AD-A084 386 INTERNATIONAL SOCIETY OF BIORHEOLOGY NEW YORK F/G 6/5
PROCEEDINGS OF THE INTERNATIONAL CONGRESS OF BIORHEOLOGY (3RD), --ETC(U)
1978 Y FUNG, J G PINTO N00014-78-G-0018

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BIORHEOLOGY

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U. S. NATIONAL SCIENCE FOUNDATION
OFFICE OF NAVAL RESEARCH
UNIVERSITY OF CALIFORNIA, SAN DIEGO
NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

EDITORS

Y. C. FUNG J. G. PINTO

I.S.B

(Library of Congress Catalog Card Number 78-67490)

THE INTERNATIONAL SOCIETY OF BIORHEOLOGY

15 N00014-78-G-0018

6 Proceedings of the ~~THE THIRD~~

INTERNATIONAL CONGRESS OF BIORHEOLOGY (3rd), La Jolla, California, 28 August-1 September 1978,

HONORARY CHAIRMAN: Roy Swank

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ACKNOWLEDGMENTS

The Organizing Committee wishes to express appreciation to the following individuals and organizations whose contribution towards the planning of the Congress has been invaluable.

Roy H. Swank, Professor Emeritus, University of Oregon

Helmut H. Hartert, Chefarzt, Professor Dr. Med. University Kaiserslautern, FR Germany

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T.Y.T. Wu, California Institute of Technology, Pasadena

INVITED SPEAKERS

(In addition to the following list, all symposia speakers are invited)

M. ABE, Jikei University, Tokyo, Japan

T. AZUMA, Shinshu University, Matsumoto, Japan

D. E. BROOKS, University of British Columbia, Vancouver, Canada

C. G. CARO, Imperial College of Science & Technology, London, England

L. C. CERNY, Masonic Medical Research Laboratory, Utica, New York

S. E. CHARM, Tufts University, Boston, Massachusetts

H. CHMIEL, Institut fur Grenzflachen und Bioverfahrenstechnik, Stuttgart, Bundes Republic, Deutschland

T. H. COOK, Pennsylvania State University, University Park, Pa.

N. DAVIDS, Pennsylvania State University, University Park, Pa.

L. DINTENFASS, Sydney Hospital, Sydney, Australia

I. FATT, University of California, Berkeley, Ca.

W. P. GRAEBEL, University of Michigan, Ann Arbor, Mich.

J. F. GROSS, University of Arizona, Tucson, Ariz.

H. HARTERT, University of Kaiserslautern, Germany

R. H. HOCHMUTH, University of Washington, St. Louis, Mo.

C. R. HUANG, New Jersey Institute of Technology, Newark, N.J.

T. IWAZUMI, University of Washington, Seattle, Wa.

W. G. KNAUSS, California Institute of Technology, Pasadena, Ca.

B. KUMMER, Universität zu Köln, Lindenburg, Germany

G. S. KURLAND, Harvard Medical School, Boston, Mass.

R. F. LANDEL, California Institute of Technology, Pasadena, Ca.

Y. LANIR, Israel Institute of Technology, Haifa, Israel

G. C. LEE, State University of New York, Buffalo, N.Y.

J. S. LEE, University of Virginia, Charlottesville, Va.

P. S. LINGARD, The Children's Hospital, Sydney, Australia

R. LITTLE, Michigan State University, East Lansing, Mich.

L. V. McINTYRE, Rice University, Houston, Tex.

J. W. MELVIN, University of Michigan, Ann Arbor, Mich.

M. ROACH, University of Western Ontario, Ontario, Canada

A. H. SACKS, Palo Alto Medical Research Foundation, Palo Alto, Ca.

H. SCHMID-SCHÖNBEIN, Rein,-Westf. Techn. Hochschule Aachen, Aachen, West Germany

M. G. SHARMA, Pennsylvania State University, University Park, Pa.

S. USAMI, Columbia University, New York, N.Y.

A. VIIDIK, University of Aarhus, Aarhus, Denmark

H. WAYLAND, California Institute of Technology, Pasadena, Ca.

V. M. ZAIKO, Institute of Organ and Tissue Transplantation, Moscow, U.S.S.R.

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MONDAY A.M. SESSION 1 SYMPOSIUM

MOLECULAR FORCES IN THE MECHANICS OF CELL MEMBRANE

Room 1105 Basic Science Bldg.

CHAIRMEN - RICHARD SKALAK, Columbia University, New York
SHELDON WEINBAUM, City University of New York

9:00 Structural and Dynamic Aspects of Red Cell Membranes (1.1)
R.F. BAKER, University of Southern California, School of Medicine, Los Angeles, Ca.

9:35 Molecular Movements of Cell Surface Receptors (1.2)
M. POO, University of California, Irvine, Ca.

10:05 Mechanical Calorimetry of Red Cell Membrane (1.3)
E.A. EVANS, Duke University, Durham, N.C.

10:35 INTERMISSION

10:50 Molecular Forces Between and Within Lipid Membranes (1.4)
V.A. PARSEGIAN[1], R.P. RAND[2], N. FULLER[2] and M. McALISTER[2], [1]NIH, Bethesda, Md.; [2]Brock University, St. Catharines, Ontario, Canada.

11:20 Theoretical Models of Vesicular Transport and Endothelial Membrane Interaction (1.5)
S. WEINBAUM, The City College of the City University of New York, N.Y.

MONDAY A.M. SESSION 2 SYMPOSIUM

SOFT TISSUES AROUND A DIARTHRODIAL JOINT

Room 2100 Basic Science Bldg.

CHAIRMEN - SAVIO WOO, University of California, San Diego, Ca.
STEVE KUEI, University of California, San Diego, Ca.

9:00 Biorheology of Soft Tissues: The Need for Inter-Disciplinary Studies (2.1)
S. WOO, University of California, San Diego, Ca.

9:10 The Multicomposite Structure of Tendon Collagen-Relationships between Ultra-Structure and Mechanical Properties (2.2)
E. BAER, Case Western Reserve University, Cleveland, Oh.

9:40 Collagen: Its Structure and Function in Normal and Pathological Connective Tissues (2.3)
M.E. NIMNI, P.D. BENYA, C. KENNEY and A.J. KEYSER, University of Southern California, School of Medicine, Los Angeles, Ca.

10:10 INTERMISSION

10:30 Biphasic Rheological Analysis of Cartilage Creep and Stress Relaxation (2.4)
V.C. MOW[1], S.C. KUEI[2] and W.M. LAI[1], [1]Rensselaer Polytechnic Institute, Troy, N.Y., and [2]University of California, San Diego, Ca.

11:00 Application of Enzyme Probes in Connective Tissue Biomechanics (2.5)
A.S. HOFFMAN, University of Washington, Seattle, Wa.

11:30 Mechanical Imperatives for Synovial Joint Homeostasis: The Present Potential for their Therapeutic Manipulation (2.6)
W.H. AKESON, D. AMIEL, S.L -Y. WOO and F. HARWOOD, University of California, San Diego, Ca.

MONDAY P.M. SESSION 3 **SYMPOSIUM**

MUCO-CILIARY TRANSPORT

Room 1105 Basic Science Bldg.

CHAIRMEN - THEODORE Y.T. WU, California Institute of Technology, Pasadena, Ca.
STANLEY A. BERGER, University of California, Berkeley, Ca.

1:30 The Rheology and Molecular Organization of Epithelial Mucus (3.1)
A. SILBERBERG, The Weizmann Institute of Science, Rehovot, Israel.

2:00 Tracheal Muco-Ciliary Clearance (3.2)
A.T.W. CHEUNG and A.T. CHWANG, California Institute of Technology, Pasadena, Ca., and University of Iowa, Iowa City, Ia.

2:30 Flagellar Propulsion of Sperm in Cervical Mucus (3.3)
D.F. KATZ and S.A. BERGER, University of California, Berkeley and Davis, Ca.

3:00 INTERMISSION

3:15 Chemical Aspects of Mucus Rheology (3.4)
M. LITT, University of Pennsylvania, Philadelphia, Pa.

3:45 Fluid Propulsion in a Muco-Ciliary Channel (3.5)
J.R. BLAKE and H. WINET, Division of Mathematics and Statistics, CSIRO, Australia; and Southern Illinois University, Carbondale, Ill.

4:15 Cervical Mucus as a Sustained-Release Hydrogel System for Spermatozoa (3.6)
R.M. NAKAMURA, M. SAGA, F. FLORIANI, D. TREDWAY, V. DAVAJAN and G. BERNSTEIN, Univesrity of Southern California (USC), Los Angeles, Ca.; St. Marianna University, Kawasaki City, Japan; Kaiser Permanente Hospital, Bellflower, Ca.; University of Chicago; USC; and USC, Los Angeles, Ca.

MONDAY P.M. SESSION 4

CELL MEMBRANE AND CHROMATIN

Room 2100 Basic Science Bldg.

CHAIRMEN - BRUNO ZIMM, University of California, San Diego, Ca.
V.I. VOROB'EV, Institute of Cytology, Academy of Sciences, USSR

1:30 Effect of Temperature on the Viscosity of Red Cell Membrane (4.1)
R.M. HOCHMUTH, E.A. EVANS and K. BUXBAUM, Duke University, Durham, N.C.

1:50 Membrane Mechanical Properties of ATP-Depleted Human Erythrocytes (4.2)
H.J. MEISELMAN, E.A. EVANS and R.M. HOCHMUTH, University of Southern California, School of Medicine, Los Angeles, Ca.; Duke University, Durham, N.C.; and Washington University, St. Louis, Mo.

2:10 Viscoelastic Properties of Red Cell Membrane (4.3)
S. CHIEN, K.-L.P. SUNG, R. SKALAK and A. TOZEREN, College of Physicians and Surgeons, Columbia University, N.Y.; and Department of Civil Engineering and Engineering Mechanics, Columbia University, N.Y.

2:30 Buckling of the Red Blood Cell Membrane (4.4)
T.M. FISCHER[1], C.W.M. HAEST,[1] M. STOHR-LIESEN[1], H. SCHMID-SCHONBEIN,[1] and R. SKALAK[2], [1]Medizin.-Theoret. Institute der RWTH, Aachen, West Germany; and [2]Columbia University, N.Y.

2:50 INTERMISSION

3:05 Charge Relaxation Effects in Membrane Breakdown (4.5)
J.M. CROWLEY, University of Illinois, Urbana, Ill.

3:25 Rheological Changes of Growing Cells: Effect of Auxin and Fusicoccin on Collenchyma (4.6)
M. JACCARD and P.E. PILET, Institute of Plant Biology and Physiology of the University, Lausanne, Switzerland.

3:45 Rheological Studies of Chromatin (4.7)
V.I. VOROB'EV and L.V. KUKHAREVA, Institute of Cytology of the Academy of Sciences of the USSR, Leningrad, USSR.

4:05 The Dynamic Equilibrium Model of Cytoplastmic Microtubules and the Oxalate-Induced Radial Segmentation of the Nuclei of Mononuclear Blood Cells (4.8)
B. NORBERG and A. NORBERG, University Hospital of Lund, Lund, Sweden.

MONDAY P.M. SESSION 5

BIORHEOLOGY OF LUNG, AIRWAY AND SKIN

Room 274 Clinical Science Bldg.

CHAIRMEN - SIDNEY S. SOBIN, University of Southern California, Cardiovascular Research Lab., Los Angeles, Ca.
CLIFFORD ASTILL, National Science Foundation, Wash. D.C.

1:30 Homogeneity and Isotropy of Lung Parenchyma (5.1)
G.C. LEE and R. TAI, State University of New York at Buffalo.

1:50 Elastic Properties of Lung Parenchyma: The Effect of Pressure-Volume Hysteresis on the Behavior of Large Blood Vessels (5.2)
S.J. LAI-FOOK, Mayo Clinic, Rochester, Minn.

2:10 A Finite Element Analysis of the Whole Lung (5.3)
D.L. VAWTER, Virginia Polytechnic Institute and State University, Blacksburg, Va.

2:30 On the Measurement of the Elasticity of the Airway (5.4)
T. NAKAGAWA, Y. SEGUCHI and Y.C. FUNG, University of California, San Diego, Ca.

2:50 Possible Aerodynamic Instability in the Airway Due to Flow Separation and Interaction of Flow with Elastic Wall (5.5)
Y. MATSUZAKI and Y.C. FUNG, National Aerospace Laboratory, Japan; and University of California, San Diego, Ca.

3:10 INTERMISSION

3:30 Mechanical Properties of Human Skin (5.6)
T.H. COOK, The Pennsylvania State University, University Park, Pa.

3:50 The Rheological Behavior of the Skin: Experimental Results and a Structural Model (5.7)
Y. LANIR, Technion-Israel Institute of Technology, Haifa, Israel.

4:10 The Role of the Microcirculation on the Dynamic Mechanical Behavior of Human Skin (5.8)
S.T.J. PENG,[1] R.F. LANDEL,[1] G.S. BRODY[2] and G. GARSIDE,[2] Jet Propulsion Laboratory, [1]California Institute of Technology, Pasadena, Ca.; and [2]Rancho Los Amigos Hospital, Downey, Ca.

TUESDAY A.M. SESSION 6 **SYMPOSIUM**

RECENT ADVANCES IN HEMORHEOLOGY

Room 1105 Basic Science Bldg.

CHAIRMEN - SHU CHIEN, Columbia University, New York, N.Y.
HERBERT MEISELMAN, University of Southern California, Los Angeles, Ca.

8:45 Flow of Blood through Narrow Capillaries: Rheological Mechanisms Determining Capillary Hematocrit and Apparent Viscosity (6.1)
P. GAEHTGENS, Universitat, Köln, W. Germany.

9:25 Red Cell Interactions in Macromolecular Suspensions (6.2)
K.-M. JAN, Columbia University College of Physicians and Surgeons, N.Y.

10:00 Viscoelastic Study of Aggregation of Red Blood Cells (6.3)
E. FUKADA and M. KAIBARA, The Institute of Physical and Chemical Research, Saitama, Japan.

10:35 INTERMISSION

10:50 Parameters for Blood Rheology (6.4)
G.B. THURSTON, The University of Texas at Austin, Austin Tx.

11:25 Platelet Motions and Interactions in Tube Flow (6.5)
H.L. GOLDSMITH, McGill University Medical Clinic, Montreal, Canada.

RHEOLOGY OF BLOOD VESSELS

Room 2100 Basic Science Bldg.

CHAIRMEN - KITTY FRONEK, University of California, San Diego, Ca.
HANS WERNER WEIZSÄCKER, University of Graz, Austria

8:45 Viscoelastic Characteristics and Architecture of Venous Walls (7.1)
M. HASEGAWA and T. AZUMA, Shinshi University Medical School, Matsumoto, Japan.

9:25 Mathematical Characterization of the Nonlinear Rheological Behavior of the Vascular Tissue (7.2)
R.N. VAISHNAV, The Catholic University of America, Washington, D.C.

10:00 Mechanical Properties of Arteries as a Function of Topography and Age (7.3)
K. FRONEK and Y.C. FUNG, University of California, San Diego, Ca.

10:35 INTERMISSION

10:50 Mechanical Properties of Human Cerebral Arteries (7.4)
K. HAYASHI,[1] K. MORITAKE,[1] A. OKUMURA,[1] S. NAGASAWA,[1] H. NIIMI[2] and H. HANDA,[1] [1]Kyoto University, Kyoto, Japan; and [2]National Cardiovascular Center, Osaka, Japan.

11:25 Regional Species and Age-Related Variations in the Mechanical Properties of Arteries (7.5)
R.H. COX, Bockus Institute, University of Pennsylvania, Philadelphia, Pa.

TUESDAY A.M. SESSION 8

MUCUS RHEOLOGY

Room 274 Clinical Science Bldg.

CHAIRMEN - MICHAEL LITT, University of Pennsylvania, Philadelphia, Pa.
ALEX SILBERBERG, Weismann Institute, Rehovot, Israel.

8:45 Tracheal Mucus Viscosity and Elasticity (8.1)
L.A. GATTO and E. AIELLO, Fordham University, Bronx, N.Y.

9:05 Transport and Rheology of Bronchial Secretions in Chronic Bronchitis (8.2)
E. PUCHELLE and J.M. ZAHM, U. 14 Inserm Vandoeuvre-les-Nancy, France.

9:25 Effect of Pharmacologic Interventions on the Relationship between the Mechanical Properties of Mucus and Mucociliary Transport (8.3)
M. KING, Meakins-Christie Labs., McGill University, Montreal, Canada.

9:45 In Vitro Drug Induced Changes in Mucus Rheology (8.4)
C. MARRIOTT, M. LITT and C.K. SHIH, University of Pennsylvania, Philadelphia, Pa.

10:05 In Vivo Drug Effects on the Physicochemical Properties of Canine Tracheal Mucus (8.5)
C.K. SHIH, M. LITT and L.W. CHAKRIN, University of Pennsylvania, Philadelphia, Pa.; and Smith Kline and French Laboratories, Philadelphia, Pa.

10:25 Ciliary Inhibitory Factor in Sputum of Asthmatic Patients (8.6)
T.M. CHEN and M.J. DULFANO, Veterans Administration Hospital, Brooklyn, N.Y.

10:45 The Effect of Sodium 2-Mercapto-Ethane Sulphonate and Hypertonic Saline Aerosols on Bronchial Clearance in Chronic Bronchitis (8.7)
S.W. CLARKE, M.T. LOPEZ-VIDRIERO, D. PAVIA and M.L. THOMSON, The Royal Free Hospital; the University of London; the Royal Free Hospital; and the London School of Hygiene and Tropical Medicine, London.

11:05 Studies on the Viscosity of Human Cervical Mucus (8.8)
M. SAGA, R.M. NAKAMURA, H. HAMADA and G. MATSUMURA, St. Marianna University, Kawasaki, Japan; University of Southern California, Los Angeles, Ca.; St. Marianna University, Japan; and Showa University, Tokyo, Japan.

11:25 Flow Permeation Studies of Cervical Mucus (8.9)
P.Y. TAM, D.F. KATZ and S.A. BERGER, University of California, Berkeley and Davis, Ca.

11:45 The Clinical Parallel Tube Sputum Viscometer (8.10)
S.R. HIRSCH, J.H. LINEHAN and R.T. BALMER, VA Center, Milwaukee; Marquette University; and University of Wisconsin, Milwaukee, Wis.

12:05 A Material Ratchet - The Pedal Mucus, the Slug *Ariolimax columbianus* (8.11)
M. DENNY, Dept. of Zoology, the University of British Columbia, Vancouver, B.C., Canada.

TUESDAY P.M. SESSION 9

DYNAMICS OF THROMBOSIS AND PLATELETS

Room 1105 Basic Science Bldg.

CHAIRMEN - HELMUT H. HARTERT, University of Kaiserslautern, FR Germany.
EUGENE F. BERNSTEIN, University of California, San Diego, Ca.

1:30 The Molecular Mechanism of Erythrocyte Aggregation (9.1)
D.E. BROOKS, J. CHARALAMBOUS and J. JANZEN, University of British Columbia, Vancouver, Canada.

1:50 Platelet Response to Shear Stress: Changes in Serotonin Uptake, Serotonin Release, and ADP-Induced Aggregation (9.2)
G.H. ANDERSON,[1] J.D. HELLUMS,[1] J.L. MOAKE,[2] and C.P. ALFREY, Jr.,[3] [1]Rice University; [2]University of Texas Medical School; and [3]Baylor College of Medicine, Houston, Tx.

2:10 Rheological and Morphological Studies on the Structure of Fibrin Network (9.3)
M. KAIBARA,[1] E. FUKADA[1] and K. SAKAOKU,[2] [1]The Institute of Physical and Chemical Research, Saitama, Japan; and [2]Tokyo University of Agriculture and Technology, Tokyo, Japan.

2:30 Thromboscillography, A Method to Differentiate Physiological Qualities of the Blood Clot (9.4)
H.H. HARTERT, Stadt. Krankenhaus, University of Kaiserslautern, FR Germany.

2:50 INTERMISSION

3:05 The Action of Differeing Heparin Preparations on the Visco-elasticity of Surface Layers of Fibrinogen (9.5)
R.G. KING and A.L. COPLEY, Polytechnic Institute of New York, Brooklyn, N.Y.

3:25 Rheological Investigations on Fibrin Clots (9.6)
H.A. UNGER and H.H. HARTERT, Universitat Kaiserslautern, Federal Republic of Germany.

3:45 Fibrinolysis and Coagulation in Human Plasma (9.7)
J.P. KIRKPATRICK,[1] L.V. McINTIRE[1] and J.L. MOAKE,[2]
[1]Rice University; and [2] The University of Texas Medical School at Houston, Houston, Tx.

4:05 Influence of Some Antibiotics of the β-Lactam Group upon Rheological Properties of Blood and Plateelet Aggregation (9.8)
L. HOUBOUYAN, S. GAILLARD, A. GOGUEL and J.F. STOLTZ, Centre de Transfusion Sanguine-Brabois, Vandoeuvre-Les-Nancy, France.

4:25 Platelet Function Abnormality as Measured by the Platelet Count Correlation (PCC) Technique (9.9)
K.V. BENNER, H. BOEHME and E. HUETTEL, Technical University, Munich; and Central Clinic, Gauting, Germany.

TUESDAY P.M. *SESSION 10*

BIORHEOLOGY OF MUSCLES

Room 274 Clinical Science Bldg.

CHAIRMEN - JAMES W. COVELL, University of California, San Diego, Ca.
ALLAN J. BRADY, University of California, Los Angeles, Ca.

1:30 Series-Coupled Myogenic Behavior of the Arteriolar Network (10.1)
P.C. JOHNSON, M.E. BURROWS, S.M. SULLIVAN and B.J. LaLONE, University of Arizona, College of Medicine, Tucson, Ariz.

1:55 Modelling of the Mechanical Response of Endothelium and Smooth Muscle Layers in Arterioles (10.2)
J. LEE, B.R. DULING and R.W. GORE, University of Virginia, Charlottesville, Va.

2:20 Assessment of Cardiac Mechanics during Isovolumic Systole (10.3)
M. LANDOWNE and E.W. ROSS, Jr., U.S. Army Res. Inst. Env. Med.; and U.S. Army Res. & Develop. Command, Natick, Ma.

2:45 INTERMISSION

3:00 Macroscopic Inhomogeneities in the Mechanical Response of Papillary Muscle (10.4)
J.G. PINTO, University of California, San Diego, Ca.

3:25 Cardiac Muscle Mechanics (10.5)
P.J. HUNTER, University of Oxford, England.

3:50 Stress-Strain-History Relation of Passive *Taenia coli* Smooth Muscle (10.6)
J.M. PRICE,[1] P. PATITUCCI[2] and Y.C. FUNG,[2] [1]Dept. of Physiology, College of Medicine, University of South Florida, Tampa, Fla.; and [2]University of California, San Diego, Ca.

4:15 An Examination of Isometric Contraction of Uretal Smooth Muscle (10.7)
P.F. ZUPKAS, Y.C. FUNG and J.G. PINTO, University of California, San Diego, Ca.

TUESDAY P.M. SESSION 11

MATHEMATICAL BIOFLUID DYNAMICS

Room 2100 Basic Science Bldg.

CHAIRMEN - OTTO H. MAHRENHOLTZ, Instit für Mechanik, Technische Universität Hannover, FR Germany
GEORGA K. LEA, National Science Foundation, Wash. D.C.

1:30 The Influence of Wave Shape on Peristaltic Transport (11.1)
O.H. MAHRENHOLTZ, M.G. MANK and R.U. ZIMMERMANN, Institute für Mechanik, Technische Universität, Hannover, FR Germany.

1:50 Finite Element Methods for Studying Mechanical Factors in Blood Flow (11.2)
N. DAVIDS, Pennsylvania States University, University Park, Pa.

2:10 Effect of Fluid Filtration on Apparent Blood Viscosity in the Microcirculation (11.3)
H.D. PAPENFUSS and J.F. GROSS, Ruhr-University Bochum, Bochum, West Germany; and University of Arizona, Tucson, Ariz.

2:30 A Re-examination of the Lighthill-Fitzgerald Theory (11.4)
J. AROESTY, W. KING and J. LAMAR, The Rand Corporation, Santa Monica, Ca.

2:50 INTERMISSION

3:05 Pressure-Flow Relationships of Blood in the Mammalian Kidney (11.5)
A.H. PURDY, National Institute for Occupational Safety and Health, Rockville, Md.

3:25 Indirect Determination of Rheological Properties of Fluid-Filled Viscoelastic Tubes Modelizing Arterial Hemodynamics (11.6)
D. GEIGER, P. FLAUD and C. ODDOU, Laboratoire de Biorheologie et d'Hydrodynamique Physiologique, Universite Paris, France.

3:45 A Rotated Disc Electrode for Characterization of Transport in Membranes (11.7)
D.A. GOUGH, J.K. LEYPOLDT and M. DAVIS, University of California, San Diego, Ca.

4:05 Mathematical Simulation of Axisymmetric Biological Liquids (11.8)
A.M. SHCHERBAKOV, M.J. NEGINSKI, I.V. SHIRKO and V.M. ZAIKO, Institute of Transplantation of Organs and Tissues, Moscow, USSR.

4:25 Mathematical Simulation of the Motion of a Catheter in a Vascular Channel (11.9)
I.V. SHIRKO, Institute of Transplantation of Organs and Tissues, Moscow, USSR.

4:45 Pulsatile Blood Flow with Couple Stress Theory (11.10)
P. CHATURANI and V.S. UPADHYA, Indian Institute of Technology, Bombay, India.

5:05 Mathematical Model of the Blood Flow in the Artificial Ventricle Cavity during Systole (11.11)
V.M. SHUMAKOV and V.M. ZAIKO, Institute of Transplantation of Organs and Tissues, Moscow, USSR.

WEDNESDAY A.M. SESSION 12

HEMORHEOLOGY: VISCOELASTICITY

Room 1105 Basic Science Bldg.

CHAIRMEN - EIICHI FUKADA, Institute of Physical & Chemical Research, Wako-Shi, Saitama, Japan.
PETER GAEHTGENS, Institut für Normale und Pathologische Physiologie der Universität, Köln, FR Germany.

8:45 Rheological Equations for Whole Human Blood (12.1)
C.R. HUANG, New Jersey Institute of Technology, Newark, N.J.

9:05 Yield Stress Measurements in Red Cell Suspensions (12.2)
H. KIESEWETTER, G. KOTITSCHKE and H. SCHMID-SCHONBEIN, Rein-Westf. Techn. Hochschule, Aachen, FR Germany.

9:25 Low Shear Rate Viscosity of Fresh Blood (12.3)
A. DOWNS, M. LITT and R.E. KRON, University of Pennsylvania, Philadelphia, Pa.

9:45 Rheological Hysteresis of Blood at Low Shear Rate (12.4)
M. BUREAU,[1] J.C. HEALY,[1] D. BOURGOIN[1] and M. JOLY,[2] [1]Faculte de Medicine Pitie-Salpetriere, Paris; and [2]Faculte de Medecine, Strasbourg, France.

10:05 Mathematical Analysis of the Hysteresis Rheogram of Human Blood (12.5)
W. FABISIAK and C.R. HUANG, New Jersey Institute of Technology, Newark, N.J.

10:25 INTERMISSION

10:40 Rheological Modeling of Fresh Blood from Transient Flow Measurements (12.6)
G. YEPSON, D. BOUTIN and M. LITT, University of Pennsylvania, Philadelphia, Pa.

11:00 The Mechanical Transfer Function of Blood: Modifications by Some Biological Factors (12.7)
B. OBRECHT,[1] P. RUSCH[2] and J.C. HEALY,[2] [1]Universite Louis Pasteur, Strasbourg; and [2]Faculte de Medecine, Strasbourg, France.

11:20 Influence of the Various Plasma Substitutes upon the Visco-elastic Properties of Blood. Comparison with Albumin (12.8)
S. GAILLARD, A. LARCAN and J.F. STOLTZ, Centre de Transfusion et d'Hematologie, Brabois et Service de Reanimation, Nancy, France.

11:40 In Vivo and In Vitro Viscosity Influences of Different Plasma Substitutes (12.9)
D. INGEMAR, University of Gothenburg, Surgery Dept. I, Sweden.

WEDNESDAY A.M. SESSION 13

ATHEROSCLEROSIS

Room 2100 Basic Science Bldg.

CHAIRMEN - MARGOT R. ROACH, University of Western Ontario, London, Canada.
SYOTEN OKA, National Cardiovascular Center, Osaka, Japan.

8:45 Flow Factors in Atherosclerosis (13.1)
M.R. ROACH, University of Western Ontario, London, Ontario, Canada.

9:05 Interaction of Blood Pressure and Flow with Arterial Wall (13.2)
C.G. CARO, Imperial College, London, England.

9:25 Effects of Oscillatory Strain on Macromolecular Uptake by Artery Wall (13.3)
S. CHIEN,[1] S. USAMI,[1] K.-M. JAN,[1] S. WEINBAUM[2] and C.G. CARO,[3] [1]Columbia University College of Physicians and Surgeons, New York; [2]City College of New York, CUNY; and [3]Imperial College of Science and Technology, London.

9:45 Flow Separation and Vortex Formation in Blood Vessel Models (13.4)
K. KIKUCHI, T. AZUMA and T. FUKUSHIMA, Shinshu University Medical School, Matsumoto, Japan.

10:05 Turbulence Generation in Stenotic Blood Vessel Models (13.5)
T. AZUMA and T. FUKUSHIMA, Shinshu University Medical School, Matsumoto, Japan.

10:25 INTERMISSION

10:40 Human Blood Cells in Models of Stenoses and Bifurcations (13.6)
T. KARINO and H.L. GOLDSMITH, McGill University Medical Clinic, Montreal General Hospital, Montreal, Canada.

11:00 Flow Disturbance at Branching Sites in the Abdominal Aorta (13.7)
T. FUKUSHIMA, K. KIKICHI and T. AZUMA, Shinshu University Medical School, Matsumoto, Japan.

11:20 Role of Stress Concentration in Arterial Walls in Atherogenesis (13.8)
H. NIIMI, National Cardiovascular Center, Research Institute, Suita, Osaka, Japan.

11:40 Numerical Study on Bifurcating Flow in a Blood Vessel (13.9)
M. KAWAGUTI and A. HAMANO, Dept. of Physics, Keio University, Yokohama, Japan.

WEDNESDAY A.M. SESSION 14

CAPILLARY BLOOD FLOW

Room 274 Clinical Science Bldg.

CHAIRMEN - BENJAMIN ZWEIFACH, University of California, San Diego, CA.
JEN-SHIH LEE, University of Virginia, Charlottesville, Va.

8:45 The Role of Blood Cellular Elements as Determinants of Apparent Viscosity in the Microcirculation (14.1)
H.H. LIPOWSKY, S. USAMI and S. CHIEN, Dept. of Physiology, Columbia University, N.Y.

9:05 The Interaction of White and Red Blood Cells in Capillary and Postcapillary Vessels (14.2)
G.W. SCHMID-SCHOENBEIN, S. USAMI and S. CHIEN, Dept. of Physiology, Columbia University, N.Y.

9:25 Microcirculation by Model Material (14.3)
R. TAKAKI and K. YASUZAMI, Tokyo University of Agriculture and Technology, Japan.

9:45 Hematocrit Distribution in Microvasculature (14.4)
R.T. YEN and Y.C. FUNG, University of California, San Diego, Ca.

10:05 The Interaction between Oxygen Tension Levels and the Flow of Sickle-Cell Blood in the Capillaries (14.5)
S.A. BERGER and W.S. KING, University of California, Berkeley; and the RAND Corporation, Santa Monica, Ca.

10:25 INTERMISSION

10:40 Erythrocyte Motion through a Narrow Capillary Constricted by Surrounding Tissue Pressure from Optic Disc Edema in Anterior Ischemic Optic Neuropathy (14.6)
S. E. MOSKOWITZ, The Hebrew University, Jerusalem, Israel.

11:00 Blood Flow in Curved Capillary Glass Tubes (14.7)
T.-C. HUNG, T.-K. HUNG and G. BUGLARELLO, University of Houston; University of Pittsburgh; and Polytechnic Institute of New York.

11:20 Pulsatile Blood Flow in Arteriole of Frog Web (14.8)
M. HORIMOTO, T. KOYAMA, H. MISHINA and T. ASAKURA, The Research Institute of Applied Electricity, Hokkaido University, Sapporo, Japan.

11:40 Basic Hydrodynamic Resistance Behaviour of Erythrocyte Suspensions in Capillaries from 5-7 µm Diameter (14.9)
P.S. LINGARD, Children's Medical Research Foundation, Sydney, New South Wales, Australia.

THURSDAY A.M. SESSION 15

RED BLOOD CELLS

Room 1105 Basic Science Bldg.

CHAIRMEN - MARCOS INTAGLIETTA, University of California, San Diego, Ca.
EVAN EVANS, Duke University, Durham, N.C.

8:45 Method to Determine the Deformability (Pore Passage Time) of Single Erythrocytes (15.1)
K. MUSSLER, H. KIESEWETTER and H. SCHMID-SCHÖNBEIN, Medizin.-Theoret. Institut. der RWTH, Aachen, West Germany.

9:05 Deformation of a Red Blood Cell in a Simple Shear Flow. II. Experimental Study with Optical Methods (15.2)
J.F. STOLTZ, J.C. RAVEY, M. GUILLOT and P. MAZERON, Centre Régional de Transfusion - Brabois, Vandoeuvre-Lès-Nancy, France.

9:25 Deformation of a Red Cell in a Simple Shear Flow: I. Theoretical Study, Case of a Sphered Cell (15.3)
D. BARTHES-BIESEL and B. GUERLET, UTC, BP 233 Compiegene, France, and Groupe d'Hemorheologie, CRTS 5400 Nancy, France.

9:45 Apparent Elastic Constant and Adhesiveness of Red Cells from Calf, Dog and Human (15.4)
L.W. SHEN, T.C. HUNG and N.H.C. HWANG, Institute for Cardiovascular Studies, University of Houston, Houston, Tx.

10:05 INTERMISSION

10:20 Application of Centrifugal Flexibility Measurements to Sickle Cell Anemia Erythrocytes (15.5)
B.F. CAMERON and P.E. SMARIGA, Cincinnati Comprehensive Sickle Cell Center, Cincinnati, Oh.

10:40 Material Properties of Erythrocytes in Muscular Dystrophy (15.6)
Y.F. MISSIRLIS and M.C. BRAIN, McMaster University, Hamilton, Ontario, Canada.

11:00 Influence of Pentoxifylline on Erythrocyte Filtrability and Microrheology - A Pharmacological Study (15.7)
J.F. STOLTZ, M. GUILLOT and G.A. MARCEL, Centre Régional de Transfusion - Brabois, Vandoeuvre-lès-Nancy, France.

11:20 Analysis of Flow Velocity by Means of Fluorescent Angiography and Low Light Level Video System (15.8)
B. ENDRICH and M. INTAGLIETTA, University of California, San Diego, Ca.

11:40 A.C. Electrophoresis of Human Red Blood Cells (15.9)
P.C.Y. CHEN, University of California, San Diego, Ca.

THURSDAY A.M. SESSION 16

MECHANICAL PROPERTIES OF ARTERIES AND VEINS

274 Clinical Science Bldg.

CHAIRMEN - TAKEHIKO AZUMA, Shinshu University School of Medicine, Matsumoto, Japan.
RAMESH N. VAISHNAV, Catholic University of America, Wash. D.C.

8:45 Chairman's Review on the Present Status of Arterial Mechanics
R.N. VAISHNAV, Catholic Univ. of America, Wash. D.C.

9:10 An Investigation into the Fracture Mechanics of Cerebral Arteries and Aneurysms (16.1)
A.D. HARMAN, University of British Columbia, Vancouver, B.C., Canada.

9:35 Alteration of Rheological Properties of Canine Thoracic Aorta in Experimental Hypertension (16.2)
M.G. SHARMA and J.P. JACOBUS, Pennsylvania State University, University Park, Pa.

10:00 INTERMISSION

10:15 Identification of the Rheological Properties of the Arterial Wall: Problems Arising from Reflexions (16.3)
C. KOPP, Groupe de Biomecanique et Institut de Mecanique des Fluides, Strasbourg, France.

10:40 A Rubber-Like Protein from Octopus Arteries (16.4)
R. SHADWICK, University of British Columbia, Vancouver, B.C., Canada.

11:05 On a Problem of Arteries (16.5)
C. PALLOTTI and G. PALLOTTI, Gruppo Nazionale per la Fisica Matematica del C.N.R. Istituto di Fisica "A Righi" e Istituto di Fisiologia Veterinaria del Universita di Bologna, Italy.

11:30 Review on the Mechanics of Vein
T. AZUMA, Shinshu University, Matsumoto, Japan.

Nonlinear Viscoelastic Properties of Arteries (16.6)
A.G. HUDETZ, E. MONOS and A.G.B. KOVACH, Experimental Research Institute, Semmelweis Medical University, Budapest, Hungary.

Stress-Strain Relationship for Human Arteries (16.7)
S. STOYCHEV, Institute of Mechanics and Biomechanics Bulgarian Academy of Sciences, Sofia, Bulgaria.

THURSDAY A.M. SESSION 17

HEMORHEOLOGY AND HEMODYNAMICS

Room 2100 Basic Science Bldg.

CHAIRMEN - HARRY L. GOLDSMITH, McGill University and Montreal General Hospital, Montreal, Canada.
J. F. STOLTZ, Centre de Transfusion Sanguine - Brabois, Vandoeuvre-les-Nancy, France.

8:45 Quantitative RBC Aggregation Deduced from Viscometry (17.1)
D. QUEMADA, Laboratoire de Biorheologie et d'Hydrodynamique, Physiologique UER Physique, Universite Paris VII, Paris, France.

9:10 A New Look at the Erythrocyte Sedimentation Rate (17.2)
D.M. STASIW, L.C. CERNY, R. WILLIAMS and M. ZONGRONE, Utica College and Masonic Medical Research Laboratory, UTICA, N.Y.

9:35 The Influence of Normal and Rigid Red Blood Cells on Suspension Rheology - Viscometric Flows and Instability Measurements (17.3)
W.M. PHILLIPS and W.A. DANIELS, The Pennsylvania State University, University Park, Pa.

10:00 INTERMISSION

10:15 Blood Flow through Columns of Rigid Spheres: A Tissue-Perfusion Analog (17.4)
G.R. COKELET, R. MOUNTAIN, P. KIMMET and M. EVONIUK, Dept. of Chemical Engineering, Montana State University, Bozeman, Mt.

10:40 Effects of Red Cell Rigidity and Aggregation on Resistance to Flow (17.5)
A.H. SACKS, K.W. KIRK, P.N. NORTH and R. SUE, Palo Alto Medical Research Foundation, Palo Alto, Ca.

11:05 Some Biophysical Properties of Artificial and Whole Blood Mixtures (17.6)
L.C. CERNY and D.M. STASIW, Utica College and Masonic Medical Research Laboratory, Utica, N.Y.

11:30 On Thermal Hemolysis and Heat Transfer in Blood Rheology (17.7)
T. ARIMAN, University of Notre Dame, Notre Dame, Ind.

11:55 Non-Newtonian Flow in Tube - Determination of the Shear Dependent Apparent Blood Viscosity (17.8)
M. ARPAD and F. KORNEL, Biophysical Institute Medical University, Pecs, Hungary.

THURSDAY P.M.

CONVOCATION

Room 2722 Undergraduate Science Bldg.

CHAIRMAN - ALEX SILBERBERG, Weizmann Institute, Israel
President of the International Society of Biorheology

1:30 Chairman's Address

1:35 From Colloidal Science to Biorheology - A Historical Remi-niescence
B. TAMAMUSHI, Nezu Chemical Institute, Musashi University, Tokyo, Japan.

1:55 Prospects of Biorheology
A.L. COPLEY, Polytechnic Institute of New York, Brooklyn, N.Y.
Past President, International Society of Biorheology

2:10 Presentation of Poiseuille Medal to the 1978 Awardee:
M. JOLY.
Introduction by A. SILBERBERG, President, Int. Society of Biorheology.
Presentation by S. OKA, previous Poiseuille Medal Awardee

2:15 Poiseuille Lecture: Biorheology, a Factor of Scientific Progress
M. JOLY, Laboratoire de Biophysique, Faculté de Médicine Pitié - Salpêtrière, Paris, France.

THURSDAY P.M. SESSION 18

NEW HYPOTHESES IN HEMORHEOLOGY AND MUSCLE CONTRACTION

Room 2722 Undergraduate Science Bldg.

CHAIRMAN - ROY SWANK, University of Oregon, Portland, Ore.

3:00 Rheology of Thrombotic Processes Occurring in Flow: The Interaction of Erythrocytes and Thrombocytes (18.1)
H. SCHMID-SCHÖNBEIN, P. RICHARDSON, G.V.R. BORU, H. RIEGER, R. FROST and I. ROHLING-WINKEL, Rhein-Westf. Techn. Hochschule, Aachen. FR Germany.

3:40 Physical Theory of Permeability of Vascular Walls in Relation to Atherogenesis (18.2)
S. OKA, National Cardiovascular Center, Research Institute, Suita, Osaka, Japan.

4:20 Biorheology of Muscle: A Synthetic Approach (18.3)
T. IWAZUMI, University of Washington, Seattle, Wa.

HEMORHEOLOGY IN ASTRONAUTICS

Room 1105 Basic Science Bldg.

CHAIRMEN - GEOFFREY V.F. SEAMAN, Univ. of Oregon Health Sciences Center, Portland, Ore.
ROBERT S. SNYDER, Chief, Separation Processes Branch, Marshall Space Flight Center, Ala.

3:00 A Review of Hematology Studies Associated with Space Flight (19.1)
S.L. KIMZEY, Johnson Space Center, Houston, Tx.

3:20 Biorheology in Space: Some Speculations (19.2)
G.V.F. SEAMAN, University of Oregon Health Sciences Center, Portland, Ore.

3:40 Aggregation of Red Cells and Blood Viscosity under Near-Zero Gravity (19.3)
L. DINTENFASS, Kanematsu Memorial Institute, Sydney Hospital, Sydney, Australia.

4:00 Certain Aspects of Hemorheology in a Near-Zero Gravity Environment (19.4)
A.L. COPLEY, Polytechnic Institute of New York, Brooklyn, N.Y.

4:20 Interpretation of Fluid Phenomena in Weightlessness (19.5)
D. SAVILLE, Princeton University, Princeton, N.J.

4:40 Panel Discussion
A.L. COPLEY, L. DINTENFASS, H. GOLDSMITH, S.L. KIMZEY, D. SAVILLE and L. VROMAN.

BONE AND CARTILAGE

Room 274 Clinical Science Bldg.

CHAIRMEN - WAYNE AKESON, Univ. of Calif., San Diego, Ca.
VAN C. MOW, Rensselaer Polytechnic, Troy, N.Y.

3:00 Permeability and Transport Properties of Articular Cartilage (20.1)
S.S. GORDON[1], V.C. MOW[1], R. LEE[2], and A.J. GRODZINSKY[2],
[1]Rensselaer Polytechnic Institute, Troy, N.Y. and
[2]Massachusetts Institute of Technology, Cambridge, Ma.

3:25 A Theory of Strength for Bone and Wood (20.2)
S. COWIN, Tulane University, LA.

3:50 The Effects of Pressure and Time on the Permeability of Articular Cartilage (20.3)
J.P. RENAUDEAUX, Universite Pierre et Marie Curie, Orsay, France

4:15 Rheological Measurement of Interarticular Cartilage Surface Shearing Forces In Vitro (20.4)
L.L. MALCOM, F.R. CONVERY, S.L-Y. WOO and W.H. AKESON, University of Calif., San Diego, Ca.

4:40 Rheological Study of Human Knee Joint (20.5)
T. TATEISHI, Y. SHIRASAKI and Y. MIYANAGA[2],
Mechanical Engineering Laboratory, Igusa 4-12, Suginamiku, Tokyo; [2]Faculty of Medicine, University of Tokyo, Japan.

Evaluation of the Adaptation of Long Bones to Bending Stress (20.6)
B. KUMMER, Anatomisches Institut der Universitat, Koln, Germany.

Quadripole Model of Bone Piezoelectricity (20.7)
G. BRANKOV and N. PETROV, Institute of Mechanics and Biomechanics, Bulgaria.

THURSDAY P.M. SESSION 21

TISSUE SPACE

Room 2100 Basic Science Bldg.

CHAIRMAN - HAROLD WAYLAND, California Institute of Technology
Pasadena, Ca.

3:00 Macromolecular Transport in Connective Tissue (21.1)
H. WAYLAND, California Institute of Technology, Pasadena, Ca.

3:25 Protein Movements in the Extravascular Space (21.2)
S. WITTE, Diakonissen-Krankenhaus, West Germany.

3:50 Water Movement Through Swelling Connective Tissue (21.3)
I. FATT and P. TAM, University of Calif., Berkeley, Berkeley, Ca.

4:15 Blood Flow Properties in Human Veins Under Various Hydrostatic Conditions (21.4)
A.M. EHRLY, University Medical School, Frankfurt, West Germany

4:40 Mathematical Model of Substance Diffusion in Tissue with Nonlinear Absorption (21.5)
V.M. ZAIKO and A.N. SHARIKOV, Institute of Transplantation of Organs and Tissues, Moscow, U.S.S.R.

FRIDAY A.M. SESSION 22

ELASTIN, COLLAGEN AND TENDONS

Room 274 Clinical Science Bldg.

CHAIRMEN - ERIC BAER, Case Western Reserve University, Cleveland, Oh.
ANDRUS VIIDIK, Univ. of Aarhus, Aarhus, Denmark

8:45 Rheological Analysis of Collagen - with Reference to Morphology and Experimental Techniques (22.1)
A. VIIDIK, H. OXLUND and T. ANDREASSEN, Institute of Anatomy, University of Aarhus, Denmark.

9:15 Electromechanochemical and Reaction-Diffusion Dynamics in Collagen Membranes (22.2)
N.A. SCHOENFELD, J.H. NUSSBAUM, and A.J. GRODZINSKY, Massachusetts Institute of Technology, Cambridge, Ma.

9:45 The Dynamic Mechanical Properties of Elastin (22.3)
J.M. GOSLINE, University of British Columbia, Vancouver, B.C.

10:15 INTERMISSION

10:30 Effect of Water on the Mechanical Relaxation of Human Intervertebral Disc Material (22.4)
N.D. PANAGIOTACOPULOS, R. BLOC, and W.G. KNAUSS, California Institute of Technology, Pasadena, Ca.

11:00 Dynamic Viscoelastic Behaviour of Human Tendon In Vitro (22.5)
H. SCHWERDT, A. CONSTANTINESCO, and J. CHAMBRON, Groupe de Biomecanique, Institut de Physique Biologique, Strasbourg, Cedex, France.

