that likely occurs through water filled pores. Caveolae although they may contain plasma proteins are not necessary to describe plasma protein transport but they may contain docking sites for circulating molecules in plasma that regulate specific endothelial cell messenger functions.

UNDERSTANDING LYMPHATIC STRUCTURE AND FUNCTION: MAJOR ADVANCES BY MICROCIRCULATORY SOCIETY MEMBERS

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In this historical review, we have featured a few of the meritorious contributions members of the American Microcirculatory Society have made in advancing our knowledge of the lymphatic system. These contributions include 1) the first studies to correlate physiological lymphatic function with ultrastructural morphology on the same vessel, and demonstrations 2) of anchoring filaments which prevent the collapse of lymphatic capillaries in edema, 3) of the functional importance of lymphatic valves in lymph propulsion, 4) that lymph protein concentration does not remain constant as it passes through the lymph nodes 5) that the intestinal mucosal, submucosal, and serosal layers have extensive lymphatic plexuses largely devoid of valves 6) that the contraction frequency and the underlying pacemaker potentials in lymphatic vessels is regulated by the lymphatic endothelium, 7) that VEGF-C induces selective hyperplasia of the lymphatic endothelium and is involved in lymphangiogenesis, 8) that contractions of the pleural lymphatics generate pressure oscillations, which drive fluid from the subatmospheric pleural space into the lymphatic network even while pressure in the lymphatics are subatmospheric, 9) a primary valve system in the endothelial cells of initial lymphatics that allows for the unidirectional flow of lymph during the periodic compression and expansion of the lymphatic, and 10) that flow/shear inhibit the active lymph pump in both mesenteric lymphatics and in the thoracic duct via an endothelium-dependent mechanism.

These studies and others by members of the American Microcirculatory Society have been fundamental in the development of the current knowledge of lymphatic physiology and pathophysiology.