11:30 Nonlinear Viscoelastic Behavior of Human and Canine Flexor Tendons in Simple Elongation (22.6)
F.K. KO, A. PASTORE and F. COLE, Philadelphia College of Textiles and Science; University of Pennsylvania; and Thomas Jefferson University, Philadelphia, Pa.

12:00 Rheological Properties of Natural and Reconstituted Collagen Fibers (22.7)
L.V. KUKHAREVA and V.I. VOROB'EV, Institute of Cytology of the Academy of Sciences of the U.S.S.R., Leningrad, U.S.S.R.

FRIDAY A.M. SESSION 23

CLINICAL HEMORHEOLOGY I

Room 2100 Basic Science Bldg.

CHAIRMAN - LEO DINTENFASS, Kanematsu Memorial Institute, Sydney, Australia

8:45 Clinical Applications of Blood Viscosity Factors and Functions (Invited Lecture) (23.1)

9:15 Clinical Use of Hemorheometry (23.2)
B.Y. LEE, F.S. TRAINOR, D. KAVNER, J.A. CROSOLOGO, L.R.M. DEL GUERCIA and J.L. MADDEN, Veterans Administration Hospital, Castle Point, N.Y.

9:35 Clinical Blood Rheology (23.3)
H. CHMIEL, I. ANADERE, H. HESS[2] and G.B. THURSTON[2]; Institut fur Grenzflachen-und Bioverfahrenstechnik, FR Germany; Medizinische Poliklinik der Universitat Munchen, FR Germany; [2]University of Texas at Austin, Austin, Tx.

9:55 Reduced Erythrocyte Deformability in Diabetes (23.4)
D.E. McMillan, N.G. UTTERBACK and J. LA PUMA, Sansum Medical Research Foundation, Santa Barbara, Ca.

10:15 INTERMISSION

10:30 Hemorheological Considerations on Diabetic Microangiopathy: What Can be Good Indices for Its Management? (23.5)
Y. ISOGAI, A. IIDA, K. MOCHIZUKI, T. YOKOSE, H. OKABE, M. ASHIKAGA, S. IDEMOTO, T. MAEDA and M. ABE, Department of Internal Medicine, Jikei University, Minato-ku, Tokyo, Japan.

10:50 Abnormal Red Cell Membrane Fluidity in Zieve's Syndrome (23.6)
K.M. GOEBEL, R. SCHUBOTZ, and J. SCHNEIDER, Department of Medicine, University of Marburg, Marburg, Germany.

11:10 Fast Determination of Water Mobility in Blood Plasma: Investigation of Clinical Significance (23.7)
A. GANSSEN, H. SCHMID-SCHOENBEIN[2], H. MALOTTA[2] and R. SCHNEIDER[2], Siemens AG UB Med., Erlangen, Germany; [2]Abt. Physiologie, T.H. Aachen, Germany.

11:30 The Rheological Behavior of the Abnormal Porteinemia Due to Temperature Change and its Clinical Significance (23.8)
S. SHIGEHIRO, Kitasato University School of Medicine, Kanagawa-ken, Japan.

FRIDAY A.M. SESSION 24

BIOFLUID DYNAMICS

Room 1105 Basic Science Bldg.

CHAIRMAN - COLIN G. CARO, Imperial College of Science and Technology, London, U.K.

8:45 The Characteristics of Secondary Flow and Turbulence in a Cone-Plate Apparatus (24.1)
C.F. DEWEY, JR., S.R. BUSSOLARI and H.P. SDOUGOS[2], Massachusetts Institute of Technology, Cambridge, Ma.; [2]Institut fur Biomedizinische Technik, Zurich, Switzerland.

9:05 The Wall-Shear-Stress Intensification Due to Pulsatile Blood Flow (24.2)
Y. MATUNOBU, Keio University, Hiyoshi, Yokohama, Japan.

9:25 The Fluid Dynamic Evaluation of the Outflow Tract Stenosis in Cardiac Surgery (24.3)
T. TSUJI, K. SUMA, M. SUGAWARA, and Y. SAKURAI, Tokyo Women's Medical College, Tokyo, Japan.

9:45 Model Experiment on Genesis of the Korotkoff Sounds (24.4)
M. ARAKAWA and Y. MATUNOBU, Keio University, Kiyoshi, Yokohama, Japan.

10:05 INTERMISSION

10:20 Flow of Blood Through a Curved Duct (24.5)
V.S. PRATAP, D.B. SPALDING and V.L. SHAH[2], Imperial College, London, England.
[2]University of Wisconsin, Milwaukee, Wi.

10:40 Chains of Spheres in Poiseuille Flow: Their Equilibrium Position, Slip-Velocity and Hydrodynamically Induced Forces - A Model for the Rouleaux Formation and Plasma Transport (24.6)
K. BAUCKHAGE, Universitat Bremen, Bremen, FR Germany.

11:00 Experimental Investigation on the Mass Transfer of CO_2 in Aqueous NaCl Solution Containing Solid Particles (24.7)
A. OBERMAYER, Institut fur Thermische Verfahrenstechnik-der TU Clausthal, Leibnizstrasse 15, FR Germany.

11:20 Particle Movements and Transverse Fluid Transport - Rates In a Poiseuille Flow of a Suspension of Low Concentration in a Tube with Membraneous Wall - Their Influence on O_2 and CO_2 Mass Transfer as a Model for Blood Flow (24.8)
K. HIRSCHMANN and K. BAUCKHAGE, Universitat Bremen, Bremen, FR Germany.

11:40 Sensitivity Analysis of the Physical Factors Affecting Flow in a Vascular Segment (24.9)
K.P. TEWARI, H.P. Medical College, Simla, India.

Long Chain Polymers: Their Effect on Pulsatile Blood Flow in Elastic Tubes (24.10)
S. EINAV and M. ROSHU, Tel Aviv University, Israel.

FRIDAY P.M. SESSION 25

PROPERTIES OF BIOSOLIDS

Room 274 Clinical Science Bldg.

CHAIRMEN - WILLIAM P. GRAEBEL, Univ. of Michigan, Ann Arbor, Michigan
YORAM LANIR, Julius Silver Inst. of Biomedical Eng. Sciences, Technion, Israel.

1:30 Biaxial Membrane Inflation Techniques for Identification of Constitutive Equations and Failure Criteria for Soft Biological Tissues (25.1)
J.W. MELVIN, N.M. ALEM, and A.S. WINEMAN, The University of Michigan, Ann Arbor, Mi.

1:50 Rheology of Biomembranes (25.2)
D. BOURGOIN, M. JOLY, D. ROBAGLIA, and W. SHANKLAND, Faculte de Medecine, Universite Paris, Paris, France.

2:10 Biomechanics of the Uterine Cervix (25.3)
R.W. LITTLE, Michigan State University, East Lansing, Mi.

2:30 The Study of Surface and Interfacial Kinetics of Biopolymers Using a Normalized Resonance Oscillatory Surface Rheometer (25.4)
B. WARBURTON, The School of Pharmacy, University of London, London, England.

2:50 Materials Properties of the Living Human Cornea (25.5)
W.P. GRAEBEL, B.E. COHAN and A.C. PEARCH, The University of Michigan, Ann Arbor, Mi.

3:10 Mechanical Stresses and Piezoelectricity of Dental Tissues (25.6)
R. OGOLNIK, B. PICARD and D. GEIGER, Universite Paris VII, France.

3:30 Influence of Freeze-Drying and Gamma Sterilization on the Mechanical Properties of Human Dura Mater Grafts (25.7)
N. PETROV and ST. MECHKARSKY, Institute of Mechanics and Biomechanics, and Tissue Bank to the Pirogov Institute for Urgent Medical Aid, Sofia, Bulgaria.

FRIDAY P.M. SESSION 26

CLINICAL HEMORHEOLOGY II

Room 1105 Basic Science Bldg.

CHAIRMEN - HOLGER SCHMID-SCHONBEIN, Rhein.-Westf. Techn. Hochschule, Aachen, FR Germany.
STANLEY CHARM, Tufts University, Boston, Ma.

1:30 The History of the Measurement of the Viscosity of Human Blood Serum and Plasma in Relation to Disease (26.1)
J. HARKNESS, Dept. of Clinical Pathology, Musgrove Park Hospital, Taunton, England.

1:50 Changes in the Oxygen Pressure of Human Muscle Tissue by Variations of the Flow properties of Blood (26.2)
A.M. EHRLY, and W. SCHROEDER, Dept. of Physiology, University Medical School, Frankfurt, West Germany.

2:10 Fundamental Mechanisms Controlling Hemorheology (26.3)
H.L. DAVIS, Depts. of Surgery and Biochemistry, University of Nebraska, College of Medicine, Omaha, Ne.

2:30 Red Blood Cell Aging as a Model to Influence Pharmacologically the Red Cell Deformability (26.4)
H.-G. GRIGOLEIT, H. LEONHARDT[2], R. SCHROER and F. LEHRACH, Hoechst AG, Werk Albert, Wiesbaden, Germany;
[2]Klinikum Steglitz der Freien Universitat, Berlin, Germany.

2:50 The Behavior of Different Types of Materials in the Dynamic Physiological Environment (26.5)
S.D. BRUCK, Stephen D. Bruck, Associates, Inc., 11300 Rockville Pike, Rockville, Md.

3:10 Evaluation of Blood Microfilter Performance (26.6)
C.H. TAMBLYN, R.J. KNOX, F.J. NORDT, G.V.F. SEAMAN, R.L. SWANK and C.F. ZUKOSKI IV, Dept. of Neurology, University of Oregon Health Sciences Center, Portland, Or.

3:30 Effects of Exercise and Conditioning on Properties of Red Blood Cells Significant for Blood Flow (26.7)
R.E. LOVLIN, L.S. SEWCHAND, J.S. BECK and S. ROWLANDS, Division of Medical Biophysics, The University of Calgary, Calgary, Alberta, Canada.

3:50 Lower Plasma Viscosity of Joggers vs Non-Joggers (26.8)
S.E. CHARM, H. PAZ and G.S. KURLAND [2], Tufts University, School of Medicine, Boston, Ma.
[2]Harvard Medical School, Boston, Ma.

FRIDAY P.M. SESSION 27

ULTRASOUND APPLICATIONS, BIOFLUIDS AND VISCOELASTIC BODIES

Room 2100 Basic Science Bldg.

CHAIRMEN - SIEGFRIED WITTE, Diakonissen-Krankenhaus, FR Germany
DAVID GOUGH, Univ. of Calif., San Diego, La Jolla, Ca.

1:30 Contribution to the Study of Blood Flow Using Low Frequency Spectral Analysis of Doppler Ultrasonic Waves. Application to a Pulsed Model (27.1)
J.C. VERA, M. LEFORT and J.F. STOLTZ, Groupe d'Hemorheologie, Ecole des Mines, Nancy, France.

1:50 Studying the Formation of Red Blood Cell Aggregates Using an Ultrasonic Resonating Technique (27.2)
D. CATHIGNOL, C. FOURCADE, M. HEITZ[2], J.C. VERA[2] and J.F. STOLTZ[2], Centre d'Etude et Technologie Appliquees a la Clinique, Bron, France; [2]Centre Regional de Transfusion de d'Hematologie, Vandouvre, France.

2:10 Ultrasonic Velocity Measurements and Phase Transitions in Liposome Suspensions (27.3)
A. SAKANISHI, University of Tokyo, Tokyo, Japan.

2:30 The Microrheology of Colloidal Dispersions: Some Biological Applications (27.4)
K. TAKAMURA, H.L. GOLDSMITH and S.G. MASON, McGill University, Montreal, Canada.

2:50 The Viscoelasticity of Normal and Pathological Synovial Fluid (27.5)
I. ANADERE, H. CHMIEL and W. LASCHNER[2], Institut fur Grenzflachen - und Bioverfahrenstechnik, Stuttgart, FR Germany; [2]Abteilung fur orthopadische Rheumatologie, Stuttgart, FR Germany.

3:10 The Viscosity of the Urine from Catheterized Patients - Problems and Possibilities (27.6)
U. PARKHEDE, A. NORBERG and B. NORBERG, University Hospital of Lund, Lund, Sweden.

CONVOCATION ADDRESSES

CONVOCATION ADDRESS 1

FROM COLLOIDAL SCIENCE TO BIORHEOLOGY - A HISTORICAL REMINISCENCE

B. Tamamushi
Prof. Emer. of Chemistry
Nezu Chemical Institute, Musashi University
1-26 Toyotama-Kami, Nerima-Ku
Tokyo, 176, Japan

Biorheologists are certainly familiar with such terms as anomalous viscosity, viscoelasticity, thixotropy, rheopexy, streaming double refraction, tactoid formation, and mesomorphic state of matter. The phenomena relating to these terms were discovered or investigated originally by colloid and surface chemists such as Bingham, Hatschek, Freundlich, Ostwald, Zocher and their collaborators in the period of 1920-1935.

As one of pupils of Freundlich I studied in his laboratory in Berlin during 1927-1929, when I was able to have personal contacts with most of these investigators and to acquire some knowledge about their findings and discussions. After returning to my homeland I began to make research on some of those phenomena, particularly thixotrophy, dilatancy, rheopexy and related properties of some colloidal systems during 1930-1941, which later gave a stimulation for the further development in rheological research in Japan.

As Scott Blair writes in his latest book on Introduction to Biorheology the term "Biorheology" was first proposed by Dr, Copley at the First International Congress on Rheology held in Scheveningen (Holland) in 1948. With Dr. Copley I met for the first time in 1960 when he delivered a lecture on "Hemorheology, An Introduction" in the International Congress on Blood Transfusion held in Tokyo, His lecture aroused interests in biorheological research in my country, particularly through Dr. Oka who attended the lecture with myself.

My recent interest mainly lies in the study of mesomorphic states of matter from the viewpoint of colloid and surface chemistry as well as rheology. In this lecture I would like to make a sketch of lineage of the colloid and surface chemical approach to biorheology and, if possible, touch on researches in mesophases in connection with biological and biorheological problems.

CONVOCATION ADDRESS 2

PROSPECTS OF BIORHEOLOGY

Alfred L. Copley
Laboratory of Biorheology
Polytechnic Institute of New York
Brooklyn, New York 11201

The biorheological exploration of life processes is of great significance among the perspectives pertaining to the future of biorheology as an organized science. Biorheological experimentation and treatments are bound to be more and more included in multidisciplinary research regarding many problems in the biomedical sciences.

In recent years, experimental research on atherogenesis included hemorheological considerations and studies. Atherosclerosis is an example of multidisciplinary approach, in which hemorheological studies play an important role. A new theory of early atheroma formation was recently presented by the author (A. L. Copley, 4. Kölner Symposium on Cerebral and Coronary Vascular Disorders and Infarcts, Max-Planck-Institut für Hirnforschung, Cologne, 21.-24. June 1978. Springer-Verlag, Heidelberg, in press). It is based in great part on our surface rheological studies of β-lipoprotein-fibrinogen systems (A. L. Copley and R. G. King, Thrombosis Research 4: 193-198, 1974) and surface chemical studies by Miller et al. concerning the adsorption of lipoproteins on proteinaceous surface and their desorption from it (I. R. Miller, H. Graet and Y. F. Frei, in: Atherogenesis: Initiating Factors. Amsterdam, Assoc. Sci. Publ., 1973, pp. 251-266). This theory includes the theoretical approach to atherogenesis by Oka, involving polymer physics and hemorheology (S. Oka. In: Hemorheology and Thrombosis. Eds. A. L. Copley and S. Okamoto. New York-Oxford, Pergamon Press, 1976; Thrombosis Research 8 (Suppl. II): 305-313, 1976).

Although clinical hemorheology has been practiced since several decades more and more both diagnostically, such as the erythrocyte sedimentation rate, the viscosity of blood systems, and Hartert's thrombelastography and therapeutically, e.g., by hemodilution, it is anticipated that clinical hemorheology will be greatly expanded to include many new hemorheological techniques and treatments.

Many biorheological tests and treatment, other than hemorheological ones, will be introduced in the practice of medicine and surgery. Clinical biorheology will play an important role in more successful clinical management including therapy and in prophylactic measures. It will also be applied towards better birth control and to more effective aid to the aged. Clinical biorheology will become a major discipline and taught in medical, dental and veterinary schools. It will also have a great impact on space bio-medicine and many biorheological tests will be carried out near zero gravity in spacelab modules.

Advancement of knowledge in biorheology will likewise be applied, among others, to genetics, the differentiation of cells, embryology and growth processes including cancer. However, biorheology will not be limited to problems relating to life processes in mammals and other animals, but will be extended to micro-organisms including viruses and viroids, and, in particular, to plant organisms.

It is almost paradoxical that the flow of a non-biological simple fluid, such as water, was first studied by Poiseuille after he made his hemorheological observations about 143 years ago of the very complex microcirculation in animals. This led to what is well known as the Poiseuille law. There will be a growing number of stimuli from biorheological researches in non-biological scientific and technological areas. There will be also an augmentation of new theoretical biorheological approaches, which will be advanced for many complex biological manifestations and processes. These theoretical concepts will become available for application to medical, biological, other scientific and technological disciplines.

It is concluded that biorheology with its numerous and multitudinous applications will become one of the major life sciences and be an integral part in the further development of human society. Finally, the differentiation between life and inanimate matter may well be decided by biorheological investigation and the perennial question "what is life" may thus find an answer.

BIORHEOLOGY, A FACTOR OF SCIENTIFIC PROGRESS

M. Joly
Laboratoire de Biophysique
Faculté de Médecine Pitié-Salpêtrière
Paris, France

The characterization of biorheology as an autonomous science with a precise place in the field of knowledge should not allow the biorheologists to forget the various aspects of the importance of this kind of research in the general scientific development; in addition to the study of its own domain, biorheology behaves as a stimulative agent for other chapters of science, from fundamental rheology up to biochemistry, biology and medical engineering.

It is well known that rheology of liquids has been initiated by the work of Poiseuille on the pulmonary microcirculation. The case of this medical man who changed into a physicist in order to elucidate a biological problem is typical of the part played in science by biorheology, not only as a tool of investigation, but also as an initiator or a catalyser of new researches. Many examples of this action of biorheology appear in various fields.

The complexity of the problems studied in biorheology comes up frequently against the deficiencies of fundamental rheology, and consequently biorheology ought to act as a stimulus for the improvement of the experimental methods of rheology and the extension of its phenomenological or theoretical analysis to more complicated cases. Thus the peculiarities of blood flow have led recently to establish very general relationships for the rheological behavior of concentrated suspensions with any structure depending on the stresses.

In other fields biorheological phenomena have been often at the origin of important theoretical and technical developments, or have served as models for the elaboration of new devices or products. Besides the knowledges on muscle biology, cellular biology or protoplasm structure, for instance, are greatly indebted to the study of rheological properties of these living systems for their present state of refinement, as shown in a few examples.

At a more modest level, problems of surface rheology of biological substances, such as lipids and proteins, have led to state precisely the notions of flow induced structure or phase changes, molecular deformability, and conformational stability of biopolymers. Rheo-optical studies (flow birefringence and rheoturbidity) of denatured protein suspensions have required the investigation of the flow induced aggregation processes, and the development of a general theory of the aggregation which has permitted recently to calculate the interaction energy between the blood red cells in the rouleaux from the data given by optical retrodiffusion measurements.

The main reason of this influence of biorheology on other chapters of knowledge is the fact that the complexity and often the apparent strangeness of the rheological behavior of some biological systems are so great that they enjoin the research of the hidden causes and parameters at more and more acute scale, frequently up to the molecular scale, which leads to a series of works in biology, biophysics and biochemistry.

In order to promote such an extension of biorheology it is necessary to study and describe as accurately as possible the rheological behavior of many biological systems, whatever its intricacy may be, and to search into the cause of every observed phenomenon. For that, the mechanical properties must be analyzed, step by step, from the macro- to the microrheological level. A tentative method of approach for the study of complicated systems is proposed on the basis of the introduction of the concepts of locally equivalent systems and simple tangential systems, and of apparent rheological coefficients, the exact significance of which is to be made clear by taking into account the interactions between the constitutive particles or molecules of these systems.

PROCEEDINGS

1.1 STRUCTURAL AND DYNAMIC ASPECTS OF RED CELL MEMBRANES

Richard F. Baker, Dept. of Microbiology, USC School of Medicine
Los Angeles, Calif. 90033

The ultrastructure of the human red cell membrane has been much studied in recent years because it has become clear that many of the biochemical, biophysical and rheologic properties of the cell are directly dependent on this structure. Earlier models of the membrane based on a simple symmetric bilayer have been replaced by more sophisticated structures which include provision for lipid asymmetry, protein lipid interaction, fluidity, structural protein and ion transport mechanisms. Biophysical methods which have been recently used to explore membrane structure include thin section electron microscopy, Xray diffraction, polarized light, nuclear magnetic resonance, Xray energy dispersive analysis, freeze-fracture and labeling techniques.

These studies have led to the current concept of the red cell membrane as an asymmetric lipid bilayer which is interrupted at intervals by intercalated proteins, some of which traverse the thickness of the bilayer, affording the possibility of communication and transport across the membrane. A protein named spectrin lines the cytoplasmic surface of the bilayer and appears to be involved in the regulation of cell shape, as well as anchoring membrane-spanning proteins in place. Induced perturbations of spectrin may cause aggregation of both membrane-associated protein (MAP) as well as externally located receptors. Lateral mobility of membrane protein has been observed (1,2) as one of the steps in membrane fusion, one of the important events in cell biology.

We have investigated some of the factors controlling the fusion of intact red cells by the combined action of phosphate ion and calcium (3). Red cells agglutinate at room temperature in the presence of 13mM phosphate and 2-30mM Ca, hemolyze and undergo fusion in 10-60 min at 37C. Both fresh and metabolically depleted cells undergo fusion, indicating that ATP is not essential for fusion. In a typical experiment, ATP levels in fresh cells incubated with phosphate and calcium decreased 43 fold in one hour, while intracellular calcium increased 13 fold. Incubated with calcium alone, ATP levels decreased 4 fold in one hour, while intracellular calcium increased 4 fold. Freeze-fracture replication showed clustering of MAP and particle-free vesiculation occurring in fusing cells. Fusion occurred in the presence of DIDS-a known inhibitor of anion transport, therefore intracellular phosphate may not be necessary for fusion. Fusion was inhibited in neuraminidase-treated cells or in cells pretreated with cationized ferritin. Factors in the fusion mechanism which are common to fusion with Sendai virus and chemical agents remain under investigation.

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1.2 MOLECULAR MOVEMENTS OF CELL SURFACE RECEPTORS

Mu-ming Poo
Department of Physiology
California College of Medicine
University of California
Irvine, California 92717

One of the most convincing evidences that cell membrane is basically fluid in structure comes from the finding that many macromolecular components undergo long-range movements in the plane of cell membrane. Brownian diffusion of membrane proteins or cell surface receptors has been demonstrated for a number of cell types. In addition, we found that a uniform electric field of the order of 5 V/cm applied extracellularly along the membrane surface electrophoretically redistributes surface receptors in the plane of membrane within a few hours. Three types of receptors on the surface of embryonic *Xenopus* muscle cells have been studied. First, heterogenous groups of receptors for various plant lectins. Second, a specific charged glycolipid, GM 1. Thirdly, a specific membrane protein, acetylcholine (ACh) receptor. The topological distribution of the receptors is examined by either post-field fluorescence staining with receptor-specific ligand and/or ionotophoretic mapping. The findings can be summarized in the following: (1) For all receptors studied, the accumulation of receptors induced by the electric field occurs on the side of cell facing the cathode of the field. Preincubation with neuraminidase reverses the polarity of accumulation (i.e. toward anodal side) for some receptors (e.g. those for concanavalin A and ACh); (2) Some receptors (e.g. those for Con A) undergo back diffusion after field is removed resulting in recovery of uniform distribution within 30 min, while others (e.g. ACh receptors) form irreversible receptor aggregates after electrophoretic accumulation; (3) Pharmacological evidences suggest that both the accumulation and recovery movements, as well as the aggregate stabilization, are processes independent of cell metabolism and cyto-skeletal structure. They appear to be phenomena analogous to the electrophoretic and diffusional movements and aggregation of soluble proteins in aqueous solution.

ACKNOWLEDGEMENTS

This research is supported by USNSF.

1.3 MECHANICAL CALORIMETRY OF RED CELL MEMBRANE

Evan A. Evans
Department of Biomedical Engineering
Duke University
Durham, North Carolina 27706

Abstract

Mechano-calorimetry involves temperature dependent mechanical experiments to decompose reversible changes in membrane free energy density into internal energy and entropy density contributions. The measurements required are the membrane surface elastic properties (area compressibility and shear moduli) as a function of temperature plus the thermal area expansivity of the membrane. The results include the reversible heats of expansion and extension for the membrane as well as the energetic contributions. Consequently, the approach directly assesses the thermodynamic state of the membrane, in situ; comparison with well defined chemical systems (i.e. specific vesicle combinations of lipids, proteins, etc.) provides insight into the chemical state of the composite or natural membrane "mixture". For the human red cell membrane, the thermal area expansivity has been found to be $1.2 \times 10^{-3} C^{\circ -1}$. The heat of expansion is determined to be 110-200 ergs/cm^2; the heat of extension is 2×10^{-3} ergs/cm^2 for unit extension of the red cell membrane. The heat of expansion is a measure of the thermal repulsive forces acting in the membrane surface; the heat of expansion measured for the red cell membrane is of the order anticipated for a lipid bilayer idealized as twice the behavior of a monolayer at an oil-water interface. On the other hand, the heat of extension measured for the red cell membrane is five orders of magnitude smaller than the heat of expansion. Assuming that the red cell membrane shear rigidity and heat of extension is associated with "spectrin", unit extension of the membrane increases the configurational entropy of spectrin by about 500 cal/mole; this is opposed by enthalpic increases of 600-700 cal/mole produced by extension.

1.4 MOLECULAR FORCES BETWEEN AND WITHIN LIPID MEMBRANES

V. A. Parsegian, R. P. Rand, N. Fuller and M. McAlister
NIH, Bethesda, MD, USA, Brock University, St. Catharines, Ont., Canada

Governed by a hierarchy of short-range and long-range physical forces, electrically neutral phospholipid molecules in water aggregate to form bilayer membranes which in turn form a multilayer lattice of bilayers alternating with aqueous layers. We use x-ray diffraction to determine the bilayer thickness d_l, average molecular cross-sectional area A and bilayer separation d_w. As water is removed from the lattice not only do the bilayers come closer together but they deform to decrease area A and to thicken the bilayer.

We measure the work of water removal and divide this work into that of overcoming long-range bilayer repulsion and that of causing bilayer deformation. Electrically neutral membranes of egg lecithin, dipalmitoyl lecithin (above and below the melting temperature of its hydrocarbon chains), and egg phosphatidylethanolamine all exhibit a very strong repulsion at less than 20 to 30 Angstrom separation. For $d_w < 10$ Angstroms the repulsive pressure exceeds 100 atmospheres. This force varies roughly exponentially with a decay distance of 2 to 3 Angstroms and presents a formidable barrier to close contact between membranes.

The lattices are stabilized at 20 to 30 Angstroms separation by van der Waals attraction between bilayers whose magnitude can also be estimated. This attraction is of the correct magnitude expected from the general theory of van der Waals forces.

Preliminary comparison of the work of membrane deformation with monolayer data suggests that the lateral pressure to compact molecules on the same bilayer is not related simply to the analogous surface pressure of lipids in monolayers. The lateral pressure is necessarily zero at the equilibrium packing area of the phospholipids and increases to the order of 25 dyne/cm for 25% change in area. The low work of lateral compression (relative to thermal energy) might permit fairly large lateral fluctuations in packing if the work of lateral expansion is comparably small. Our ability to measure the work of rearranging lipids makes it possible to test and compare theories of bilayer mechanical properties and their stability, phase transitions between disordered and ordered states of the hydrocarbon chains, and phase separation of lipids in mixed systems.

1 5 THEORETICAL MODELS OF VESICULAR TRANSPORT AND ENDOTHELIAL MEMBRANE INTERACTION

by Sheldon Weinbaum
The School of Engineering
The City College of The City University of New York
New York, N. Y. 10031

Existing mechanical models to predict biological membrane deformation and biophysical models to predict molecular level long range membrane interaction have been based on membranes with homogeneous structure and uniformly distributed molecular level force fields. These simplified models are unable to explain, e.g., how a vesicle neck can form in a vesicle plasmalemma interaction or why in the intercellular cleft between adjacent endothelial and epithelial cells there are localized regions in which different types of junctional complexes are observed with large variations in the intercellular spacing. Freeze cleavage electron microscopic studies of the membrane bilayer have shown that in these localized regions of strong membrane interaction the intramembranous proteins are not uniformly dispersed but have a highly specialized ultrastructure.

To explain this diversity of behavior a new theory is advanced which attempts to take into account the heterogeneous internal structure of the membrane, the deformation of the membrane due to the spatially varying molecular level force fields generated by this structure and the resulting mechanical membrane bending stresses. The starting premise of the new theory is that each intramembranous particle provides a long range force field which is of London-van der Waals type and a short range electrostatic force field which causes the particles to behave in the near field as either (i) electrically neutral (ii) an electric dipole or (iii) an electric quadrapole. The near range forces are responsible for the packing configuration of intramembranous proteins within a given membrane whereas the inhomogeneous long range attractive force between adjacent membranes is due to the spatial variation in density of the particles, which in the theoretical formulation is treated as a continuum density distribution. The above assumptions are incorporated into a continuum model in which membrane bending stresses, electric bilayer forces and the non-uniform London-van der Waals forces described above are considered in static equilibrium. The resulting fourth order equation to determine the equilibrium membrane configuration is of similar type to that arising in non-linear beam theory. Sample solutions will be presented for the intercellular spacing between cells and for tight junctions.

2.1 BIORHEOLOGY OF SOFT TISSUES: THE NEED FOR INTERDISCIPLINARY STUDIES

Savio L-Y. Woo, Ph.D.
Division of Orthopedic Surgery

University of California, San Diego
La Jolla, California 92093

A detailed knowledge of the mechanical properties of various soft tissues around diarthrodial joints is a necessary prerequisite to understanding the complexity of their mechanical behaviors and functions. Those investigators who are interested in the study of the biomechanical properties of these soft tissues need advanced understanding of the relationship between the ultrastructure, biochemical structure, and the biomechanical properties to aid in the problems which arise in biomechanical testing, such as defining the state of zero stress, the preconditioning effect of these tissues, preparation of tissue test samples and test conditions, variability and nonhomogeneity of tissues, nonlinear, anisotropic and time-dependent behavior, etc. On the other hand, the experimentalist must also have advanced knowledge of the mathematical analyses of individual tissues and whole joint behavior and function so that proper experiments and meaningful data are obtained. Unfortunately, at the present time, the relationship between the detailed ultrastructure, biochemical structure and function, and biomechanical properties of any single joint tissue, such as ligament and tendon, has not been well established. It is therefore difficult for further advanced analyses of the complicated joint function.

The purpose of this symposium is to introduce interdisciplinary approaches that are necessary in order to gain further knowledge of soft tissues, to illustrate the current advances in technology and methodology used by the leading scientists in this field. The lecturers include one macromolecular scientist, one biochemist, one biomechanician, one biochemical engineer, and one clinical scientist. With the contribution of a group of investigators with wide, but relevant backgrounds, it is hoped that a better understanding of the tissue ultrastructure, biochemical constituents, biomechanical properties, and the mechanical behavior of joints in normal and pathological conditions may be achieved, and enzyme probes and therapeutic manipulation to alter joint functions in clinical situations may be applied in clinical conditions. As a result of these lectures, we hope to demonstrate the need for interdisciplinary approach in the study of soft tissues around diarthrodial joints to encourage rigorous studies related to problems such as arthritis and degenerative joint diseases. Ultimately, this knowledge should give clinical scientists and physicians suitable recommendations for therapeutic manipulation and treatment in patient care.

2.2 THE MULTICOMPOSITE STRUCTURE OF TENDON COLLAGEN-RELATIONSHIPS BETWEEN ULTRASTRUCTURE & MECHANICAL PROPERTIES

E. Baer
Department of Macromolecular Science
Case Western Reserve University
Cleveland, Ohio 44106

A revised morphological model for the crimp structure of tendon is presented. The 300-500μ diameter tendons of the mature rat tail are comprised of from one to more than ten substructures, called fascicles, of 80-320μ diameter. Fascicles each possess a "crimp structure" demonstrable in the polarizing microscope and neighboring fascicles within a tendon usually exhibit crimp registry.

The fascicle itself is shown to be a cylindrical array of planar-zig-zag crimped 500-5000Å diameter collagen fibrils. The approximate cylindrical symmetry of the fascicle is demonstrated by SEM and polarizing optical microscopy. A method of replacing native water with other liquids of refractive index near to that of collagen is utilized to reduce or eliminate light diffusion and thereby greatly improve OM observations. Small bunches of collagen fibrils removed from the tendon are shown to exhibit the simple planar zig-zag morphology described in previous literature. The planar crimping of collagen fibrils and their assemblage into cylindrically symmetric fascicles is verified by small angle x-ray diffraction.

The stress-strain behavior of rat tail tendon can be considered in three regions: a toe region, a linear region, and a yield and failure region. Both stress-strain and microscopic measurements showed that the deformation in the linear region was reversible and, for ages above three months, independent of age. Deformation in the yield and failure region was partly by irreversible damage of the collagen fibrils, resulting in weakening of the stress-strain curve and alteration of the waveform. The amount of damage decreased sharply with age.

The stress-strain behavior for ages above three months has been explained by a simple composite model containing oriented viscoelastic fibers embedded in a viscoelastic matrix. The fibers are independent, while the shear modulus of the matrix increases with age. For deformation in the yield and failure region, fiber breakage which reduces the effectiveness of the fibers is assumed to occur and thus reduces the overall stiffness of the composite. Examples are given to show how the model can be used to analyze changes in the tendon structure with age.

2.3 COLLAGEN: ITS STRUCTURE AND FUNCTION IN NORMAL AND PATHOLOGICAL CONNECTIVE TISSUES

Marcel E. Nimni, Paul D. Benya, Cristina Kenney, Anthony J. Keyser.
University of Southern California, School of Medicine, Department of Medicine - Rheumatology, Los Angeles, California 90033.

Collagen fibers represent the primary structural element of connective tissue. They are responsible for the functional integrity of such tissues as bone, cartilage, skin, and tendon, where they account for the overwhelming majority of the proteins present, and for the structural integrity of many other structures such as blood vessels and most organs, to which they contribute a framework within which the tissue functions. A variety of human conditions, normal and pathological, involve the ability of tissues to repair and regenerate this collagenous framework. Some are characterized by excessive deposition of collagen (liver cirrhosis, scleroderma, keloid, glomerular nephritis). Following trauma or surgery, abnormal deposition of collagen may impair function (adhesions following repair of long tendons, scar formation during healing, etc.). In addition, many disabling conditions result from changes in the nature and organization of collagen (heart-valve lesions, osteoarthritis, rheumatoid arthritis, and congenital collagen diseases such as Marfan's syndrome and Ehlers-Danlos syndrome, osteogenesis imperfecta, etc.).

In the last several years various collagen types have been described. Some, like type II are synthesized exclusively by chondrocytes and found only in cartilage. Others like type III are found in blood vessels and skin. Type I is the only collagen present in bone, yet it is also the most ubiquitous off all collagen types (skin, blood vessels, tendon, ligaments, etc.). A more complex mixture of collagens (type IV) is characteristic of basement membranes. What are the functional significance of these different collagen types? Experiments to be discussed will attempt to shed some light on this question.

2.4 BIPHASIC RHEOLOGICAL ANALYSIS OF CARTILAGE CREEP AND STRESS RELAXATION

Van C. Mow, Steve C. Kuei* and W. Michael Lai
Rensselaer Polytechnic Institute, Troy, New York 12181
*University of California, San Diego, La Jolla, CA 92093

Articular cartilage is a biphasic material consisting of a porous and deformable solid matrix, ~ 20% of the total tissue weight, whose interstices are filled with an intrinsically incompressible fluid, ~80%. The intrinsic mechanical properties of the solid matrix govern the hydration of the tissue and the rates of fluid transport throughout the tissue. Thus it is important to be able to measure the intrinsic properties of the solid matrix. The constitutive equations for articular cartilage were formulated from the general mixture theory. The theory was specialized to a binary mixture of an intrinsically incompressible, linearly elastic, nondissipative solid and an intrinsically incompressible, nondissipative fluid. The only dissipation of the mixture is due to the diffusional drag of permeation. The layer inhomogeneity of fluid content of cartilage is represented by a layer variation of the initial solid content ratio.

Under a one-dimensional configuration, the theory was used to simulate the creep and stress relaxation behavior of cartilage. The final governing equation for the solid displacement is a variable coefficient linear diffusive equation. A regular perturbation method was employed to obtain first order approximation solutions for the problems. The results of the analyses were used to determine two of the intrinsic moduli of the constitutive equations. A mean aggregate elastic modulus of the matrix, determined from the equilibrium displacements at 3000 sec on ten creep experiments, is $0.79 \pm .09$ MN/m^2. The same modulus obtained from six stress relaxation experiments is $0.76 \pm .03$ MN/m^2. The average permeability k, obtained from a nonlinear regression analysis of the creep portion of the curve for $t < 3000$ sec, is 0.76×10^{-14} m^4/N-s.

The experimental biphasic creep and stress relaxation results verified the linearity assumptions made in our constitutive model. Further, it was shown that the stress and strain behavior of the solid matrix is linear up to ~30% compressive strain! The permeability coefficient obtained here is greater than those obtained via steady direct permeability measurements. This is due to the observed decrease of permeability as a function of applied compressive strain. The value obtained here is the value averaged over a variable strain field. In conclusion, a binary mixture theory has been shown to be capable of describing most, if not all, of the viscoelastic behavior of cartilage and the movement of the interstitial fluid is the most important process governing its creep and stress relaxation responses.

This work was sponsored by NSF Grant No. ENG 75-20866 and NIH Grant No. AM 19094.

2.5 APPLICATION OF ENZYME PROBES IN CONNECTIVE TISSUE BIOMECHANICS

A. S. Hoffman
Center for Bioengineering
Dept. of Chemical Engineering
University of Washington
Seattle, Washington 98195

Soft connective tissues may be viewed as composite structural materials, containing a crimped, but stiff elastic reinforcing fiber (collagen) a soft and rubber-like elastic reinforcing fiber (elastin), a soft matrix gel (glycosaminoglycans and water), and, sometimes, a contractile element (muscle cells). The individual or joint contributions of such components to the overall biomechanical responses of soft tissues may be investigated *in vitro* by using specific chemical or biochemical probes for each component.

Collagenase and elastase are enzymes which may be obtained in reasonable purity and which are specific to the two major stress-bearing elements in soft connective tissues, collagen and elastin. Such enzyme probes may be used to elucidate the biomechanical behavior of soft tissues by three general techniques:

(1) Pre-treat the tissues in a control buffer or active enzyme solution for varying times in the absence of applied stress, and then test mechanically. Any biomechanical differences between the buffer control and the enzymolysed specimen may be directly ascribed to the degraded tissue component.

(2) Pre-equilibrate the tissues in buffer solution, then place under stress in the same buffer solution plus or minus the particular enzyme of choice. In this case, the time-dependent biomechanical process is occurring simultaneously with two other time-dependent processes: enzyme diffusion into the specimen and enzymolysis of the particular tissue component. Such concurrent processes can greatly complicate the interpretation and analysis of the biomechanical data.

(3) Pre-equilibrate the tissues in the absence of applied stress in control buffer solutions or in enzyme solutions under pH and temperature conditions where there will be insignificant enzymolysis occurring. After the sample is saturated with enzyme, perform mechanical tests under conditions where the imbibed enzyme will be activated. In this situation, if time-dependent biomechanical processes such as stress relaxation are run, the resulting behavior can be interpreted in terms of the kinetics of breakdown by enzymolysis of one particular tissue component.

Examples of these techniques with various soft connective tissues will be compared and contrasted.

2.6 MECHANICAL IMPERATIVES FOR SYNOVIAL JOINT HOMEOSTASIS: THE PRESENT POTENTIAL FOR THEIR THERAPEUTIC MANIPULATION

W.H. Akeson, D. Amiel, S.L.-Y. Woo and F. Harwood
Division of Orthopedics & Rehabilitation
University of California, San Diego
La Jolla, California

Introduction. Fibrous connective tissue homeostasis is motion and stress dependent in a manner analogous to bone where the functional response to loading is widely recognized in the eponym Wolff's Law. The dependence of fibrous connective tissue on stress and motion has been demonstrated in exercise and immobilization experiments. Clinically, the stress and motion dependence typically creates complications when casts are required for immobilization in the treatment of fractures or other injuries. The time required for casting is often several weeks or months. When the case is removed joint stiffness is experienced. Exercise and other forms of physical therapy sometimes correct this problem, but too frequently residual stiffness remains as a permanent disability. This problem is recognized in legal proceedings where disability is usually judged by the measured degrees of joint stiffness.

Results and Discussion. The biochemical events underlying the joint contracture process have been studied in our laboratory and have been correlated with the secondary mechanical changes. We have observed two major constituent changes: 1. Loss of proteoglycan and water (the lubricants of the connective tissue matrix), and 2. Changes in the pattern of collagen cross linking. We believe the loss of lubricant is a permissive effect which allows collagen fibers to contact at critical intercept points, and permits fibers to become cross linked in a stationary attitude. This could occur by cross link reactions between molecules of adjacent fibers in the immobilized network, or by randomly disposed newly synthesized collagen which inserts new fibrils between existing fiber bundles in a non-functional attitude. Some of the stress and motion dependent biochemical effects can be moderated by drugs or hormones to minimize the constituent changes and subsequent mechanical phenomenon. Drugs demonstrated to successfully impede this process in our model system include: penicillamine, 17-β estrakiol and hydrocortisone. Penicillamine blocks the reactive aldehydes implicated in collagen cross linking and hydrocortisone reduces collagen synthesis, but the mechanism of action of 17-β estradiol on the connective tissue matrix is not clearly understood. Therapeutic manipulation of the connective tissue cells to favor maintenance of matrix mechanics post fracture should soon be possible.

ACKNOWLEDGEMENT

This project was supported by Grants AM 14918 and AM 00304 awarded by the National Institutes of Health.

3.1 THE RHEOLOGY AND MOLECULAR ORGANIZATION OF EPITHELIAL MUCUS

A. Silberberg
The Weizmann Institute of Science
Rehovot, Israel

In most instances where sliding transport has to occur over an epithelial tissue surface, the surface is covered by a system of cells capable of secreting a thick flowing fluid mucus. The sliding motion can involve the transport of the whole organism, the transfer of food, the facilitation of sperm or ovum movement, the clearance of respiratory air way, etc. There is considerable evidence that the major biopolymeric component involved is a glycoprotein, 80% of whose weight is carbohydrate and only 20% is protein. The carbohydrate is attached in the form of short oligomeric side chains to about 2/3 of the protein backbone leaving 1/3 of its length bare. The bare part of the protein involves cystein bridges which may or may not be intramolecular. These glycoproteins are crosslinked into a reversible gel i. e. a system which is viscoelastic and is endowed with very long, if not infinite, mechanical relaxation times.

Where, as is often the case, mucus is in mechanical contact with an array of metachronously beating cilia it acts as essential coupler in facilitating transport by ciliary propulsion. In relation to the period of the ciliary beat its relaxation times are very long and the response of the mucus layer lying on top of the bed of beating cilia is that of a semi-solid sheet having an essentially rigid interaction with the moving wave. It can be shown that the requirements are rather complex and strongly linked to ciliary shape and beat characteristics. While solid-like properties are essential they must fall into a certain class and the characteristics of an incipient gel are the most favourable in establishing transport.

While other materials having these properties can substitute for mucus, mucus itself possesses a variety of further properties whose effect and purpose is not yet fully understood. Mucus, for example, is unstable and its gel-like structure declines spontaneously. This occurs the more rapidly the higher the temperature. Hence the crosslinks of mucus are labile and of a character not yet fully established.

The muco-ciliary system will be discussed in the light of recent results both with respect to its molecular, structural aspects and the rheological and other physico-chemical properties which result. The functional role of these systems will be examined in the light of these new insights and attempts will be made to establish direct links between molecular properties and the physio-pathology of the organs involved.

3.2 TRACHEAL MUCO-CILIARY CLEARANCE

Anthony T. W. Cheung
Division of Engineering and Applied Science
California Institute of Technology, Pasadena, California

and

Allen T. Chwang
Institute of Hydraulic Research
University of Iowa, Iowa City, Iowa

Tracheal clearance represents the only means of transport and defense in the respiratory tract against hazardous foreign particles, cellular debris and harmful bacteria. Clearance is mucus-dependent, muco-ciliary in nature and is achieved through a continuous escalation of the mucus layer by ciliary movement and serous-fluid interactions in a conveyor-belt manner.

The unique beat characteristics of tracheal cilia (which significantly differ from all types of micro-organism cilia), the effective uni-directional fluid movement (ciliary current) as a result of the unique forward strokes, the periodic penetration of the mucus layer by the tips of the cilia, the muco-ciliary interactions, the particulate transport rate of the mucus layer and its functional characteristics have been quantitatively studied in great detail.

The loading-unloading characteristics of the mucus blanket have also been experimentally investigated. Mucus (and particulate) transport was found to nearly stop when the mucus layer of a muco-ciliary surface was completely removed (with the serous fluid layer intact) and effective transport resumed when the mucus layer was artificially restored. Mucus transport rate was observed to decrease by a substantial amount of its normal value when only the serous fluid was depleted and the mucus blanket remained intact. Such quantitative experimental data are then interpreted and compared with our theoretical model.

The model adopted for predicting the mucus transport rate is based on the conveyor-belt mechanism as described quantitatively by Cheung and Jahn (1975, 1976). The cilia are assumed to have periodic penetration contact with the bottom of the overlying mucus blanket during the early stage of the planar forward strokes. The unique bent (resting) configuration of the tracheal cilia and the effective uni-directional movement of the surrounding fluid (ciliary current) all help to contribute to the overall mucus transport. The predicted average mucus transport rate is found to depend linearly on the beat frequency of the tracheal cilia and also on the contact time between the tips of the cilia and the bottom of the mucus layer.

The theoretical predictions are in good agreement with the experimental observations.

3.3 FLAGELLAR PROPULSION OF SPERM IN CERVICAL MUCUS

D.F. Katz[1,2] and S.A. Berger[1]
1 Department of Mechanical Engineering
University of California, Berkeley

2 Department of Obstetrics & Gynecology
University of California, Davis

The spermatozoa of many mammals must negotiate a mucus-filled cervical canal while en route to the egg(s). The cervical mucus is a dilute gel, whose backbone is comprised of fibrous glycoprotein macromolecules exhibiting both non-homogeneity and polydispersity. Biomechanical interactions between spermatozoa and the mucus are microscale events. Consequently, relationships between sperm migration through the mucus and continuum, macrorheologically - defined, mucus properties are understood in only the grossest sense, and may obscure the essence of the sperm transport process.

Experimental studies of sperm locomotion in cervical mucus will be presented, in which the details of the motion are determined by high-speed cinemicrography. Film analysis focuses on the relationship between sperm swimming speed and the undulations of the cell's flagellum. Emphasis is placed upon the dispersion in this relationship, and thus the applicability of distributed, global concepts to characterize the sperm-mucus interaction. On the basis of these results, analytical approaches will be discussed. Continuum mucus models employ a modified constitutive equation for the medium suspending the spermatozoa. Discrete models place a spermatozoon in a two-phase environment, in which sperm locomotion is modulated directly by details of the mucus microstructure.

3.4 CHEMICAL ASPECTS OF MUCUS RHEOLOGY

M. Litt
University of Pennsylvania
Philadelphia, Pennsylvania 19104

The rheological properties of mucus secretions have assumed increasing importance for understanding physiological functions since the demonstration that a finite elastic modulus is necessary for transport by cilia. It had already been shown that the elastic properties of the mucus gel are due to the glycoprotein or mucin fraction. Recent work on the chemical composition and structure of these mucins has shown that they consist of proteins containing both glycosylated portions of the chain and naked portions containing no carbohydrate. These latter portions are rich in cysteine residues, which provide the basis for crosslinking the molecules into larger entities. However, the gel behavior of the mucins is also due to non-covalent interactions in these polyelectrolyte solutions, leading to dependence of the rheological properties on pH and ionic strength as well as composition and concentration.

Chemical characterization of mucus secretions from many sources has indicated an overall similarity of structure as well as a similarity in the content of individual amino acids and carbohydrates. However, there may be large variations in the rheological behavior of these secretions from various sources, depending on compositional and physiological factors. These points will be elucidated with rheological and chemical data on mucus from various sources, including tracheal, cervical and middle-ear mucus.

3.5 FLUID PROPULSION IN A MUCO-CILIARY CHANNEL

J. R. Blake
Division of Mathematics and Statistics
CSIRO, Australia

and

H. Winet
Physiology Department
Southern Illinois University
Carbondale, Illinois

The study of fluid propulsion by a stationary ciliated surface is extended experimentally and theoretically to include two ciliated surfaces propelling a mucin suspension, i. e. a muco-ciliary channel.

The experimental data have been gathered from a system in which two strips of frog palate epithelium are mounted in a closed chamber so as to form a channel lined on two opposite sides with cilia. Flow velocity profiles are obtained from cine records of suspended 0.5 μm styrene butadiene spheres which are propelled by the cilia. The normal epithelial mucus which has been removed by blotting is replaced with bovine submaxillary mucin at concentrations in the range 1 - 3% w/v. In all cases flow velocity profiles are generated as functions of the reduced gap $2Y/\ell$ (where Y is the wall-to-wall gap and ℓ the cilium length) between the ciliated walls.

The theoretical model tested by these experiments is based on the mean-field volume-force model of muco-ciliary transport to include the condition of deep ciliary penetration into the mucus layer such that the entire cilium experiences some extra loading. For simplicity the fluid is taken to be divided into three zones of different mucus concentration as measured from the wall to the lumen midpoint (Y/ℓ). The model predicts that in order to avoid a discontinuity in the flow velocity profile, the cilia must alter their beating pattern in response to the extra loading. It appears that the predominant mechanism for mucus propulsion is the penetration of cilia into the more concentrated mucus zones. Moreover, since the difference between effective stroke loading and recovery stroke loading in a mucus gradient is so much greater than that in a Newtonian fluid, the backflow at the base of the cilium will be correspondingly greater. This increased backflow would be of considerable benefit to objects being propelled near the wall. A possible case in point may be spermatozoa in certain regions of the female reproductive tract.

3.6 CERVICAL MUCUS AS A SUSTAINED-RELEASE HYDROGEL SYSTEM FOR SPERMATOZOA

R. M. Nakamura,* M. Saga, F. Floriani, D. Tredway
V. Davajan,* and G. Bernstein*
*University of Southern California, Los Angeles, Calif.
St. Marianna University, Kawasaki City, Japan
Kaiser Permanente Hospital, Bellflower, Calif.
University of Chicago, Chicago, Illinois

During the investigation of the dynamics of sperm transport in the midcycle of human female it became apparent that sperm were released from the cervical mucus into the genital tract for over 48 hours post insemination. The midcycle cervical mucus is a hydrogel containing 2% solid and the remaining 98% is aqueous. After insemination the total column of cervical mucus in the endocervical canal was equilibrated with sperm within 3 hours. The pattern of sperm released from the cervical mucus is analogous to the "burst" followed by the so-called steady state release observed from a sustained release device such as steroids released from the organogel, the silastic platform. Within 10 minutes, the burst was observed when the number of sperm recovered in the oviducts was significantly elevated for approximately an hour. After this time, the level decreased to a lower rate which was maintained for the next 40 hours. The need for a sustained release system at the level of the cervical canal will be correlated with the endocrine events leading to ovulation.

4.1 EFFECT OF TEMPERATURE ON THE VISCOSITY OF RED CELL MEMBRANE

R.M. Hochmuth, E.A. Evans and K. Buxbaum
Department of Biomedical Engineering
Duke University, Durham, NC 27706

Large extensions in the plane of the red cell membrane are produced by the application of equal and opposite forces at diametrically opposite "points" on the red cell rim. The force-free extensional recovery of the cell is measured as a function of time. The results are analyzed with a nonlinear theory which describes the finite deformation behavior of a two dimensional viscoelastic solid. The nonlinear theory describes closely the time dependent recovery of a single cell for a single fixed value of the time constant t_R of 0.1 sec at 25°C (1). In the viscoelastic theory, the time constant is the ratio of membrane surface viscosity η to membrane surface elasticity μ. Recent measurements indicate that $\mu = 0.006$ dyne/cm at 25°C (2). Thus, $\eta = \mu t_R = 6\times10^{-4}$ dyne·sec/cm (poise·cm). Studies at 5°, 15°, 25° and 37°C indicate that $t_R \approx 0.30$, 0.17, 0.10 and 0.06 sec, respectively. Since μ decreases only by about 33% over this temperature range (2), the viscosity at 5° relative to that at 37° is about 7:1 - a ratio characteristic of viscous oils like castor oil or olive oil. The results indicate that the red cell membrane behaves as a two-dimensional viscoelastic solid over the range of temperatures, times, and large extension ratios in these experiments.

Acknowledgment: Supported by HL21803(RMH), HL16711 (EAE) and Research Career Development Awards HL70612 (RMH) and HL00063 (EAE)

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4.2 MEMBRANE MECHANICAL PROPERTIES OF ATP-DEPLETED HUMAN ERYTHROCYTES

H.J. Meiselman, E.A. Evans and R.M. Hochmuth. Department of Physiology, USC School of Medicine, Los Angeles, Ca. 90033; Department of Biomedical Engineering, Duke University, Durham, N.C. 27706; Department of Chemical Engineering, Washington University, St. Louis, Mo. 63130.

Although the relations between the metabolic state and the mechanical properties of human red blood cells (RBC) continue to be of current interest, literature reports in this area are not in agreement: a) consequent to metabolic depletion via 24 hour incubation at 37°C, Weed, La Celle and Merrill (1) indicate a twelve to fourteen fold decrease in membrane deformability as judged by the negative pressure necessary to produce hemispherical deformation of the RBC membrane into a 3 micron pipette; b) employing membrane hemisphere deformation into a 1.5 micron pipette, Leblond (2) reports an identical two-fold increase in negative pressure for fresh, echinocytic RBC produced by shape altering agents and for echinocytes produced by incubation at 37°C for 20 hours; c) using 1 to 2.5 micron pipettes, Heusinkveld and co-workers (3) indicate no difference in negative pressure for membrane hemisphere formation between fresh RBC and RBC incubated at 37°C for up to 45 hours.

The present investigation was designed to determine several intrinsic material constants of human RBC membranes before and after metabolic depletion via incubation at 37°C for 24 hours. Using micropipette and flow channel techniques, three properties were measured: i) μ, surface shear modulus of elasticity; ii) K, elastic area compressibility modulus; iii) η_p, shear viscosity in the plastic domain. Our results indicate <u>no</u> significant differences in these parameters between fresh and ATP-depleted human RBC membranes. These present data are thus in disagreement with those reports indicating large changes in membrane mechanical properties following metabolic depletion and suggest that total cellular deformability and circulatory behavior of depleted RBC may be related to as yet unmeasured membrane mechanical factors. In addition, they lend credence to viscometric and morphologic data demonstrating that the rheologic properties of ATP-depleted RBC can be simulated using crenated, ATP-fresh RBC and that restoration of the biconcave shape, without biochemical restoration, returns the flow behavior of ATP-depleted RBC to normal (4).

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SUPPORTED BY: NIH Grants HL 12839, HL15162, HL15722, HL16711; AHA 76-1043; AHA/GLAA 537IG2; NIH RCDA HL00063, HL70569, HL70612.

4.3 VISCOELASTIC PROPERTIES OF RED CELL MEMBRANE

Shu Chien, Kuo-Li Paul Sung, Richard Skalak
and Aydin Tözeren
Department of Physiology, College of Physicians and Surgeons, and Department of Civil Engineering and Engineering Mechanics, School of Engineering and Applied Sciences, Columbia University, New York City

The purpose of this study is to obtain elastic and viscous coefficients which define normal red blood membrane properties. The deformation of a portion of red blood cell during aspirational entry into a micropipette has been analyzed on the basis of a constant area deformation of an infinite plane membrane into a cylindrical tube. Consideration of the equilibrium of the membrane at the tip of the pipette has generated the relation between the aspirated length and the dimensionless time during deformational entry as well as during relaxation following the removal of aspiration pressure. Experimental studies on deformation and relaxation of normal human red cells were performed with the use of micropipettes and a video dimension analyzer which allowed the continuous recording of the time courses. The deformation consisted of an initial rapid phase with a membrane viscosity (range 0.6×10^{-4} to 4×10^{-4} dyn sec/cm) varying inversely with the degree of deformation and a later slow phase with a high membrane viscosity (mean 1.89×10^{-2} dyn sec/cm) which was not correlated with the degree of deformation. The membrane viscosity of the recovery phase after 20 seconds of deformation (mean 4.98×10^{-4} dyn sec/cm) was also independent of the degree of deformation. When determined after a short period of deformation (e.g., 2 sec), however, membrane viscosity of the recovery phase became lower and agreed with that of the deformation phase. These results suggest that the rheological properties of the membrane can undergo dynamic changes depending on the extent and duration of deformation, reflecting molecular rearrangement in response to membrane strain.

ACKNOWLEDGMENT This investigation was supported by NHLBI grant HL 16851.

4.4 BUCKLING OF THE RED BLOOD CELL MEMBRANE

T. M. Fischer, C. W. M. Haest, M. Stöhr-Liesen,
H. Schmid-Schönbein and R. Skalak
Abteilung Physiologie, Medizin.-Theoret. Institute der RWTH,
Melatenerstr. 211, D-5100 Aachen, West Germany

One of the unique mechanical properties of the RBC membrane is its ability to resist high shear strains without buckling. This phenomenon was explained by the relatively low shear modulus and high bending modulus of the membrane (1). To study the importance of this phenomenon we increased the shear modulus of the membrane by chemical modification of its proteins. This can be achieved by various SH-reagents (2). Our observations of RBC were done in a transparent counter-rotating cone-plate-chamber adapted to a microscope. Through careful rotation of the cone-plate-chamber by hand it is possible to turn a native cell under microscopic control and to get a three-dimensional impression of its resting shape. With this technique we studied the morphology of cells which were first modified in the biconcave state and then swollen osmotically. The observed rim buckling was similar to that which Fung obtained with macroscopic rubber models (3). We also studied cells which were modified in the nearly spherical state and then placed back into isotonic medium. The cells showed various shapes which resembled those of rubber models (4) or theoretically computed shapes (5). By driving the cone-plate-chamber with constant speed the RBC suspension was subjected to preselected shear rates. The viscosity of the suspending phase was about ten times that of plasma to obtain a stationary orientation of the RBC in the shear field. Under these conditions the velocity gradient is transmitted into the cytoplasm of the cell via the so-called tanktread motion of the membrane. The frequency of this periodic motion increases linearly with the apparent shear rate of the cone-plate-chamber. The modified cells showed the same dependence of tanktread frequency on shear rate as the control cells. The elongation of RBC in the shear field, however, was reduced for the modified cells at all shear rates. In addition the modified cells showed stationary bucklings parallel to the flow direction irrespective of the superimposed tanktread motion of the membrane. In conclusion: (1) The occurrence of buckling in general demonstrates that the protein modification by SH-reagents increases mainly the shear modulus of the RBC membrane whereas the bending modulus is increased much less (if at all!). (2) The fact that cells with a decreased elongation are still driven into the tanktread motion emphasizes the great importance of this phenomenon for the flow adaptation of the RBC.

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4.5 CHARGE RELAXATION EFFECTS IN MEMBRANE BREAKDOWN

Joseph M. Crowley
Department of Electrical Engineering
University of Illinois
Urbana, Illinois 61801
USA

In a Coulter counter, blood cells pass through a region of high electric field, which may cause electrical breakdown of the membrane. Measurements of the critical voltage have been used to test the proposed electromechanical breakdown mechanism under the assumption that changes in external voltage immediately change the membrane voltage, and that the membrane ruptures as soon as the critical voltage is reached. In the present paper, the first assumption is modified to allow for electrical charge relaxation effects. Even with instantaneous mechanical response, the applied voltage must be significantly increased to achieve breakdown in times that are on the order of the charge relaxation time of the cell, which suggests that the actual breakdown voltages are lower than the reported values.

4.6 RHEOLOGICAL CHANGES OF GROWING CELLS: EFFECT OF AUXIN AND FUSICOCCIN ON COLLENCHYMA

M. Jaccard and P. E. Pilet
Institute of Plant Biology and Physiology of the University
6, Place de la Riponne, 1005 Lausanne, Switzerland

Creep relaxation tests have been used to determine the relationship between cell growth and cell wall extension (1,2). Collenchyma is a choice material for testing the effect of a longitudinal force on the rheological behavior of plant tissues.

It has been shown (2,3) that rheology (including rheological parameters and low pH effect on extension rate) of isolated collocyte bundles changed during growth and differentiation of tissues. In order to test only the interactions between growth and rheology of collocyte walls, fusicoccin (FC) and α-naphtyl acetic acid (ANA) were used (5). High growing and low growing petioles were prepared from *Apium graveolens* plants as previously reported (3,4). The basal part of the petioles was cut, the initial length of the collocytes being 30 ± 0.5 mm. Agar blocks containing buffer ± FC ± ANA were used to cover the two cut ends. After a chosen incubation time, the length of the collenchyma bundles was measured and collocytes were carefully excised, quickly frozen and kept at -20°C. When bundles were needed, they were thawed at room temperature and washed with buffer. Rheological parameters (including total stain, time dependent strain, elastic strain and permanent strain) and low pH effect on extension rate values were calculated (force applied F = 10 gp) as previously reported (2,3).

The growth of the collocyte bundles (treated or not with FC or ANA) was analyzed. Differences between FC (at a 5.10^{-7}M), ANA (at a 10^{-5}M) and control treatments were significant after 6 hrs of incubation. In contrast, the FC effects on rheological parameters were not obtained before 12 hrs, while ANA changed some rheological parameters already after 3 hrs of incubation. Different concentrations of FC were tested and comparisons with ANA effects were discussed. It was thus concluded (a) that FC and ANA changed - according to different kinds of processes - the extensibility and the rheology of the cell wall (b), that the change in growth was rather correlated with total and permanent strains than with time dependent and elastic strain modifications. The significance of these results was analyzed in relation to the rheological behavior of the cell wall.

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4.7 RHEOLOGICAL STUDIES OF CHROMATIN

V. I. Vorob'ev and L. V. Kukharvea
Institute of Cytology of the Academy of Sciences of the U.S.S.R.
Leningrad 190121, U.S.S.R.

Interphase chromatin of the cell nuclei during cell cycle undergoes a reversible structural transition to the densely packed metaphase chromosomes. The nature of changes in the state of chromatin condensation anyhow remains unknown. We have shown earlier that purified chromatin isolated from cell nuclei is a non-fluid and elastic gel the properties of which are strongly dependent on the ionic environment (1). The fibers prepared from native and reconstituted chromatin show a considerable mechanical strength and elasticity. A particular role in the structure of chromatin is played by lysin-rich histone H1. There is some indirect evidence which indicates that this histone promotes condensation of elementary chromatin threads composed of linearly arranged subunits - nucleosomes. Moreover, histone H1 is likely to accomplish interaction between adjacent chromatin threads. At the same time, our investigations show that dissociation of histone H1 does not influence rheological properties of dispersed chromatin in solutions of low ionic strength (2,3). It appears, however, that in such condition chromatin particles have a loose uncoiled structure with nucleosomes divided by stretches of internucleosomal DNA. Therefore, it may be suggested that in this case histone H1 is not able to display its potential structure-forming properties. A study of native chromatin gels by means of Weissenberg rheigoniometer allowed to check this suggestion. It was found that selective extraction of histone H1 causes drastic changes of chromatin gel-forming properties. After complete removal of histone H1 chromatin practically loses its ability to form gels.

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4.8 THE DYNAMIC EQUILIBRIUM MODEL OF CYTOPLASMIC MICROTUBULES AND THE OXALATE-INDUCED RADIAL SEGMENTATION OF THE NUCLEI OF MONONUCLEAR BLOOD CELLS

B. Norberg and A. Norberg
Department of Internal Medicine, University Hospital of Lund,
S-221 85 Lund, Sweden

The contractile events of cell division are thought to be due to a superficial membrane-associated contractile cell layer, which is blocked by cytochalasins, and a deep centriole-associated fibrous system composed of microtubules, which is blocked by antitubulins, e.g. colchicine and vinca alkaloids.

By incubation with oxalate at room temperature, a segmentation of the nuclei of mononuclear blood cells is induced - the oxalate-induced radial segmentation (RS). The oxalate-induced RS can be interpreted in terms of the dynamic equilibrium model of cytoplasmic microtubules proposed by Inoué; during slow disintegration, cytoplasmic microtubules contract and fold the nucleus in. At conditions of rapid microtubule disintegration, the development of RS nuclei is inhibited (1,2,3).

The oxalate-induced RS provides a convenient screening test of anti-tubulin activity with approximately the same sensitivity as the metaphase of cell division (4).

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5.1 HOMOGENEITY AND ISOTROPY OF LUNG PARENCHYMA

G. C. Lee and R. Tai
State University of New York at Buffalo
Buffalo, New York 14214

This report will be centered on the results of a program of experimental observation on lung tissue cubes stretched three-dimensionally. It may be regarded as the continuation of an earlier study conducted by Hoppin, Lee and Dawson. The purpose of this present study is aimed at the determination of the mechanical properties of the lung parenchyma with respect to its possible locational- and/or directional-dependency. A better understanding of the regional differences in mechanical properties will enable us to model and predict the gross lung behavior with more confidence.

Tissue cubes of dog's lung of approximately 1 cm^3 are stretched both in air and in saline. The locations of the cubes considered include those near the apex, near the diaphragm, and those in the middle portion of the lung. Furthermore, certain cubes are selected to be mostly free of airways and blood vessels, while others include purposely, a major airway in one of its axes of deformation. Certain cubes are also selected so that one or two of its six surfaces coincide with the pleural surface of the lobe. A further attempt in this present series of experiments is to compare the mechanical properties of lungs of the young with those of the aged.

Some of the planned experiments are yet to be carried out as of this writing. However, they are expected to be completed by August, 1978.

5.2 ELASTIC PROPERTIES OF LUNG PARENCHYMA: THE EFFECT OF PRESSURE-VOLUME HYSTERSIS ON THE BEHAVIOR OF LARGE BLOOD VESSELS

S. J. Lai-Fook, Mayo Clinic, Rochester, Minn. 55901

The elastic constants of lung parenchyma were measured for states of uniform inflation. The bulk modulus was determined from small quasi-static pressure-volume (PV) perturbations and the Young's modulus by indentation tests at fixed lung transpulmonary pressures. Both linear elastic constants were almost unique functions of transpulmonary pressure, and independent of the volume which may be different at the same pressure due to PV hysteresis. A second-order strain energy function was derived for which the elastic constants were linear functions of the pressure. Large deformation solutions for the symmetric inflation of a cylindrical hole in the parenchyma were computed. The solutions were used to explain changes in diameter of large pulmonary blood vessels when transpulmonary and vascular pressures were varied. Estimates of perivascular pressure, the pressure acting on the outside of blood vessels, were obtained for both inflation and deflation limbs of the PV curve. (Supported by grants HL18354 and HL19205 from NHLBI)

5.3 A FINITE ELEMENT ANALYSIS OF THE WHOLE LUNG

D. L. Vawter
Engineering Science and Mechanics
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061

A numerical analysis of the regional distribution of stress, volume expansion, and surface expanding pressures in a whole lung loaded by gravity and changes in thoracic cavity shape was undertaken using a finite element technique. Both elastic and surface tension forces were considered. The strain energy formulation and surface tension idealization are discussed elsewhere (1).

<u>Regional Lung Volume</u> It was found that for a given overall lung volume the regional distribution of lung volume (i.e., alveolar expansion) was independent of surface tension, with the apical portion of the lung more highly expanded than the base.

As in previous analyses (West and Matthews (2)) it was found that regional differences in lung volume decreased with increasing overall lung volume suggesting gravitational loading has less effect at high lung volumes where the lung is "stiff".

We found that the apical lung volume increased monotonically with overall lung volume. West et al. found that at lung volumes near FRC apical volume decreased with increasing overall volume. It should be noted that they found this phenomenon only for a few lung shapes.

<u>Distribution of Surface Expanding Pressures</u> We found that the pressure at the pleural surface required to keep the lung at a given volume varied from the apex to the base and was higher when surface tension was present. In the absense of surface tension it was higher at the apex and decreased monotonically toward the base. When surface tension was considered the surface pressure trend was similiar to the purely elastic case at low lung volumes but at higher lung volumes the maximum surface pressure occured not at the apex but at some distance down the lung. As lung volume increased, the point of maximum surface pressure moved further toward the base. At an overall lung volume of four (4) times the stress-free volume the maximum pressure occured about midway between the apex and base. It was found that this basal movement of the maximum pressure point was present whether or not the diaphram was lowered during expansion. Lateral movement of the thoracic cage moved the maximum pressure point toward the base even without the presence of surface tension.

<u>Conclusions</u> We found that the presence of surface tension did not alter the regional lung volumes but increased the surface pressure at any lung volume and profoundly affected the distribution of pressure.

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5.4 ON THE MEASUREMENT OF THE ELASTICITY OF THE AIRWAY

T. Nakagawa, Y. Seguchi and Y. C. Fung
Department of AMES/Bioengineering
University of California, San Diego
La Jolla, California 92093

The airway elasticity must be known in order to solve many problems of breathing. For example, a popular clinical test of pulmonary function is the measurement of "resistance" to breathing by small perturbations of flow and pressure at the mouth; but it is shown recently (1) that this so-called "resistance" is greatly influenced by airway elasticity. Other examples are the frequency dependent behavior of lungs, flow limitation in forced expiration, high velocity flow in sneezing or coughing, wave speed limitation, and the possibility of airway wall flutter or divergence due to aeroelastic interaction. As a basic step toward solving these problems, this article reports on the measurement of pressure-diameter relationship of the bronchi of the rabbit.

Past works have either reported measurements of airway lengths and diameters as function of transpulmonary pressure (e.g. Ref. 2,3) or of the pressure-volume relationship of dissected airway segments (e.g. Ref. 4) or uniaxial stretching of dissected airway tissue (e.g. Ref. 5). In the first method, the airways in the lung are distended by the lung parenchyma, and only limited transmural pressure difference across the airway wall can be obtained. In the other two methods the structures are disturbed and the effect of lung parenchyma cannot be considered.

To avoid excessive dissection and to obtain desirable transmural pressure in situ, we propose an occlusion technique, in which airway segments are isolated by occluding the lower bronchi. An excised lung is hung in a moist box and supported by a transparent tube connected to the trachea. A mixture of silicone oil and small glass beads is used as the occluding medium, which has a relatively high viscosity (of the order of 100 poise). The airway is first perfused with a certain amount of this medium. Then a radio-opaque fluid of low viscosity is used to fill the airway, and to push the viscous fluid forward until complete occlusion is obtained. Once the pushing action is properly controlled, occlusion is very stable. The applied transmural pressure is controlled by changing the fluid head of radio-opaque solution. The lung is then photographed in x-ray. The diameters of various bronchi are measured from the photographs and correlated with the applied pressure.

It is observed that the bronchial diameter is sensitive to the pressure changes up to about 30 mm H_2O. By this method it is relatively easy to obtain the pressure-diameter relationship of the bronchi. By further dissection and measurement of bronchial wall thickness the stress-strain relationship is obtained.

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5.5 POSSIBLE AERODYNAMIC INSTABILITY IN THE AIRWAY DUE TO FLOW SEPARATION AND INTERACTION OF FLOW WITH ELASTIC WALL

Y. Matsuzaki
National Aerospace Laboratory
Chofu, Tokyo, Japan

Y. C. Fung
University of Calif., San Diego
La Jolla, Calif. 92093

In the preceeding article (paper No. 5.4) it is shown that the modulus of elasticity of the upper airway wall is quite small. The compliance is of the order of 1% change of diameter per 1 cm water pressure change. In Ref (1) it is shown that the respiratory resistance is greatly influenced by the airway compliance. In the present paper the aerodynamics of the flow and the aeroelastic interaction between the flow and the elastic wall are studied in greater detail, with a particular attention to the question of possible instability.

First, possible separation of a divergent flow from a solid wall at moderate Reynolds numbers is studied (2). Experimental data on a divergent flow through a two-dimensional water tunnel in the Reynolds number range 1000 to 6000 are presented. It is shown that in a lower range of divergence angle flow separation is characterized by a sharp decrease in the mean pressure differential when the flow rate is increased continuously and gradually; whereas recovery from separation is signaled by a discontinuous increase in pressure when the flow rate is decreased again. The critical Reynolds numbers for separation and reattachment are detectably different.

Next, the aeroelastic instability of flow and wall interaction is investigated (3,4 and new results). Both two-dimensional channels and circular cylindrical tubes, symmetric and antisymmetric modes, incompressible and compressible fluids, and linear and nonlinear oscillation analyses with analytical and numerical integration methods have been studied. The results show that a critical flow rate exists at which the wall becomes buckled aerodynamically, but the instability is of the divergence type, and not flutter.

These stability analyses are applicable to blood flow in arteries with stenosis or aneurysm and to veins. But the geometry and flow conditions are highly idealized to steady flow and straight tube.

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5.6 MECHANICAL PROPERTIES OF HUMAN SKIN

T. H. Cook, Department of Engineering Science and Mechanics
The Pennsylvania State University, University Park, PA. 16802

The objectives of this study are to determine the mechanical properties of living human skin and quantitate these properties through the development of appropriate constitutive relations predictive of the *in vivo* behavior.

To accomplish these objectives a strip-biaxial test system, capable of running constant strain rate and stress relaxation tests has been used. The system is similar to *in vivo* methods employed successfully by other investigators (1,2). However, the method of data reduction used in the present study differs from those used previously. The biaxial resting tension and stretch states are determined. This enables the stresses and strains applied to the skin with the strip-biaxial system to be referred to a unique undeformed state i.e., the state the sample would assume if it were cut free from the body. The method requires determining the principal directions of existing tension and stretch in the plane of the skin (these directions have been shown to be coincident (3)) followed by strip-biaxial tests in each of these directions. The skin sample (typically 8mm x 50mm) is unloaded past the point of wrinkling and then loaded to the preexisting state. This data is used in a least squares curve fitting routine to quantitate the point of zero tension in each of the two test directions. This information is used with the general form of a finite elastic constitutive relation in terms of a strain energy function and necessary conditions for coincidence of principal axes of stress and strain to solve for the dimensions of the undeformed sample. This analysis assumes the *in vivo* skin behaves as an elastic, isotropic and incompressible material in the range of stretch less than the resting (preexisting) stretch state.

Results of a series of biaxial constant strain rate and relaxation experiments run at a number of sites on the body e.g., back and forearm, and reduced as described above, have demonstrated the nonlinear stress-strain and nonlinear viscoelastic response of living human skin which is typical of many soft biological tissues.

Major obstacles to a complete mechanical characterization of living human skin still exist for example the unknown affect of surrounding tissues and the inability to measure the instantaneous skin thickness. These affects are currently under investigation.

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Acknowledgement: financial support by the National Science Foundation Grant No. ENG 7704993 is gratefully acknowledged.

5.7 THE RHEOLOGICAL BEHAVIOR OF THE SKIN: EXPERIMENTAL RESULTS AND A STRUCTURAL MODEL

Y. Lanir
Department of Biomedical Engineering
Technion - Israel Institute of Technology
Haifa, Israel

From results of biaxial mechanical tests of the skin it is apparent that the skin is anistropic and viscoelastic. The biaxial stress-strain relationships under constant rate of stretch tests are nonlinear and have significant hysteresis. The effect of the rate of stretch is small. From stress relaxation tests under constant strain it is observed that stress relaxation curves at different strain levels cannot be normalized to a single curve. Hence the skin is nonlinear viscoelastic.

An attempt is made to develop a rheological model for the skin which is based on the observed structure of its constitutents and their experimentally determined mechanical properties. The basic assumptions are:

a. The collagen and elastin fibers are arranged in two separate networks, with some corsslinks between them.
b. The collagen network consists of fibers of considerable undulation. The fibers become gradually straight upon stretch. Each undulated fiber has a characteristic overall direction (which is related to its direction upon stretch).and a characteristic "straightening strain". The collagen fibers have tensile strength but negligible compressive and bending strengths.
c. The elastin network consists of straight and linear elastic fibers which are under tension at equilibrium.
d. The directional distributions of the collagen and elastin fibers and the "straightening strain" distribution of the collagen can be expressed by continuous functions due to the large number of fibers.
e. The gelatinous ground substance is a matrix in which the fibers are embedded. Its sole contribution to the mechanical response of the tissue is through the hydrostatic pressure. The fiber-matrix interactions are insignificant.

The constitutive equations of the whole tissue is obtained from equilibrium considerations: The stress acting on a unit area in the tissue is equivalent to the sum of the forces exerted on it by the fibers which cross it.

The stress-strain-time relationships are developed in detail for cases of some simple angular distribution functions and a simple linear viscoelastic model for the collagen.

It is shown that the predictions for the tissue's behavior under common experimental conditions are in qualitative agreement with the above experimental observations. In particular the model predicts nonlinear stress-strain relations and nonlinear viscoelastic behavior.

Furthermore, a specific experimental procedure is developed through which the material functions and constants for a given specimen can be obtained.

5.8 THE ROLE OF THE MICROCIRCULATIOCN ON THE DYNAMIC MECHANICAL BEHAVIOR OF HUMAN SKIN

S. T. J. Peng,[1] R. F. Landel[1], G. S. Brody,[2] and G. Garside[2]
[1]Jet Propulsion Laboratory
California Institute of Technology
Pasadena, Ca. 91103
[2]Rancho Los Amigos Hospital
Downey, Ca. 90242

Normal living human skin strained in the physiological range does not behave like any other material; mechanically it behaves like a complex, dynamic structure.

Evidence:

1. In some test conditions, it is time independent, e.g. below certain strains (approximately 10%) or in descending steps of stress relaxation at large strains.

2. In other test conditions it is highly time dependent, e.g. at large strains or in ascending relaxation.

3. Stress-strain response is rate insensitive, yet shows large hysteresis.

4. There is a large difference between the first stress-strain cycle and all subsequent cycles, and the hysteresis loop decreases steadily with cycling.

5. There is a stress-strain crossover during unloading if the strain is carried above a certain triggering strain. The descending curve crosses the ascending curve, implying a net energy input at the end of the cycle.

These phenomena are not seen in pathologic situations where the dermal circulation is disturbed, e.g. in burn scars, with lymphedema, on the application of a simple tourniquet (blood pressure cuff), or after inducing tissue swelling by fluid injection. This circumstantial evidence implies that the microcirculation controls the mechanical response of the dermis to preserve its homeostasis.

ACKNOWLEDGMENT

This abstract represents one phase of work performed at the Jet Propulsion Laboratory, California Institute of Technology, sponsored by the National Aeronautics and Space Administration under Contract NAS7-100.

6.1 FLOW OF BLOOD THROUGH NARROW CAPILLARIES: RHEOLOGICAL MECHANISMS DETERMINING CAPILLARY HEMATOCRIT AND APPARENT VISCOSITY

P. Gaehtgens
Institute für Normale und Pathologische Physiologie der Universität
D-5000 Köln-41, West Germany

Experiments were performed on glass capillaries (I.D. 3.4 to 11.0 μm) during perfusion with suspensions of human RBC in buffered Ringer's solution in order to study the mechanisms determining intra-capillary hematocrit. These mechanisms include (a) phenomena limiting the number of cells entering the orifice as a result of either phase separation in the feeding vessel (plasma skimming) or size limitation at the orifice (screening effect); (b) phenomena which occur exclusively within the capillary (Fahraeus effect). These mechanisms can be differentiated by determining (a) the ratio of discharge to feed hematocrit (H_D/H_F), or (b) the ratio of tube to discharge hematocrit (H_T/H_D), respectively.

Experiments performed at variable H_F (0.1 to 0.6) and variable capillary shear stress (τ_T, range 0 to 25 dyn/cm^2) included determinations of cellular (v_c) and suspending fluid (v_p) flow velocity (dual slit technique), determination of H_T (from microphotographs and photoelectric signal recordings), and pressure drop across the capillaries.

The present results indicate that the Fahraeus effect ($H_T<H_D$) decreases with capillary diameter from $H_T/H_D = 0.67 \pm 0.04$ (11 μm) to 0.94 ± 0.07 (3.4 μm). Significant flow dependence of H_T/H_D (range of v_c 0.1 to 3 mm/sec) was not seen. The Fahraeus effect was hematocrit-independent in capillaries ≤ 6 μm, whereas an increase of H_D resulted in a decrease of the Fahraeus effect in the larger capillaries where hematocrit-dependent transition from single-file to multi-file flow occurred.

At a given H_F the screening effect ($H_D<H_F$) was a function of τ_T with $H_D/H_F \to 0$ as $\tau_T \to 0$. At high τ_T the ratio H_D/H_F approached unity provided that plasma skimming in the feed was absent. Under these conditions the screening effect was seen to increase with decreasing capillary diameter, with increasing flow rate in the feeding vessel, and with decreasing H_F.

The Fahraeus-Lindqvist effect showed a maximum at a capillary diameter of 5 μm; in even smaller capillaries the apparent viscosity increased significantly with H_T.

ACKNOWLEDGEMENTS

Supported by the Deutsche Forschungsgemeinschaft.

6.2 RED CELL INTERACTIONS IN MACROMOLECULAR SUSPENSIONS

Kung-ming Jan

Div. of Circulatory Physiology and Biophysics, Dept. of Physiology
Columbia Univ. College of Physicians and Surgeons
New York, NY 10032

Aggregation of red blood cells (RBC) results in acceleration of erythrocyte sedimentation rate and elevation of low-shear blood viscosity. Investigations on RBC aggregation may provide information for the analysis of force balance in cell-to-cell interactions induced by macromolecules.

RBC aggregation was quantified by various methods including direct microscopic observation and light reflectometry. The dynamic process of aggregation and disaggregation under shear was observed in a flow channel. The ultrastructure of RBC aggregates was investigated with the use of light microscopy, transmission and scanning electron microscopy.

In the presence of macromolecules, e.g. dextrans, polylysines, heparin, or various plasma proteins, RBC aggregate to form rouleaux. The mechanism of rouleau formation has been postulated to be due to macromolecular bridging between adjacent cell surfaces. The bridging energy is a function of the nature of binding and the number of binding sites between the macromolecules and cell surfaces. RBC surface is negatively charged due to the presence of sialic acids. The interaction of surface potentials results in a significant mutual repulsion between cells, especially in the presence of macromolecules. The magnitude of the repulsion is a function of surface charge density and ionic composition of fluid medium. RBC aggregation occurs when the bridging force due to surface adsorption of macromolecules overcomes the electrostatic repulsive force, membrane bending resistance, and disaggregating shear force. Studies on the ultrastructure of RBC aggregates showed that the intracellular distance is a function of macromolecular dimensions and that the shape of RBC aggregates is determined by the net aggregation energy.

Understanding the force balance in red cell interaction serves to establish the physicochemical principles of cell-to-cell interactions induced by macromoleculars. It also provides basic information for the micromechanics of RBC aggregation in blood rheology.

Supported by USPHS Research Grant HL 16851 and Research Career Development Award HL 00036 from the National Heart, Lung and Blood Institute.

6.3 VISCOELASTIC STUDY OF AGGREGATION OF RED BLOOD CELLS

E. Fukada and M. Kaibara
The Institute of Physical and Chemical Research, Saitama, Japan

Dynamic rigidity and viscosity were determined at 1 Hz for bloods of rabbit, horse, cow and man. The blood collected from human umbilical cord was also tested. The microscopic observation showed that at a stationary state no rouleaux is formed for red blood cells of rabbit and cow, but rouleaux and their lateral association are formed for red blood cells of man and horse. Red blood cells in human cord blood form rouleaux which are short and do not associate laterally.

The flow curve showed no hysteresis for bloods of rabbit and cow, but considerable hysteresis for bloods of man and horse during a cyclic change of shear rate. Slight hysteresis was observed for cord bloods.

To eliminate aggregation of red blood cells originally present in the sample, a steady flow with a shear rate of 66 sec^{-1} was applied for 1 minutes. Sinusoidal vibration was applied when the steady flow was stopped. With the lapse of time, the real component(G') and imaginary component(G") of the rigidity of blood remained constant for bloods of rabbit. No erythrocytes sedimentation(ES) was observed for 1 hr. The values of G' and G" increased and then decreased with time for bloods of man and horse. The obvious ES was observed. G' and G" for cord bloods increased initially and remained constant with very little ES.

Experiments for bloods with different dilution of plasma showed that the rate of decrease of G' and of G" is linearly related to the rate of ES. The time when G' and G" reach maxima is related reciprocally to the rate of ES.

The experimental results may be interpreted as follows. The initial increase of G' and G" is caused by the formation of rouleaux and weak association between them. For bloods of man and horse lateral association is gradually formed between rouleaux and introduces a nonuniformly aggregated structure such as islands in sea, which results in the decrease of G' and G" as well as the increase of SE. For bloods of rabbit and cord, neither rouleaux nor their lateral association take place and hence no inhomogeneous structure is formed which results in the constant values of G' and G" and absence of SE.

6.4 PARAMETERS FOR BLOOD RHEOLOGY

George B. Thurston
Biomedical Engineering Program
Mechanical Engineering Department
The University of Texas at Austin
Austin, Texas 78712 U.S.A.

The parameters for blood rheology may be divided into two classes, rheological and physiological. The primary rheological parameters are shear stress, strain rate, and time. Rheological tests under steady flow conditions give the viscosity, while for oscillatory flow the viscoelasticity is obtained, and for flow transients relaxation times result. In contrast, physiological parameters often originate from clinical interests and include such factors as hematocrit, osmolarity, erythrocyte rigidity, aggregation tendency, state of health of the donor. Paradoxically, while the physiological flow condition is pulsatile, the physiological parameters are more often correlated with steady flow or oscillatory flow. In the present work, a distinction is drawn between the analysis of blood rheology by these two different classes of parameters.

Using the rheological parameters only, a generalized Maxwell model serves to tie together several basic experiments. The individual elements of the model are assumed to be degradable with increasing shear rate. In this way the model can represent the variable internal structure of the blood. This model provides relationships for the shear rate dependence of steady flow viscosity, frequency dependence of viscoelasticity, and shear rate dependence of viscoelasticity. Relaxation times are key factors in these functions.

The viscoelasticity of blood is very responsive to the physiological parameters. Both the viscous and elastic components are strongly dependent upon hematocrit. Changing osmolarity of the plasma produces cell volume changes and consequently hematocrit changes. The resulting change in viscoelasticity is very similar to that obtained while changing hematocrit at constant osmolarity. Hardening of the erythrocytes, which occurs in bank-stored blood, or can be induced by aldehyde treatments, produces large increases in the viscoelasticity. The tendency for cell aggregation can be moderated by Dextran of varying molecular weight and also by changes in the composition of the blood plasma. Such moderation of aggregation has a strong influence on the viscoelasticity. The elastic component serves to provide an estimate of the strength of the aggregates.

6.5 PLATELET MOTIONS AND INTERACTIONS IN TUBE FLOW

Harry L. Goldsmith, McGill University Medical Clinic,
Montreal General Hospital, Montreal, Canada

Platelet motions in concentrated suspensions: Studies from this laboratory have described motions of tracer human red cells and 2 μm latex microspheres (modeling platelets) in concentrated suspensions of transparent ghost cells undergoing tube flow (1). Using photo-optical techniques and a traveling microtube (2) it was observed that shear dependent, continual collisions between the cells resulted in appreciable radial dispersion of the paths of tracer particles. With the aid of interference phase contrast microscopy it has now been possible to observe platelet motions in ghost cells. The results show that, as with the microspheres, the cell paths exhibit greater amplitudes in radial dispersion than those of red cells. When these are analysed in a manner similar to Brownian motion, the radial dispersion coefficients over time intervals ~0.2 sec at shear rates $< 10\ \mathrm{sec}^{-1}$ are up to 100× greater than the platelet translational diffusion coefficient. Whereas in platelet-rich plasma there are few cell-wall collisions, these occur frequently in the ghost cell suspensions.

Platelets in regions of disturbed flow: Sites of flow disturbance in the circulation, such as arterial bifurcations, stenoses and venous valve pockets have been associated with the deposition of platelet thrombi. We have studied the behavior of red cells and platelets in idealized models of such geometry, as in the flow at an abrupt expansion of a 150 μm tube opening squarely into a 500 μm tube. In the annular vortex which exists at the expansion, the formation and accumulation of platelet aggregates was observed. This occurred in platelet rich plasma, washed platelet suspensions and in whole blood, in the absence of aggregating agents, although the rate and extent of aggregation markedly increased when ADP or thrombin were added in amounts sufficient to sphere the cells. In a given suspension, platelet aggregation was only observed in a narrow range of Reynolds number Re. From the known distribution of shear rate in the vortex and 2-body collision theory, it was estimated that > 5000 2-body collisions/sec occurred at Re corresponding to maximum aggregation. At higher Re at a mean vortex shear stress ~2 Nm^{-2}, the formation and growth of aggregates was prevented despite a 50% increase in the collision rate. Measurements of platelet wall adhesion on collagen fibers in and downstream of the vortex were also made. The effect of red cells in augmenting the effective platelet diffusivity in tube flow was strikingly manifested by the large increase in adhesion in going from 0 to 40% hematocrit.

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7.1 VISCOELASTIC CHARACTERISTICS AND ARCHITECTURE OF VENOUS WALLS

M. Hasegawa and T. Azuma
Department of Physiology, Shinshu University Medical School,
Matsumoto, Japan

Static and dynamic viscoelasticities were studied of longitudinal and circumferential strips taken from different large veins of dogs. Rheological properties in longitudinal direction could be regarded as elastic, while those in circumferential direction as viscoelastic. No distinct regionality was observed either among longitudinal strips or among circumferential ones. In order to elucidate the above-mentioned properties of venous walls from the architectural viewpoint, static measurements were performed on each of the main components of venous walls (smooth muscle, elastin and collagen fibers). Noradrenaline and papaverine did not alter the elastic property of longitudinal strips. In circumferential direction, noradrenaline caused a considerable decrease in stress relaxation and some increase in slope of the ascending limb of hysteresis loop. Papaverine did not affect the circumferential characteristics. Venous walls were incubated in a formic acid solution which removed smooth muscle and collagen fibers, leaving elastin fibers intact. The pretreatment did not make any change in longitudinal properties, but caused the disappearance of hysteresis loop and a remarkable decrease in stress relaxation in circumferential direction. This indicates that elastin fibers may be a principal determinant for longitudinal properties. Elastic moduli of venous walls pretreated with elastase, which digested elastin fibers, amounted to the order of 10^8 dynes/cm^2 which is about 1000 times as high as those of the control. Accordingly, collagen fibers seemed not to make any appreciable contribution to rheological properties of venous walls under physiological conditions. The inference was supported by optical and electron microscopic observations of venous walls under unstretched and stretched states. Structural arrangements of constitutive fibrous elements in venous walls were proposed based on the findings obtained. An attempt was made to construct rheological models for venous walls. For this purpose, relaxation moduli and distribution functions of relaxation time (τ) were obtained from stress relaxation curves. Longitudinal characteristics were represented by a single spring, while circumferential ones were simulated by a simplified model consisting of one spring and three Maxwell elements (τ = 1, 10 and 100 sec) coupled in parallel.

7.2 MATHEMATICAL CHARACTERIZATION OF THE NONLINEAR RHEOLOGICAL BEHAVIOR OF THE VASCULAR TISSUE

Ramesh N. Vaishnav, Professor, The Catholic University of America, Washington, D.C. 20064

To understand the mechanics of the circulatory system in health and disease, and to design vascular prosthesis more intelligently, it is necessary to characterize the rheology of the vascular tissue as realistically, and in as much detail as possible. While earlier attempts at characterization of the vascular rheology were based on elementary application of the classical theory of isotropic materials, considerable progress has been made by various investigators towards characterizing the vascular tissue more fundamentally, taking into consideration its capability of undergoing rather large deformations. We report here our own attempts at such characterization of the arterial tissue, treating it as incompressible and orthotropic. At various levels, we consider the tissue to be elastic, viscoelastic, or thermoviscoelastic. For the elastic characterization, we assume that there exists for the tissue a strain energy density (SED) function which, for the usual physiologic loading consisting of an intravascular pressure and a longitudinal tethering force, can be represented as a polynomial of the second or third degree in the Green-St.Venant strains in the circumferential and longitudinal directions. This involves 3 constitutive constants for the 2nd degree and 7 for the 3rd degree representation of the SED function. In vitro experiments on canine middle descending thoracic aortic segments indicate that the 3- and 7-constant formulations (particularly the latter) satisfactorily characterize the large elastic deformations of this tissue, and yield orthotropic incremental moduli quantitatively consistent with those obtained directly. For characterizing the nonlinear viscoelastic behavior, it is assumed that the circumferential and the longitudinal stresses are functionals of the histories of the two Green-St.Venant strains. Expressing these functionals in terms of series of multiple integrals and truncating these series at the first two levels yields nonlinear viscoelastic characterizations involving 4 and 10 constitutive functions. In vitro experiments on canine aortic segments again substantiate the applicability of the proposed formulations to this tissue. Finally, theoretical analysis based on considering the stress, entropy, internal energy, and heat flux in the tissue as functionals of the histories of its strain and temperature, has been carried out. From the general structure of the theory, it appears that with careful experimentation it will be possible to obtain a quantitative thermoviscoelastic characterization of the arterial tissue.

Acknowledgements: Thanks are acknowledged to my former students Drs.J.T. Young and E.M. Ahmad for collaboration in various aspects of this work; to Dr. D.L. Fry, in whose laboratory at NIH the experimental work was conducted; to Dr. D.J. Patel, who has been my collaborator in most of my work in vascular rheology. Support of HEW Grant HL-15270 and NSF Grant ENG 76-02911 and its forerunners is gratefully acknowledged.

7.3 MECHANICAL PROPERTIES OF ARTERIES AS A FUNCTION OF TOPOGRAPHY AND AGE

Kitty Fronek, M.D., Ph.D. and Y. C. Fung, Ph.D.
Department of AMES-Bioengineering
University of California, San Diego
La Jolla, California 92093

The arterial wall mechanical properties in rabbits were studied as functions of topography and age. Common carotid artery (CA), common iliac artery (ILA) and abdominal aorta (Ao) from rabbits 6 months and 36 months old were analyzed. Isolated vessel segments were pressurized in calcium-free Krebs solution with EGTA, and the changes in diameter and length were continuously monitored with a closed circuit TV and a video dimension analyzer. The stress-strain relationship and the incremental elastic moduli were calculated for each type of vessel.

In both age groups, the CA presented the lowest incremental modulus (calculated at the pressure of 100 mmHg) and the stress-strain curve was shifted to the right. The incremental elastic modulus increased caudadly in the hind limbs; the stress-strain curve of the ILA was shifted to the left. However, when the elasticity of the vessels from young and old rabbits was compared, the CA became significantly stiffer with age, while the ILA elasticity did not change. The vessel wall thickness increased with age in all arteries, and so did the ratio of the midwall radius to the wall thickness. The increase in vessel wall stress to which old arteries are exposed is determined by the increase in radius/wall thickness ratio.

7.4 MECHANICAL PROPERTIES OF HUMAN CEREBRAL ARTERIES

Kozaburo Hayashi, Kouzo Moritake*, Atsushi Okumura*,
Hideyuki Niimi,** Hajime Handa* and S. Nagasawa*

Department of Engineering Science, and
*Department of Neurosurgery, Kyoto University, Kyoto, Japan
**Research Institute, National Cardiovascular Center, Osaka, Japan

Saccular aneurysms are common in the cerebral arteries and rather rare elsewhere in the body. There are many theories on the etiology of cerebral saccular aneurysms, which are either congenital hypotheses, acquired hypotheses, or a combination of both. From the standpoint of biomechanics, the formation of aneurysms is considered to be a breakdown of the arterial wall caused by a force. Some morphological features peculiar to the cerebral arteries have been given a considerable amount of attention. However, there have been few studies which relate the mechanical properties of the cerebral arteries with their structural characteristics. In this study, the stiffness of human cerebral arteries was quantitatively compared with the extracranial arteries based upon pressure-radius data.

Tubular segments of basilar, renal, mesenteric and common carotid arteries were obtained at necropsies. The distension ratio was defined as the ratio of external radius at each pressure to that at a standard pressure (100 mmHg), and was used to represent the deformation of blood vessels due to the pressure change. Linear relations were observed between the distension ratio and the logarithm of relative pressure, the ratio of each pressure to a standard pressure, in the physiological pressure range. The slope of each line was defined as the stiffness parameter, and was used to express the stiffness of blood vessels.

The value of the stiffness parameter of the basilar artery, representing the large cerebral arteries, was found to be much larger than that of the extracranial arteries of almost the same diameter. This mechanical characteristic of cerebral arteries is attributable to the paucity of elastic fibrils in the medial and adventitial coats. All arterial walls used in this study become stiffer with age, corresponding to an increase of collagen and decrease of smooth muscle with age. However, the stiffness of basilar artery reaches a maximum vale approximately at the age of 30, and does not progress thereafter. The stiffness parameter of common carotid artery increases gradually with age even after the parameter of the previous artery has approached a fairly constant value. This observation endorses the common occurrence of aneurysms not only in the elderly but in the middle aged person.

Effect of the stiffness of blood vessels on blood flow dynamics was also studied. Using a pulsatile flow in polymer tubes, each of a different stiffness, the role of the mechanical properties peculiar to the cerebral arteries in the pathogenesis of cerebral aneurysms was investigated.

7.5 REGIONAL, SPECIES AND AGE-RELATED VARIATIONS IN THE MECHANICAL PROPERTIES OF ARTERIES

Robert H. Cox
Bockus Institute, Graduate Hospital and
Department of Physiology, University of Pennsylvania
Philadelphia, PA. 19146

Several studies have been conducted using intact arterial segments in vitro in order to relate active and passive mechanical properties (MP) with wall composition. Transmural pressure, external diameter and axial force measurements were made on these segments under conditions of active (5 μg/ml norepinephrine) and passive (0-Ca^{++} and 2 mM-EGTA) smooth muscle (SM). The data were used to compute stress-strain relations, and values of incremental elastic modulus. Active SM responses were quantitated in terms of active stress development versus muscle length and active diameter response versus transmural pressure. Determinations of series elasticity (SE) were made using incremental releases during an isometric response to norepinephrine. Arteries were used from a) different anatomical regions in the same animal (5,6), b) animals during growth and development (1,2), c) same site in different animal species (4), and d) animals during aging (3). Segments were used for chemical analysis of collagen (C) and elastin (E) content. Results indicate a complex relation between passive MP and connective tissue (CT) with the former determined by a) ratio of C/E (1-4), b) total CT=C+E (1), c) ratio of C+E to extracellular water content (1), and d) the recruitment of collagen fibers with increasing wall strain (5). In a given animal, there was not a good correlation between passive MP and C/E ratio (5). No simple relation could be found between active stiffness (SE) and connective tissue (CT) composition (6). However, in a given artery, a close correspondence was found between passive mechanics and SE mechanics. That is, arteries with stiffer MP also had stiffer SE. The active responses of SM showed substantial differences in the various studies. Arteries with the largest stress response did not always exhibit the largest diameter response and vice versa (2-4,6). The results suggest that stiffer passive mechanics increase the efficiency of the contractile system in SM, allowing for a greater diameter response than predicted from the stress response. It is concluded that the active (SM) and passive components (C and E) of arteries functionally interact in some way as to influence the overall properties and responses of activated arterial muscle. (Supported by DHEW grant HL-17840.)

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8.1 TRACHEAL MUCUS VISCOSITY AND ELASTICITY

Louis A. Gatto and Edward Aiello
Department of Biological Sciences,
Fordham University, Bronx, N.Y. 10458

A methodology for capillary viscosimetry was developed. A detailed description of the flow of samples of rat tracheal mucus, ranging in volume from 0.06 to 0.2 $\mu\ell$, was obtained during uniform shearing in a microcapillary tube. Viscosity and elasticity were computed for different stress conditions. The flow curves show plateau regions that correspond to repeatable viscosity computations. Such computations are, by Newtonian standards, absolute viscosities: 121 ±16 (SD) poise. An initial viscosity gain in all trials, prior to the attainment of a plateau, characterized tracheal mucus as a rheopectic material. Elastic moduli, computed from measurements of elastic recoils, were 3 ±1 (SD) $dyne \cdot cm^{-2}$. Short flows that were fully reversed during recoil were interpreted as elastic flows. Viscosity computations reported by others correspond to points in the flow curve of our samples. Although viscosity showed no correlation with elasticity when all data were plotted, a linear relationship between these two parameters was found for each sample, since successive increases in viscosity corresponded to concomitant decreases in elastic recoil as consecutive shearing of the sample took place. A spring-and-dashpot model helps explain the data in that plateaus are states of equilibrium between viscous drag and elastic load, during that part of the flow, as both shear stress and shear rate remained constant. An arrangement of this sort would illustrate the duplex behavior of this viscoelastic material, where viscosity quantitations expose elasticity as a concomitant phenomenon. The plot of shear stress versus shear rate for all plateau computations shows a zero y-intercept, not reflecting the fact that this material has a yield stress, and thus illustrating a state of equilibrium. Mucus secreted after pilocarpine injection had a viscosity of 171 ±16 poise and an elastic modulus of 3 ±1 $dyne \cdot cm^{-2}$.
(Supported by grant HL-16730 from NHLBI.)

8.2 TRANSPORT AND RHEOLOGY OF BRONCHIAL SECRETIONS IN CHRONIC BRONCHITIS

E. Puchelle and J. M. Zahm
U 14 INSERM, C.O. 10
F-54500 Vandoeuvre-les-Nancy, France

The transport of secretions by mucociliary clearance and coughing has been analyzed in 27 patients with chronic bronchitis and compared to 19 normal non-smokers by measuring the rate of removal of inhaled monodisperse particles of an anionic resin (diameter (8.1 + S.D. : 3.5 μm) tagged with ^{99m}Tc. The particles were uniformly deposited on the proximal part of the bronchial tree. The deposition pattern was comparable in the healthy subjects and patients. Mucociliary clearance was calculated as the percentage of initial bronchial radioactivity cleared after 1 hour. Mucociliary clearance was significantly slower (21.8 ± S.D. : 7.8%) in the elderly non-smokers (>53 years old) than in the young (21 to 37 years old) non-smokers (34.1 ± S.D. : 14.1%). In the comparison with chronic bronchitics (39 to 77 years of age), the normal non-smokers younger than 37 years were excluded. In chronic bronchitics, the mucociliary clearance was within the normal range for 10 patients with a mean value of 26.6 ± S.D. : 10.4 while in 17 patients it was much lower with a mean value of 4.1 ± S.D. : 4.2%).

In vitro, the relative transport velocity of the secretions collected by coughing was measured on the ciliated frog palate. The transport was significantly slower ($p < 0.05$) in the group of 17 patients with low mucociliary clearance.

A positive correlation ($r = 0.525$, $p < 0.01$) was observed between the in vivo and in vitro measurements of mucociliary transport. The comparison of the percentage of bronchial radioactivity cleared by mucociliary clearance and coughing showed that in chronic bronchitis, the impairment of the mucociliary clearance could be compensated for by coughing.

The rheological properties of sputum collected in patients have been analyzed in vitro with a rotational rheometer and compared to the in vitro values of mucus transport. The optimal conditions for mucociliary clearance were characterized by an apparent viscosity (η_o) ranging from 50 to 180 poises and a strain recovery (S_R) ranging from 4 to 12 units. Outside these limits, an increase or fall in the viscoelasticity of the secretions appeared to be a limiting factor in mucociliary clearance.

8.3 EFFECT OF PHARMACOLOGIC INTERVENTIONS ON THE RELATIONSHIP BETWEEN THE MECHANICAL PROPERTIES OF MUCUS AND MUCOCILIARY TRANSPORT

Malcolm King
Meakins-Christie Labs, McGill University, Montreal, Canada

The relationship between the mechanical properties of tracheal mucus and its rate of transport on the mucus-depleted frog palate was investigated. Mucus samples were obtained from dogs subjected to a variety of physiological interventions — barbiturate anesthesia, tranquilization, cholinergic stimulation, and dehydration. For each sample, the storage and loss components, G' and G", of the complex shear modulus G* over the frequency range 1 to 100 rad/sec were determined by means of the magnetic rheometer technique, and the relative frog palate transport rate, Tr, was determined by previously described methods. For 140 tracheal mucus samples, a correlation was found relating the relative transport rate to both the shear modulus and the loss tangent, $\tan \delta$ (= G"/G'), measured at 1 rad/sec. At constant $\tan \delta$, Tr *vs.* log G*, log G', or log G" all gave partial correlation coefficients of *ca.* -0.48, the correlation coefficient between Tr and log G' being slightly higher than the other two. Tr *vs.* linear G gave marginally smaller (less negative) correlation coefficients than the correlations with logarithmic G. At constant G*, the partial correlation with either $\tan \delta$ or log $\tan \delta$ was also negative, the former being more negative ($r = -0.46$).

None of the physiological interventions used to produce changes in the mechanical properties of tracheal mucus led to any essential difference in the interrelationship of mucociliary transport on the frog palate and mucus mechanical properties. Anesthesia induced by sodium pentobarbital resulted in large increases in G*, but little change in $\tan \delta$. This tended to emphasize the effect of G* vis-à-vis $\tan \delta$. Dehydration and rapid rehydration experiments induced relatively large changes in $\tan \delta$ with little change in G*. In this case, the effect of $\tan \delta$ on transport was emphasized. Treatment with cholinergic drugs (methacholine or histamine) induced significant changes in both G* and $\tan \delta$, and in this case both parameters were found to be important in determining the changes in transport rate.

This dual correlation of transport with mucus mechanical properties satisfies the intuitive expectation that, when the available ciliary energy is fixed, the rate of transport should decrease as the deformability of the mucus decreases, and for a fixed shear modulus, the rate of transport should decrease as the rate of energy dissipation (*i.e.* $\tan \delta$) increases. The former relationship has been previously demonstrated by various authors. The latter relationship is in agreement with the prediction of Ross and Corrsin (J. Appl. Physiol.,1974, 37,333), namely that at constant mucus viscosity, transport increases with increasing elastic modulus.

(Supported by M.R.C. of Canada)

8.4 IN VITRO DRUG INDUCED CHANGES IN MUCUS RHEOLOGY

C. Marriott,* M. Litt and C.K. Shih
University of Pennsylvania
Philadelphia, Pennsylvania 19104

Previous studies have indicated that the tetracycline group of antibiotics are capable of inducing gel structure in sputum and gastric mucin sols. However, because of the complex biochemical and physical nature of both these systems, no indication of the mechanism of this interaction could be obtained. In this work we have examined the effect of six different tetracycline molecules on the rheological properties of canine tracheal mucus.

Mucus gels were reconstituted at 3% w/v nondialyzable solids content from mucin powder which had been produced by dialysis and by lyophilization of the mucus obtained from the tracheal pouch of a healthy adult male beagle dog. Phosphate buffer was used as the reconstituting medium and to this was added the required amount of tetracycline and/or other additives. Rheological determinations were carried out using a magnetic microrheometer over the frequency range 0.02 to 40 Hz. Transport studies were carried out using the upper palate of the bullfrog.

No alteration in the rheological properties of mucus gels was apparent when the tetracyclines were used in concentrations of up to 0.5% w/v. This was also the case if the tetracycline was added to the gel after reconstitution.

When either serum albumin or globulin was added in conjunction with the tetracycline, a reduction in the dynamic moduli was produced. It is considered likely that this effect was due to the binding of tetracycline to the serum protein, since both albumin and globulin alone were found not to affect the mucus rheology. Certainly, the increase in gel structure of sputum produced by the tetracyclines does not appear to be associated with the presence of exuded serum proteins.

However, the inclusion of 5×10^{-4} M calcium ions in the reconstitution buffer resulted in marked increases in the rheological properties of the mucus gels. These increases were associated with a concomitant decrease in transport rate on the frog palate. Both effects were dependent upon tetracycline concentration.

*Present address: Department of Pharmacy
University of Nottingham
Nottingham NG7 2RD, England

8.5 IN VIVO DRUG EFFECTS ON THE PHYSICOCHEMICAL PROPERTIES OF CANINE TRACHEAL MUCUS

C.K. Shih, M. Litt and L.W. Chakrin
University of Pennsylvania
and Smith Kline and French Laboratories
Philadelphia, Pennsylvania

Four beagles equipped with canine tracheal pouches were used in a study of the physicochemical properties of mucus secreted following the chronic administration of methacholine chloride and atropine sulfate. Dogs were subjected to the following sequential stages: control; methacholine chloride (0.3 mg/kg); methacholine chloride (0.5 mg/kg); and atropine sulfate (0.5 mg/kg) with methacholine chloride (0.5 mg/kg). Each stage lasted three months. Drugs were administered subcutaneously, daily, five days per week. Pouch mucus samples were aspirated once every week. G' (storage modulus) and G" (loss modulus) of both fresh and reconstituted mucus were measured. In addition to rheology, pH, solids content, nondialyzable solids content, total mucus output, mucin content and amino acid composition of fractionated mucin samples were also monitored.

The results showed that there were no significant long-term effects of the drugs on mucus rheology, secretion rate and composition. An acute study showed that methacholine chloride (0.5 mg/kg) did indeed enhance the secretion of mucus in the first hour after injection; however, the secretion rate was reduced to a level even lower than the control after two hours. In the chronic studies, the effects were not significant because the pouch mucus represented an average over a one-week period.

Complete rheological and physicochemical studies cannot be made on acute studies because of small sample size; however, investigation of the effects on composition and secretion rate are now being undertaken using tagged precursors.

8.6 CILIARY INHIBITORY FACTOR IN SPUTUM OF ASTHMATIC PATIENTS

T.M. Chen and M.J. Dulfano

Sputum Laboratory and Respiratory Care Center

Veterans Administration Hospital

800 Poly Place

Brooklyn, New York 11209

Some patients with acute symptoms of bronchospasm have been found to have a sputum factor capable of causing ciliary dyskinesia in frog palates. Patients sputa were collected in iced containers over a period of less than 3 hours, spinned down and few drops of the supernatant placed in contact with a folded piece of frog palate mucosa. The preparation was kept at 28°C. Control values using sputum from a variety of patients with C.O.P.D. (excluding asthmatics) showed that the ciliary beat frequency remains basically undisturbed for at least 60 minutes. In 7 of the 9 acute asthmatic patients studied, their sputum samples decreased or totally inhibit the underlying ciliary activity within 2 to 60 minutes. These effects were more noticeable with the sputa obtained during the time of most acute symptoms as the inhibition decreased or disappeared completely as the clinical condition improved. As expected, mucus transport rate decreased or stopped when the ciliary inhibition was present.

8.7 THE EFFECT OF SODIUM 2-MERCAPTO-ETHANE SULPHONATE AND HYPERTONIC SALINE AEROSOLS ON BRONCHIAL CLEARANCE IN CHRONIC BRONCHITIS

S. W. Clarke,[1] M. T. Lopez-Vidriero,[2] D. Pavia[1]
and M. L. Thomson[3]
[1]Department of Thoracic Medicine, The Royal Free Hospital
London NW3 2QG, England
[2]Department of Experimental Pathology
Institute of Diseases of the Chest (London University)
London SW3 6HP, England
[3]T.U.C. Centenary Institute of Occupational Health
London School of Hygiene and Tropical Medicine
London WC1E 7HT, England

The efficacy of a mucolytic agent, 2-mercapto-ethane sulphonate (MISTABRON[R]), administered in the form of an aerosol was evaluated in a group of 11 patients (8 men and 3 women) with chronic bronchitis in a controlled, double-blind, cross-over study. Saline aerosol isotonic (1.21M, 7.1%) to the drug was used as a placebo. The efficacy of the drug was assessed by its effect on (1) lung function, (2) rheological and chemical properties of sputum, (3) clearance of bronchial secretions and (4) by subjective assessment.

The mean ± S.D. age of the study group was 62.8 ± 8.0 years and height 1.67 ± 0.03 metres. There were 10 smokers who had smoked an average 38.0 ± 12.3 pack-years. Their mean ± S.D. ventilatory indices together with the percentages of predicted on sex, age and height in parentheses were: Forced Expiratory Volume in 1 sec, 1.29 ± 0.48 litres (50 ± 7%); Forced Vital Capacity, 2.76 ± 0.74 litres (81 ± 6%) and Peak Expiratory Flow, 202 ± 22 litres/min (48 ± 19%).

Approximately 1 ml of drug-placebo was inhaled in arosol form (mass median diameter: 6.5 μm) by the patients twice a day for 3 days and a final dose was given on the mornings of the drug-placebo trial runs. A third, control run was also carried out in all the patients. Existing therapy was maintained with the exception of mucolytic and expectorant drugs which were discontinued for one week before and throughout the trial period.

The results were as follows: (1) Lung function was unchanged. (2) The viscosity of sputum as measured with a Ferranti-Shirley cone and plate viscometer, the dry macromolecular weight and the N-acetyl neuraminic acid/fucose ratio remained unaltered throughout the study. (3) Clearance of bronchial secretions was enhanced with respect to the control run following the administration of either drug or placebo aerosols although statistical significance ($P < 0.01$) was only achieved for the placebo. This was attributed to an increase in sputum volume containing more radioactivity in the placebo than the control run. (4) Subjective assessment showed no change.

In conclusion therefore, hypertonic saline had a greater effect than MISTABRON[R]. It is of interest to reflect that saline was formerly a traditional expectorant.

8.8 STUDIES ON THE VISCOSITY OF HUMAN CERVICAL MUCUS

M. Saga,[1] R. M. Nakamura[2], H. Hamada,[1] and G. Matsumura[3]
[1]Department of OB-Gyn, School of Medicine
St. Marianna University
Kawasaki, Japan
[2]Department of OB-Gyn, School of Medicine
University of Southern California
Los Angeles, California
[3]School of Pharmaceut.
Showa University
Tokyo, Japan

Cervical mucin is known as a sialoglycoprotein(s). Due to the low pk_a value of sialic acid, many sialoglycoproteins behave as polyelectrolytes in phsyiological medium. Though Meyer and his coworkers had reported that the neuraminidase treatment of bovine cervical mucus did not affect rheological behaviors of the mucus (1), Daunter found that sialic acid was an important structural integrity of the mucin by scanning electron microscopy (2).

The present study was made to elucidate the role of sialic acid in physicochemical properties of the mucin by rheological approach.

Mucins were prepared from human cervical mucus of midcycle following Gibbons' method essentially. Viscosity was measured with a Cannon-Manning capillary viscometer, a Beckman Low-Shear Viscometer or a Shimazu Rheometer equipped with cone and plate.

Viscosity of mucin solution highly depended on the ionic strength of the solution like usual polyelectrolyte solutions. The treatment with neuraminidase reduced the high viscosity of aqueous solution of the mucin remarkably, but less significantly at high ionic strength. Dependency of viscosity on shear rate was also decreased by neuraminidase treatment at low ionic strength. The enzyme treatment affected the viscoelasticity of the mucus also. The maximum stress at a fixed oscillation condition was significantly reduced by this treatment. The mucin may behave as a polyelectrolyte at low ionic strength at least.

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8.9 FLOW PERMEATION STUDIES OF CERVICAL MUCUS

P.Y. Tam[1], D.F. Katz[1,2], S.A. Berger[1]

1 Department of Mechanical Engineering
University of California, Berkeley

2 Department of Obstetrics and Gynecology
University of California, Davis

The uterine cervix plays an important role in reproductive processes. Sperms deposited in the vagina must traverse this organ in order to reach the site of fertilization. In most mammals, the cervical canal is filled with mucus not unlike that of the bronchial tract. The cervical mucus is a gel, 95% (of which) or more of liquid components. The mucins, which constitute the solid component, are arranged in a network of fibrous macromolecules. This network presents a physical barrier which sperms must negotiate in order to traverse the cervix. This study seeks to determine quantitative information about the microarchitecture of the macromolecular network, particularly for mucus in the native state. Experiments consist of expressing the liquid components from the mucus by applying various pressures, and monitoring the corresponding flow rates of the liquid so expressed. The relationship between pressure and flow rate is an indication of the resistance encountered by the liquid while flowing through the network openings or "pores". The degree of hydration of the mucus is also experimentally determined. These measurements are incorporated into mathematical models of the fluid dynamics of the flow permeation process. Such models take into account the degree of mucus hydration as well as qualitative aspects of the macromolecular network architecture. Resulting computations consequently provide information about mucin filament diameters as well as interstitial sizes. Estimations of the interstitial sizes and filament diameters are obtained for native mucus of various degrees of hydrations and for mucus with its network cross-links chemically perturbed. Effects of aging of mucus on pore and filament sizes are also studied.

AD-A084 386 INTERNATIONAL SOCIETY OF BIORHEOLOGY NEW YORK F/G 6/5
PROCEEDINGS OF THE INTERNATIONAL CONGRESS OF BIORHEOLOGY (3RD),--ETC(U)
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8.10 THE CLINICAL PARALLEL TUBE SPUTUM VISCOMETER

S. R. Hirsch, M.D., VA Center, Milwaukee, WI
J. H. Linehan, Ph.D., Marquette University, Milwaukee, WI
R. T. Balmer, Sc.D., University of Wisconsin, Milwaukee, WI

Clinical sputum viscometry requires the measurement of a significant quantity of a heterogeneous and infectious fluid. The resultant data must be rheologically, physiologically and clinically significant. This work reports the results of a study of non-Newtonian fluids with an instrument of proven clinical capability (1,2). The parallel tube viscometer consists of a 12 ml brass barrel enclosed in a temperature regulating water jacket with a pressure transducer at the lower end connected to a potentiometric strip short recorder. A close fitting hollow brass plunger with plates of varying thicknesses fastened at the lower end containing 8 holes (parallel tubes) is driven at a constant velocity through the specimen contained in the barrel. The resulting time-varying pressure measured at the bottom of the barrel has been shown to be related to the viscosity of Newtonian fluids by

$$\Delta P_i = \frac{8\mu L}{\pi R^4} \dot{Q} \left(1 + \frac{C\pi R}{8L}\right)$$

wherein ΔP_i = pressure drop across the tubes and the latter term represents the entrance correction for creeping flow in short tubes (3). The ΔP_i, found by extrapolating the linear portion of the ΔP_i-time tracing to zero time, was used to calculate the viscosity of Newtonian liquids. Comparison of this measurement with the viscosity measurement of the same fluids in the falling-ball viscometer agreed within ± 4% at the 95% confidence limit.

The viscosity of polyacrilamide liquids, carboxymethylcellulose and pooled, reconstituted, dialyzed, lyophilized sputum which are all non-Newtonian were measured in the parallel tube viscometer at shear rates of 3 to 312 sec^{-1} and at the same temperature and shear rates in a Weissenberg Rheogoniometer. Values of ΔP_i from the parallel tube viscometer and μ from the Rheogoniometer were correlated by linear regression analysis. We conclude that the sputum viscometer is a clinically utilizable device which measures apparent non-Newtonian viscosity.

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8.11 A MATERIAL RATCHET - THE PEDAL MUCUS THE SLUG ARIOLIMAX COLUMBIANUS

M. Denny
Department of Zoology
The University of British Columbia
Vancouver, B.C., Canada

Gastropod snails locomote using a single appendage - the foot. For many gastropods the power for locomotion is provided by muscular waves moving along the ventral surface of the foot, the force of these waves being coupled to the substratum by a thin layer of mucus (1,2). This mucus acts as a glue which causes the animal to adhere to the surface upon which it crawls, but none the less allows forward movement of the beast. In order to better define the role of mucus in gastropod locomotion the physical properties of the pedal mucus were examined in the pulmonate slug, *Ariolimax columbianus*.

The pedal mucus is a gel consisting of 96-97% water restrained by a network formed of a high molecular weight glycoprotein. The glycoprotein is a polyelectrolyte, charged groups being present on the glutamic and aspartic acids of the protein and the uronic acids of the carbohydrate fraction. The gel network is stabilized, at least in part, by disulfide bonds between protein moieties.

The physical properties of the pedal mucus were measured by shearing in a dynamic testing apparatus. At extension ratios of <5 the gel shows the properties of a viscoelastic solid. G' is 10^2 Nm^{-2} and $\tan \delta$ is 0.08; both are virtually constant from 0.1-100 Hz. The gel stress relaxes without reaching equilibrium, indicating that the disulfide bonds present do not act as permanent crosslinks.

At an extension ratio of about 5 the gel yields and with further extension acts as a viscous fluid with a viscosity of 3 poise. If this fluid is allowed to stand unstressed the gel will "heal". The network will reform in much less than a second and the mucus will again behave as a solid. This "yield-heal" cycle can be repeated numerous times. The precise mechanism of the "healing" process has not been elucidated.

These physical properties are ideally suited to gastropod locomotion. Under the moving portions of the foot (the muscular waves) the mucus is present in the form of a viscous liquid, lubricating forward motion. Under the stationary parts of the foot (the interwaves) the mucus has "healed" and, as a solid, serves as an effective adhesive. The mucus thus acts as a material ratchet allowing for effective adhesive locomotion.

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9.1 THE MOLECULAR MECHANISM OF ERYTHROCYTE AGGREGATION

D.E. Brooks, J. Charalambous and J. Janzen, Department of Pathology, University of British Columbia, Vancouver, Canada V6T 1W5

The mechanism by which plasma constituents cause erythrocytes to aggregate into rouleaux, or into the more compact aggregates seen in various pathological conditions is not firmly established. A reasonable working hypothesis, based on the established mechanism of dextran-induced aggregation, is that fibrinogen molecules can adsorb simultaneously to two adjacent cell surfaces in sufficient number and with a high enough binding energy that a bond is formed between the cells. To partially test this hypothesis we have begun studying the adsorption of fibrinogen to human erythrocytes and correlating this adsorption with an aggregation index derived from the flow behaviour at low shear rates of cell suspensions (1).

Pure human fibrinogen is prepared by a procedure which includes barium citrate adsorption, multiple precipitations by polyethylene glycol and affinity chromatography on lysine-sepharose. The product is 95-100% thrombin clottable and is pure as judged by polycrylamide gel electrophoresis. Lactoperoxidase-labelled ^{125}I-fibrinogen is equilibrated with fresh washed human erythrocytes and the cells pelleted and separated from their supernatants by centrifugation for 6×10^6 g-min. under an immiscible organic phase whose density is intermediate between that of the cells and the suspending medium. The pellet is then washed up to seven times with protein-free buffer and counted at each step. Anlysis of the data so obtained, corrected for carryover and adsorption to the tubes, indicates that fibrinogen adsorbs to at least two types of kinetically-distinct sites, one of which allows more rapid desorption than the other. The adsorption isotherms for both types of sites are typical for weak binding, showing no saturation over the physiological concentration range. The degree of aggregation increases with increasing fibrinogen concentration, but it is not yet possible to tell if both types of binding sites are involved in the aggregation reaction.

Supported by the Canadian Medical Research Council and the B.C. Heart Foundation.

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9.2 PLATELET RESPONSE TO SHEAR STRESS: CHANGES IN SEROTONIN UPTAKE, SEROTONIN RELEASE, AND ADP-INDUCED AGGREGATION

G. H. Anderson,* J. D. Hellums,* J. L. Moake,+ and C. P. Alfrey, Jr.±

*Biomedical Engineering Laboratory, Rice University, Houston,TX 77001
+Department of Medicine, University of Texas Medical School, Houston TX 77030.
±Department of Medicine, Baylor College of Medicine, Houston,TX 77030

Thrombocytopenia and thromboembolism are complications encountered in the use of extracorporeal circulatory devices and cardiac prostheses. There is some evidence of platelet injury or stimulation by shear stress as a mechanism for the complications. Therefore, in the present study a special purpose rotational viscometer was used to study the effects of shear stress on platelets in human platelet-rich plasma (PRP). Evidence of platelet response was taken from changes in serotonin uptake rate by platelets on incubation with radiolabelled serotonin after exposure to shear stress, from measurements of serotonin release induced by exposure to the shear field, and from impairment of the aggregation function in response to addition of ADP.

Exposure of PRP to the shear field for 5 minutes yielded no significant changes for stress levels of 50 dynes/cm^2 or less. A stress of 100 dynes/cm^2 caused marked decreases in serotonin uptake rates (40%) but only slight changes (2%) in serotonin release and in aggregation response (2%). Stresses in the range of 150 dynes/cm^2, corresponding to incipient lysis, caused marked changes in serotonin release and aggregation response, as well as in serotonin uptake rate. Exposure times of 30 sec yielded results qualitatively similar to those for 5 min. However, the effects were smaller and occured at higher stress levels. For example, the serotonin uptake rate for a stress level of 100 dynes/cm^2 was reduced by only 20% for 30 sec exposure.

Experiments were carried out with three different viscometer configurations so that the shear stress level and the solid surface area access were varied independently. It was found that surface access was not a significant variable in the conditions of the experiments. Thus, impairment of platelet function as well as platelet stimulation may be caused by stress effects alone, as well as by solid surface interaction. The results also show that the response of platelets to shear stress is strongly dependent on exposure time.

9.3 RHEOLOGICAL AND MORPHOLOGICAL STUDIES ON THE STRUCTURE OF FIBRIN NETWORK

M. Kaibara, E. Fukada and K. Sakaoku*
The Institute of Physical and Chemical Research, Saitama Japan,
*Tokyo University of Agriculture and Technology, Tokyo, Japan

Gelation of fibrin is influenced by a number of environmental conditions. Fibrin gels have been classified into two types called coarse and fine clots(1). In the present paper, the structures of fibrin network formed at various conditions in fibrinogen-thrombin system are investigated from the mesurement of viscoelasticity during the gelation of fibrinogen solution and the observation of fibrin gel by an electron microscope.

The dynamic rigidity modulus G' and loss modulus G" of the sample during clotting were measured by a multiple viscoelastorecorder(2). The observation of the fibrin gel by electron microscope was carried out by using an extraction replica method.

The time change of dynamic rigidity can be represented by the superposition of two processes of the first order reaction as follows(3):

$$G' = G_1' + G_2' = G_{1s}'[1 - \exp(-k_1 t)] + G_{2s}'[1 - \exp(k_2 t)]$$

where G_{1s}' and G_{2s}' are the saturated values of G_1' and G_2', k_1 and k_2 the respective rate constants and t=0 is taken at the time of sharp rise of the curve. The first process is the crosslinking reaction between fibers, which results in the formation of network. The second process is the gradual increase of rigidity due to the lateral association of fibrin fibers at crosslinked regions, which takes place after the initial formation of network. The value of G_{2s}'/G_{1s}' indicates the degree of the lateral association of fibrin fibers after the initial formation of crosslinks.

At low ionic strengths, the resulted clot is coarse and the value of G_{2s}'/G_{1s}' is nearly zero. This indicates that the lateral association of fibrin fibers at crosslinks hardly takes place, because the network consists of thick fibrous bundles, which are not flexible enough to make lateral associations.

At high ionic strengths, the resulted clot is fine and the value of G_{2s}'/G_{1s}' is high and decreases with the increase of fibrinogen concentration. The lateral association at crosslinks may easily occur contrary to the coarse clot. With increase of fibrinogen concentration, the degree of lateral association would decrease because the increase of the number of crosslink in the network causes the decrease of the flexibility of fibers.

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9.4 THROMBOSCILLOGRAPHY, A METHOD TO DIFFERENTIATE PHYSIOLOGICAL QUALITIES OF THE BLOOD CLOT

H. H. Hartert
Med. Klinik I, Städt. Krankenhaus
University of Kaiserslautern, West Germany

The thromboscillograph (TOP) is a development closely related to the rheosimulator (RS), (Hartert, 1972). Its machinery is reduced from four moving parts to only one in the new device. The integral part is a pendulum, electronically driven in an orbital kind of movement. Attached to it the blood containing cylindrical cup is swinging around a cylindrical rod. Both encircle a cylindrical gap, where the clotting substrate is subject to some kind of a fulling action, similar to that in the RS. It brings about an appreciable increase of fibrin elasticity module, if it acts during the phase of cross-linking.

The typical thromboscillogram (TOG) taken from a recalcified platelet rich plasma is realized by a shift of the self-frequency of the elastically suspended pendulum towards its forced frequency, caused by the growing fibrin structure variations by resonance effect, that the physiologic action of platelets is producing a reaction in the TOG, which is rather different from that brought about by fibrin formation. A lack of factor XIII on the other hand again furnishes another feature of the TOG, which is distinguishable from the parameters given by platelet activity and/or fibrin(ogen) level.

9.5 THE ACTION OF DIFFERING HEPARIN PREPARATIONS ON THE VISCOELASTICITY OF SURFACE LAYERS OF FIBRINOGEN

R. G. King and A. L. Copley
Laboratory of Biorheology
Polytechnic Institute of New York
Brooklyn, New York 11201

In earlier studies (1) using a modified Weissenberg Rheogoniometer, we found (2,3) decreased rigidity or torque values (τ) in surface layers of heparin plasma, when compared to τ of oxalate plasma from the same blood withdrawal. In subsequent studies of the viscoelasticity of surface layers of highly purified fibrinogen of bovine and human origins, we found with some heparin preparations a marked lowering of viscosity (ηM) and of elasticity (γM). These decreased values were not related to the anticoagulant activities of the heparin preparations used. In some heparins no changes in ηM and γM occurred. Our findings suggest that certain heparin preparations counteract the clotting of fibrinogen without thrombin participation. These findings may be explained on the basis of Copley's concept on the initiation of thrombus formation (4) in which fibrinogen polymerizes without thrombin interaction and forms gel structures. The well established antithrombotic action of heparins is therefore not dependent upon their anti-coagulant action.

ACKNOWLEDGEMENT

Aided in part by Grant HL 19013 of the National Institute of Health and by the Office of Naval Research Contract N00014-75-C-0222.

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9.6 RHEOLOGICAL INVESTIGATIONS ON FIBRIN CLOTS

H. A. Unger and H. H. Hartert
Universität Kaiserslautern, Fachbereich Maschinenwesen
6750 Kaiserslautern, Pfaffenbergstrasse 95
Federal Republic of Germany

The rheological behavior of clotting blood can be characterized either by Thrombelastography (shearmodulus) or Rheosimulation (impedance). A modified Rheosimulator allows additional measurements of resonance-force- and free vibration (coaxial cylinder system). This new construction enables us to simulate and combine all four methods. With a mechanical model analogous the system and material properties can approximately be described. The present paper shows results of rheological studies on fibrin clots with platelet poor and platelet rich plasma. The behavior of elasticity and damping modulus, including their nonlinearity are represented and discussed. For example, a very simple and effective differentiation of the natural angular frequency with the equation $\omega(t,\varphi) = \overline{\omega}(t) + a(t)\varphi + b(t)\varphi^2$ is possible, where $\overline{\omega}(t)$ is the basic value and a(t), b(t) the coefficients of nonlinearity. Additional differentiation of the above mentioned rheological properties are possible and contribute to the results of Thrombelastography and Rheosimulation.

9.7 FIBRINOLYSIS AND COAGULATION IN HUMAN PLASMA

J. P. Kirkpatrick, L. V.McIntire, and *J. L. Moake: Biomedical Engineering Laboratory, Rice University and *Department of Medicine, The University of Texas Medical School at Houston, Houston, Texas.

The goal of this study is to determine the effects of fibrinogen-fibrin degradation products (FDP) on coagulation and the kinetics of fibrinolysis in platelet-free and platelet-rich human plasma (PFP and PRP). To activate plasmin and produce FDP, PFP was incubated at 37°C with streptokinase (SK), soybean trypsin inhibitor added at the end of the incubation period to prevent further fibrinolysis, and the samples quick frozen for later analysis. By methods previously described[1],dynamic measurements of shear storage and loss moduli (G', G'') were made for recalcified 1:1 mixtures of normal fresh PFP or PRP and the SK incubated samples. For PFP, the mixtures containing plasma incubated 3' with 100 or 50 units/ml SK showed a significantly greater maximum G' (G'_{max}) than the control (0' incubation period).For longer incubation times G'_{max} decreased to 30-40% that of the control. For normal PFP, G'_{max} was directly proportional to fibrinogen concentration. Samples incubated up to 150' with 10 units/ml SK did not show a significant change in G'_{max} compared to the control. Addition of 20 units/ml in the absence of SBTI resulted in a clot which rapidly lysed. Low levels of SK (<10 units/ml) had no effect on clot structure unless Factor XIII crosslinking was inhibited (with hydroxylamine). Fibrin monomer aggregation was not significantly lengthened by FDP. In PRP mixtures containing plasma incubated with 100 units/ml of SK, G'_{max} was in all cases less than that of the control. The minimum G'_{max} occured in the samples with plasma incubated 20'-34' with 100 units/ml SK (G'_{max} 30%-40% of control). For a 50% decrease in fibrinogen concentration by dilution of normal PRP with constant platelet count, G'_{max} was 75%-80% than of the control. Platelet aggregation to thrombin, ADP, and polymerizing fibrin monomer was unimpaired by FDP. These results indicate: 1) uncrosslinked fibrin is more susceptible to attack by plasmin that either fibrinogen or cross-linked fibrin polymer, 2) FDP interferes with the thrombin-fibrin interaction, 3) PFP treated with SK for short incubation periods yields a clot with a much higher elastic modulus, indicating a change in structure caused by fibrin conformational changes or FDP, and 4) fibrin-platelet interaction is adversely affected by FDP.

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9.8 INFLUENCE OF SOME ANTIBIOTICS OF THE β-LACTAM GROUP UPON RHEOLOGICAL PROPERTIES OF BLOOD AND PLATELET AGGREGATION

L. Houbouyan, S. Gaillard, A. Goguel and J. F. Stoltz
Groupe d'Hémorhéologie-Centre de Transfusion Sanguine - Brabois -
54500 Vandoeuvre Lès Nancy et Laboratoire d'Hématologie -C.H.U.
A. Paré - 92100 Boulogne Billancourt - France

Since their discovery, antibiotics have been occupying a more and more important place among therapeutic substances. Nevertheless, besides their great efficiency, some secondary effects may occur, which must not be neglected.

The aim of the present study is to make clear the influence of different antibiotics of the β-lactam group (Penicillin, carbenicillin, metampicillin, ampicillin, cefalotin) upon the rheological properties of blood (apparent viscosity and yield stress) and also on platelet aggretation.

The study has consisted in:

- determination of blood viscosity using a viscosimeter with coaxial cylinders $(0.1 < \dot{\gamma} < 50 s^{-1})$,
- measurement of screen filtration pressure of whole blood and of PRP in presence of ADP,
- study of platelet photometric aggregation.

The results have then shown that:

1) The screen filtration pressure of whole blood is not significantly modified (for the 5 antibiotics studied).

2) Some antibiotics induce important change of the apparent viscosity. Thus, ampicillin does not significantly modify the rheological properties of blood, even when very high doses of the antibiotic were added. On the other side, metampicillin leads to an increase of the apparent viscosity (about 10%). The effect of cefalotin is more important and related to the does, the value of the yield stress is strongly increased for a dose of 5 mg/ml; the same with carbenicillin. The modifications of blood rheological properties induced by Penicillin were very important, justifying a more searching study. Thus, for a hematocrit of 40%, the viscosity is not significantly modified for Penicillin concentrations inferior to 5000 U/ml, but doses ranging from 5000 to 10,000 U/ml induced a strong increase of the apparent viscosity, depending upon the dose and the shear rate. This hyperviscosity is the more evident as the hematocrit is elevated. These results might be compared to the studies on the interactions of Penicillin G with some phospholipids (Kellaway and Coll) with modifications of the rheological properties.

3) Platelet aggregation, either performed by photometric technic or by screen filtration pressure in presence of ADP, is always impaired, for these five antibiotics, with a relation to the dose.

An in vivo study has also been realized with some of these antibiotics (especially Penicillin G and carbenicillin).

This work was supported by DRME (Grant 76.34.146.00.480.75.01).

9.9 PLATELET FUNCTION ABNORMALITIES AS MEASURED BY THE PLATELET COUNT CORRELATION (PCC) TECHNIQUE

Klaus U. Benner, Heinz Boehme, and E. Huettel
Anatomical Institute, Technical University of Munich, Germany and Department of Angiology, Central Clinic of the LVA, Gauting, Germany

Using a fixation method Wu and Hoak (Lancet 2:924, 1974) tried to demonstrate indirectly the existence of platelet aggregates in venous blood, the number of which is probably elevated significantly in several diseases. Subsequently, other authors (e.g. Prazich, J.A. et al., Thrombos. Haemostas. 38:597, 1977; Rohrer, T.F. et al., Blut 36:15, 1978) have raised doubts on the diagnostic and predictive value of the Wu and Hoak method. The present study was designed to test this fixation technique with a group of patients suffering from mild (type I and II) and severe (type III and IV) arterial occlusive diseases (AOD).

The technique consists of a comparative platelet count in two different blood samples taken from the same person. Venous blood (0.5 ml) is collected in 2 plastic syringes one of which is prefilled with 2 ml of a phosphate-buffered EDTA-formaldehyde-solution and the second with 2 ml of the buffered EDTA-solution alone. After gentle mixing and 15 min incubation at room temperature both samples are centrifuged at 150 g for 8 min and a platelet count is performed on the supernatant fluid. The quotient of count in the EDTA-formaldehyde-solution and in the EDTA-solution gives the so-called PCC.

In healthy volunteers (n=6) and in patients with thromboembolic venous diseases (n=5) the PCC ranged between 0.62 and 1.20 with a mean value (±s.d.) of 0.96 ± 0.18, and 0.85 ± 0.20, respectively. Comparable counts were observed in patients with AOD I/II (n=21), for which the PCC averaged 0.87 ± 0.09 (single values between 0.73 and 1.05). However, in patients with AOD III/IV (n=12) the mean value of PCC was found to decrease to 0.63 ± 0.16 (single values between 0.26 and 0.83), which differs significantly from the other groups ($p<0.01$). Pilot experiments with patients of low PCC suggested that this decrease can be eliminated by a 5-10 day oral administration of aspirin and/or dipyridamole.

From these results one should not conclude directly that a significant number of platelets are aggregated intravascularly in the patients with severe AOD. Rather it should be assumed that platelets in those cases are in a more activated state. This relatively strong activation of platelets, which can be inferred to be present to a lesser degree in healthy volunteers, may be the reason for the well known extreme variations in normal human platelet counts as determined by the usual laboratory techniques. Supported by Deutsche Forschungsgemeinschaft (Be 625/4).

10.1 SERIES-COUPLED MYOGENIC BEHAVIOR OF THE ARTERIOLAR NETWORK

P.C. Johnson, M.E. Burrows, S.M. Sullivan,
and B.J. LaLone
Department of Physiology, University of Arizona,
College of Medicine, Tucson, Arizona 85724

The arterioles of cat mesentery and cat sartorius muscle dilate when arterial pressure is reduced. This has been suggested to be caused by reduction of the intravascular pressure. Intravascular pressure is believed to provide a stimulus to the vascular smooth muscle (the myogenic hypothesis). This theory has been tested by measuring intra-arteriolar pressure along with arteriolar flow and diameter during changes in arterial and venous pressure. These studies (in cat mesentery) are largely in accordance with the myogenic hypothesis but demonstrate a greater arteriolar constriction with venous pressure elevation than with arterial pressure elevation. A second series of experiments in cat sartorius muscle has compared the responses of large and small arterioles with arterial pressure reduction. Modest decreases in arterial pressure cause dilation only of the large arterioles. Greater pressure reductions lead to dilation of the small arterioles as well. We interpret these findings as indicating that the arterioles constitute a series coupled network of independent myogenic effectors. With small reductions in arterial perfusion pressure the large arterioles dilate, which restores pressure in the small arterioles to the normal level. Thus there is no change in the pressure stimulus in these small vessels and therefore diameter does not change. With greater pressure reduction, dilation of the large arterioles cannot restore downstream pressure to its normal levels. Therefore the small arterioles dilate due to a decrease of the pressure stimulus.

ACKNOWLEDGEMENTS

This study is supported by NIH Grants HL 17421, HL 15390 and HL 07249.

10.2 MODELLING OF THE MECHANICAL RESPONSE OF ENDOTHELIUM AND SMOOTH MUSCLE LAYERS IN ARTERIOLES

Jen-shih Lee, Brian R. Duling, and Robert W. Gore
Division of Biomedical Engineering and Department of Physiology
University of Virginia
Charlottesville, Virginia 22901

A method has been developed by Duling et. al for the mechanical study of isolated arterioles under in vitro condition which permits a study of regional variations of smooth muscle along the arterial network. It would be desirable to identify further the role of endothelium and smooth muscle in the passive and active response of the isolated arteriole. The inner layer of the present mechanical model, the endothelium, is assumed to be a passive tissue. The smooth muscle cells form the outer layer. A third order power series is used to describe the stress-strain relation of the endothelium and passive behavior of the smooth muscle layer. The active tension developed in the stimulated muscle is assumed to be a parabolic function of the strain. A procedure has been developed to select the appropriate constants in the stress-strain relations of the model to match the pressure-diameter relations obtained from the in vitro experiment under the conditions of complete relaxation and various levels of stimulation. From the model analysis, a set of dimensionless variables controlling the deformation of the arterioles was identified. The model predicted that during vessel constriction, compression of the endothelium layer, instead of the intraluminal pressure, may be the major factor resisting complete closure of the arteriole.

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Acknowledgements: This study is supported partly by NIH Grant HL 12792 and HL 16812.

10.3 ASSESSMENT OF CARDIAC MECHANICS DURING ISOVOLUMIC SYSTOLE

M. Landowne* and E. W. Ross, Jr.**
*U.S. Army Research Institute of Environmental Medicine
and **U.S. Army Research and Development Command
Natick, Massachusetts 01760

In seeking to apply the force-velocity relationship of muscle fibers to analysis of the intact mammalian heart and to an assessment of clinical disorders, the choice of basic assumptions has frequently overspecified the results, and introduced inconsistencies. Fung (1970) has consolidated theoretical and experimental information to develop a comprehensive yet simplifying formulation which removes logical inconsistencies and, in addition, considers the time-dependence of tension development when a fiber is activated. With this formulation, for example, the development of fiber tensile stress may be quantitated for isometric contraction as a function of time, with 11 characterizing parameters.

Additional complexities appear necessary to the description of pressure development of an intact heart; here force is generated by sequenced fractionate contractions within a thick walled architectually complex structure, where the force-time pattern results from a temporal, spatial, and individual ventricular fiber distribution of properties. This distribution is probably unique to the particular anatomical and functional situation.

If both fiber characterization and ventricular organization are reduced to the simplest possible terms, and consideration is limited to the period of isovolumic ventricular systole, the velocity of shortening of the contractile element of a lumped, equivalent three-element model, requiring only two descriptive parameters, might be considered to approximate a gamma distribution function:

$$\frac{dp/dt}{b(p+k)} = t^{a-1} \cdot e^{-t/c}.$$ This, upon integration yields

$$p = (p_o + k)e^{bc^a \gamma(a,t/c)} - k$$

where $\gamma(a,t/c)$ is the incomplete gamma function.

With careful attention to measurement and computational detail, the time course of left ventricular pressure during isovolumic systole in unanesthetized goats is quite accurately described by this expression (average rms deviations range .6 to 1.4 mm Hg). However, the parameter estimates may not be sufficiently well specified, i.e., the values derived for the 4 or 5 parameters may depend upon the particular strategies used for measurement and curve fitting. Only two parameters are used to define the constitution of the whole ventricle in terms of its fibers and yet the descriptive function may be over-parameterized for the available data. That is, the complexities of fiber organization and activation pattern serve to limit deductions drawn from pressure measurements on intact heart as to its mechanical behavior, or implications of subtle alterations of clinical relevance.

10.4 MACROSCOPIC INHOMOGENIETIES IN THE MECHANICAL RESPONSE OF PAPILLARY MUSCLES

J. G. Pinto
University of California, San Diego
La Jolla, Calif. 92093

Mechanical experiments performed on papillary muscle in the past provided the scientific framework for making mechanistic deductions on the mechanical behavior of the intact heart. However, recently the methodology of mechanical experiment on muscle bundles has come under debate and doubt. The difficulties introduced by terminology, methods of testing, artifacts from testing machines and specimen clamps etc. have all added up to create a dilemma in papillary muscle research.

Measurements of segmental deformation made on papillary muscles in our laboratory suggest that by far the serious difficulty arises from the nature of the specimen itself. We measured deformational pattern in resting papillary muscles of cats and rabbits by marking the specimen surface with ink spots and measuring their separation distance as the specimen was strained by pulling at its ends. In stimulated (twitching) muscles whose overall (end-to-end) length was maintained isometric, the changes in the length of segments due to contraction elicited by electrical stimulation were measured using an electronic camera (Optron Inc.). Measurements were made on long and cylindrical specimen obtained from canine and pig hearts. Consideration of shape and size of the specimen was important in selecting it for the test. Uniform cylindrical geometry avoided the effect of stress concentration while long muscles minimized the artifact due to end fixtures on segments away from ends. Our measurements indicate that the deformation is non-uniform in resting as well as stimulated papillary muscles. More important, the non-uniformity observed here manifests beyond a macroscopic scale-size of 1.0 to 1.5 mm and may be primarily attributed to structural non-uniformities. These observations when coupled with those of Lakatta and Jewel (1), who showed length dependent inotropy, suggest that inotropic state of the muscle is also inhomogeneous along the specimen length. Thus, the mechanical response of the papillary muscle in general is non-uniform. This aspect is particularly significant when segments of small size are considered.

In view of the above, in formulating the mechanics of papillary muscle, it is important to establish a minimum size of segment "sufficiently" far from the disturbing influence of end conditions. The segment size should be large enough to integrate out the non-uniform aspects. Our measurements suggest a minimum size of 2.5 mm for the length of segment. These mechanical considerations on length and the viability considerations on the diameter (<1 mm) of the specimen suggest that most of cat and rabbit papillary muscles are unsuitable for mechanical experiments.

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Acknowledgement This study is supported by NIH Grant HL 19460-02.

10.5 CARDIAC MUSCLE MECHANICS

P. J. Hunter
Department of Engineering Science
Parks Road, Oxford

An optical system for measuring the length changes in a central segment of a cardiac muscle preparation will be described. The application of the method to the servo control of 0.5 mm segments of rat and rabbit right ventricular papillary muscle will be discussed and the twitch response of these segments under isometric conditions will be reported.

Non-uniformities in cardiac muscle preparations, arising partly from geometric factors (tapering ends and non-parallel fibres) and partly from cell damage caused by the muscle clamps, have a significant effect on the measurement of the mechanical properties because the ratio of length to diameter in these muscles is seldom greater than four. Two techniques for measuring the length of a uniform, undamaged part of the preparation have been reported: the "spot-follower" method (1), and a laser diffraction method (2). The first is subject to the criticism that the surface length changes which it measures are not the same as internal length changes and the second can only be applied to very thin muscles ($\lesssim$ 150 μm diameter) which are available in the rat but not in other species, such as the rabbit and cat, more relevant to the physiology of man. The technique described below is designed to measure internal length changes in muscles of any diameter but typically in the range 0.2 - 0.5 mm.

Two glass fibres (diameter 10-20 μm) are inserted vertically into the horizontally mounted muscle about 0.5 mm apart. A lens, focussed in the plane of the glass fibres, casts a magnified image onto a silicon diode array tube in which the fibres appear as shadows against the bright background provided by a pulsed light emitting diode mounted behind the muscle. By repetitively scanning the tube face along a single line adjacent to the muscle the video signal is processed digitally to give the distance between the glass fibres with an accuracy of 1 part in 500 at a sampling rate of 7.4 kHz. The mechanical properties of the muscle segment are then measured with the distance between the glass fibres held under servo control as the muscle develops tension following an electrical stimulus.

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ACKNOWLEDGEMENTS

The author is indebted to Dr. D.H. Bergel and Dr. B. Rajagopalan for their assistance in this study.

10.6 STRESS-STRAIN-HISTORY RELATION OF RESTING TAENIA COLI SMOOTH MUSCLE

J. M. Price*, P. Patitucci**, and Y. C. Fung**
*Department of Physiology, College of Medicine
University of South Florida
Tampa, Florida 33612
**Department of AMES-Bioengineering
University of California, San Diego
La Jolla, California 92093

Stress-relaxation characteristics and stress-strain relationship have been analyzed in resting guinea pig taenia coli (TC). Mechanical tests were performed with an electromechanical testing device which can impose a step stretch on the specimen within 10 ms without oscillation or overshoot. Three methods were used to suppress spontaneous activity in this muscle: the use of calcium free solution containing disodium ethyleneglycolbis-(β-aminoethylether) - N, N-tetraacetic acid (EGTA), the lowering of the bath temperature, and the use of epinephrine. The stress response to a step increase in strain was measured in spontaneous TC and in the same specimen after the spontaneous contractions were arrested. Each step stretch began from the length at a 100 mg. preload. A comparison of these responses suggests that the epinephrine method is the least harmful to the muscle. The following mathematical expression for the relaxation function in epinephrine was examined: $K(\varepsilon, t) = G(t)\, T^{(e)}(\varepsilon)$.The normalized stress relaxation function, $G(t)$, was found to be independent of the degree of stretch. The form of $G(t)$ has a continuous spectrum of relaxation constants, and corresponds to a mechanical model of viscoelasticity consisting of an infinite number of springs and dashpots. This $G(t)$ is specified by three parameters computed computed from the experimental data. The values of these parameters are: $c = 2.25$, $\tau_1 = .003$ s, and $\tau_2 = 3.38$ s. The theoretical expression agrees with experimental results quite well. The "elastic" response, $T^{(e)}(\varepsilon)$, is a function of the magnitude of stretch, and is experimentally determined by stress-strain tests at high strain rates. The stress-strain relationship is nonlinear. It is different in loading and unloading. It depends on the previous strain history. The mathematical expression for the stress-strain relationship in the loading process consists of two power laws of the form $T = \beta\varepsilon^{\alpha}$. Computed mean values of α ranged from .2 to 2.79, and β ranged from 4.97 to 8001. x 10^4 dynes/cm^2 for strain rates of .01 to 20. Hertz. The normalized relaxation function of resting TC is similar to those of nonspontaneously contracting tissues. The stress-strain relationship is similar to that of the aorta, but different from the exponential relation of papillary muscle, mesentery, and ureter.

10.7 AN EXAMINATION OF ISOMETRIC CONTRACTION OF URETAL SMOOTH MUSCLE

P. F. Zupkas, Y. C. Fung and J. G. Pinto
University of California, San Diego
La Jolla, California 92093

In this study we examined the isometric contractions of uretal smooth muscle. Uretal segments from dog and rabbit were exposed and carefully removed immediately after sacrificing the animal. Segments were exposed with the animal lying on its back, in situ length was measured prior to removal by making two ink marks on the ureter. The dissected ureter was placed in an oxygenated Kreb's solution for approximately five minutes. A segment of approximately 1.25 cm was tied with 3-0 silk thread at both ends and mounted in the testing chamber of an electro-mechanical servo device (1). The specimen was left quiescent in the chamber for fifteen minutes, allowing it to equilibrate and recover from mechanical trauma (2). The specimen was then stretched to its in situ length and stimulated at 20 volts for 2 seconds at twenty-second intervals for sixty minutes to stabilize the tension development. Following this procedure, reference measurements of length and diameter were made. During reference measurements, a small load was imposed on the specimen (10 mg for rabbit and 50 mg for dog), to ensure vertical alignment of the specimen. After reference measurements, the voltage, duration and frequency of stimulation were selected to obtain maximum repeatable active tension. The segment was then stretched at a constant rate while maintaining stimulation. The tension and changes in length were recorded on a strip chart recorder. The active tension curve versus the time change of this curve was also recorded for increasing length of the segment on an x-y plotter.

The data from every experiment was normalized with respect to the maximum active tensions generated for each experiment and the reference length. A mathematical expression was obtained to fit the active and passive tension versus length curves of each experiment. The influence of the length on the shape of the active tension curve is shown in a comparison of the phase plots of the curves at different lengths.

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ACKNOWLEDGEMENT

This study is supported by USPHS IT 32 HL 7089.

11.1 THE INFLUENCE OF WAVE SHAPE ON PERISTALTIC TRANSPORT

O.H. Mahrenholtz, M.G. Mank and R.U. Zimmermann
Institut für Mechanik, Technische Universität Hannover, FR Germany

Peristalsis as a physiological pumping process takes place in various hollow organs of the body. The aim of this contribution is to extend existing models (1, 2) by allowing for unsymmetric wave forms, higher amplitude ratios and higher Reynolds numbers. Theoretical and experimental investigations have been carried out under plane flow conditions.

The theoretical part is based on a finite element approach with nodeless pressure variables, using a modified Galerkin procedure. The experimental setup consists of a straight channel with a flexible bottom, transversally moved by a belt on which cams of different heights form the wave shape. Flow rate, pressure rise and pressure distribution are measured dependent on the shape of the flexible wall. Flow patterns have been registered by filming individual floating particles.

In the case of low Reynolds numbers a high degree of concordance between calculation and experiment could be noticed. It can be seen that a change of the wave form strongly influences the pressure recordings in the channel. However, the shape of the wave at least in the case of low Reynolds numbers has no significant influence on pressure rise and flow rate. Only under the influence of inertia forces the calculation shows an increase of the flow rate or the pressure rise if the steep slope of the wave precedes. But the experimental verification of this result has still to be done.

The finite element methods reduces the modelling restrictions and leads to satisfying results. In order to apply this technique to the peristalsis of the ureter special boundary conditions have to be integrated into this problem.

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11.2 FINITE ELEMENT METHODS FOR STUDYING MECHANICAL FACTORS IN BLOOD FLOW

Norman Davids, Department of Engineering Science and Mechanics
The Pennsylvania State University, University Park, PA. 16802

This paper reviews some biomechanical analyses of blood-flow in large arteries, by use of the computer-based finite element method and describes some recent developments in it. It presents the computational features of the method and stresses the mechanics-based features of the problems, such as the effect of geometric complexities, material non-linearities and the non-Newtonian rheology of the blood. The specific mechanical and fluid dynamic factors analyzed are wall shear stress, flow profiles, and pressure variations. After simulating tubes of circular cross-section, we apply the analysis to a number of physiological situations of significance including blood flow in the entrance region, at bifurcations, in the annular region between an inserted catheter of varying diameter and the vessel, with a view to delineate some of the above factors as causative for atherosclerosis and injuries to blood vessel intima.

A model study was completed of pulsatile flow in a 60°-bifurcated channel for measurement of velocity profiles, with special emphasis on reversed or disturbed flow conditions.

Velocity profiles were taken in four positions (pre-branch, just downstream of it, 4 diameters further in the daughter branch, and far downstream, respectively). Among the highlights suggested by these measurements are: rapid fluid movements occur due to pressure pulses, which may further increase wall shear stress, and that vessel capacitance significantly alters the velocity field, and hence shear stress. Although bifurcations are generally considered to be relatively rigid, the profile through them is dependent on both pre-branch and post-branch vascular segments, which are more capacitive.

The corresponding analysis was extended to the situation where flow separates and reverses in the neighborhood of stagnation points. This required developing the exact, non-linear expression for the convective velocity change in which ΔV^2 is not negligible compared with ΔV. A computer algorithm was developed to handle the simultaneous effects of pressure and viscous forces on velocity change across the element, and applied to the canine pre-branch arterial segment.

For mean physiological flow conditions, low shear stresses (0-10 dynes/cm^2) are predicted near the wall in the diverging plane, higher values (50 dynes/cm^2) along the converging sides of the wall, backflow is predicted along the outer wall, pressure recovery prior to and into the branches, and a peak shear stress at the divider lip.

Comparison with the experiments is in progress.

Financial support by the National Heart, Lung, and Blood Institute, Grant No. IR-1-HL-11289, is gratefully acknowledged.

11.3 EFFECT OF FLUID FILTRATION ON APPARENT BLOOD VISCOSITY IN THE MICROCIRCULATION

Heinz D. Papenfuss
Ruhr-University Bochum, Institute for Thermo and Fluid Dynamics 4630 Bochum, West Germany

Joseph F. Gross
University of Arizona, Department of Chemical Engineering, Tucson, Arizona 85721

This theoretical study is concerned with changes of apparent blood viscosity in capillaries due to transmural fluid exchange (1). Two effects resulting from fluid loss are considered: (i) Variation of plasma protein concentration along the capillary axis which changes the plasma viscosity and (ii) Increase of the tube hematocrit along the capillary axis with a concomitant increase in relative apparent blood viscosity. The mathematical formulation of transcapillary fluid exchange is based on Starling's hypothesis. With regard to the intraluminal axial transport of blood, several models of the single-file flow of red cells are employed. The red cells are assumed to be rigid discs or spheres in order to calculate the relative apparent blood viscosity. Viscosity values which were determined by Skalak et al. (2) by using the actual shape of undeformed red cells are employed in the present analysis. Recent experimental rheological data for capillary blood by Albrecht (3) are also used. A fictitious reservoir approach is proposed to determine the Fåhraeus and Fåhraeus-Lindqvist effects for permeable blood vessels. Results for the rat renal glomerulus show an axial increase of apparent blood viscosity due to filtration by as much as 60%. From the present work it can be concluded that in-vivo studies of apparent blood viscosity from capillary networks may lead to uncertainties when fluid filtration is ignored.

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11.4 A RE-EXAMINATION OF THE LIGHTHILL-FITZGERALD THEORY

J. Aroesty, W. King and J. Larm
The Rand Corporation, Santa Monica, Ca. 90406

The Lightfill-Fitzgerald theory of erythrocyte motion has been widely cited and poorly understood for more than ten years. Recent findings suggest that both the theory and its applications are questionable. The original Lighthill analysis combined lubrication theory for the plasma flow and a linear relation between red cell deformation and local pressure. The deformation-pressure relations were, however, only appropriate for a compressible cell. Fitzgerald's modifications included an axisymmetric version of lubrication theory to describe the plasma motion, and a compatibility condition between erythrocyte configuration and the average pressure acting over the cell membrane. This compatibility condition relaxed Lighthill's assumption of particle compressibility. However, Fitzgerald's application of the theory for estimating pressure drop is suspect due to three factors: (1) As shown by Tözeren and Skalak, the Lighthill-Fitzgerald force balance is not consistent with known asymptotic results. (2) The numerical integration of the equations of motion is incorrect and, (3) For a given hematocrit, the number of red cells in single file capillary flow is underestimated.

This paper presents a new application of the Lighthill-Fitzgerald theory that corrects these three factors. Of particular importance in determining non-Newtonian characteristics is the way in which the pressure drop contributions of the individual cells are summed to determine the pressure drop-velocity relations for an entire capillary (of diameter $5 \sim 7\mu$). The additional pressure drop due to the presence of an individual red cell is computed, and then multiplied by the number of red cells in single file flow. The number of red cells is estimated on the basis of volume considerations alone. The formula for the effective viscosity, η^*, then becomes

$$\eta^* = \mu \left(1 + \frac{H \cdot \pi \cdot r_o^3}{V_{cell}} \; \frac{(D - 16)}{8(\kappa r_o)^{\frac{1}{2}}} \right)$$

where μ is the plasma viscosity, r_o is the capillary radius, κ is a red cell curvature, V_{cell} is the volume of the individual red cell, H is the hematocrit, and D is the resistance parameter defined by Fitzgerald and Lighthill.

Our calculation of effective viscosity exhibits one disturbing feature: when the hematocrit is specified, the effective viscosity may not increase monotonically with decreasing capillary radius. This occurs because of two opposing effects; a decrease in the number of red cells due to volume constraints, and an increase in the additional pressure drop across each red cell. A comparison of the present results and those already in the literature will be presented, along with suggestions for refining the theory in the light of modern ideas about the erythrocyte membrane in sickness and health.

11.5 PRESSURE FLOW RELATIONSHIPS OF BLOOD IN THE MAMMALIAN KIDNEY

Alan H. Purdy, Ph.D., C.C.E.
Department of Health, Education, and Welfare
National Institute for Occupational Safety and Health
5600 Fishers Lane
Rockville, Maryland 20857

This paper deals with the problem of quantification of the properties and activities of living tissue in the peripheral vasculature. The object of this study was to show that the mammalian peripheral vasculature, specifically the dog's kidney, meets the conditions necessary for lumped hydraulic impedance analysis.

This was an experimental and theoretical study to demonstrate that the relationship between blood pressure and flow is linear and that the physical size of the vasculature involved is small enough to meet the requirements of the lumping theory.

The experimental method used was the injection of hydraulic sine waves into the blood flow system of the dog's kidney. By this means, two proofs of linearity were derived. One method of proof was to examine the pressure flow relationships of the blood by means of cross correlation. The other method was to compare the velocities of the pulse waves of different mean blood pressures. Pulse wave velocities were also measured as a means of demonstrating the length of the system with respect to the wave length and thus, show the degree of lumping.

The observed facts in this investigation show: 1) the relationship between pressure and flow of blood in the dog's kidney is linear as shown by a mean cross-correlation coefficient of .9792. 2) the physical length of the vascular bed of the kidney is shown to be small enough with respect to the pulse wave length to apply lumped hydraulic analysis with an error of less than 6.5% to quantify the following properties: A. Pulsatile resistance, B. Total reactance, C. Inertance reactance, D. Compliance reactance, E. Lumped depth of wave penetration, F. Lumped vessel radius, G. Pulsatile real work, H. Pulsatile reactive work.

In theory, the equations developed in this experiment can be used to better understand the distribution of blood flow within an organ when it is subject to a toxin, hormone, or change in blood pressure.

11.6 INDIRECT DETERMINATION OF RHEOLOGICAL PROPERTIES OF FLUID-FILLED VISCOELASTIC TUBES MODELIZING ARTERIAL HEMODYNAMICS

Geiger, D., Flaud, P., Oddou C.
Laboratoire de Biorheologie et d'Hydrodynamique Physiologique
Universite Paris 7
2 Place Jussieu - 75221 Paris Cedex 05

The knowledge of the rheological behavior of the vessel wall to pathophysiology is of great interest to both fundamental hemodynamics and to pathophysiology. So far only a few methods have been developed in order to perform in vivo measurements of rheological parameters of the wall material. Among them, propagation studies of small amplitude and high frequency artificial wave trains permits the evaluation of the complex Young modulus of the blood vessels (1), (2). This method requires both phase shift and attenuation measurements between two transducers (pressure or wall displacement or fluid flow rate).

By using a numerical computation to modelize the pressure wave train propagation in fluid-filled viscoelastic tubes, it is shown that an optimal wave train length exists that allows phase shift and attenuation measurements of good accuracy. The interest of this result, is that for this optimal wave train length, drawbacks related to reflection phenomena, and deformation of the wave train during its propagation are avoided. An experimental confrontation is carried out in the test section of a hydrodynamical model, on which directs measurements of pressure and radius are performed. A rheological model is deduced in terms of complex Young modulus. Direct measurements of wall mechanical behavior, obtained by extensiometric analysis, validate this approach.

Finally, it is shown that the accuracy of the method is dependent upon the pressure wave train length and that this accuracy can be improved in order to obtain better knowledge of the rheological parameters describing the wall material which is a fundamental requirement in arterial hemodynamics studies.

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11.7 A ROTATED DISC ELECTRODE FOR CHARACTERIZATION OF TRANSPORT IN MEMBRANES

by
D. A. Gough, J. K. Leypoldt, and M. Davis

Department of Applied Mechanics and Engineering Sciences
Bioengineering Group
University of California, San Diego

In recent years, there has been a growing interest in the development of biochemical-specific sensors for analytical applications. Most of these devices function either by (1) selective transport of the chemical of interest across a membrane to an electrode where it is quantitated by an electrochemical process, or (2) the "enzyme electrode" principle where the chemical undergoes catalytic reaction in the membrane to produce or consume species that can be quantitated at the electrode. The phenomena involved are complex, including: transport, both in the membrane and in the external solution; heterogeneous catalysis in the case of the enzyme electrodes; and electrochemical processes.

A rotated disc electrode on which a membrane could be mounted would offer some unique advantages for characterization of transport in membranes, for sensor development, and for study of related electrochemical phenomena. With such an electrode, a well-defined transport regime could be established that would be analogous to that of the classical rotated disc electrode in which the disc surface is uniformly accessible to reactant and the diffusion boundary layer thickness precisely defined. At low rotation rates, the diffusion boundary layer would be relatively large, so that transport through solution would be a major contribution to total diffusional resistance. Under such conditions, the current would be proportional to the square root of rotation rate. At high rotation rates, however, the resistance of the solution would be negligible, making the diffusion current independent of rotation rate and determined by the properties of the membrane.

In this communication, we will describe some preliminary experiments with membrane-covered, rotated disc electrodes. We will report studies with two electrode configurations: (1) the working and reference electrodes mounted behind a hydrophilic membrane, and (2) the working reference and counter electrodes mounted behind hydrophilic or hydrophobic membranes. We will demonstrate the use of these electrode systems to evaluate transport of simple solutes in well-studied model membranes.

11.8 MATHEMATICAL SIMULATION OF AXISYMMETRIC BIOLOGICAL LIQUIDS

A.M. Shcherbakov, M.J. Neginski, I.V. Shirko, V.M. Zaiko
Institute of Transplantion of Organs and Tissues
Moscow 123436, U.S.S.R.

A numerical method of quasi-stationary axisymmetric isothermal flow of viscous-plastic-elastic media with a complex rheology described by the following rheological relationship is presented:

$$\epsilon_{ij} = \Psi_1 \cdot S_{ij} + \Psi_2 \cdot \dot{S}_{ij} \quad (1)$$

$$\sigma = K \cdot (1 - \rho / \rho_o) \quad (2)$$

where ϵ_{ij} is a tensor deviator of deformation velocities, S_{ij} is a deviator of a stress tensor, Ψ_1, Ψ_2 are scalar functions of the invariants of the above tensors, $\dot{S}_{ij}$ is time derivative of components of a stress deviation tensor in convective transport, expressing pure deformation which is not influenced by the rotation of the vicinity of a material point as a rigid body.

The numerical method is a modification of a stationary one of the flows. The method permits one to consider the flow of media in axisymmetric channels with boundaries as well as the forces acting upon the channel walls.

As an example, the problem of peristaltic movement of such a medium in a cylindrical channel is considered.

Plotted are stress and velocity fields for different kinds of functions Ψ_1 and Ψ_2.

The method involved can be used for the investigation of conformity of different rheological models with experimental data.

11.9 MATHEMATICAL SIMULATION OF THE MOTION OF A CATHETER IN A VASCULAR CHANNEL

I. V. Shirko
Institute of Transplantation of Organs and Tissues
Moscow 123436, USSR

A problem of the motion of a catheter or a zond (probe) in a vascular channel consists of determining the external forces to be applied to an originally rectilinear rod for it to assume tha given shape of the vascular channel.

On the basis of Kirchgof-Love's hypotheses a system of differential equation defining strained and deformed states of a special curved rod of a circular or ring cross section is derived. Mechanical properties of the catheter material are supposed to be described by the following equation:

$$\sigma_{ij} = \Psi . \varepsilon_{ij} + \phi . \varepsilon_{ij} \qquad (1)$$

where σ_{ij} , ε_{ij} are stress and strain tensors, respectively, ψ and ϕ , are known invariant functions of the above tensors. The dot stands for the differentiation with respect to time or some other parameter defining the course of the process.

The results obtained permit one to define the deformations of the catheter when passing through a vascular channel, the forces acting upon vascular walls the changes,of these quantities with time during a prolonged catheter passing in a vascular channel and the feasible residual catheter deformations etc. As an example, the problem of a catheter deformation for the case when a vascular channel has a special spiral shape is solved.

11.10 PULSATILE BLOOD FLOW WITH COUPLE STRESS THEORY

P. Chaturani and V. S. Upadhya
Mathematics Department
Indian Institute of Technology, Bombay 400 076 INDIA

A new method has been developed for the study of the pulsatile flow of couple stress fluid (blood) through circular tubes. The first, second and third approximation solutions for flow velocity v, wall shear, flow rate Q and relative viscosity η_r have been obtained in closed form in terms of couple stress parameters $\overline{\alpha}$ and $\overline{\eta}$, pulsatile Reynolds number α, phase ϕ and time factor nt. The second approximation solution correspond to the steady state solution [1]. From the analytic solution, up to third approximation, it is observed that pressure gradient and other flow variables (v, Q etc.) are not in phase. The numerical computations of these solutions, shown through figures, show that the contribution from third approximation solution is small, in particular is very small, for small values of $\overline{\alpha}(\alpha=1)$ which is pertinent to blood flow. Hence, it is concluded that the flow variables are almost in phase with pressure gradient like Bugliarello and Sevilla [2]. A method has been suggested to determine experimentally the value of pulsatile Reynolds number for blood. The variation of flow variables and relative viscosity with $\overline{\alpha}$, $\overline{\eta}$, α, and ηt has been shown graphically and discussed. The obtained results are compared with the other theoretical and experimental results and are in good agreement.

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11.11 MATHEMATICAL MODEL OF THE BLOOD FLOW IN THE ARTIFICIAL VENTRICLE CAVITY DURING DIASTOLE

V. M. Shumakov and V. M. Zaiko
Institute of Transplantation of Organs and Tissues
Moscow 123436, USSR

A mathematical model of blood flow in an artificial ventricle working on hydraulic drive of an ideal incompressible fluid is proposed. The model is based on the following assumptions: blood is considered as a viscous homogeneous Newton incompressible fluid; the ventricle membrane and the entry valve have the rotation symmetry. Then the blood flow is described by the three-dimensional Navier-Stokes system of equations with the rotation symmetry:

$$\frac{\partial w}{\partial t} + \frac{\partial}{\partial z}(v_\tau w) + \frac{1}{\tau}\frac{\partial}{\partial z}(v_z w) = \frac{1}{Re}\Delta_{\tau,z}\, w \qquad (1)$$

$$\frac{1}{\tau}\frac{\partial^2 \psi}{\partial z^2} + \frac{\partial}{\partial z}\left(\frac{1}{\tau}\frac{\partial \psi}{\partial z}\right) = -w \qquad (2)$$

$$\text{with } v_z = -\frac{1}{\tau}\frac{\partial \psi}{\partial z}\ ;\quad v_z = \frac{1}{\tau}\frac{\partial \psi}{\partial \tau}\ ;\quad w = \frac{\partial v_z}{\partial z} - \frac{\partial v_z}{\partial \tau} \qquad (3)$$

v_z, v_τ - axial and radial components of linear blood flow rate; ψ , w - flow and rotor functions; Re- the Reynolds number. The boundary conditions for the system (1,2) are taken on the surfaces of the membrane and the entry valve of the artificial heart.

The uniform rectangular network was introduced in the domain of calculation and the derivatives of the system (1,2) were approximated by the second order of accuracy directed differences. Curved boundaries were replaced by piece-wise straight lines with links parallel to coordinate axes. For the approximation of the system (1,2) the effective implicit scheme of variable directions was used. The solution of the difference equations was obtained by means of implicit domains method.

Distributions of pressures, viscous tensions, blood flow rates and different integral working characteristics of artificial heart ventricle provided by model allow evaluation to what degree constructions of membrane or entry valve fulfil the requirement of minimal deviations of values of local gradients of pressures and viscous tensions from their physiological normal values.

12.1 RHEOLOGICAL EQUATIONS FOR WHOLE HUMAN BLOOD

C.R. Huang

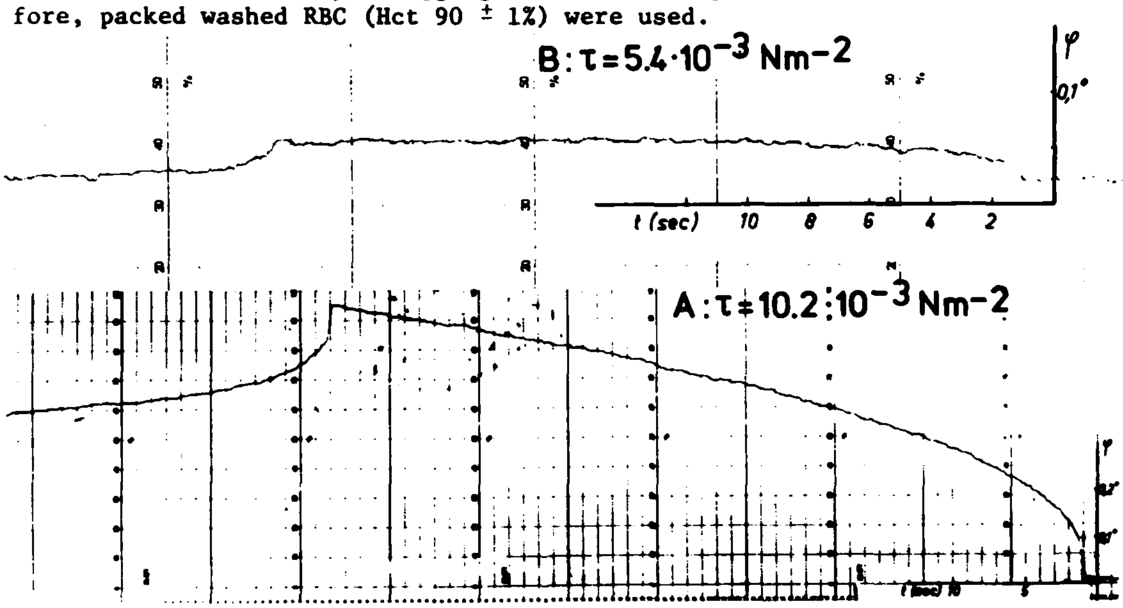
Department of Chemical Engineering and Chemistry
New Jersey Institute of Technology
Newark, N. J. 07102

The documental investigation of the flow of blood dated back to 1835, when Poiseuille observed the blood flow through capillaries obeying Newton's law of viscosity. This one parameter rheological equation was used to represent the rheological behavior of blood, and blood was considered as a Newtonian fluid. With the advancement of precision viscometer, it was found that the apparent viscosity of blood varies with the rate of shear. Because of this new finding, more life scientists and engineers are attracted to the area of hemorheology. In the early sixties, Merrill and co-workers employed Casson's equation to represent this shear rate dependency of blood viscosity. The limitation of this two parameter equation is that it can be applied in a region of shear rates less than 10 reciprocal seconds. In 1972 Huang and co-workers reported the measurement of a hysteresis loop and a torque-decay curve of whole human blood from a modified Weissenberg Rheogoniometer. This finding verified that blood is a thixotropic fluid whose apparent viscosity is shear rate dependent as well as time dependent. Huang, et al, introduced a thixotropic equation in 1974 to represent the hysteresis loop and the torque-decay curve of a blood sample. The equation was derived from a mathematical model based on the progressive breakdown and formation of rouleaux. It was found later that the five thixotropic parameters of the equation can be used to characterize the chemical and physical properties of blood samples beyond their rheological properties. In 1977, Huang and Fabisiak reported at the International Symposium on Biorheology in New York that this thixotropic equation can be used to represent both the thixotropic behavior and the steady state shear rate dependency of viscosity of blood with a wide range of shear rates. The next phase of our research on hemorheology will emphasize on the application of our findings. The following are some of the topics under investigation currently: (1) The establishment of the range of thixotropic parameters of blood from apparently healthy human subjects. (2) Correlation of thixotropic parameters and other clinical tests of blood of middle age men with high risk factors of cardiovascular disorders. (3) The altered rheological properties of blood during cardiopulmonary bypass.

12.2 YIELD STRESS MEASUREMENTS IN RED CELL SUSPENSIONS

H. Kiesewetter, G. Kotitschke, H. Schmid-Schönbein
Department of Physiology
Melatenerstr. 211, RWTH Aachen
Fed. Rep. Germany

Whether or not blood possesses a yield shear stress is still a matter of debate. Most workers using rotational rheometers employing preselected shear rates (γ), have measured shear stresses (τ); from their computation of apparent viscosities (η_{app}) they have denied the existence of a yield shear stress of whole blood. Red cell aggregates, the cause of structural viscosity and thixotropy of whole blood, clearly exhibit elastic properties when subjected to microrheological tests. Recently, an instrument has become available (DEER-rheometer, J.J.DEER, 2 Chessington Close, West Ewell, Surrey 01-3933659, England) in which preselected τ (0-2.8 Nm^{-2}) is applied, γ is derived from the measured rotational speed (rad/s). The instrument incorporates a FERRARIS motor (torque proportional to voltage irrespective of rotational speed), air-bearing and guardring. A yield shear stress (τ_y) is not seen in blood at normal Hct, but does exist when Hct $>$ 55%: despite $\tau < 10^{-3}$ Nm^{-2}, $\gamma \to 0$, $\eta_{app} \to \infty$. τ_y showed strong interindividual variability depending on hematocrit, tendency to aggregation, blood lipid status, etc. Therefore, packed washed RBC (Hct 90 $\pm$ 1%) were used.



Typical registrations of ϕ (t) for τ = 5.4 and 10.2 x 10^{-3} Nm^{-2} are seen above: (1) $d\phi/dt$ is initially high and decays to a finite value (A) or to zero (B). (2) Upon sudden removal of τ, a typical elastic recoil is seen. Observation of the same samples in a "rheoscope" suggest that the initial high shear rate is caused by a rearrangement and orientation of the RBC, following which flow is achieved by a gliding and tanktreading motion of red cells that remain oriented. When the shear stress is removed, the cells resume irregular shapes; we assume that this rearrangement is the cause of the elastic recoil found in the sample.

12.3 LOW SHEAR RATE VISCOSITY OF FRESH BLOOD

A. Downs,* M. Litt and R.E. Kron
University of Pennsylvania
Philadelphia, Pennsylvania 19104

The viscosity of fresh blood of normal subjects has been measured at shear rates below 5 sec^{-1}. Viscosity was measured using a ramp function variable flow capillary viscometer which gives a continuous measure of viscosity versus shear rate on a single 3 ml sample. A complete viscosity shear rate curve can be obtained within 15 seconds, and the run completed in less than one minute from venipuncture. Multiple repeats on the sample can be made at 15 second intervals.

Blood samples were collected daily on three successive days from healthy young adults. Fresh blood samples were tested, followed immediately by EDTA anticoagulated samples of the same blood. The range of hematocrits measured was from 32 to 55. It was found that the viscosity-hematocrit relations for both fresh and anticoagulated blood were both linear on a semilog plot but of significantly different slope. It was also found that the daily variations in viscosity for some individuals could be as great as 30%, although in most individuals day to day variation of fresh blood viscosity was not significant.

*Present address: Stauffer Chemical Company
Visalia, California 93277

12.4 RHEOLOGICAL HYSTERESIS OF BLOOD AT LOW SHEAR RATE

M. Bureau, J.C. Healy, D. Bourgoin and M. Joly
Laboratoire de Biophysique
Faculté de Médecine Pitié-Salpêtrière
Paris, France
and
Laboratoire de Biorhéologie
Faculté de Médecine
Strasbourg, France

A Couette type servo-controlled microviscometer associated with a low frequency generator modulating the rotational speed of the viscometer outer cylinder (1) has been used to plot the rheological hysteresis curves of blood (2). It has been shown that the shape of these curves largely depends on the values of the parameters α and t_m characterizing the linear variation of the rate of shear with time (3): $\dot{\gamma} = \alpha t$ for $0 < t < t_m$ and $\dot{\gamma} = \alpha(2t_m - t)$ for $t_m < t < 2t_m$. Two sets of α and t_m have been selected in order to obtain rheograms showing preferentially the viscoelastic or the thixotropic behavior of blood (4). This technique is used to compare normal human bloods with bloods submitted to various physical or chemical treatments, or with different pathological bloods. Some interpretations are proposed from considerations on changes in the deformability or aggregability of blood cells.

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ACKNOWLEDGEMENT

This work was supported by the following contracts: INSERM No. 73.1.438.17 and DGRST No. 74.7.0953.

12.5 MATHEMATICAL ANALYSIS OF THE HYSTERESIS RHEOGRAM OF HUMAN BLOOD

W. Fabisiak and C. R. Huang*
Department of Chemical Engineering
Manhattan College
Riverdale, New York 10471

and

*Department of Chemical Engineering and Chemistry
New Jersey Institute of Technology
Newark, New Jersey 07102

Human blood is a thixotropic fluid whose apparent viscosity is a function of the shear rate and the duration of shear. One of the most important characteristics of human blood is that its rheogram of shear stress versus shear rate exhibits a hysteresis loop. This hysteresis loop is obtained from a plot of shear stress vs. shear rate in which the shear rate is steadily and linearly increased to a maximum value, and then immediately decreased at the same rate toward zero. Recently, hysteresis loop analysis has been used to characterize the thixotropic behavior of human blood. In this communication, we obtain an analytical solution of the Navier-Stokes equation for the case of a hysteresis loop having a time-dependent boundary condition for the shear rate using a Couette geometry. Analysis of the solution shows that it is possible for a Newtonian fluid to exhibit a hysteresis loop under certain experimental conditions. The size and shape of the hysteresis loop generated by a Newtonian fluid was found to be controlled by a dimensionless group. From this analysis, we are able to determine the real hysteresis loop for human blood. Our analysis can also be used to detect and eliminate presence of artificial hysteresis loops generated by Newtonian fluids.

12.6 RHEOLOGICAL MODELING OF FRESH BLOOD FROM TRANSIENT FLOW MEASUREMENTS

G. Yepsen, D. Boutin and M. Litt
University of Pennsylvania
Philadelphia, Pennsylvania 19104

A methodology has been developed capable of rheologically modeling fresh blood at low shear rates. The technique consists of analyzing the transient response of a capillary-fluid system when subjected to a step function input in the flow rate. The flow rates used corresponded to maximum shear rates of 5 sec^{-1} or less. The procedure requires solution of the first-order step response equation for the capillary flow of a suitable model fluid, such as a power law or Casson fluid. The theoretical response is fit to step response data for a fresh blood sample by non-linear regression and the optimum fluid model parameters are found.

Data were obtained using a 0.12 cm diameter capillary 35 cm long. Transient pressure was monitored using a variable reluctance membrane differential transducer whose compliance was such as to give first-order time constants for the system of 0.15 to 0.6 seconds over a viscosity range from 5 to 20 centipoise. This yields a short data acquisition time (actual step response $<$ 3 seconds) and, combined with small sample size (4 ml), makes this methodology ideal for rheometric determinations on fresh blood in a clinical environment.

As a first model, the power law, $\tau = K\dot{\gamma}^n$, was chosen. The model parameters, K and n, were shown to be sensitive to physiological variables such as the presence of anticoagulants, hematocrit, fibrinogen levels and red cell deformability. Anticoagulants (dry EDTA) significantly depressed the parameter K relative to the fresh blood value. The coefficient K was found to be a linear function of hematocrit, while n was only weakly dependent on hematocrit. On the other hand, the exponent n was influenced by red cell-red cell interactions, changing significantly with fibrinogen levels (which control aggregability) and with red cell deformability. The whole blood viscosity calculated using experimentally determined power law parameters correlated very well with the viscosity found from steady state pressure vs. flow data. The step response technique is easily adaptable to other fluid models, including those with a yield stress, such as the Casson model.

12.7 THE MECHANICAL TRANSFER FUNCTION OF BLOOD: MODIFICATIONS BY SOME BIOLOGICAL FACTORS

B. Obrecht*, P. Rusch**, J. C. Healy**
*Laboratoire de Mécanique des Fluides
Université Louis Pasteur
Strasbourg, France
and
**Laboratoire de Biorhéologie
Faculté de Médecine
Strasbourg, France

The static rheological properties of blood can be obtained by many methods, but the complex structure of this system can be studied really only by dynamic methods. In a Couette geometry, we have devised an instrument which can apply a pseudo-random shear motion superimposed on a steady rotation. The input signal is therefore a superposition of a pseudo random shear rate and a steady shear rate. The output signal is the shear stress obtained on-line through a servo-controlled device. A fourier transformation is made on these signals. The algebraic quotient of the Fourier transforms of the input and output signals is the transfer function of the sample. This transfer function depends on the mean shear rate. Many results can be presented: the real and complex parts of the transfer function, the modulus and phase versus frequencies, and so on. The frequencies used in this study lie in the range between zero and 20 Hz. The dependence of the transfer functions on some factors (hematocrit, temperature, aggregability and deformability of erythrocytes...) allow us to correlate the transfer function to the structure of the blood. For example, very important modifications of this function are obtained when the cells form rouleaux. The experimental data are shown, and some theoretical diagnostic and therapeutic consequences are discussed.

12.8 INFLUENCE OF THE VARIOUS PLASMA SUBSTITUTES UPON THE RHEOLOGICAL PROPERTIES OF BLOOD IN TRANSIENT FLOW. COMPARISON WITH ALBUMINE

S. Gaillard, A. Larcan and J. F. Stoltz
Groupe d'Hémorhéologie
Centre de Transfusion et d'Hématologie
Brabois et Service de Réanimation
C.H.U. 54000 Nancy, France

After proposing a viscoelastic model to represent the behavior of normal blood in transient flow at low shear rates

$$(\tau + a \; d\tau/dt = b \; (\dot{\gamma} + c \; d\dot{\gamma}/dt) \qquad (1)$$

where b represents the apparent viscosity at the established rate, and a and c represent parameters corresponding to the relaxation time of the shear stress (at zero rate) and of the shear rates (at zero tension)[1] the authors studied the modifications induced by the main plasma substitutes used in France (Dextran 80, Dextran 40, Subtosan, Haemacel, Plasmion, human albumine, fluid gelatins, polyvinylpyrolidone) under the same in vitro conditions. The study was carried out in transient flow for various values of the shear rate. The recording of graphs [τ=f(t)] was carried out with a coaxial cylinders micro-viscometer. Each substitute was studied after adding blood taken from EDTA, adapted to an hematocrit at 40% and to a final concentration at 25%. The results prove that the apparent viscosity in established regime is significantly modified at low shear values for all the substitutes. It is highly increased for the Dextran 80 and reduced for the Dextran 40. The study in transient flow reveals important modifications of the graphs τ=f(t), obtained for normal blood: increase in the response for certain substitutes (Dextran 80), suppression of the viscoelastic behavior by Dextran 40. Concerning the parameters a and c of the equation (1), an increase compared with normal values is generally noticed, which shows an increase in the relaxation time of the shear stress due to a network of "rouleaux", which is more difficult to dissociate. On the contrary, albumime which produces the dispersion of "rouleaux" induces a decrease of the values a and c at low shear rates inferior to 3 sec^{-1}.

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ACKNOWLEDGMENT

This work was supported by D.R.M.E Grant 76.34.14600.480.75.01.

13.1 FLOW FACTORS IN ATHEROSCLEROSIS

Margot R. Roach
Departments of Biophysics and Medicine
University of Western Ontario
London, Ontario, Canada

The localized nature of atherosclerotic lesions can be explained only by the presence of local differences in the arterial wall, or by local differences in the flow field there. In general, aortic lesions in rabbit are distal to the orifices except for those around coronary orifices which encircle the orifice. Large lesions tend to occur beyond large branches, and the lesions grow steadily if the animal is left on a high cholesterol diet. The location of the lesions can be changed by modifying the flow either into the branch, or approaching the branch. The first change appears to be in the endothelial cells, and the next, the passage of lipid into the wall. Raised lesions alter the flow, and secondary deposits occur in areas where eddies shed from the first lesion may reattach to the wall. We require much more detailed maps of the exact three-dimensional shape and location of the relation of these lesions to branch points, before realistic mathematical and/or physical models can be devised to determine what flow factor is involved.

ACKNOWLEDGMENT

This research is supported by the Ontario Heart Foundation.

13.2 INTERACTION OF BLOOD PRESSURE AND FLOW WITH THE ARTERIAL WALL

C. G. Caro
Physiological Flow Studies Unit, Imperial College
London, England

Consideration of the literature reveals scope for further work on the interaction of arterial mechanics and mass transport, with account being taken of the detailed structure and ultrastructure of the artery wall. A prime requirement is a suitable experimental preparation. An artery perfused *in situ* has the advantages over one *in vivo* that the fluid mechanics can be controlled and over a perfused excised artery that its endothelium and adventitial connections can be intact and that it can be studied at normal luminal hydrostatic pressure when stresses in the wall and pressures in the vasa vasorum can be physiological. In order to separate the effects of luminal hydrostatic pressure on vessel dimensions and mass transport arteries have been prevented from expanding by external restraint, but this approach is subject to the criticism that the wall tends to be compressed. Observations at luminal hydrostatic pressures just above atmospheric have revealed high curvature regions in arteries *in situ* with extensive corrugation of the inner lamellae of the wall, severe deformation and possible loss of related endothelial cells and changes in wall permeability.

13.3

EFFECTS OF OSCILLATORY STRAIN ON MACROMOLECULAR UPTAKE BY ARTERY WALL

S. Chien, S. Usami, K.-M. Jan, S. Weinbaum and C.G. Caro
Columbia Univ. College of Physicians and Surgeons
New York, New York 10032
City College of New York, CUNY
New York, New York 10031
and
The Imperial College of Science and Technology
London SW 7, England

The uptake of ^{125}I-albumin by isolated segments of canine common carotid arteries was studied in vitro with a technique modified from that described by Caro and Nerem(1). The artery was cannulated from both ends with stainless steel tubings fixed to a splint to avoid alterations in vessel geometry when the segment was removed from the pentobarbitalized dog. After mounting the isolated segment on a rig in a 37°C bath, the splint was removed and the lumen was filled with autologous serum containing ^{125}I-albumin. Sinusoidal variation in vessel length by 4% (100% to 96% in vivo length peak-to-peak) was achieved by the use of a motor-cam system with frequency ranging from 1 to 10 Hz. Control arterial segments were prepared in the same manner, but not subjected to oscillation. Fifteen minutes following the serum introduction, the oscillation was stopped. The contents of the oscillated and control segments were rinsed with 0.9% NaCl. After fixation with glutaraldehyde, segments were used for ^{125}I counting and diameter measurement.

^{125}I uptake was calculated from the ratio of ^{125}I activity per unit weight of artery to that per unit volume of serum. The ratio of uptake between the oscillated and control segments was not significantly different from 1.0 at frequencies of 1 and 2 Hz, but it increased significantly to 1.4 at 5 and 10 Hz.

These results can be compared with our theoretical model on the enhancement of endothelial vesicle transport by periodic mechanical disturbances(2). According to the theory, in order to obtain a ratio of transport between the oscillated and control conditions of 1.4, the ratio of free versus attached vesicles should equal 0.4.

Oscillatory variations in vessel length at 5 and 10 Hz caused also an increase in the apparent luminal circumference to 1.3 times that of control arteries. Therefore, the increase in albumin uptake by oscillation may result in part from an increase of the area available for macromolecular transport.

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ACKNOWLEDGMENTS

Supported by USPHS Grant HL 19454 and NSF Grant ENG 75-19243

13.4 FLOW SEPARATION AND VORTEX FORMATION IN BLOOD VESSEL MODELS

Katsuyori Kikuchi, Takehiko Azuma and Takayoshi Fukushima
Department of Physiology, Shinshu University Medical School,
Matsumoto, Japan

The purpose of the present study is to obtain greater understanding of the local disturbances in flow due to stenotic change of blood vessel lumen. Three kinds of straight cylindrical tubes were used as the models of normal and morbid blood vessels ; i.e. a tube with no distortion of the lumen, tubes with an axisymmetric constriction, and tubes with a protuberance protruded from one wall of the tube. Water was substituted for blood. Patterns of flow were visualized and filmed by one of the following three methods : the dye injection method, aluminium dust method, and hydrogen bubble method. At Reynolds numbers above the critical value, vortices were formed at the distal end of the wake, shed downstream in succession, and broken down into turbulence. The steady flow pattern around the protuberance was very comlicated. A vortex tube called the horseshoe vortex was formed in front of the protuberance. It passed round the front of the obstacle in both directions and led to a vortex pair trailing downstream. The stream adjacent to the bottom wall stagnated just before the top of the horseshoe vortex. Then it was divided into two flows which passed around the front and side of the vortex tube in both directions. The divided streams were rolled inside the separated region, curled into the existing wake eddies, and passed downstream. These flow patterns changed entirely as the steady flow was switched over to the pulsatile flow. During the accelerating phase, the stream brought into collision with the converging surface of the axisymmetric constriction was pressed toward the tube wall and wake vortex was formed just behind the constriction. During the subsequent decelerating phase, the wake vortex curled up toward the tube axis while growing rapidly in size. Then it was shed downstream as a vortex ring which in turn broke down into turbulence immediately. In steady flow, turbulence occurred at much higher Reynolds number than in the pulsatile. During the accelerating phase, a pair of wake vortices and the horseshoe vortex were formed behind and in front of the protuberance, respectively. During the subsequent decelerating phase, the wake vortices grew up rapidly as the stream past the protuberance was rolled inside the separated region. At the same time, the stream near the opposite wall of the tube separated from the surface to form another vortex. Immediately, these vortices were broken down into turbulence. The contraction and expansion of the horseshoe vortex were repeated periodically. The flow behavior of blood in the major central arteries has so far been conjectured from the knowledge obtained by experiments on steady flow. The present study revealed that the conjecture was invalid.

13.5 TURBULENCE GENERATION IN STENOTIC BLOOD VESSEL MODELS

Takehiko Azuma and Takayoshi Fukushima
Department of Physiology, Shishu University
Medical School, Matsumoto, Japan

Abnormal hemodynamic forces related to distortions of blood vessel lumen have been thought to play an important role in the pathogenesis of focal vascular lesions such as atherosclerosis, mural thrombus and poststenotic dilatation. The purpose of the present study is to investigate the structure of turbulence generated in steady and pulsatile flows past moderate stenoses and to elucidate the possible roles of the turbulence in the development of focal vascular lesions. Metacrylate tubes with an axisymmetric constriction of varying degrees were utilized as the models of stenotic arteries. A downstream position from the constriction along the flow axis was expressed in a dimensionless value relative to the length of the constriction. The range of Reynolds number (Re) used in experiments with steady flow was between 500 and 5000. In experiments with pulsatile flow, the instantaneous mean velocity (U) was given by $U = \bar{U} - \tilde{U} \cos\omega t$, where $\bar{U}$ was the mean velocity of steady flow component, $\tilde{U}$ was the amplitude of oscillatory component and ω was the angular frequency of oscillation. Similarity parameters were set as follows: $\bar{R}e$=1200, 1500 and 1800; $\beta = \tilde{U}/\bar{U} = 1.0$; $\alpha = R\sqrt{\omega/\nu} = 22$, where R and ν stood for the tube radius and the kinematic viscosity of the fluid. Velocity measurements were made by the use of a hot-film anemometer, the output of which was led to a real time spectrum analyser with a digital integrator. Turbulence observed in steady flow past a stenosis was generated by shedding and breakdown of the vortices formed in a shear layer produced by flow separation just behind the constriction. The vortices were shed with a certain fixed wave length which was specific to each model. The strength of the turbulence was dependent upon Reynolds number and the degree of constriction. The station at which the strongest turbulence was observed was far downstream from the constriction, e.g. at position 6 in the tube with the most mild stenosis and at position 4 in the model with the narrowest constriction. In pulsatile flow, large vortices were formed in the separated region near the constriction with the progress of acceleration. The vortices were shed and broken down into turbulence in the succeeding decelerating phase. The station of the maximum turbulence was much closer to constriction than that in steady flow, i.e. at position 2 in every one of the models. In both the steady and pulsatile flows, the generated turbulences were damped out at short distance downstream from the stations, indicating localized nature of the disturbance produced by moderate stenoses. Measurements were also performed of the spatial distribution of turbulent intensity across the tubes.

13.6

HUMAN BLOOD CELLS IN MODELS OF STENOSES AND BIFURCATIONS

Takeshi Karino and Harry L. Goldsmith
McGill University Medical Clinic, Montreal General Hospital, Montreal, Canada

This work is concerned with the behavior and interactions of human blood cells and model particles in flow through idealized models of stenoses and bifurcations. It is motivated by an interest in sites of flow disturbance in arteries where atherosclerotic lesions develop and platelet thrombi are deposited onto the wall. In a model of a stenosis consisting of an abrupt concentric expansion of a 150 into a 500 μm glass tube we have already shown the formation of an annular vortex, migration of single cells out of it, trapping of large aggregates, and formation and growth of platelet thrombi in the vortex (1,2). More recently, the role of fluid mechanical factors on the initial wall adhesion of platelets in the vortex was studied. A larger expansion consisting of a 0.92 mm into a 3.00 mm tube coated with collagen fibers was used. Suspensions of washed platelets containing red cells flowed through for 1 to 3 min at Reynolds numbers Re between 28 and 113, after which the adhering platelets were fixed, stained and counted under a microscope. In steady flow, there was a pronounced peak in platelet number density N in the vortex followed by a local minimum at the reattachment point and a smaller second peak just downstream, after which N asymptoted to a constant value. At Re = 38, N increased 6× as the hematocrit increased from 0 to 40%. With increasing Re, both primary and secondary peaks decreased in value, while the local minimum remained and the asymptotic N was almost constant.

The localization of platelet adhesion may be explained by considering the transport of platelets to and from the wall along radially directed streamlines in the vortex and downstream of the reattachment point. To test the validity of this hypothesis in other flow situations, T-bifurcations of 3 mm glass tubes were constructed. Prior to measuring platelet adhesion, the streamlines were mapped out using latex sphere suspensions with one of the daughter tubes partially occluded to facilitate vortex formation in the bifurcation. The existence of paired spiral secondary flow patterns and complex vortices on either side of the common median plane of parent and daughter tubes was demonstrated. Pronounced radial flow of suspended particles toward the tube wall was observed around the carina and the reattachment points of the vortices.

It appears therefore, that a vortex region can provide favorable conditions for the genesis, growth and trapping of platelet aggregates as well as for an enhanced adhesion of cells to the vessel wall.

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13.7 FLOW DISTURBANCE AT BRANCHING SITES IN THE ABDOMINAL AORTA

Takayoshi Fukushima, Katsuyori Kikuchi and Takehiko Azuma
Department of Physiology, Shinshu University Medical School,
Matsumoto, Japan

In order to explore the significance of hemodynamic factors in atherogenesis, model studies were carried out on flow patterns and velocity distributions in the median cross-section of the abdominal aorta which had been known as the favored site for the development of atherosclerotic plaques. Flow patterns of water through a glass model of the abdominal aorta were visualized by means of the dye injection method. Velocity measurements were made by the use of a hot-film anemometer. Flow parameters and corossectional area ratios between branch vessels and the main trunk were made close to those in the abdominal aorta. A dye streak entered into each daughter vessel curled round on itself and formed a vortex pair trailing downstream. No flow separation was observed at the outer wall of the vessel at its branching site. The secondary flow generated in a dauter vessel affected the flow in the main trunk as if there had existed a hydrodynamic sink associated with vortex region at the site corresponding to the orifice of the vessel, thereby leading to the formation of complicated flow patterns in the main trunk. Regions of high and low wall shear were anticipated to appear around the orifice: a region of high wall shear in the proximal portion and that of low wall shear in the both sides as a result of the sink-vortex flow. Flow supply to the daughter vessels corresponding to the celiac and superior mesentric arteries made the flow in the main trunk separate from the posterior wall and form a separated region between the wall and a vortex tube connecting the orifices of the daughter vessels corresponding to the bilateral renal arteries. A part of the posterior wall facing to the vortex tube would be subjected to a high adverse shearing stress. Turbulence due to the vortex tube was given rise to in the adjacent downstream segment of the main trunk. The results of the velocity measurements by the hot-film anemometer coincided well with those of the flow visualization experiments. A steep velocity gradient thus generated gave rise to a high shearing stress at the wall. In the adjoining segment extending from the first to the last branchings, wall shear stresses would be generally high at the anterior wall. Excepting the area opposite to the vortex tube mentioned above, they would be commonly low at the posterior wall where the separation of flow took place. A few flow visualization experiments were also carried out by using pulsatile flow. Vortices similar in appearance to those observed in stenotic blood vessel models were generated at every pulsation at the outer wall of each daughter vessel. The separated region at the posterior wall of the main trunk was not as stable as that in the steady flow.

13.8 Role of Stress Concentration in Arterial Walls in Atherogenesis

Hideyuki Niimi

National Cardiovascular Center, Research Institute
Suita, Osaka, Japan

It is well known that atherosclerotic plaques are prone to develop at arterial branchings. Although a number of hemodynamic theories on atherogenesis have been presented, the localizing factor seems to remain unclear yet. The purpose of this paper is to elucidate a local phenomenon of high stress concentration at the intimal surface in the branched segment and to propose the wall stress concnetration in the arterial branching as an important localizing factor of atherosclerosis.

The arterial wall may be stretched or deformed in branching more easily than other portions because there does not exist any elastic medium to resist blood pressure and axial tetherings. Nonuniform stress and deformation in the neighborhood of branching are demonstrated, using a simple model of branching, that is an infinitely large plate of homogeneous, isotropic, Hookean wall with a circular hole. Stress and deformation in more realistic branched vessels are analyzed on basis of "thin shell theory" in solid mechanics. It is shown that there exists, at the intimal surface of branching, high stress concentration which depends on its branching specification. In views of wall stress, arterial branchings may be considered to be locally under hypertension in such a sense that their walls are subjected to high tension with large stress pulsation.

Although the mechanism of formation of atherosclerosis is very complicated, the transport of substances in blood across the arterial wall will certainly play an important role. As it is shown experimentally by Fry and others, and theoretically by Oka, the permeability of arterial wall is enhanced by mechanical disturbances such as wall stress, stretch or pulsatile strain. Our predicted high stress concentration at the intimal surface may work to increase the permeability of arterial wall. It is concluded that high stress concentration in arterial branchings is responsible for the predilection of atherosclerosis. Our conclusion is supported by the common knowledge that chronic hypertension may accelerate the progress of atherosclerosis.

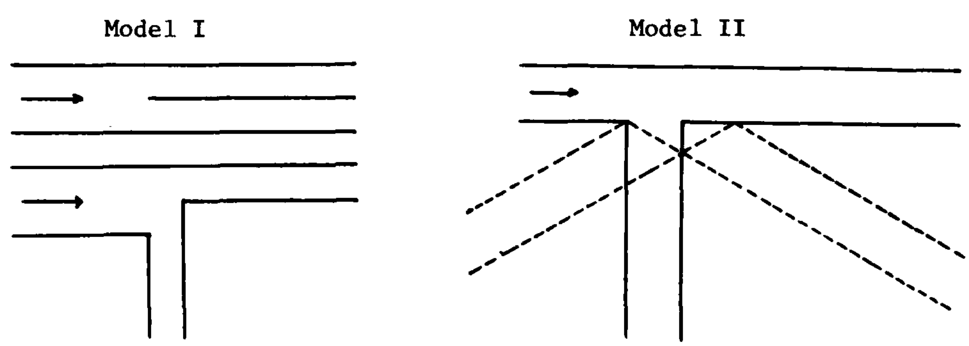
13.9 NUMERICAL STUDY ON BIFURCATING FLOW IN A BLOOD VESSEL

M. Kawaguti and A. Hamano
Department of Physics
Keio University
4-1-1, Hiyoshi, Kohoku-ku
Yokohama, Japan

As is well known, vascular lesion appears usually downstream of constricted portion (post-stenotic dilatation), in the neighborhood of a branch, in the region whose curvature is very large (e.g. aortic arch) and so on. But its origin has not been conclusively elucidated, in spite of many theoretical and experimental studies. The present series of numerical study is aimed at searching for the origin of vascular lesion from the hydrodynamic point of view. Concerning the post-stenotic dilatation, the authors studied numerically the two-dimensional pulsatile flow through constricted artery, and suggested strongly that the hydrodynamic cause of endothelial lesion of artery and of post-stenotic dilatation can be found in the large temporal variation of shearing stress behind a constricted portion of artery.

Now, the two-dimensional model of blood flow in an artery with branch was studied numerically. Steady flows of a viscous fluid through a branch were investigated for various parameters (width of branched flow, angle of bifurcation, Reynolds number, ratio of flow quantities downstream of bifurcation), as preliminary study of pulsatile flow in a bifurcation.

Concerning the width of branched flow, two models were studied: in Model I, width of branched flow is a half of that of upstream flow, and it is equal to that of upstream in Model II (cf. Fig.). For Model I, angles of bifurcation are selected at 0°, 90°, but they are 30°, 90° and 150° for Model II. Reynolds number range is 32~64. The ratio of flow quantities downstream of birfurcation is chosen as 1:1 or 7:13.



14.1 THE ROLE OF BLOOD CELLULAR ELEMENTS AS DETERMINANTS OF APPARENT VISCOSITY IN THE MICROCIRCULATION

H. H. Lipowsky, S. Usami and S. Chien
Dept. of Physiology, Columbia University
New York, N.Y. 10032

Simultaneous measurements of pressure drops, red cell velocities, microvessel dimensions and optical density were performed *in situ* in single unbranched arterioles of the mesentery (cat), to delineate the rheological behavior of blood as a function of hematocrit and leukocyte-endothelium adhesion. These techniques (detailed previously (1)) permitted computation of apparent viscosity, η, defined as that value required to satisfy Poiseuille's equation. Intravascular hematocrit, H_{micro}, was determined from on-line measurement of optical density using an *in vitro* calibration (2). Leukocyte-endothelium adhesion was monitored by video tape during the experiment.

Apparent viscosities were obtained in six arterioles, D = 24-47 μm, as microvessel hematocrit was reduced by systemic hemodilution, and grouped together for trend analysis. During these measurements, wall shear rate remained high, as reflected by values of the computed Newtonian wall shear rate. No leukocyte adhesion to the endothelium was observed at these shear rates. The resulting trend of η vs H_{micro} was established over a range of $2.0\% \leq H_{micro} \leq 24\%$, and represented by linear regression as $\eta = 1.39cP + 0.066H_{micro}$. At the maximum H_{micro} observed (24%) η equalled 3.97cP. In comparison, *in vitro* determinations of η by Couette viscometry at $\gamma > 200\ sec^{-1}$ yielded a regression of $\eta = 1.24cP + 0.045H$. While the 12% greater *in vivo* plasma viscosity (extrapolated value) is not statistically significant, the 27.5% (greater *in vivo* value of η at $H_{micro} = 24\%$ is significant ($P < 0.5$). This disparity is attributed to geometric irregularities of the microvessel lumen and deviations from a circular cross-section. To illuminate the effect of white cell-endothelium adhesion on *in vivo* viscosity, arteriolar flow rates were reduced by systemic hemorrhage. Adhesion of leukocytes attendant to the reduced shear rates resulted in higher computed values of η (dependent on diameter).

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ACKNOWLEDGEMENTS

Supported by USPHS Research Grant HL 16851 and NRSA HL 07114.

14.2 THE INTERACTION OF WHITE AND RED BLOOD CELLS IN CAPILLARY AND POSTCAPILLARY VESSELS

G.W. Schmid-Schoenbein, S. Usami, S. Chien

Dept. Physiology, Coll. Physicians & Surgeons, Columbia U.

New York, NY 10032

In capillaries the velocity of white cells is lower than that of red cells. This is mostly due to the larger volume and less deformable cytoplasm in the white cells. Observation of single file capillary blood flow in the rabbit ear-chamber by means of high speed microcinephotography shows that upstream of a white cell the red cells accumulate to high hematocrits, whereas a cell-depleted region is formed downstream. When the white cell flows into a postcapillary venule with increased diameter (about 9-15 μm) the red cells upstream overtake the white cell. At that instant the white cell is displaced close to the endothelium. It reduces significantly its axial velocity and begins rolling along the endothelium. All leukocytes make attachments to the endothelium of postcapillary venules after this interaction with the red cells.

To study in detail the hydrodynamic interaction of red and white cells a large scale model of capillary blood flow was built based on the principle of geometric and dynamic similarities. A capillary and postcapillary venule were simulated with a straight tube and a diverging cylindrical cone, the white cells by rigid spheres (sphere/tube diameter: $\lambda = 0.82$, and 0.63), the red cells by flexible pellets ($\lambda = 0.69$ and 0.79; thickness/ diameter $\simeq 0.2$), and the plasma by a Newtonian oil. Measurements of mean velocity, the cell axial and rotational velocities and displacements were obtained. The results show that pellets do not pass the spheres in a straight tube, but they always pass in the cone at a larger tube diameter. At the instant the first pellet passes, the sphere is displaced radially (in the sense of cylindrical coordinates) very close to the tube wall and remains in the same radial position afterwards. These model experiments extend the *in vivo* observations and provide a system for quantitation of the interaction between the spherical leukocytes and discoid red cells.

The interaction of white and red cells in postcapillary vessels forms a mechanism for systematic displacement of leukocytes from the vessel center to close proximity of the endothelium so that adhesion can occur. The ensuing attachment of white cells to the endothelium is the first step towards the emigration across the endothelium and into the interstitium.

Supported by USPHS, NIH GRANT HL-16851

14.3 MICROCIRCULATION BY MODEL MATERIAL

Ryuji Takaki and Kazuo Yasuzumi
Tokyo University of Agriculture and technology
Fuchu-shi, Tokyo 183, Japan

The purpose of this paper is to show that an observation of a microscopic flow of the latex suspension is a powerful method in order to understand behaviors of the blood especially in the micro-circulation. In the experiment latex particles with diameter 0.3 microns were suspended in a electrolyte solution with pH 9, the volume concentration of which was about 20 %. This fluid was put in a closed cell made of plate glass with sizes 2x2 cm and a spacer with thickness 10 microns. A flow inside the cell was made by deforming the plate glass and was observed through optical microscope. The particles have a tendency to form agglomerations just like the blood if the shear rate of the flow is weak.

The figure below shows a flow (from top-right to down-left) around a bubble with diameter 40 microns, which has entered occasionally into the cell. A triangular clear region is seen to appear at the rear stagnation point on the bubble surface. Particles are rare inside it, but the solvent was observed to flow quite slowly to the downstream direction. The area of this region increased as the flow around the bubble decreased.

The area is considered to be related to the size of the agglomerations because each agglomeration moves along a streamline around the bubble which is apart from it by more than the radius of the agglomeration. Hence, from measurement of this area one can obtain *directly* an average size of agglomerations of suspended particles, and also a dependence of this size upon the shear rate of the flow.

This phenomenon has an analogy with those in the microcirculation such as the plasma-skimming. The technics of observation will be applied also to fundamental sciences such as chemical engineering or liquid state physics.

This work was supported by the Grant-in-Aid for Specified Reseach from the Ministry of Education.

14.4 HEMATOCRIT DISTRIBUTION IN MICROVASCULATURE

R. T. Yen and Y. C. Fung
University of California, San Diego
La Jolla, California 92093

In vivo blood flow in microvasculature is characterized by non-uniform distribution of hematocrit (volume fraction of red blood cells in whole blood) in capillary blood vessels. The question is "why"?

We suspect that the reason for this phenomenon is each red cell must move as an integral body, and not just as a part of a homogeneous fluid. The crucial region for this individuality to reveal itself is the entrance region of each capillary blood vessel. If a capillary is joined to an arteriole, or to another capillary, the point of junction (or bifurcation) is the entrance region. At such a junction a red cell is subject to forces which tend to pull it into the branching capillary, and also to forces which pushes it along the main channel. The balance of these forces decides to which side the cell goes.

To explore this point of view in detail, we constructed two kinematically and dynamically similar models for testing. Blood is simulated with disk shaped gelatin pellets (3.2 mm dia, 1 mm thick) in silicone fluid (100 cp). In one model, a capillary is simulated with a cylindrical tube of square end, which is immersed in a main flow with velocity perpendicular to the tube axis. This simulates a branching capillary from an arteriole. The result shows that the ratio of the hematocrit in the tube to that in the main flow, H_T/H_F, depends on the velocity ratio U_F/U_T, and the diameter ratio D_c/D_T, (subscripts F = feed or main flow, T = tube, c = cell). The smooth muscle action at the junction thus controls the flow and the hematocrit.

In another model, a cylindrical tube is bifurcated into two equal daughter branches. The hematocrits in the two branches are measured while the flow rates in the branches are varied. The results show that the hematocrit ratio depends on the difference in velocities of flow in the daughter branches. For velocity ratios smaller than a certain critical value, we obtain

$$\frac{H_1}{H_2} - 1 = a\left(\frac{v_1}{v_2} - 1\right)$$

where v_1, v_2 and H_1, H_2 denotes the cell velocities and tube hematocrits in branches 1 and 2 resp. "a" is a constant depending on D_c/D_T, the shape and rigidity of the cell, and H_F. For velocity ratios beyond a critical value, nearly all cells flow into the faster branch. The smaller the feeding tube hematocrit is, the smaller is the critical velocity ratio at which this phenomenon occurs.

14.5 THE INTERACTION BETWEEN OXYGEN TENSION LEVELS AND THE FLOW OF SICKLE-CELL BLOOD IN THE CAPILLARIES

S.A. Berger
University of California, Berkeley
and
W.S. King
The RAND Corporation

Sickle cell disease appears to be a disease whose profound clinical symptomology is primarily a manifestation of abnormal events occuring in the microcirculation, and more particularly, mainly in the capillaries. In this study we look at some aspects of the flow of sickle cell disease blood in the capillaries in an attempt to elucidate some of the mechanisms at work at this level and the interplay among them. One of our aims is to understand the origin of the stasis (of red cells) in the capillaries, which in its less acute manifestation occurs to some extent all of the time, leading to localized tissue death, and when more pronounced leads to intense pain and greater disability and tissue damage. In the literature of sickle cell disease the so-called viscous cycle plays a prominent role in explaining stasis. Underlying the explanation is the well-known fact that blood from patients with sickle cell anemia exhibits an increase in viscosity at oxygen levels that lie within the physiological range, or, more particularly, at oxygen levels that are found in the capillary bed. This can lead to the following scenario. As such blood flows through the capillaries and releases oxygen its oxygen tension decreases, leading to an increase in viscosity, this in turn leads to a decrease in velocity, allowing more time for oxygen release, a further decrease in oxygen tension, a resulting further increase in viscosity and so on, the ultimate result being possibly a static mass of sickled cell blocking the circulation. Two principal differences between sickle and normal blood are that the former has a lower hematocrit (about half as high) and an oxyhemoglobin dissociation curve shifted significantly rightward. Although both of these can be regarded as compensating mechanisms working against stasis, the extent to which they can prevail against the oxygen tension-viscosity effect is not clear. To this end we have analyzed the coupled problem of blood flow and oxygen transport in a capillary using the Krogh model. Lubrication theory is used to provide a relationship between the velocity of red cells and their membrance compliance. With an assumed relationship between this compliance and oxygen tension, the oxygen convection-diffusion equation, including production and destruction terms, is solved to determine oxygen tension levels in the capillary, and these are compared to the case for normal blood. The results show that if the pressure drop across the capillary is maintained at normal levels that oxygen tension levels remain fairly high, but, because of the non-linear relationship between cell velocity and pressure drop predicted by lubrication theory, moderate decreases in the latter can cause very large decreases in cell velocity, leading possibly to stasis.

ACKNOWLEDGEMENT

This work was supported by NIH Grant 5-R01-HL16580;03

14.6 ERYTHROCYTE MOTION THROUGH A NARROW CAPILLARY CONSTRICTED BY SURROUNDING TISSUE PRESSURE FROM OPTIC DISC EDEMA IN ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Samuel E. Moskowitz
The Hebrew University, Graduate School of Applied Science and Technology, Division of Applied Mathematics, Jerusalem, Israel

The posterior ciliary arteries supply blood to the optic nerve head through a communicating network of capillaries. A sudden elevation in intraocular pressure relative to differential perfusion pressure in the posterior ciliary arteries can produce anterior ischemic optic neuropathy (1), a group of systemic disorders including infarction of the optic nerve head with accompanying visual loss. The exact mechanics of the ocular disorder are unknown, but it appears that tissue pressure from optic disc edema constricts the capillaries in the prelaminar region, the most anterior portion of the optic nerve head where nerve fibers arranged in bundles are separated by trabeculae of glial tissue which also support the capillaries.

The purpose of this investigation was to develop a mathematical model by which to determine pressure, velocity and gap profile relationships in a constricted narrow capillary through which erythrocytes pass in single file. Data on pressure differential and erythrocyte velocity in a single unbranched microvessel in the mesentery of the cat (2) were utilized to determine the resistance parameter (3,4) and whole blood apparent viscosity.

It is shown that the resistance within a capillary increases significantly under moderate levels of tissue pressure, of the order of elevated intraocular pressure encountered in clinical practice, if available estimates of wall elasticity (5) are used, with marked reduction in velocity.

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14.7 BLOOD FLOWS IN CURVED CAPILLARY GLASS TUBES

Ting-Cheng Hung, Tin-Kan Hung, and George Bugliarello
University of Houston, University of Pittsburgh, and
Polytechnic Institute of New York

This study extends the knowledge of in vitro behavior of human blood by focusing on the effects of orientation and curvature of glass capillaries on peripheral resistance, peripheral plasma layer (PPL), and velocity profiles. Starting with a symmetric velocity profile (on the diametric plane) in an upstream straight segment, the peak erythrocyte velocity in a 90^{o} curve of the tube is found to occur in the inner wall region--in agreement with the characteristics of creeping flow in a coiled tube or in a two-dimensional curved channel. The degree of asymmetry of the mean erythrocyte velocity profile increases with curvature and hematocrit. At a 40% hematocrit the thickness of the peripheral plasma layer adjacent to the outer region of the diametric plane is about 20% larger than that adjacent to the inner wall. At lower hematocrits (20% and 10%), the outer layer thickness is about 10% larger than the inner one. The thickness is controlled largely by the curvature effect. In the straight segment immediately downstream of the curve, the peak velocity shifts toward the outer region. Gravitational effects on the velocity profile in the curved segment are generally small compared with the curvature effects. The resistance coefficient for a downward flow in a straight capillary tube is about 18% smaller than that for an upward flow. An additional 10% increase was found for curved capillary tubes with a 6.8 ratio of radius of curvature to tube diameter. The reduction of hematocrit of blood flowing in capillary tubes (the Fåhraeus effect) is stronger for blood in small capillary tubes than for rigid sphere suspension when the particle to tube diameter ratio is larger than 0.05. An opposite trend occurs when this ratio is smaller than 0.05. An approximately linear relationship was found between the relative peripheral layer thickness and the relative particle size. The qualitative similarities between Bugliarello and Hayden's in vitro observations in 1963 and the in vivo observations by Block in 1962 give us no reason to believe that the in vivo effects of curvature and gravity would not result in a similar behavior as we observed in this study.

14.8 PULSATILE BLOOD FLOW IN ARTERIOLE OF FROG WEB

M.Horimoto, T.Koyama, H.Mishina and T.Asakura

The Research Institute of Applied Electricity, Hokkaido University, Sapporo, JAPAN

The velocity profile of blood flow in the arteriole has never been studied in relation with cardiac events. To measure the pulsatile velocity profile, a method was introduced, which enabled obtaining a pulsatile velocity contour in a small probing area of the arteriole. The method enabled a comparison of the blood flow property with Newtonian fluid.

Blood flow velocity was measured in the arteriole of anesthetized frog web by means of a laser Doppler microscope. The obtained velocity signals were transmitted via time-sharing circuit triggered with R-wave of ECG. They were time-shared for sequential 60 msec time intervals after R-wave and separately stored in 16 memory-channels of the computer system. The sampling was repeated during 10 minutes over a number of cardiac cycles to produce 16 independent velocity-appearance frequency histograms for each time interval. Mean value of each histogram and its arrangement in the time sequence, which visualized the pulsatile velocity contour, were readily made by a selection of the programs of the computer system.

The measurements were made at the central, median and marginal portions of the arterioles. Pulsatile blood flow corresponding to the cardiac cycle was observed in all of the examined arterioles whose diameter ranged from 35 to 90 μm. The flow velocity decreased gradually after R-wave, attaining the minimum value at the time of 132 ± 94 msec after R-wave, then turned to increase sharply and reached the maximum at 471 ± 162 msec after R-wave. Thereafter, the velocity decreased slowly, returning to the initial value. In the central portion of the arteriole the maximum and minimum velocity and the difference between them were 5.52 ± 1.39, 4.64 ± 1.15 and 0.89 ± 0.34 mm/sec on an average, respectively.

Since the laser Doppler method summarized and averaged the virtual velocities prevailing in the probing area as mentioned by Baker and Wayland on the double-slit method, an effort was made to find a virtual velocity contour from the obtained contours by a repetition of a trial and error numerical calculation and constructed sets of velocity profiles changing with cardiac cycle. To estimate the velocity profile of Newtonian fluid flowing through a vessel of a comparable diameter, a pressure gradient curve was obtained from the center line velocity contour and put into a simplified Navier-Stokes equation. The virtual velocity profile was found to show a little more blunt configuration than parabola over the whole cardiac cycle. Furthermore, the pulsatile amplitude of the virtual flow velocity was larger than that of Newtonian fluid. These results suggested that the property of the pulsatile blood flow in the frog arteriole was somewhat different from that of Newtonian fluid.

14.9 BASIC HYDRODYNAMIC RESISTANCE BEHAVIOUR OF ERYTHROCYTE SUSPENSIONS IN CAPILLARIES FROM 5-7 μm DIAMETER

P. S. Lingard
Children's Medical Research Foundation
Crown Street, Sydney, New South Wales, 2010, Australia

Methods: A Capillary Pore Rheometer was designed embodying a pump providing precise (4% abs., 1% setting) speed control in the range 0.02-1 mm/sec. This drives erythrocyte (RBC) suspensions through a resistance element across which pressure drop is measured to $\pm$ 0.04 mmH_2O. The resistance elements are either Nuclepore filters (pore diam: 5 & 7 μm; length: 12-13 μm) or Glass Capillary Arrays (GCAs: pore diam. 5 μm; length: 500 μm). Suspensions were made in buffered (pH: 7.4) isotonic albumin-containing media after removing microclots and white blood cells which cause obstruction of the capillary pores. The prepared suspensions flow freely and continuously through both resistance elements without obstruction at greater than 60% haematocrit. Pressure drop - velocity data were collected both sequentially and reversibly in continuous flow experiments with velocity as independent variable.

Results: Pressure drop - velocity relations for Newtonian media are straight lines passing through the coordinate origin indicating constant resistance determined by the fluid viscosity. Both Nuclepore filter and GCA pore diameters calculated from Poiseuille's law agree within 2% of the micrometer measurement, showing that entrance losses are small or negligible. RBC suspensions of haematocrit 20-80% give unusual two-limbed linear pressure drop-velocity relations. The low velocity limb passes through the origin of coordinates, but abruptly changes slope at a velocity beyond which the second linear zone begins. Projected back, the second zone produces a finite pressure drop intercept. The hydrodynamic resistance is thus a constant maximum below the critical velocity and decreases as one-upon-velocity beyond. Relative resistance increases significantly with haematocrit; maxima of 4.7 and 2.5 being found at haematocrit 40% for Nuclepore filters and GCAs, respectively of pore diameter 5 μm. At 0.4 mm/sec effective pressure gradients for Nuclepore filters and GCAs are about 54 and 14 cmH_2O/mm length, respectively: comparable to micropuncture estimates from living capillaries.

Conclusions: The constant resistance, apparently hydrodynamic, "cushioning" at low velocities has no comparison in blood flow theory. It suggests an elastic state of quasi-relaxation of the sliding, squashed-up cells. The one-upon-velocity behaviour is predictable from the large-scale bowing model of Fitz-Gerald for elastic cell distortion by hydrodynamic forces. Similar results were obtained recently by Zarda et al. using finite element theory. Hence erythrocyte mechanical properties, especially membrane bending resistance, may play an important role in governing resistance to red cell movement in the capillaries.

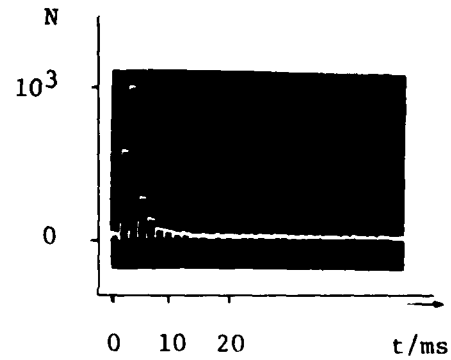
15.1 METHOD TO DETERMINE THE DEFORMABILITY (PORE PASSAGE TIME) OF SINGLE ERYTHROCYTES

K. Mussler, H. Kiesewetter and H. Schmid-Schönbein
Abteilung Physiologie, Medizin.-Theoret. Institute der RWTH
D-5100 Aachen, West Germany

Pathological Red Blood Cells Rigidity (RBC) has been claimed crucial in the pathophysiology of a number of clinical conditions. Most methods available to date to assess the "deformability" of RBC utilize shear stresses of approx. 50 N/m^2 and provide an integrative information (an average value) for a given population, not a statistical analysis of single cell behavior.

Based on the method of Schlick and Schmid-Schönbein (1), an apparatus has been developed to determine the "deformability" of single erythrocytes from a RBC suspension in albumin-containing phosphate-buffered isotonic saline. The passage time of a single RBC through a single pore (diameter approx. 4 μm, length 10-40 μm) at shear stresses as low as 1 N/m^2 is measured optoelectronically as a function of variable driving pressures. A special flow cell was constructed to mount the pores. The actual pores have been realized by submitting a sheet of polypropylene 10-40 μm thick to bombardment with heavy ions, followed by the subsequent etching of the obtained channel (Gesellschaft fur Schwerionenforschung, Darmstadt, W. Germany). The pressure gradient necessary to drive the cells through the pore is achieved by means of a newly developed system allowing its simultaneous adjustment and measurement. During the passage of a RBC through the pore, the resulting change of light transmission in the projection of the pore is measured with an optoelectronic device. The signals are processed with a multichannel analyzer connected to a computer and displayed as histograms of passage time distribution. The signal is thereby normalized with respect to its height during the cell passage through the pore. The obtained frequency distribution is compared to a standard distribution obtained empirically with cells from normal blood, in order to detect eventual abnormalities. In addition to this frequency distribution curve, an average pore passage time is also computed. A typical normal histogram is presented on Figure 1.

When comparing the pore passage times of erythrocytes from patients with different disorders (including recent cerebral ischemic attacks) to those in normal controls a significant increase was found ($p < 0.025$).



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15.2 DEFORMATION OF A RED BLOOD CELL IN A SIMPLE SHEAR FLOW II. EXPERIMENTAL STUDY WITH OPTICAL METHODS

J. F. Stoltz, J. C. Ravey, M. Guillot and P. Mazeron
Groupe d'hémorhéologie - Centre Régional de Transfusion -
Brabois - 54500 - Vandoeuvre-lès-Nancy - France

Recently a new technique based upon light diffraction was proposed by Bessis and Mohandas[1] to evaluate red blood cell (rbc) deformability. It consists in sending a laser beam through a (rbc) suspension, subjected to a shear flow, and observing the diffraction spectra of the beam. So far, the interpretation of the corresponding diffraction spectra is rather qualitative.

This paper attempts to present a quantitative interpretation of those spectra by taking into account both the mechanical and physical phenomena involved. The mechanics of the suspension is described by a theoretical model, recently developed [2] in the case of sphered cells. This model predicts that the cell assumes an ellipsoidal shape whose axes are oriented with respect to the streamlines.

Using those results, we evaluate the small angle light scattering by an ellipsoidal particle. The orientation is given by the mechanical model. The refraction index of the internal hemoglobin solution is assumed to be known. An approximation similar to that used in optical physics is used rather than the Rayleigh-Gan Debye theory. It consists in computing the electromagnetic field on the surface by applying locally Fresnel's laws. The theoretical scattering patterns must be compared to those calculated from Mie's theory, and also to those obtained experimentally.

Simultaneously we have undertaken an experimental study of those phenomena. Two viscometric systems are used. The first one, similar to the ektacytometer, [1] consists in a Couette device. The second one consists in two counter-rotating parallel discs. In the former system, it is possible to observe diffraction spectra, by changing the incidence angle of the laser beam. Furthermore a direct observation of the cells in the stationary plane by high speed microcinematography is considered.

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Acknowledgement: Research supported by C.N.R.S. ATP 25.82

15.3 DEFORMATION OF A RED BLOOD CELL IN A SIMPLE SHEAR FLOW: I. THEORETICAL STUDY, CASE OF A SPHERED CELL

D. Barthes-Biesel,* and B. Guerlet**
*UTC, BP 233, 60206 Compiègne France
**Groupe d'hémorhéologie, CRTS 54000 Nancy, France

The behavior of a red blood cell (r.b.c) freely suspended in a linear shear flow is presently used by many authors (1,2) as a means to evaluate its deformability. One of the drawbacks of the experimental results is that the cell is observed from one direction only, and that it is difficult to distinguish between a change in the orientation of the cell and a change in its deformation. We present here a simple mathematical model where the deformation and the orientation can both be expressed exactly in terms of the relevant physical parameters. This model is valid for the particular case where the cell is sphered but it gives qualitative information on the respective influence of orientation and deformation in the general case.

The r.b.c. is modeled as a thin spherical elastic membrane enclosing a newtonian viscous fluid (the hemoglobin solution). It should be noted that this model differs from the liquid droplet model because of the nature of the interface, and from the elastic sphere model because of the behavior of the cell contents. The cell is freely suspended in a simple shear flow. Its motion is described by Stoke's equations inside and outside the cell. On the deformed surface of the membrane, we require continuity of velocities and equilibrium of viscous and elastic forces. Since this problem is highly non-linear, a regular perturbation solution is sought in the limiting case where the deviation from sphericity is small. In order to assess the role of the internal viscosity on the motion, it is necessary to compute at least the first two terms of the expansion. This leads in particular to a regular perturbation expansion of the non-linear theory of membrane shells up to second order terms.

Consequently we obtain an explicit expression for the deformation and orientation of the cell as a function of the shear rate, the elastic coefficients of the membrane, the ratio of internal to external viscosities. In particular, it appears that the very viscous cells orient at nearly 45° to the streamlines, whereas the less viscous cells are more parallel to the streamlines. Finally the tanktreading motion of the membrane around the hemoglobin contents, is predicted by the model. It is shown to be a consequence of a solid body rotation superimposed upon a constant elastic deformation. The expression obtained for the rate of rotation of the membrane is in good agreement with experimental measurements of Fischer and Schmid-Schonbein (3). (Research supported by CNRS, ATP 2609).

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15.4 APPARENT ELASTIC CONSTANT AND ADHESIVENESS OF RED CELLS FROM CALF, DOG AND HUMAN

L.W. Shen, T.C. Hung, and N.H.C. Hwang
Institute for Cardiovascular Studies
University of Houston, Houston, Texas

Understanding of the behaviors of blood elements under shearing stress is important to the evaluation of artificial organs using animal models. In this study an in vitro experiment is employed to compare the mechanical properties of erythrocyte membranes for dog, calf and human. The experimental procedures follow those developed by Hochmuth et al in 1973. Venous blood, drawn and collected in heparinized vacutainers, was centrifuged at 3000 rpm. The red blood cells were washed twice in phosphate-buffered saline (PBS), and were resuspended, at a hematocrit of 0.3%, in 0.1% dextrose PBS. The suspension of red cells was introduced into a rectangular channel (10 mm. wide, 0.12 mm. deep, and 40 mm. long) for RBC settling onto the bottom glass plate. A steady flow of cell free suspending medium was then produced in the channel. For shear stress less than 20 dynes/cm^2, two deformed shapes were studied for comparing the membrane distensibility and adhesiveness among the red cells of dog, calf and human. For cells stretched by the flow to a tongue shape with a line attachment onto the bottom plate, the membrane extension ratio of calf's RBC is about 40% larger than that of dog's RBC when the shear stress is below 7.5 dynes/cm^2. Another 40% increase in the extension ratio is seen for the human red cell. The apparent elastic constant of red cell membrane calculated from the theory of Hochmuth et al for calf, dog and human are found to be 0.025, 0.0443 and 0.0245 dynes/cm respectively. For human red cell, this elastic constant increases rapidly when shear is greater than 7.5 dynes/cm^2. Similar non-linear relationships between the membrane extension ratio and shear do not occur for dog and calf erythrocytes until the shear stress exceeds 12 dynes/cm^2. When RBC is deformed into a tear-drop shape due to a single point attachment onto the channel bottom, the assumption of uniform membrane stress is no longer adoptable. The extension ratio varies non-linearly with the flow induced shear even as low as 1 dyne/cm^2. To compare the adhesiveness of dog, calf and human erythrocytes, the initial rate of cell detachment was calculated from a series of experiments characterized by steady flow over a period of one minute followed by a step increase in discharge. The wall shear for a sequence of steady stream varies from 1 dyne/cm^2 to 42 dynes/cm^2. The critical shear stress needed for washing away the attached RBC from the channel bottom surface is 5 dynes/cm^2 for calf, 21 dynes/cm^2 for dog and 9.7 dynes/cm^2 for human. The addition of 0.1% bovine serum albumin into the RBC suspension reduces the aforementioned critical shear stress to 2, 3 and 5 dynes/cm^2 respectively.

15.5 APPLICATION OF CENTRIFUGAL FLEXIBILITY MEASUREMENTS TO SICKEL CELL ANEMIA ERYTHROCYTES

B. F. Cameron and P. E. Smariga
Cincinnati Comprehensive Sickle Cell Center
Cincinnati, Ohio

A method for determining erythrocyte flexibility by centrifugation has been described by Sirs (1) and applied to blood samples from normal individuals (2). This consists of spinning a blood sample in a micro-hematocrit tube in the centrifugal force region of 200-600 g, and then spinning at full speed to obtain a packed hematocrit. The initial centrifugation yields a partially packed cell mass, with the extent of packing as compared to full speed centrifugation as a function of cell flexibility. An inflexible cell will pack to a lesser proportion of its final packed volume under a short-term low-speed spin.

We have applied this methodology to sickle cell blood samples. The problems associated with this are primarily due to the fact that sickle cell samples are from anemic individuals and hence normally have hematocrits less then 35. The technique of Sirs, when extended to hematocrits below 35, yields a non-linear relationship of PPV (partial packing volume) to hematocrit. Empirically, a centrifugation protocol was determined in which PPV is linear with hematocrit over the hematocrit range 5-55. Using this protocol, 37 sickle cell patients (homozygous SS) were studied, as well as AS heterozygotes and SC double heterozygotes. The mean flexibility factor (percentage decrease in flexibility from normal controls) for 60 SS samples was -14.2, and for 14 SC patients was -13.2, with a range from about -18% to -5%. Heterozygous sickle cell trait individuals were not significantly different from normal.

Upon deoxygenation, the flexibility of SS cells decreased by approximately 20%. Thus the method does show the expected relationship to sickling.

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15.6 MATERIAL PROPERTIES OF ERYTHROCYTES IN MUSCULAR DYSTROPHY

Y.F. Missirlis and M.C. Brain
Departments of Engineering Physics and Medicine, McMaster University
Hamilton, Ontario, Canada

Erythrocytes from patients with muscular dystrophy have altered membrane lipid composition (1) and protein Kinase (PK) activity (2). PK phosphorylates spectrin, which forms a network in the cytoplasmic side of the membrane, and is thought to play a major role in the mechanical properties of the membrane. In particular the elastic properties of the membrane are an as yet undetermined function of the physical state of spectrin.

One such elastic property, the shear modulus, has been measured by the micropipette aspiration technique. In a blind study coded samples of erythrocytes from control subjects (C), patients with non-dystrophic neurological disease (NC) and from patients with the following forms of muscular dystrophy: Duchenne (DMD), Myotonic (MD), Limb Girdle (LG) and Fasioscapulohumeral (FSH) were tested, with the following results:

Diagnostic Category	No. Patients	No. Cells	Shear Modulus Mean Value (dyn/cm)	S.D. ±	P
C	21	60	0.011	0.006	-
NC	24	59	0.013	0.006	N.S.
DMD	11	39	0.030	0.008	<0.01
MC	10	21	0.019	0.010	N.S.
LG	11	32	0.028	0.018	<0.05
FSH	1	2	0.015	0.003	N.S.

These results suggest that erythrocytes from patients with DMD are significantly different from normal ones with respect to their elastic deformation at constant area. The significantly different degree of phosphorylation of spectrin in these erythrocytes (2) suggests that there may be a correlation between the phosphorylation of the protein and thus the physicochemical state of spectrin and the elastic behaviour of the whole membrane.

Furthermore the same studies were done on erythrocytes from obligatory carriers of DMD. The shear modulus was 0.023 ± 0.008 dyn/cm (N=65) and this was signifcantly different from normal but not from DMD erythrocytes. Populations of cells are currently studied with the cells being aspirated in polycarbonate filters in an effort to increase the cells/sample/time ratio.

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15.7 INFLUENCE OF PENTOXIFYLLINE ON ERYTHROCYTE FILTRABILITY AND MICRORHEOLOGY - A PHARMACOLOGICAL STUDY

C. Guillot, G. A. Marcel and J. F. Stoltz

Groupe d'hémorhéologie - Centre Régional de Transfusion -
Brabois - 54500 - Vandoeuvre-lès-Nancy - France

In addition to plasma viscosity, haematocrit and red cell aggregation, red cell deformability affects blood viscosity. A decrease in this parameter can lead to obstruction of small capillaries. The aim of this work was to study the effect of pentoxifylline [3-7 dimethyl-1 (5-OXO-hexyl)-Xantine] on red cell deformability. The deformability was approached by different methods:

- Filtration pressure of a 2% suspension of washed erythrocytes, through 5μ and 8μ filters at constant flow
- Filtration volume of whole blood through 5 μ Nuclepore filters, under negative pressures varying from 5 to 30 cm H_2O. In this case we have used a hyperosmolar model (Ionic strength 0,20 M).
- Diffraction diagrams of a laser beam crossing the gap of a coaxial cylinder viscometer allowing shear stress up to 2000 dyn/cm^2 (Bessis and Mohandas method (Blood cell 1975 , 1 : 315)). At rest the diffraction diagrams are circular, whereas when the erythrocyte is submitted to shear stress, the diagram becomes elliptical.
- As well as these measures of deformability we studied blood viscosity, erythrocyte osmotic fragility, and erythrocyte ATP levels.

Results show, for amounts of drug from 20 to 100 γ/ml and after two hours incubation:

- a decrease in filtration pressure of erythrocytes through 5μ or 8μ filters
- and increase of filtrability of erythrocyte in hyperosmolar model
- a 10 to 15% elongation of the diffraction diagram of red blood cells in hyperosmolar medium when treated cells are compared to non-treated at the same shear stress;
- a decrease in ismotic fragility and an increase in erythrocyte ATP level.

The mechanism of this effect can be achieved by improving the energy status of the red blood cell. However, the link between the increase of ATP and the increase in deformability is not certain. Incubation of red cells in hyperosmolar blood with adenosine does not normalize deformability. On the other side, pentoxifylline can normalize deformability in peripheral arterial disease where red cell ATP is depleted.

15.8 ANALYSIS OF FLOW VELOCITY BY MEANS OF FLUORESCENT ANGIOGRAPHY AND LOW LIGHT LEVEL VIDEO SYSTEM

Bernhard Endrich and Marcos Intaglietta
Department of AMES-Bioengineering
University of California, San Diego
La Jolla, California 92093

Blood vessels and blood cells are normally not accessible to light, but become exposed to light during experimental procedures for in vivo studies of microcirculatory phenomena. At the present, these effects are presumed to be negligible compared to effects of microsurgical trauma and exposure. As the "physiological condition" of the preparation is improved, it becomes desirable to maintain light levels at the minimum.

Experiments were performed in the microvasculature of adipose tissue in the hamster omentum. The image of the microcirculatory bed under observation was televised by means of a silicon intensified target tube (SIT) Camera and recorded on videotape. The preparation was epiilluminated by a vertical illuminator for fluorescence microscopy using a 50 watt mercury vapor lamp and selected filters. A collector lens directed the light to the exciter filter. A dichroic beamsplitter filter directs the light through the objective and to the preparation. Fluorescent materials in microscopic blood channels of the preparation react to excitation wave length and emit longer wave lengths. The barrier-filter passes the emitted light from the omentum preparation and blocks unwanted background illumination. Flow velocity measurements were carried out after i.v. injection of 0.4 ml of 5% FITC-Dextran 150 by means of a video photometric analyzer and on-line crosscorrelation.

In the adipose tissue, the contrast between blood cells, blood capillaries and surroundings is quite poor; the combination of optical elements and low amounts of FITC-Dextran improves the contrast of the televised image without changing macro- and microhemodynamics to such an extent that red blood cells and blood vessels are delineated as bright structures against a substantially darker background. This permits the study of practically all the blood vessels within a given field, and shows that the flow velocity in arterioles is in the order of 0.8 - 1.2 mm/sec, in midcapillaries in the range of 0.3 - 1.0 mm/sec, and reaches up to 0.7 mm/sec in venules.

Supported by Grants HL-12493 and HL-17421

15.9 A.C. ELECTROPHORESIS OF HUMAN RED BLOOD CELLS

Peter Chung-Yick Chen
AMES-Bioengineering
University of California, San Diego
La Jolla, California 92093

An A.C. micro-electrophoresis technique in the frequency range of 2-10 Hz has been developed for measuring the surface charge density of human red blood cells (RBC). Measurement of charge density is essential for identification of charged groups on the cell surface and is useful in understanding how a natural membrane is constructed.

The A.C. electrophoretic chamber is made from plexiglas with cover glass as the observation window. The flow channel has a dimension of 1.28 cm by 0.2 cm and is 0.015 cm deep. It contains two platinum wires (reference grade, 0.01 cm diameter) placed 0.125 cm apart. An A.C. field is applied across these electrodes using a function generator. Blood obtained from finger prick and diluted to 0.05% with a $NaHCO_3$ buffered normal saline is used. The amplitude of oscillation of the individual RBC at the stationary level under the A.C. field is recorded by a 16 mm movie camera mounted over a Mach-Zehnder interference microscope. A magnification of 500X is used. Mobility μ_m is calculated using the expression $\mu_m = wA/E$, where w, A, E are the angular frequency, amplitude and field strength, respectively.

The A.C. method offers several advantages over the standard D.C. method. The amplitude of oscillation can be measured over a time period inversely proportional to frequency. This will enable one to work with unstable (chemically or enzymatically attacked) cells where a quick determination of mobility is essential. With this short-time period, most of the drifting and gravity effects are minimized. Electrode polarization is also minimized. This simplifies the construction of the chamber. The electroosmotic flow profile under a frequency range of 2-10 Hz with our chamber design is found to be identical to the D.C. case. An extension of the theoretical analysis shows that with a chamber thickness of 1 mm and a frequency of 10 Hz, there is a large region in the center of the chamber where the electroosmotic velocity is almost constant. This is ideal for following large particles, because they experience some electroosmotic velocity in spite of their settling due to gravity.

With the present A.C. electrophoretic method, the mobility of RBC in normal saline is found to be 1.07 ± 0.02 µm/sec/volt/cm. This compares very well with the D.C. method (1). (The author gratefully acknowledges the guidance and encouragement of his thesis advisor, Dr. Y. C. Fung, during the course of this study. Supported by NIH Training Grant No. T32 HL-07089.)

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16.1 AN INVESTIGATION INTO THE FRACTURE MECHANICS OF CEREBRAL ARTERIES AND ANEURYSMS

A. D. Harman
Biomechanics Group, Zoology Department
University of British Columbia
Vancouver, B.C., Canada

The mechanical properties of cerebral arteries are dominated by elastin and collagen fibers, whilst the aneurysm has to depend on collagen alone to support the blood pressure. Due to its increased diameter and reduced wall thickness, the aneurysm operates at around 10 times the wall stress experienced by the artery, and is very prone to rupture catastrophically sometime in middle age. The study reported here extends classical fracture mechanics to compare the fracture energies of these two composite materials, using a modified Griffith criterion to predict critical crack lengths in both structures. Fracture energies were assessed using notched test pieces, taken at post mortem and strained uniaxially to failure in a buffered saline solution. Results show that normal cerebral arteries are, weight for weight, as tough as steel, whilst the aneurysms studied vary between 1/10 and 1/100 of this value. Both materials are extremely notch-insensitive, rounding out their pre-cut notches to give a stress concentration of 2 at the notch tip when failure occurs. Critical crack lengths at physiological stresses are tens of centimetres for cerebral arteries, and only millimetres for aneurysms. These figures are rather higher than expected, implying that the notch rounding mechanism may be impaired in vivo, where any critical defect would be introduced under load in a biaxial strain field. Further experiments on rubber models confirms this, showing that critical crack length estimates made from uniaxial tests are around 40 times too high. The discrepancy appears to be caused by formation of a transitory stress concentration at the tips of a crack introduced suddenly into a biaxially strained membrane.

16.2 ALTERATION OF RHEOLOGICAL PROPERTIES OF CANINE THORACIC AORTA IN EXPERIMENTAL HYPERTENSION

M. G. Sharma and J. P. Jacobus
Pennsylvania State University, University Park, Pennsylvania 16802

The primary objective of the investigation is to evaluate the changes in the rheological properties which occur in the canine thoracic aorta under experimental hypertension and to discuss the possible physiological mechanisms underlying the changes. To this end segments of thoracic aortas of two week, four week hypertensive and sham (control) operated animals were subjected to *in vitro* uniaxial stress relaxation experiments at various stretch ratios within the physiological range and uniaxial stress-strain experiments at various deformation rates ranging from 10 to 40 mm/min. From the experimental results the incremental relaxation modulus distribution along the whole length of hypertensive and control animals were compared. It was found that the modulus values on an average were 15 percent higher for two week hypertensive animals and 40 percent higher for four week hypertensive animals. The amount of increase in modulus was found to depend upon the location of aortic segment. Stress-strain results were found to be rate independent for both hypertensive and control animals. From these results, strain energy density distribution for the thoracic aorta was determined and found to be appreciably higher for four week hypertensive animals.

A quantitative estimation of aortic protein uptake by a fluorescent method[1] indicated that the arterial wall permeability to plasma proteins of hypertensive animals increases almost 100 percent in the upper and about 60 percent in the lower regions of the aorta. Finally, a mathematical model has been developed for correlating the observed changes in rheological properties to permeability changes in the wall accompanying hypertensive conditions.

ACKNOWLEDGEMENTS

The investigation was supported by the National Science Foundation. The protein uptake study by the fluorescent method and the induction of hypertension in dogs were performed by Dr. T. M. Hollis, Biology Department of the Pennsylvania State University.

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16.3 IDENTIFICATION OF THE RHEOLOGICAL PROPERTIES OF THE ARTERIAL WALL: PROBLEMS ARISING FROM REFLEXIONS

C. Kopp
Groupe de Biomecanique et
Institut de Mecanique des Fluides CNRS ERA 594 Strasbourg

The mechanical properties of the vascular system are closely related to the histological and macroscopic structures of walls. The filtering properties vis a vis pressure waves of arteries are determined by the wall's rheological parameters, the filling liquid being newtonian in the larger vessels involved here.

Conversely, if the behavious of the actuel filter is known by an experiment (the measure of his pressure-transfer function) on principle, the parameters of the wall may be determined by identification with those of an equivalent filter, for example those of (1).

Biotransferometric techniques indicated in (2) and related in detail in (3) have been applied to the arterial bed of human leg (4). Results obtained by external rheography (using natural cardiac-, and external stimulation), show that reflexion problems are not negligible.

To overcome this difficulty, the study of a simple model of short elastic tube of the kind described in (2) with proximal and distal reflexion sites, shows that the crude result of measurements is the pseudo transfer function

$$H(f) = \frac{H_1(f)(1 + H_3(f))}{1 + H_1^2(f) \cdot H_3(f)}$$

where $H_1(f)$ is the true transfer function of a tube segment, and $H_3(f)$ the transfer function of the downstream system. The deconvolution in the time domain resulting from the divisions in the frequency domain shows that the inverse Fourier transform of H(f) does not comply with the causality rule. Nevertheless, it is shown that the use of truncated correlation functions of input and output signals, in the case of an adapted stimulus (3), is the right way to get $H_1(f)$.

If kind and location of reflexion sites are suitably chosen it is shown that results of theoretical model, actual short elastic tube, and in vivo experiment on healthy leg are in good agreement.

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16.4 A RUBBER-LIKE PROTEIN FROM OCTOPUS ARTERIES

R. Shadwick
Department of Zoology
University of British Columbia
Vancouver, B.C., CANADA

The importance of elastin in vertebrate arteries is well known. However, this protein is not present in the invertebrates (1). Cephalopod molluscs have a well developed, closed circulatory system. Based on blood pressure profiles of the octopus (2) one would expect the aorta to function as an elastic reservoir or "Windkessel" element. To test the hypothesis that the octopus aorta has rubber-like properties and that a fibrous protein mechanically similar to elastin is present, the following study was carried out.

Pressure-volume tests on aortic segments from Octopus dofleini shows that this vessel is an elastic tube. The static circumferential wall modulus increases from about 10^4 Nm^{-2} to 10^5 Nm^{-2} over the physiological pressure range. Simusoidal inflations at 0.2 to 0.5 Hz (the resting heart rate) indicate that the dynamic modulus is several times greate~ than these static values. The aorta has a ratio of wall thickness to diameter of around 0.25. Much of the wall is muscle arranged in crossed helices with low pitch. Collagen fibres and longitudinal muscle cells are also present. In addition, there is a network of fine fibres throughout the wall that stains with aldehyde-fuchsin but not with Verhoff's elastin strain. It is presumed that these fine fibres provide the rubber-like component of the artery.

An insoluble fibrous protein was isolated from the aorta by extraction either with formic acid or with guanidine hydrochloride/ mercaptoethanol. The fibres range from 5 to 10 μm in diameter and comprise 5 per cent of the tissue dry weight. The fibres are birefringent only when stressed. Bundles of 5 to 10 fibres were tested in tension and found to be reversibly extensible up to strains of at least 0.85, with a Young's modulus of 10^6 Nm^{-2}. The amino acid composition of this protein is very different from elastin. The glycine content is low (7 per cent) as is the total hydrophobic content (37 per cent). There is no hydroxyproline, while lysine and cystine are relatively abundant (7 and 2 per cent respectively).

It has been shown that the octopus possesses arteries with elasticity based on a rubber-like protein that is not elastin. This is another example of the parallel evolution that has occurred between the Cephalopods and Vertebrates.

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16.5 ON A PROBLEM OF ARTERIES

C. Pallotti and G. Pallotti
Gruppo Nazionale per la Fisica Matematica del C.N.R.
Istituto di Fisica "A. Righi" e Istituto di
Fisiologia Veterinaria dell'Universita di Bolognà, Italy

The characteristics of the viscoelasticity of large arteries have been studied, starting from experimental tests performed by Anliker et al. studying forced oscillations in vessels of dogs; data are given.

The blood-wall system was shematized in our research through a Voigt's element and a Zener's element arranged in series. The numerical results of this investigation are reported in Table 1.

Therefore we can conclude the Young's modulus of vessels presents different values according to the different types of oscillations, with a ratio of 1:2 for radial and axial waves. Furthermore we have Young's modulus increasing with frequency, as represented in Table 1.

TABLE 1

	Young's Modulus	
Frequency in Hertz	Radial wave $dyn/cm^2 \times 10^4$	Axial wave $dyn/cm^2 \times 10^4$
20	3.10	5.92
30	6.96	13.32
40	12.38	23.69
50	19.34	37.01
60	27.86	53.30
70	37.91	72.55
80	49.52	94.77
90	62.67	119.94
100	77.38	148.09

16.6 NONLINEAR VISCOELASTIC PROPERTIES OF ARTERIES

A. G. Hudetz, E. Monos and A. G. B. Kovăch
Experimental Research Institute
Semmelweis Medical University
1082 Budapest, Üllői ut 78/a, Hungary

The aim of this study was to find stress-strain relations which can model adequately the nonlinear viscoelastic behavior of arteries with contracting smooth muscle. Main difficulties were that smooth muscle activity and material properties change rapidly in time and they are complexly affected by dynamics of loading.

Cylindrical segments of isolated canine carotid arteries were activated by norepinephrine (0.5-5.0 μg/ml) and subjected to large deformation stress-relaxation tests by rapid injection of physiological saline solution into the lumen and quasi-static inflation-deflation cycles at axial isometry. During the experiments vessels were immersed into oxygenated Krebs-Ringer buffer solution thermostated at 37°C.

Arteries behaved like materials with fading memory. Moreover their relatively stable hysteresis indicated that they are not materials of the rate type. Therefore in further analysis several simplified forms of the Green-Rivlin integral polinomial constitutive equations of simple materials with fading memory were considered. Tensorial relations were rationally reduced to scalar forms assuming cylindrical orthotropy, incompressibility and plane strain conditions.

It was found that stress-relaxation increased both in amplitude and time with increasing steps of strain. Relaxation curves could not be described by single exponential or power-law functions. Thus, relaxation functions were determined from one-step tests applying numerical methods. For satisfactory modelling of the equilibrium response at least 5 terms in the integral polinomials had to be maintained. However, a higher than 3rd order approximation resulted in unstable relaxation functions.

It is concluded that neither frequently used differential nor integral polinomial forms of constitutive equations can be applied for describing nonlinear viscoelastic properties of arteris. Instead, a constitutive equation consisting of two integral terms, each of them nonlinear in strain is suggested for identification. This model is expected to give satisfactory prediction of the viscoelastic behavior during both loading and unloading. As a following step, more sophisticated nonlinear models which reflect biological effects as well have to be developed.

16.7 STRESS-STRAIN RELATIONSHIP FOR HUMAN ARTERIES

Stoyan Stoychev
Institute of Mechanics and Biomechanics
Bulgarian Academy of Sciences, 1113 Sofia
Acad. G. Bonchev str. Bl. 8, Bulgaria

Two-dimensional static experiments are carried out on the following arteries: carotis, iliaca communis, iliaca externa, and femoralis. The experimental stress-strain relationships are determined in terms of Cauchy's stress and Almansi's strain tensor. The results obtained show that: (i) the effect of circumferential stress to axial deformation, i.e. $\sigma^2(\varepsilon_1)$ is negligibly small and $\sigma_2(\rho)$ does not depend on ε_1; (ii) the dominating relationship is $\sigma_2(\varepsilon_2)$; (iii) it is established that every blood vessel is characterized by such longitudinal deformation $-\varepsilon_1^*$, at which the axial force F does not depend on ε_2 in isometric experiments; when $\varepsilon_1 > \varepsilon_1^*$ the axial force represents an increasing function of ε_2 and when $\varepsilon_1 < \varepsilon_2$ the axial force is a decreasing function of ε_2.

On assuming the blood vessel to be a thin orthotropic and incompressible tube, the stress-strain relationship in loading procedure is analyzed by the following strain potential:

$$W = 2B\,\varepsilon_1^*\varepsilon_1 - B\varepsilon_1^{*2}(\alpha\varepsilon_2+1) + A\,\varepsilon_1^4 + B(\varepsilon_1-\varepsilon_2^*)^2\exp(\alpha\varepsilon_2)$$

$$+ C\,\{\exp[\gamma(\frac{\varepsilon_1}{2} + \varepsilon_2)] - \frac{\gamma}{2}\varepsilon_1 - \gamma\varepsilon_2 - 1\}$$

The six constants A, B, C, α, γ, ε_1^* are determined from the experimental data.

17.1 QUANTITATIVE RBC AGGREGATION DEDUCED FROM VISCOMETRY

D. Quemada
Laboratoire de Biorheologie et d'Hydrodynamique Physiologique UER Physique
Universite Paris VII, T33/34, 2 Pl. Jussieu
75005 Paris, France

OBJECTIVE - The aim of the present work is to obtain a quantitative index for RBC aggregation using viscometric methods (1).

METHOD - A relationship giving the relative viscosity η_r vs. hematocrit H and shear rate γ has been developed (2) after generalization of a newtonian viscosity equation $\eta_r = (1 - \frac{1}{2}kH)^{-2}$ (3). This generalization, based on a semi-empirical kinetic model, leads to a shear dependent intrinsic viscosity k. As a structural parameter, the latter depends on three parameters, which characterize the structure of the system. One of them is the zero shear intrinsic viscosity k_o.

Fitting the relation $\eta_r(H,\gamma)$, at fixed H, to experimental data, leads to value of the structural parameters, especially k_o which appears closely associated with RBC aggregation. If the latter does not occur under particular conditions (mainly related to the physico-chemical properties of the suspending fluid), the corresponding k value, called k_{oo} hereafter, can be taken as a reference value. Then, one can define an (overall) RBC aggregation index as $A = k_o/k_{oo}$.

RESULTS AND DISCUSSION - Fig. 1 displays the variations of A versus molar ion concentration C_m deduced from the best fit of the proposed viscosity equation on viscosity measurements performed in (1), for RBC in saline and RBC in saline +3% Dextran T70. Corresponding variations of the index of aggregation R introduced in (1) are compared in Fig. 1. This index R has been defined as the ratio $\eta_r(Dx)/\eta_r(Saline)$. Indeed, variations of R vs. C_m are strongly shear dependent and critical values of C_m (when R=1) appear independent of shear rate only below $\gamma = .3\ sec^{-1}$. On the contrary A values are by definition shear rate independent and this seems the main motive for using A instead of R as a RBC aggregation Index.

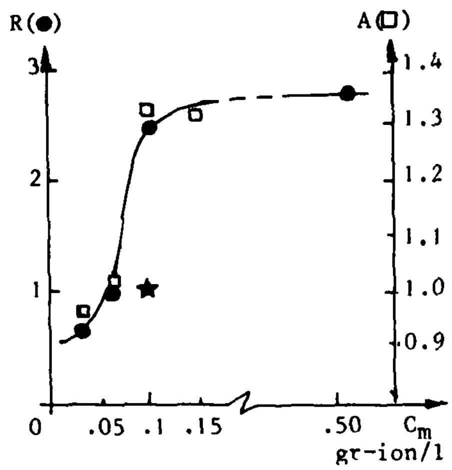

Fig. 1. Comparison of RBC - Aggregation Indexes R (from (1) and A (present work) vs. ionic strength C_m, RBC in Dextran T70 + Saline
(Control in Saline).

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17.2 A NEW LOOK AT THE ERYTHROCYTE SEDIMENTATION RATE

D. M. Stasiw, L. C. Cerny, R. Williams and M. Zongrone
Utica College and Masonic Medical Research Laboratory
Utica, New York

Several years ago, we developed an automic sedimentimeter which used an optical tracking system to follow the plasma-red cell boundary in a tube. This unit utilized a two-pen plotter to record the erythrocyte sedimentation rate (ESR). One pen continuously records the position of the liquid-solid separation boundary to provide a settling curve. The other pen is driven by a rate of change mechanism and records the first derivative on the role of change of the separation boundary with time (1). This automatic sedimenter has currently been modified:

First, it is now possible to determine the ESR and its derivative when the settling tube is at angle with the horizontal plane.

Second, the settling tube is rotated at a controlled angular velocity in both the vertical and angular positions.

Third, it is possible to use tubes up to 500 mm in length.

Data will be presented on hardened red cells, normal blood and diseased red blood cells relating the ESR to the angle of inclination of the settling tube. The effect of rotation of the tube and the tube length will also be documented.

The settling process will be discussed in terms of a semi-empirical theory for ESR (2).

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17.3 THE INFLUENCE OF NORMAL AND RIGID RED BLOOD CELLS ON SUSPENSION RHEOLOGY--VISCOMETRIC FLOWS AND INSTABILITY MEASUREMENTS

Winfred M. Phillips, Associate Professor and W. A. Daniels, Graduate Assistant, The Pennsylvania State University, 233 Hammond Building, University Park, Pennsylvania 16802.

The influence of the state and concentration of red blood cells on suspension rheology was first examined by comparing viscometric data on fixed and normal bovine erythrocytes at various hematocrits. Similar suspensions were then compared using a Couette-Taylor instability experiment in a device specially designed in our laboratory to study blood rheology. The point of instability is found to be a function of the nature of the blood suspension and is proposed as a method to evaluate constitutive models for blood. The instability of dilute polymer solutions to the Couette-Taylor flow was also examined for comparison as a viscoelastic particulate fluid.

Suspensions of fresh and fixed bovine erythrocytes were subjected to linear shear flow in both cone and plate and Couette type viscometer. The viscosity was determined as a function of cell state, hematocrit and strain rate. The suspensions of fresh red blood cells in plasma and suspensions of fresh cells in saline exhibited shear thinning behavior, reaching asymptotic values at lower strain rates for reduced hematocrits. Cells washed, fixed in glutaraldehyde by standard techniques and resuspended in saline exhibited no observable shear thinning.

The cells were introduced into the Couette-Taylor device and the inner cylinder was rotated. The torque on an isolated section of the outer cylinder was continuously monitored. The torque versus rotation rate curve is found to change slope considerably at the onset of the first Taylor instability, being linear until then. The procedure was repeated for dilute polymer solutions of varying concentrations. Critical Taylor numbers were calculated for all suspensions.

The critical Taylor number for fixed cell suspensions were found to be consistently higher than Newtonian values indicating a stabilizing influence on the flow in this particular situation. The fresh cell suspension critical Taylor numbers were below the Newtonian value indicating a destabilizing influence. Taylor numbers for the dilute polymer solutions were higher than the Newtonian value and were of comparable magnitude to those of the fixed cell suspension.

The experiment is clearly sensitive to the nature of the suspension and gives an input to the constitutive nature of the suspension. It is believed that this is the first detailed observation of the influence of blood cell state on the stability of blood suspensions and the comparison of the constitutive behavior of blood to other viscoelastic fluids.

17.4 BLOOD FLOW THROUGH COLUMNS OF RIGID SPHERES: A TISSUE-PERFUSION ANALOG

G. R. Cokelet, R. Mountain, P. Kimmet and M. Evoniuk
Department of Chemical Engineering
Montana State University
Bozeman, Montana

Benis et al. (e.g.; (1)) have interpreted vascular bed perfusion data with the Ergun equation, which includes viscous and inertial contributions to pressure drops. They concluded that inertial effects could be significant and that the failure to consider these inertial effects could be the cause of the Whittaker-Winton effect (blood viscosity determined from tissue perfusion data ("in-vivo viscometry") is about half the value found in in-vitro viscometers). Folkow and coworkers (e.g.; (2)) disagreed with Benis et al., claiming that alterations in vessel geometry during the perfusion experiments of Benis et al. invalidated their analysis. Since the Ergun equation is used to predict the flow behavior of fluids through packed beds of rigid particles, which are of a fixed flow-channel geometry, we investigated the applicability of the Ergun equation to blood flow through such columns.

Human blood was steadily pumped through packed beds of rigid spheres (sphere diameters were 123 μm and 218 μm; equivalent pore diameters were 33 μm and 56 μm) and the pressure drop-flow rate relationships determined. The data were used to see if blood flow obeyed the Ergun equation. Because of the flow conditions, inertial effects (e.g.; separated flow behind the spheres) were found to be absent.

The conventional parallel, straight tubes model, in which each tube diameter is constant along the axis (a model basis for the Ergun equation), can successfully predict the overall (macroscopic) blood flow behavior in the sense that the generalized Reynolds number-friction factor relationship is followed by blood flow through packed beds. However, microscopic behavior is not predicted; e.g.; the apparent viscosity-shear rate relationship calculated from the packed bed flow data shows viscosities (at low shear rates) which are less than those obtained from viscometric data (similar to the results of the classical Whittaker-Winton dog hindlimb perfusion experiments).

Use of a more realistic parallel tube model, in which the tube diameter varies sinusoidally with axial distance, gives predicted viscosities which are closer to the viscometric values. The predictions are very sensitive to small variations in column geometric parameters, such as fluid volume fraction. It appears that a reasonably accurate geometric model of the flow channel should be used when predicting blood flow behavior in complex flow channels from viscometric data.

Supported by Grant HL 12723 from NHLBI of the USPHS.

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17.5

EFFECTS OF RED CELL RIGIDITY AND AGGREGATION ON RESISTANCE TO FLOW

A. H. Sacks, K. W. Kirk, P. N. North, and R. Sue
Palo Alto Medical Research Foundation, Palo Alto, California

A filtration system using a motor-driven syringe with an in-line series of five porosity-matched 10μ Swank filters has been developed in which steady, reproducible flows are established at Reynolds numbers and reduced velocities which approximate those of the living microcirculation. This system yields sufficiently high driving pressures to permit accurate measurement using a slant column manometer and has been used to separate the flow resistance effects of red cell rigidity from those of red cell aggregation. By forcing samples of red cells suspended in autologous plasma and in buffered saline through the same system, each with filters in place and with filters removed, we determined the percentages of flow resistance associated with rigidity of the cell and with its tendency to form aggregates. The pressure drop in each case is defined as the difference between proximal pressures with and without filters, and the resistance due to aggregation is defined as the difference between the red cell contribution in plasma and in saline, where the contribution is the difference between the pressure drop for the suspension and that for the suspending medium.

Measurements were made on blood samples from normal male subjects at flow rates corresponding to a Reynolds number of 0.01 and a reduced velocity (velocity/pore size) of 300 sec^{-1}. All measurements were made at 40% hematocrit and 37°C. Red cells were examined microscopically to insure the absence of echinocytes and rouleaux in the saline suspensions.

The results show wide variations in the percentage of the total flow resistance which is associated with red cell aggregation (4% to 58%) and with red cell rigidity (15% to 70%), whereas the total flow resistance due to red cells varied only $\pm 15\%$ from the mean value among the normal males studied. These results would seem to indicate that attempts to improve blood flow by reducing flow resistance should not necessarily be directed toward reducing red cell aggregation but should be tailored to the individual depending upon how much of the resistance is associated with red cell aggregation and how much with red cell rigidity.

17.6 SOME BIOPHYSICAL PROPERTIES OF ARTIFICIAL AND WHOLE BLOOD MIXTURES

L.C. Cerny and D.M. Stasiw
Utica College and Masonic Medical Research Laboratory
Utica, NY

Recently, considerable success has been achieved in formulating life-sustaining perfluocarbon based artificial bloods. However, the empirical approach used to develop the appropriate formulation has almost totally ignored the study of their basic solution and flow properties. This is a two phase study providing some comprehensive data on the biophysical properties of artificial and whole blood mixtures.

In the first part, the viscosity, osmotic pressure and hemorheological behavior of the artificial bloods will be examined. The data represents the physiological ranges of shear rate, temperature and artificial blood concentrations.

In the second part, the behavior of the artificial bloods in the presence of blood components is presented. In this study, the type and magnitude of the interactions between plasma, erythrocytes, and the artificial bloods are determined using the techniques of ESR, osmotic fragility, osmotic pressure and microcalorimetry.

17.7 ON THERMAL HEMOLYSIS AND HEAT TRANSFER IN BLOOD RHEOLOGY

T. Ariman
Professor of Aerospace and Mechanical Engineering
University of Notre Dame
Notre Dame, Indiana 46556

Heat transfer is of vital medical interest in the design of blood heat exchangers of hypothermic procedures (1). Furthermore, Goldschmidt et al. (2) studied aging due to increased red cells temperature and Karle examined thermal destruction or hemolysis of erythrocytes due to high fevers. Lloyd et al. performed experiments in vitro to determine time-temperature relationships for the various morphological stages of thermal damage to red cells. Recently, the effect of heat treatment on the mechanical properties of the human erythrocyte membrane was investigated by Rakow and Hochmuth. In spite of these clinical and experimental studies the mechanism of thermal injury to red cells is still unknown and requires the investigation of heat transfer in blood including the effect of red cells.

In this paper based on a microcontinuum modeling of blood, a basic rheological theory has been developed for the investigation of heat transfer in blood. In particular, the effect of red cells on heat transfer in blood has been studied as an initial step toward the understanding of thermal hemolysis. The temperature gradient, the concentration of red cells, their spin velocity and deformation rate are treated as additional unknown variables satisfying the corresponding additional equations. Then this model is applied to the investigation of blood flow through a heated blood vessel by varying hematocrit, salinity, pH, flow rate and temperature. The temperature distribution in blood is obtained and it is concluded that there is a considerable effect of the cellular structure of blood and heat transfer. Velocity, cell rotational velocity and shear stress are determined and results are evaluated toward the understanding of thermal hemolysis.

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17.8 NON-NEWTONIAN FLOW IN TUBE - DETERMINATION OF THE SHEAR DEPENDENT APPARENT BLOOD VISCOSITY

M. Árpád and F. Kornél
Biophysical Institute, Medical University
Pécs, Hungary

The time dependence of the gravity flow of a liquid column in a tube system is determined by the liquid viscosity, density and meniscal resistance. Keeping the geometry of tube system constant, the analysis of the flow curve gives the shear stress-shear rate relationship of the fluid of known density. The principle of the computerized numerical analysis is as follows: The derivative of the natural logarithm of the flow velocity versus time function is proportionate to the actual density/viscosity quotient, and it is independent of constant forces influencing the flow (meniscal resistance). The precise registration of the flow velocity as the function of time has been solved by a photographical method based on light reflection. End effects are minimized by the applied long capillary (L=800 R) and small Reynolds number. Correction steps are built in the program for the compensation of systemic errors. The observed shear stress-shear rate function is very similar to those of measured by rotation principle methods as proposed by (1). The presented instrument allows the simultaneous measurement of 13 samples at 37°C in the shear stress range of 0.05-1.0 Pa (capillary I.D. = 0.5 mm max. liquid column height 0.2 m). The required sample volume is 0.25 ml, reproducibility is within 2% (2S.D.). The average apparent blood viscosity of 157 healthy volunteers (measured at 0.2 Pa shear stress) was found as 4.15 ± 0.54 mPa's.

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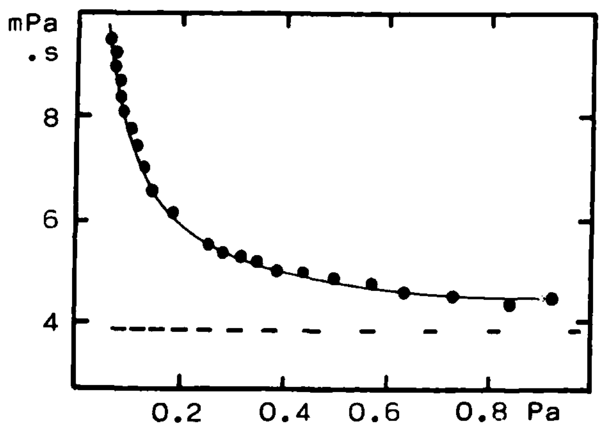

Figure: Apparent viscosity of a heparinised blood sample as a function of the shear stress (ooo), and of a 3:1 water-glycerin mixture (---). The declination of the latter is less than 2%. Continuous line: transformation of the Casson curve fitted by least squares method to the measured shear stress-shear rate plot.

18.1

RHEOLOGY OF THROMBOTIC PROCESSES OCCURRING IN FLOW: THE INTERACTION OF ERYTHROCYTES AND THROMBOCYTES

H. Schmid-Schönbein, P. Richardson, G. V. R. Born, H. Rieger
R. Forst and I. Rohling-Winkel
Department of Physiology
Rhein.-Westf. Techn. Hochschule
Aachen, West Germany

Hemostasiology in general, but also many hemorheologists, have often failed to appreciate that the vital hemostatic mechanism (primary plug formation following arterial injury) but also arterial thrombosis (wall deposition thrombus) occur in the presence of extremely high shear forces (1). Platelets are endowed with receptor-effector mechanisms that allow them to be activated instantaneously when subjected to rapid flow. As a consequence of activation, their rheological behavior is drastically changed. To study these platelet responses (e.g. activation of their contractile and secretory apparatus as an excitation in the neurophysiological sense), a number of rheological techniques were developed. Besides the "rheoscope" (2) for microscopic and the rheo-aggregometer (3) for photometric analysis of red cells, platelet and mixed suspensions subjected to controlled viscometric flow, new tube rheometers with permeable walls (Amicon^R tubes) were used. In the latter, ultrafiltrate stemming only from the marginal fluid layers are obtained and chemical agents (such as K, ADP and ^{14}C-5-HT) derived from blood cells subjected to short lasting shear forces can be measured (4). Shear exposition above 50 N/m^2 acting less than 50 msec produce ADP release from RBC and 5-HAT-release from platelets; in addition platelet phospholipids are made available. The mechanical platelet activation strongly depends on hematocrit, additional chemical stimuli, and the shear stress x shear time product.

These findings suggest that key events of thrombotic processes in areas of high flow rates might be consequence of mechanical strain of cell membranes, leading to changes in membrane permeability, transmembranal flux of species that lead to chemically activated platelets and encymatic coagulation processes that manifest themselves in regions of retarded flow.

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18.2 PHYSICAL THEORY OF PERMEABILITY OF VASCULAR WALLS IN RELATION TO ATHEROGENESIS

Syoten Oka

National Cardiovascular Center, Research Institute
Suita, Osaka, Japan

Although the mechanism of formation of atherosclerotic plaques is very complicated and has not yet been clarified, the transport of substances in blood across the arterial wall will certainly play an important role. As for the uptake of serum albumin into the endothelial surface, various experimental results have been reported recently by Fry, Carew, Nerem, Caro and others on the effects of wall shear stress, stretch, pulsatile strains, and some kinds of chemicals. It is the purpose of this paper to develop a general physical theory to explain all these experimental results based on a picture of endothelial cell junctions.

We first propose that albumin molecules pass through the junction. It is generally a slit bounded by two cell membranes in which protein molecules are embedded like a mosaic. Van der Waals bonds are formed between extruded polar groups of protein molecules on both sides of the junction. The junction is, so to speak, a two-dimensional gel. In an undisturbed state, the energy of the junction takes a minimum, that is, the attracting polar groups are as close as possible with each other. Nevertheless, albumin molecules may be transported by Brownian motion through the junction to some degree. When the junction is under mechanical disturbances, the bonds may be broken down to some degree depending upon the magnitude and duration of the mechanical disturbances. Hence, the diffusion, and consequently the permeability and the uptake, are enhanced by mechanical disturbances. Under periodic disturbances, not only the potential energy stored within the junction, but also the energy loss due to viscoelasticity of the junction should be taken into account.

Some of our results are as follows:

1) The predicted relations between the uptake and the shear stress or the stretch agree quantitatively with experiment.
2) The predicted uptake is enhanced by pulsatile flow, or vibration, or by addition of alcohol, acetone, propylene glycol, and Nembutal, or by exposure of the endothelial surface to hypotonic fluid.
3) The enhancement of the development of atherosclerosis by hypertension may be interpreted physically as a direct consequence of the increase of the circumferential tension by hypertension.

18.3 BIORHEOLOGY OF MUSCLE: A SYNTHETIC APPROACH

Tatsuo Iwazumi, University of Washington RN-10, Seattle, WA 98195

Dynamic characterization of a complex system such as biological tissue has usually been treated phenomenologically: tissues are subjected to various mechanical or other stimuli, and the responses are observed. The phenomenological characterization of muscle, however, has met with limited success so far in a sense that the characteristics ascertained under one set of conditions are hardly applicable to another set. The reason as to why it is so difficult to predict the behavior of muscle is that we still are not certain of the very physical principle on which muscle contraction works.

A theory presented here begins with a question as to what conditions must be met by a mechanism of force generation such that structural integrity of the macromolecular assembly is maintained. The importance of structural stability may be appreciated by the fact that macromolecules in muscle are flexible filaments, freely suspended in aqueous solution; yet they maintain a highly regular structure in the face of very high force and relative motion between them.

A mechanism of force generation that meets all structural stability conditions has been found. It is an electrostatic force that acts between dipole field generator and a dielectric filament. A stable structure results when dipoles are spatially arranged in such a way that the electrostatic field vector forms a helix along each dielectric filament. It has been found that there exists only one kind of spatial arrangement of dipoles to meet all stability conditions. The agreement between the theoretically synthesized structure and the ultrastructure of muscle observed by electron microscopy is striking. But more striking is the agreement between the predicted dynamic properties of this synthesized structure and observations. It explaines the peculiar viscoelastic behavior of muscle in detail. One contributing factor is electrostatic induction: a dielectric filament moving with respect to an electrostatic field experiences a force which counteracts the movement. Thus, the counteracting force is a function of the velocity and the field strength. Another factor is the steric arrangement of filament. The movement of each filament is jerky owing to the alternating stable and unstable positions: the filament jumps from one stable position to another because of the periodic arrangement of dipoles. It is possible to forcibly synchronize such filament jumping by stretching which results in responses that cannot be described adequately by viscoelastic theories.

19.1 A REVIEW OF HEMATOLOGY STUDIES ASSOCIATED WITH SPACE FLIGHT

Stephen L. Kimzey

Johnson Space Center
Houston, Texas

The most significant effect of the space flight environment relative to the blood and blood-forming tissues in man has been a consistent reduction in the circulating red blood cell mass during the flight interval. This finding was first reported during the Gemini IV, V and VII missions, and has since been a consistent observation in the Apollo, Skylab and Apollo-Soyuz flights. Similar results have been reported by Russian scientists following their Salyut missions.

It was initially proposed that the high concentration (near 100%) of oxygen in the spacecraft atmosphere was the cause of the red cell mass loss. This hypothesis was strengthened by similar observations in a chamber study utilizing a 100 percent oxygen atmosphere at a total pressure of 5 psia (identical to that of Gemini and the later portion of the Apollo flights). Studies also revealed subtle alterations in red cell membrane integrity (decreased osmotic fragility, suppression of active potassium transport, increased plasma tocopheral, decreased membrane lipid content) consistent with the concept of a mild oxygen toxicity resulting in intravascular hemolysis.

Data from the Skylab flights are not consistent with the concept of an oxygen-induced intravascular hemolysis. It would appear that some other factor characteristic of the space flight environment (weightlessness?) causes a suppression of red cell production that is not immediately relieved with a return to a normal 1-g environment, except, on longer flights, such as the 84-day Skylab 4 mission, when the red cell mass appears to begin to recover before re-entry. The variations in the magnitude of the loss in individual crewmen and the complicated postflight recovery kinetics suggest a complex relationship between the red cell mass loss and the duration of the exposure to weightlessness. This "anemia of space flight" was frequently accompanied by a reduction in plasma volume, apparently occurring early in the mission and sustained throughout the flight. Other, more subtle, effects have been observed with respect to the function and structure of red blood cells (significant changes in the distribution of red cell shapes during flight and a transient alteration in red cell specific gravity profiles postflight).

The major emphasis of this review will be to address questions relative to the regulation of blood volume during space flight and the causes of its apparent failure.

19.2 BIORHEOLOGY IN SPACE: SOME SPECULATIONS

Geoffrey V.F. Seaman
Department of Neurology
University of Oregon Health Sciences Center
Portland, Oregon 97201, USA

Analytical or preparative procedures which are adversely affected by gravity represent suitable candidates for studies in a space environment. Gravitational effects include sedimentation, bouyant convection, segregation of components by density and flows arising from the interplay of interfacial tension and density gradients. In biological systems heterogeneity in size and density increases with increasing particle size thus making biological cells especially prone to the effects of non-zero gravity fields. Approaches to solution of the convection and sedimentation problems which arise during the handling of biological cells have included density stabilization and use of high viscosity suspending media such as gels to minimize convection. However in many media cells undergo volume and shape changes and pinocytosis and moreover the polymers used in density gradient systems often produce cellular aggregation. In addition the concentration of cells which can be used is severely limited on earth by droplet sedimentation.

For low Reynolds number flows of colloidal systems, coagulation or flocculation frequently occur with concomitant rapid sedimentation of colloidal aggregates. For example, sedimentation of red blood cells is more pronounced in a variety of pathological conditions and forms the basis for the *in vitro* test of the erythrocyte sedimentation rate. The rapid sedimentation of the red cells arises from their aggregation and rapidly results in a very anisotropic system which precludes precise rheological examination under zero or low flow conditions. Does the enhanced cellular aggregation in pathological conditions *in vivo* produce a different pressure drop across a blood vessel? Simultaneous erythrocyte sedimentation precludes an answer to this question. An increase in the pressure drop might merit appropriate countermeasures whereas a decreased pressure drop would constitute a beneficial situation not requiring therapeutic intervention. The examination of biological cellular dispersions in cone-plate or coaxial cylinder viscometers at low rates of shear is rendered especially difficult under terrestrial conditions by sedimentation of cells which gives rise to a cell free zone below the upper measuring element and a non-uniform volume concentration of cells. Rheological studies carried out in zero gravity would provide information of fundamental interest especially for systems of disparate density under low flow conditions.

19.3 AGGREGATION OF RED CELLS AND BLOOD VISCOSITY UNDER NEAR-ZERO GRAVITY

Leopold Dintenfass
Haemorheology and Biorheology Department
Kanematsu Memorial Institute
Sydney Hospital, Sydney 2000
and
Department of Medicine, University of Sydney
Sydney 2006, Australia

The objectives of this investigation are: (1) to study the degree of aggregation of human red blood cells in order to define the maximum size and morphology of aggregates under conditions of weightlessness, (2) to define effect of various agents (fibrinogen, cholesterol, drugs, etc.) on the size of these aggregates, with possible development of new tests or elaboration of present diagnostic tests, and (3) to study viscosity of blood under high and low shear rates.

Anticoagulated blood samples, at original or decreased haematocrits, and of known content of proteins and lipids, will flow through a slit-capillary formed by two parallel plates made of optical quality glass. Blood samples from normal donors and patients suffering from various diseases (inter alia, diabetes, hypertension, myocardial infarction, renal failure, multiple myeloma and other forms of cancer) will be studied. The size of aggregates and the pressure drop will be recorded. The instrument will be fully automated. During the second stage of this investigation, measured amounts of agents such as fibrinogen, snake-venom preparations, paraproteins, triglycerides, etc., will be injected into the gap between plates in order to observe two phenomena: (a) diffusion of the agent with a corresponding increase/decrease of the size of aggregates, and (b) response of aggregates to these agents as modified by the type of disease and/or type of ABO blood group.

The space environment offers the advantage of weightlessness which allows formation of cell aggregates undisturbed by sedimentation. This is also an important factor in the low shear rate viscosity of blood. It should be possible to establish the maximum size of red cell aggregates (and maximum near-zero-flow viscosity) uninfluenced by gravity. The maximum aggregate size might be intrinsically linked to the concentration of ingredients of different blood samples and the various patho-microcirculatory phenomena and, thus, might be of importance in obtaining a better insight into pathology of disease and might have a potential diagnostic application.

Note: The above is an outline of NASA experiment No. MPS77F113 for the Space Shuttle No. 3.

19.4

CERTAIN ASPECTS OF HEMORHEOLOGY IN A NEAR ZERO GRAVITY ENVIRONMENT

Alfred L. Copley
Laboratory of Biorheology
Polytechnic Institute of New York
Brooklyn, New York 11201

A variety of physiological changes are induced by gravity and their field of study constitutes gravitational physiology. The rheology of blood and of the vessel wall, comprising the hemorheology branch of the science of biorheology, is bound to be affected in a microgravity environment. Since body water, constituting a predominant component of the body mass of living subjects, is mainly distributed among intracellular, interstitial and plasma compartments, gravity appears to be important in the regulation of their volumes. Exposure of human and other vertebrate subjects to weightlessness may bring about a number of hemorheological changes, affecting the blood and the vessel structures with which blood or its components come into direct contact. New advances in ground based research in hemorheology, made in my laboratory and by other investigators in recent years, will be presented. They include the following: (1) Flow properties of blood systems at varying shear rates down to 0.0009 sec^{-1}; (2) visco-elastic properties of blood and red blood cell suspensions; (3) surface layers of plasma and systems of plasma proteins including fibrinogen in steady and oscillatory shear. These researches may be applicable to an environment near zero gravity. They may be of great value for the circulation of the blood in human subjects and other vertebrates exposed to the novel microgravity environment, such as in Spacelab modules.

20.1

PERMEABILITY AND TRANSPORT OF PROPERTIES OF ARTICULAR CARTILAGE

S. S. Gordon, V. C. Mow, R. Lee* and A. J. Grodzinsky*
Rensselaer Polytechnic Institute, Troy, New York
*Massachusetts Institute of Technology, Cambridge, Massachusetts

Articular cartilage is a biphasic material composed of a highly charged solid matrix filled with an intrinsically incompressible fluid. The solid matrix is viscoelastic and permeable and the interstitial fluid contains mobile counter ions. The movement of this interstitial fluid is governed by the hydraulic permeability k and its flow through the charged matrix will entrain the mobile counter ions. The movement of these ions will induce electric fields $\vec{E}$ which may influence k. The measurements of streaming potential and conductance could reveal the effect of these $\vec{E}$ fields on the fluid flow.

Volume flow induced by a pressure gradient ΔP across a circular slice of cartilage was measured with varying amounts of applied pressure and applied strain ε_{app} (1). Transcartilage potential ΔV induced by ΔP was also measured under open circuit conditions via Ag/AgCl electrodes (2). In a separate experiment, conductance was measured via a two electrode plus four electrode a.c. phase lock technique isolating the in-phase component of impedence.

Experimental results show that k decreases exponentially for increasing strain and can be described by $k = A(\Delta P)\exp[\alpha(\Delta P)\varepsilon_{app}]$ where $A(\Delta P)$ ranges from 20.6×10^{-16} $m^4/N \cdot s$ at low pressures to 2.6×10^{-16} $m^4/N \cdot s$ at high pressures and where the decay function $\alpha(\Delta P)$ ranges from -4.2 at low pressures to -1.7 at high pressures. The cross plot of ΔP vs ε_{app} for constant k shows a linear dependence between the variables and suggests that k can be uniquely defined as a function of $\varepsilon_{actual} = \varepsilon_{app} + \varepsilon_{induced}$ where $\varepsilon_{induced}$ is the compressive strain caused by the drag of permeation (1).

In order to determine the electromechanical coupling coefficients, the experimentally accessible parameters k, ΔV, and conductance were measured. Present results show that at low pressures and low applied strains, the effect of the developed $\vec{E}$ fields on the fluid flow appears to be negligible. However, at high pressures and large applied strains, the intensified $\vec{E}$ fields, consistent with the streaming potential measurements, exert a force on the space charges which retards the flow. Thus, the observed decrease of permeability with increasing compressive strain may be due to the induced $\vec{E}$ fields as well as the compaction of the solid matrix.

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This work was supported by the NSF Grants No. Eng 75-20866 (RPI) and No. ENG 77-06973 (MIT).

20.2 A THEORY OF STRENGTH FOR BONE AND WOOD

S. C. Cowin
Department of Biomedical Engineering
Tulane University
New Orleans, Louisiana 70118

A simple theory for the stength of bone and wood is developed from the assumption that there exists a function of the stress state such that when this function is satisfied, the material will fracture. This function is then restricted by assuming that it reflects the orthotropic symmetry of bone and wood and that is is linear in the orthotropic invariants of the stress state. There are two results obtained from this theory. The first demonstrates its consistency with existing data on the directional properties of the tensile strength of bone and wood. The second is a new prediction concerning the directional property of shear strength.

The first results is a derivation of Hankinson's criterion (1). Hankinson formulated his criterion for the tensile strength empirically from test data on spruce. Many woods were later shown to obey this criterion and, more recently, Reilly and Burstein (2) showed that bone did so also. Hankinson's result is a formula for the tensile strength of a material in a direction making a specified angle with the grain in terms of the angle, the tensile strength perpendicular to the grain and the tensile strength in the direction of the grain.

The second results is a similar criterion for the directionality dependence of shear strength. It is consistent with the meager data on wood.

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20.3 THE EFFECTS OF PRESSURE AND TIME ON THE PERMEABILITY OF ARTICULAR CARTILAGE

J. P. Renaudeaux
Laboratoire de Mecanique des Fluides
Universite Pierre et Marie Curie
Batiment 502 - 91405 Orsay - France

The articular cartilage is elastic and hydrophilous. Due to these properties, its permeability is a function of both time and pressure.

Our experimental device allows the measurement of the permeability of cartilage samples under pressure differences which go from 0 to 30 bars (420 PSI).

The following empirical laws: $K = A/t^m$ at $P = Cte$ and $K = B/P^n$ at $t = Cte$, are representative of the observed phenomena. As the coefficient n is approximately equal to 1, it results from Darcy's law that the "static" flow through the cartilage is practically independent of the applied pressure.

The experimental results are compared with the consolidation theory developed by Biot. This theory is too simplified to represent exactly the comportment of the cartilage, but predicts the form of the variations and can be used as a first approximation.

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20.4 RHEOLOGICAL MEASUREMENT OF INTERARTICULAR CARTILAGE SURFACE SHEARING FORCES IN VITRO

L.L. Malcom, F.R. Convery, S.L.Y. Woo and W.H. Akeson
Division of Orthopedics & Rehabilitation
University of California, San Diego
La Jolla, California

Introduction. The rheological mechanisms which account for the efficient lubrication of human synovial joints are often hidden by the complex kinematic and geometrical conditions which are found in vivo. An electro-mechanical instrument was therefore developed which examines articular cartilage interfacial shearing friction under controlled conditions in vitro.

Method. Conformationally matched sets of bovine articular cartilage in situ with 7 mm I.D. x 12 mm O.D. cylindrically symmetric contact areas were tested. The newly constructed instrumentation consisted of a dual independent servo-feedback system capable of rotating (shearing) and loading the cartilage specimen in one of four servo modes: (1) constant normal force, (2) constant normal displacement, (3) constant shearing force, and (4) constant shearing velocity. In addition, the above experimental parameters could also be constrained to follow selected arbitrary time functions. The lubricating environment was varied between whole bovine synovial fluid and a 0.9% saline solution. Temperature and pH were controlled throughout the test.

Results. The ratio of the frictional shear force to the normal force was found to vary between 0.002 and 0.02 across an applied force range of 3.66 to 146 newtons. The magnitude of the resultant interfacial friction was shown to depend strongly on the particular load history of the applied normal force. Surprisingly, there was a very little relation between the magnitude of the frictional shear force and the velocity of shearing, showing only a factor of two increase in response to a 2000 fold variation in the shear velocity in the presence of the non-Newtonian natural lubricant: synovial fluid. At low shear velocities there was a general increase in shearing friction with a marked tendency toward an interference type of adhesion of the cartilage interfaces at zero velocity in the present of saline lubricant alone.

Conclusion. The above experimental results emphasize that the articular cartilage-synovial fluid system possesses several build-in mechanisms which control the normal and shear stresses to which the joint is subjected during normal physiological function.

ACKNOWLEDGEMENT

This project was supported by USPHS NIH Grant No. AM 20045-01.

20.5 RHEOLOGICAL STUDY OF HUMAN KNEE JOINT

T. Tateishi,[1] Y. Shirasaki[1] and Y. Miyanaga
[1]Mechanical Engineering Laboratory, Igusa 4-12
Suginamiku, Tokyo, Japan
[2]Department of Orthopedic Surgery
Faculty of Medicine, University of Tokyo
Hongo Bunkyo-ku, Tokyo, Japan

In order to disclose the rheological characteristics of human articular cartilage, cancellous bone and those composite at knee joint, regional and directional differences of dynamic viscoelasticity and strength were investigated. All the specimens were obtained from normal knee joint at operation. In normal cancellous bones of tibial condyle at 45^{o} flexion, the dynamic compressive elastic modulus was about 60 kg/mm^2 and the peak value of the phase-lag was about 10 degrees. Comparison of these measurements with those of the femoral head and condyle indicates that the larger dynamic elastic modulus and the lower degree of phase-lag of tibial condyle makes an adequate structural adaptation to dynamic weight-bearing. These facts indicate that the cartilage-cancellous bone composite tends to be ductile and effective as a shock-absorber.

In a joint such as hip and knee, the obvious strength and stiffness difference between loaded and unloaded region would also indicate that cancellous bone responds to load by remodelling.

When compared with normal bones of joint, degenerative bones generally have increased values of elastic modulus and decreased values of internal dissipation. These facts indicate that the degenerative cancellous bone tends to be brittle and ineffective as a shock-absorber as it was before. The nature of this functional adaptation was clearly illustrated as an alteration of both the amount of bone and the trabecular pattern.

20.6 EVALUATION OF THE ADAPTATION OF LONG BONES TO BENDING STRESS

B. Kummer
Anatomisches Institut der Universität zu Köln
5 Köln-Lindenthal
Lindenburg, Germany

The physiological stress for the long tubular bones is bending (1). Efforts have been made to prove that bone form and distribution of resisting material of every individual are adapted to its specific stress pattern. Vice versa, the analysis of the overall form, the distribution of material in cross-sections at different levels and of the distribution of local density allows the nearly perfect reconstruction of the kind of stresses the bone has been submitted to at lifetime.

A computer-program has been developed to determine the direction of optimal adaptation to bending for cross-sections of different shape. By the same means, it can be shown that the formation of a bony tube from a solid rod necessarily results from Pauwels' hypothesis on bone formation and functional adaptation. The distribution of local material density is determined from x-ray photographs by means of optical and photographical densitometry.

The method and results are demonstrated on the femora, tibiae and radii of 26 individuals.

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20.7 QUADRIPOLE MODEL OF BONE PIEZOELECTRICITY

G. Branko and N. Petrov
Institute of Mechanics and Biomechanics
kv. Geo Milev, bl. 8, POB 373
Sofia-1113, Bulgaria

The piezoelectric properties of bone are subject to intensive study in the last 10 years. As a result of the study of many scientists a great quantity of experimental material is obtained. From the existing experimental data it is evident that bone piezoelectricity exhibits some peculiarities differing from the classical piezomaterials.

In the present paper a quadripole model of bone piezoelectricity is proposed. With the help of this model the electric potentials generated at the bending of bone plates could be described. In the case of pure bending the application of the quadripole theory leads to participation of the stress gradient in the constitutive equations which is in good conformity with the existing experimental data.

21.1 Macromolecular Transport in Connective Tissue

Harold Wayland
Division of Engineering and Applied Science
California Institute of Technology
Pasadena, California 91125

Connective tissue consists of a "skeleton" made up of a network of collagen fibers which gives it a reference configuration — a configuration which is "remembered" after a deformative stress. Different tissues contain different percentages of collagen when in their normal configuration, as well as different percentages of elastin fibers. The interstitial space also contains proteoglycans, hyaluronic acid, chondroitin sulfate, dermatan sulfate, etc. which are relatively fixed to the matrix. The relative and absolute amounts of these various substances vary widely with the tissue type. These macromolecular components are important in determining the ease of hydration of the tissue. It is not clear whether or not the proteoglycan chains are cross-linked with each other or with the collagen network, or are merely mechanically entangled.

The apparent diffusion coefficient for various macromolecules has been studied in tissues of various compositions and in some cases in varying states of hydration. Data for tendon, mesenteric membrane and Wharton's jelly have been measured in various laboratories. Our own work in the mesenteric membrane shows such a strong dependence of the exclusion factor on molecular weight of the substance being transported that there appears to be a significant interaction between the proteoglycan network and the collagen fibril network.

21.2 PROTEIN MOVEMENTS IN THE EXTRAVASCULAR SPACE

S. Witte
Department of Medicine
Diakonissen-Krankenhaus
D-7500 Karlsruhe, W. Germany

The protein contents in the perivascular connective tissue was measured in situ by means of ultramicrospectrophotometry (1) and scanning-microfluorometery (2). In comparison to the protein of blood plasma, the perivascular protein around arterioles corresponds to 40% and around venules to 59%.

By changing the hydrostatic or colloid-osmotic pressures of the blood the protein contents within the perivascular area can be influenced. During one hour after an acute decrease or increase of the plasma protein concentration, by means of blood loss or albmin infusion, corresponding changes of the extravascular proteins were measured.

In order to obtain absolute values for the protein exchange per tissue volume, the maximal inducible protein movements in the perivascular space were calculated. Values for a maximal protein exchange within the pervascular space of ± 3 $mg \cdot ml^{-1}$ tissue during one hour were obtained.

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21.3 WATER MOVEMENT THROUGH SWELLING CONNECTIVE TISSUE

I. Fatt and P. Tam
School of Optometry and Department of Mechanical Engineering
University of California
Berkeley, California 94720

Outward movement of water through the skin is an example of water flow through swelling connective tissue. This water movement is independent of the excretion of sweat. The outward movement of water takes place when the chemical activity of water at the skin surface is less than in the deeper lying skin layers. The resultant gradient of chemical activity of water causes a gradient in skin water content and permeability, The equation describing water movement must be expressed in LaGrangian coordinates to take into account the dimensional dependence of the skin layers on water content. When properly formulated the solution of these equations gives both the water flux out of the skin and the profile of skin hydration. The complexity of the solution depends upon the model of the skin. The most realistic model treats the skin as two layers in series, the stratum corneum and the dermis. When the flow is through these two layers in series than both water chemical activity and flux must be matched at the interface. The solution of the matched equations shows how the dense stratum corneum controls loss of water from the skin and the water content profile in the skin. Addition of a thin hydrocarbon layer, from skin cream for example, further reduces water loss and results in a less steep gradient of water content across the skin. This is the explanation for the beneficial and comforting effect of skin creams on dry skin.

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21.4 BLOOD FLOW PROPERTIES IN HUMAN VEINS UNDER VARIOUS HYDROSTATIC CONDITIONS

A. M. Ehrly
Division of Angiology
Department of Internal Medicine
University Medical School Frankfurt (West Germany)

The aim of the study was to find a new experimental model for studying problems of capillary fluid transfer and venous return flow. For this purpose we investigated the behaviour of the flow properties of blood obtained from superficial veins under various hydrostatic conditions (i.e. in recumbent position and during standing).

Blood samples were taken from a) the antecubital vein and b) the vena saphena magna (ankle region) of healthy volunteers during a 20 min prone period and during a subsequent 20 min period of standing. The following blood flow parameters were measured: whole blood viscosity, plasma viscosity, red cell deformability (8 µm-Millipore-filters) and red cell aggregation (light transmission method).

As compared to the viscosity values in the recumbent position, blood and plasma viscosity markedly increase immediately after standing up (p 0,001, n = 7) reaching a plateau after 10 min. This increase in blood and plasma viscosity was markedly higher (p 0,001, n = 7) in the ankle vein compared to the antecubital vein. Red cell aggregation and erythrocyte deformability remained the same.

These results show that blood viscosity at a given shear rate markedly depends on the hydrostatic (venous) pressure existing in the punctured vein.

The increase in blood and plasma viscosity could be explained as the result of a local hemoconcentration (increase in red cell count and increase in plasma protein concentration during standing). This enables us to quantify the capillary fluid loss into the interstitial compartment. With the help of these experiments physiological (tissue fluid transfer (1)) as well as pathophysiological problems in venous diseases (2) could be answered.

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21.5 MATHEMATICAL MODEL OF SUBSTANCE DIFFUSION IN TISSUE WITH NONLINEAR ABSORPTION

V. M. Zaiko and A. N. Sharikov
Institute of Transplantation of Organs and Tissues
Moscow 123436, USSR

A mathematical model of diffusion is proposed and analytical expressions for substance concentration distributions in capillary $F(z)$ and in tissue $f(z,r)$ are obtained. The absorption rate in tissue is described by formula

$$g(f) = Af/(f+\varepsilon)$$

where it is assumed that $f \geq 10\ \varepsilon$. The stationary diffusion equation for the Krogh capillary-tissue cylinder with nonlinear absorption tissue can be written as follows:

$$D\ [\partial^2 f(z,r)/\partial r^2 + (1/r)(\partial f(z,r)/\partial r)] = Af(z,r)/(f(z,r)+\varepsilon) \quad (1)$$

and the boundary conditions are:

$$\partial f(z,b)/\partial r = 0; \ -D\ \partial f(z,a)/\partial r = h[F(z)-f(z,a)] \quad (2)$$

where D is the tissue diffusion coefficient, h is the capillary wall permeability coefficient, z,r - axial and radial coordinates, a,b - radii of capillary and Krogh tissue cylinder. Concentration distribution equation for the capillary is written as

$$U\pi a^2\ dF(z)/dz = 2\pi aD\ \partial f(z,a)/\partial r \quad (3)$$

where U is the capillary blood flow rate.

Using the deformed coordinates' method and the integral method for joint solution of equations (1,3) with set boundary conditions (2), we obtain the following expressions for concentration distributions in capillary and tissue:

$$F(z) = F_o - Iz + \varepsilon\ \ell n\ [F_o - \alpha/(F_o - \alpha - Iz)] \text{ in capillary} \quad (4)$$

$$f(z,r) = F(z) - (A/4D)(\alpha b^2\ \ell n(r/a) - r^2 + a^2)\ [1 - \varepsilon/(F(z)-\alpha)] \text{ in tissue} \quad (5)$$

where $I = \frac{A}{U}(\frac{b^2}{a^2} - 1)$; $\alpha = \frac{A}{4D}(\frac{2b^4\ \ell n(b/a)}{b^2-a^2} - \frac{3b^2-a^2}{2}) + \frac{A}{2ah}(b^2-a^2)$.

When $\varepsilon \to 0$ equation (5) is reduced to the Krogh's formula. Let us suppose that the error of Krogh's formula caused by nonlinearity of substance absorption in tissues is 100%. Then formula (5) for $f=7\varepsilon$ gives the error less than 15%, and for $f > 10\varepsilon$ less than 7%. Expression (5) can be used for evaluation of not only substance concentrations in tissue, but of oxygen concentration, if $F(z)$ is considered as an oxygen concentration on the external capillary wall.

22.1 RHEOLOGICAL ANALYSIS OF COLLAGEN - WITH REFERENCE TO MORPHOLOGY AND EXPERIMENTAL TECHNIQUES

A. VIIDIK, H. OXLUND & T. ANDREASSEN, Connective Tissue Biology Dept.
Institute of Anatomy, University of Aarhus, DK-8000 Aarhus C, Denmark.

Collagen, a fibrous protein embedded in gels of other macromolecules, has remarkable mechanical strength and exhibits visco-elasticity, which can be described in mechanical analogies and mathematical models (1,2). Correlations to various morphological components have been suggested (3,4,5), and for clarification enzymatic removal of specific components can be employed (6,7,8). Initially we tested the effects of various enzymatic preparations on film strips of purified and repolymerized collagen. Incubation with α-amylase or purified elastase diminished the strength significantly. Hyaluronidase (H-ase) had no significant effect. Collagenase (C-ase), disintegrated the strips. H-ase had no significant influence on the stress-strain curves of rat aorta and skin. For aorta mild C-ase treatment (4%, 2 hrs) decreased the strength and intensive (10%, 7 hrs) caused the stress-strain curve to break already after a slightly lowered toe part. Both C-ase treatments disintegrated the skin specimens. This confirms that collagen plays a main role for the tensile strength of aorta, while elastin is mainly responsible for the toe part (8). However, collagen and elastin interact somehow with each other - C-ase-treated specimens would otherwise have had the same extensibility as non-treated ones. In skin elastin plays a minor role, probably affecting the toe-part somewhat and restoring the normal meshwork configuration after stretching (cf. 9).

The visco-elastic properties of collagen can best be studied in parallel-fibred ligaments and tendons and be approximated by a Kelvin element in series with a non-linear Hooke element (10). The elastic and viscous components in this assembly can be evaluated (11,12). H-ase did not affect any of these components in rabbit tissue. Universal prednisone treatment stiffened the elastic part of the Kelvin element, as anticipated from previously observed enhancement of the molecular stability of collagen (13). Stress-relaxation (SR) at a given strain level and creep phenomenon (CP) at a given stress level seem to reach asymptotic levels after 5-10 minutes. There is, however, after these initial rapid SR and CP slower components. The asymptote (σ_A or ε_A) "reached" after 10 min from an initial level (σ_0 or ε_0) of 1000 is for SR 890 and CR 1080, while those calculated after 1000 min are 810 and 1180. The constitutive equation (cf. 11.12) can be written as

$$\ln(\sigma-\sigma_A) = \ln(\sigma_0-\sigma_A)-\beta t; \text{ for SR, where } \beta = -(c_K + c_E)/k, \text{ and}$$

$$\ln(\varepsilon_A-\varepsilon) = \ln(\varepsilon_A-\varepsilon_0)-\delta t; \text{ for CP, where } \delta = -c_K/k.$$

We found β_{10} to be 4.4×10^{-1} and β_{1000} 2.3×10^{-3} and δ_{10} 3.7×10^{-1} and δ_{1000} 2.5×10^{-3}. It is not presently clear whether these differences are due to a non-linear viscosity or whether they can be related to different morphological components.

(The list of references can be obtained from the authors).

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22.2 ELECTROMECHANOCHEMICAL AND REACTION-DIFFUSION DYNAMICS IN COLLAGEN MEMBRANES

N.A. Shoenfeld. J.H. Nussbaum, and A.J. Grodzinsky
Massachusetts Institute of Technology, Cambridge, Massachusetts

The charge groups of collagen mediate transduction phenomena involving mechanical, electrical and chemical energies. For example, changes in electrical repulsion forces between molecules and fibrils give rise to macroscopic stress. Previous work [1] has shown that an electric field applied across a collagen membrane can change intramembrane ionic strength and hence modulate the repulsive forces electrostatically. An understanding of transduction kinetics, involving fluxes of ions and concomitant reorientation of molecules and fibrils, is important for device applications and for certain connective tissue biophysics problems. We have compared the time dependence of changes in isometric tensile force, $\Delta f(t)$, with that of changes in average intramembrane ion concentrations $\langle \Delta c(x,t) \rangle_x$. A sinusoidal electric field $E_0 \sin\omega t$ was applied across a membrane separating baths of different NaCl concentration but of identical non-isoelectric pH. The magnitude and phase delay of the resulting $\Delta f(t)$ was measured as a function of the amplitude E_0 and frequency ω of the field. A theoretical model for $\Delta c(x,t)$ was developed, accounting for diffusion, convection and migration of mobile ions due to E_0. The magnitude and phase of $\langle \Delta c \rangle_x$ was calculated numerically.

The applied $E_0 \sin\omega t$ produced a Δf at the same ω, in the 0.005 to 5.0 Hertz range studied. The amplitude of Δf was directly proportional to E_0 (at fixed ω) for E_0 corresponding to transmembrane potentials of 20-100 mvolt. Δf decreased monotonically with increasing ω at constant E_0. A similar trend was found for $\langle \Delta c \rangle_x$. The phase of Δf decreased from -20° (@ 0.004 Hz) to -120° (@ 2 Hz); the predicted phase of Δc was similar to that of Δf, with maximum deviation of ~ 20° at the lowest frequency. When bath pH was changed from acidic to basic, reversing the sign of net collagen charge, the phase of Δf shifted by ~ 180°. The model for Δc incorporates flux and continuity relations for mobile ions, and Gauss' Law relating fixed and mobile charge to total intramembrane field. The close similarity between the frequency dependence of $|\Delta c|$ and $\angle \Delta c$ with that of Δf suggests that the forces are induced at a rate dependent on an electrodiffusion process. Reorientation of fibrils and molecules apparently occurs as fast as ion concentrations can be changed, over the frequency range studied. This is supported by recent experiments involving isometric forces induced by small changes in bath pH ($E_0 = 0$). The kinetics of these Δf are well predicted by a diffusion-limited chemical reaction model alone, accounting for changes in H^+ concentration by diffusion and by carboxyl group dissociation.

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This work was supported by NSF Grant ENG 77-06973.

22.3 THE DYNAMIC MECHANICAL PROPERTIES OF ELASTIN

J. M. Gosline
Department of Zoology
University of British Columbia
Vancouver, B.C, Canada

The elasticity of vertebrate arteries can be attributed largely to the rubber-like protein elastin. Several studies suggest that high frequency vibration can induce a structural relaxation or "fatigue" in arterial tissue, and that under physiological conditions elastin is very near to its glass transition. Since increased mechanical hysteresis might contribute to fatigue, we investigated the dynamic mechanical properties of elastin at frequencies that cause the relaxation, in order to see if there is any correlation between viscoelasticity and this apparent fatigue.

Purified elastin samples were tested in tension between 0.1 Hz and 200 Hz over a temperature range of -2°C to 75°C. The water content of elastin increases greatly with decreasing temperature over this temperature range, and water is an important plasticizer of elastin. Therefore, we hydrated elastin samples in the vapor phase over water at 37°C and then tested them while they were immersed in mineral oil so that no changes in water content were possible. Under these conditions elastin exhibits a characteristic glass transition, and master curves constructed at 37°C show that elastin is well into its transition at frequencies above about 200 Hz. For example, damping (E"/E') was 0.33 at 10^3 Hz. Temperature shift data used in constructing the master curves indicate that the activation energy for the flow process is about 35 kcal/mole, and calculations based on the WLF equation suggest that T_g for elastin hydrated at 37°C is about -20°C. Thus, viscoelastic properties may well contribute to vibration-induced fatigue in arteries.

For arteries functioning at temperatures below 37°C the glass transition should occur at much lower frequencies. However, the unusual temperature-dependent swelling properties of elastin appear to prevent this. Apparently, the increased water content counteracts the tendency of decreased temperature to bring elastin into its glass transition. Experiments carried out with elastin samples in swelling equilibrium with water showed very little change in dynamic properties over the entire range of temperature and frequency. Storage modulus (E') remains virtually constant at about 10^6 Nm^{-2}; damping changes only slightly, being about 0.01 at low frequency and high temperature and being about 0.07 at high frequency and low temperature. This suggests that the unusual swelling properties of elastin may be an important feature of the evolutionary design of this rubber-like protein, allowing primitive, cold-blodded vertebrates to function efficiently over a wide range of body temperatures.

22.4 EFFECT OF WATER ON THE MECHANICAL RELAXATION OF HUMAN INTERVERTEBRAL DISC MATERIAL

N. D. Panagiotacopulos, R. Bloc, and W. G. Knauss
Graduate Aeronautical Laboratories
California Institute of Technology
Pasadena, California 91109

The human intervertebral disc is a highly inhomogeneous fiber composite pressure vessel. It consists of two separate domains: the outer, annulus fibrosus, and the inner, nucleus pulposus. The annulus has many layers, or lamellae, which vary in thickness from about 0.1 to 1 mm. A lamella consists of collagen fibers bound by mucopolysaccharides. As assembled in the disc the layers are connected to the adjacent vertebrae via the cartilaginous end-plates with the fiber direction at approximately $\pm$ 55 with the spinal axis, the direction changing alternately from + to - in adjacent layers. There is some cross-over of collagen fibers from one layer to another, mostly in the posterior section of the disc. The nucleus pulposus consists of a network of non-oriented collagen fibrils enmeshed in a mucoprotein matrix having a gel-like consistency.

Because annulus fibrosus layers are so thin we were unable to prepare single-layer specimens. So far we have worked with two-layered samples which are sufficient to establish the mechanical properties.

We find that the relaxation behaviour is very sensitive to moisture content. Accordingly we have worked with carefully controlled environments including saline solutions claimed to represent body conditions. A major difficulty in obtaining repeatable results is the obtaining of straight test specimens and holding them in the clamps of the testing apparatus. If moisture, and temperature conditioning was repeated without re-clamping the specimen, reasonably repeatable results were obtained. No aging was observed after repeated drying and moisturizing cycles.

Water diffuses slowly in the layers; it apparently acts as a solvent in a polymer, affecting the relaxation time. Increasing water content causes shortening of relaxation times, drying having the opposite effect. Upon controlling the water content of the specimen we are able to measure the relaxation behaviour in various time domains. Data covering a wide spectrum of relaxation times is presented which includes all time scales experienced by the human body. From this we can estimate how discs respond to different rates of deformation and loading, and predict the failure modes under slow or sustained loads as compared with impact loading.

22.5 DYNAMIC VISCOELASTIC BEHAVIOUR OF HUMAN TENDON IN VITRO

H. Schwerdt, A. Constantinesco, J. Chambron
Groupe de Biomécanique
Institut de Physique Biologique
4, rue Kirschleger - F-67085
Strasbourg Cedex, France

Recent studies have confirmed the fact that tendons behave as non-linear viscoelastic bodies. Most authors have used industrial material testing machines working at different deformation speeds to study the influence of strain rate and maximal load on the stress-strain characteristics and the creep and relaxation behaviour of tendons. In order to obtain numerical values which have direct relevance to practical application (hand surgery), we have developed a new testing device which measures the dynamic elastic modulus of tendons as a function of initial strain and frequency.

In this device, the specimen (tendons of m. flexor digitorum of the human hand) are fixed between two drill chucks and prestrained from 1 to 5 percent by means of two micrometer heads mounted in a frame. The specimen is periodically deformed by an electropneumatic vibrator (frequency range from 0,5 to 15 Hz) mounted between the first micrometer and chuck. The force transducer was located between the second micrometer and chuck. The periodic deformation of the specimen, whose amplitude was 0,25 % of its initial length, was measured by means of an inductive displacement transducer.

The electrical signals of force and displacement are recorded on a digital cassette recorder and decomposed into Fourier series by means of a digital computer. The first harmonics of stress and strain were then used to calculate the modulus and phase of the dynamic elastic modulus. At a frequency of 1 Hz, values of the modulus increased from $3.10^{-9}N/m^2$ to $8.10^{-9}N/m^2$ with an increase in strain from 1 to 5 percent. The influence of frequency is less pronounced - at 1 % strain an increase from 1 to 3,5 Hz increases the elastic modulus by about 10 %. The phase does not seem to be influrenced by initial strains, but increases slightly with frequency.

22.6 NONLINEAR VISCOELASTIC BEHAVIOR OF HUMAN AND CANINE FLEXOR TENDONS IN SIMPLE ELONGATION

F. K. Ko, A. Pastore*, and F. Cole**
Philadelphia College of Textiles and Science,
Philadelphia, Pennsylvania 19144

*University of Pennsylvania
Philadelphia, Pennsylvania

**Thomas Jefferson University
Philadelphia, Pennsylvania

For the purpose of developing artificial tendons, we studied the mechanical properties of tendons by simple elongation, cyclic extension at various strain rates, and stress relaxation at various extension levels, under ambient and physiological conditions.

The tensile stress-strain behavior of human and canine flexor tendons are nonlinear and viscoelastic. Flexor tendons are strong as well as tough. The breaking strength of human and canine flexor tendons are 4.7×10^8 dyn/cm^2 and 5.5×10^8 dyn/cm^2 at elongations of 0.27 and 0.16 respectively. The energy loss in cyclic extension is fairly insensitive to strain rate. The energy loss at a strain rate of 1.67×10^{-4} sec^{-1} is only twice the energy loss at a strain rate of 1.67×10^{-2} sec^{-1}. Strain energy loss is about 30% in the first cycle and reduced to 15% in subsequent cycles. Fractional stress relaxation of the tendons depends on the strain level.

Based on our experimental results, constitutive equations are developed for the tendons using Fung's quasilinear viscoelastic model.

22.7 RHEOLOGICAL PROPERTIES OF NATURAL AND RECONSTITUTED COLLAGEN FIBERS

L. V. Kukhareva and V. I. Vorob'ev
Institute of Cytology of the Academy of Sciences
of the U.S.S.R., Leningrad 190121, U.S.S.R.

Earlier we investigated structural changes occuring during hydrothermal and chemical contraction of collagen fibers (1). However, native tendon fibers of mammalian tails (rat, kangaroo) are known to have a non-collagenous envelope - "sheath" (2). In the present study we compared the thermal contraction in physiological solution of native rat tail tendons, tendons deprived of the envelope, and reconstituted collagen fibers. The sheath was removed from the native tendons by a 4-min treatment with 0.1 M citrate buffer (pH 2) containing 0.054 M NaCl. Then the tendons were tanned by p-benzoquinone. The removel of the sheath results in a decrease of T_s (the initial temperature of thermal contraction) for the tendons in physiological saline solution as has been previously observed for the kangaroo tendons with the envelope mechanically skipped off (2). The T_s values for such fibers were practically equal to the values of T_m (equilibrium melting temperature). The difference between T_s and T_m was minimum for the reconstituted collagen fibers. The results obtained suggest that a great difference between T_s and T_m reported by a number of authors (see, for instance, 3) is accounted for by an effect of non-collagenous envelope. This envelope may influence the process of diffusion into the fiber and prevent an increase of fiber diameter during contraction.

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23.1

CLINICAL APPLICATIONS OF BLOOD VISCOSITY FACTORS AND FUNCTIONS

L. Dintenfass
Kanematsu Memorial Institute, Sydney Hospital,
Sydney 200, Australia

Our studies in haemorheology moved through a series of stages. In each of these stages, studies of blood viscosity in various diseases allowed a better insight into the microrheology of blood: by study of the abnormal we could better comprehend the normal.

The first two stages dealt with elaboration of the various blood viscosity factors (blood viscosity, plasma viscosity, aggregation of red cells, internal viscosity of the red cell, etc.), including parameters of dynamic coagulation and thrombus formation; and with phenomena specific to small blood vessels (Fahraeus-Lindqvist and "inversion" phenomena). In the third stage the viscosity factors were correlated with the levels of proteins (or their ratios), cholesterol, triglycerides, parathyroid hormone, LDH, SGOT, etc. In the fourth stage a correlation was sought between viscosity factors and exercise test, blood pressure, physical fitness, electrocardiogram abnormalities, etc.

Values of viscosity factors were established for patients with different clinical symdromes, and it was realized that an increase of blood viscosity, or plasma viscosity, or aggregation or rigidity of red cells, or apparent viscosity of artificial thrombi, is a risk factors; and a warning sign specially in the case of silent disorders. We observed an elevation of blood viscosity factors prior to arterial occlusion, prior to cancer metastasis, prior to severe kidney failure, etc. Genetic aspects were studied and found of rheologic significance in diabetes and cardiovascular disorders.

A decrease of blood viscosity factors by hemodilution or bleeding or drug therapy was beneficial in some cases, from retinal occlusion to severe anxiety.

Thus, blood viscosity factors and functions are on the way to become tools of medical diagnosis and therapy; and will allow a deeper understanding of etiology of diseases.

23.2 CLINICAL USE OF HEMORHEOMETRY

Bok Y. Lee, M.D., Frieda S. Trainor, Ph.D., David Kavner, D. Eng., J.A. Crosologo, M.D., Louis R.M. Del Guercio, M.D., John L. Madden, M.D.

Veterans Administration Hospital, Castle Point, New York and New York Medical College, New York, New York

Hemorheography is a simple, practical, noninvasive clinical technique for assessing cutaneous circulation. The sensing probe of the Hemorheograph contains a tiny light source and photosensitive cell which responds to the light reflected from arterial blood in the peripheral vascular bed over which the sensor is placed. The amount of pulsating light registered is directly proportional to the amount of pulsating arterial blood.

Blood flowing through stenotic vessels or thin collateral vessels will exhibit a significant pressure reduction. This decrease in pressure can be ascertained by noninvasive measurements of the systolic blood pressure at multiple sites in the peripheral vasculature. Extending blood pressure measurement to the digits of the hands and feet can provide quantitative means for differentiating large and small vessel disease and for assessing vasospastic peripheral vascular disease. A specially constructed digital cuff is used with the Hemorheograph to measure systolic pressure in the fingers and toes. This can be used to screen high risk population for peripheral vascular disease, before and after vascular reconstructive surgery, and for frequent follow-up testing of patient with existing peripheral vascular disease. The Hemorheograph may also be used for monitoring in the ICU after reconstructive arterial procedures and for the monitoring of skin flap vascularity after amputation.

The Hemorheograph is also used to minitor cutaneous blood flow immediately around the site of an ischemic ulcer or pressure sore. Good pulsatile waveforms are indicative of an on-going healing process at the ulcer site. Non-pulsatile blood flow waveforms are indicative of a non-healing ulcer and would point toward surgical intervention.

The Hemorheograph is a noninvasive, simple, practical device for the assessment of pulsatile blood flow as an index of tissue perfusion. It is also a simple, practical, reproducible device for evaluating wound healing in pressure sores, ischemic ulcers and post-amputation.

23.3 CLINICAL BLOOD RHEOLOGY

H. Chmiel*, I. Anadere*, H. Hess**, and G. B. Thurston***

*Institut fur Grenzflachen-und Bioverfahrenstechnik, Eierstrasse 46, 7000 Stuttgart 1, Federal Republic of Germany

**Medizinische Poliklinik der Universitat Munchen, Abteilung fur Angiologie, Pettenkofer Str. 8, 8000 Munchen, Federal Republic of Germany

***Department of Mechanical Engineering, University of Texas at Austin, Austin, Texas 78712, U.S.A.

Blood, which is a non-newtonian fluid, shows also nonlinear viscoelastic properties in oscillatory shear flow 1 . These properties were studied in vitro as a function of shear rate in oscillatory flow and in comparison to steady flow and hematocrit. The viscoelastic properties of blood can be shown with the help of oscillatory flow measurements as in the viscous component, i.e. energy dissipative and elastic component, i.e. energy storing properties. These properties of blood aredistinctly changed by almost all vascular diseases or risk factors like smoking, etc. The hematological factors of blood from 64 healthy donors were determined. The variance in the viscoelastic properties of pathological blood as in the example of 13 patients with peripheral vascular disease and healthy blood with risk factors, like smoking, by 40 donors, were also studied. The measurements were performed with an oscillating capillary rheometer. The reproducibility of this measurement is better than $\pm$ 5% for two blood samples which have been taken from the same vein one immediately after the other. The results show that both the viscous and the elastic components of pathological blood and blood with risk factors are significantly changed compared with healthy blood. Both parameters are increased by pathological blood and blood with risk factors. The mean hematocrit seemed to be also higher for pathological blood. Clinical and rheological results will be discussed in connection with hematological parameters and prospects for further work. It will be shown that this apparent increase in hematocrit is a systematical error made by the hematocrit centrifuge due to increased aggregation of erythrocytes.

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23.4 REDUCED ERYTHROCYTE DEFORMABILITY IN DIABETES

D. E. McMillan, N.G. Utterbach, and J. La Puma
Sansum Medical Research Institute, Santa Barbara, Calif.

The human erythrocyte is a pliable disc-shaped cell capable of passing through vessels considerably smaller than its own diameter. In order to do this it must be highly deformable. Past studies have suggested reduced erythrocyte deformability in diabetes but direct measurement has not been carried out. To accomplish this, micropipettes were prepared with 4μ inner diameter for a 100μ length. Single erythrocytes were introduced into the pipettes and moved in a cyclic standard velocity pattern while pressure was measured. All studies were carried out in albumin-containing Ringer's solution containing 100 mg/dl glucose. Individuals differ measurably from each other in erythrocyte deformability, but each individual erythrocyte performs within measurement error of its fellows. In seven paired studies (same micropipette) the diabetic erythrocyte required a greater pressure gradient than the control erythrocyte. The ratio of mean pressure required averaged 1.51 and ranged from 1.32 to 1.82. No relation to duration, degree of hyperglycemia, or age could be noted. The diabetic erythrocyte resists shape change considerably more than the normal. The basis for the reduced deformability is not apparent but the increased hemoglobin AI_c content and altered plasma proteins and lipids are all possible contributors. Since about half again as high a pressure gradient would be required for diabetic erythrocytes to proceed through capillaries, decreased erythrocyte deformability might induce basement membrane thickening and other microcirculation changes in diabetes. Micropipette studies of deformability of erythrocytes from 6 individuals with hereditary spherocytosis showed less resistance to flow than diabetic cells in the 4μ pipette. Chronic rheumatoid arthritics have plasma protein changes similar to those occurring in diabetes but no reduction in red cell deformability in 6 paired studies. Flow properties of erythrocytes may be analyzed using a model combining the elastic resistance of the red cell membrane and the viscous resistance of the membrane and the cell interior. Elevated flow resistance can be mediated by either increased elastic resistance or increased viscous resistance. To distinguish between these two alternatives, erythrocytes were ejected from 4μ pipettes while slow motion films were taken. All cells returned to their discoid shape, but substantial slowing of diabetic erythrocytes was found - 0.38 vs. 0.25 seconds. This slowing indicates that diabetic erythrocytes have enhanced viscous resistance to flow. The intrinsic viscosity of hemoglobin from 6 individual diabetic and control subjects was not significantly different - 2.96 ± .02 vs. 2.92 ± .03 ml/gm (mean ± S.E.). Red cell cholesterol was also found to be unchanged in diabetes. We conclude that the reduced deformability of erythrocytes is specific to diabetes, involves changes in the viscous properties of the red cell membrane or interior, and is not mediated by changes in hemoglobin conformation or membrane cholesterol content.

23.5 HEMORHEOLOGICAL CONSIDERATIONS ON DIABETIC MICROANGIOPATHY: WHAT CAN BE GOOD INDICES FOR ITS MANAGEMENT?

Y. Isogai, A. Iida, K. Mochizuki, T. Yokose, H. Okabe,
M. Ashikaga, S. Ikemoto, T. Maeda, and M. Abe
Department of Internal Medicine, Jikei University
School of Medicine, Minato-ku, Tokyo, Japan

Diabetic microangiopathy (abbreviated as DmA) is a complication characteristic with diabetes and it is generally believed that the onset and progress of DmA is closely related, whether the control of diabetes is appropriate or not, and how long diabetes has been continuing. DmA is very much associated with metabolic defects and microcirculatory disturbances. In this paper the authors place emphasis on the latter factor, thus trying to find an index for management of diabetes mellitus on the basis of cause-and-effect relations between the progress of DmA and various factors constituting hemorheologic abnormalities observed in diabetes. 23 normal subjects and 70 maturity onset diabetics were examined. The following parameters were observed: in *in vitro* studies, blood viscosity at various shear rates, plasma viscosity, platelet adhesiveness and aggregation, viscoelasticity of blood clotting (its maximum rigidity abbreviated as G'm) and plasma fibrinogen were examined. In *in vivo* studies, intravascular erythrocyte aggregation (IEA)of conjunctival blood vessels were observed with a biomicroscope, and the degree of IEA were classified into four grades. Fundoscopy was requested to the opthamologist of our institute. In comparison of all diabetic cases with normal subjects, those in the former group showed significant high levels in many factors such as blood and plasma viscosity, platelet adhesiveness and aggregation, G'm and plasma fibrinogen. A similar trend was observed by comparison of 18 cases without any retinopathy to normal subjects, and significant differences existed in factors other than plasma viscosity and fibrinogen. In the cases where the blood viscosity, platelet aggregation and G'm were all higher than normal limits, advanced retinopathy were observed remarkably in many of them. And also, in the cases where a high degree of IEA was observed, there were many advanced retinopathy or involved with hemorheological disorder. On the basis of the results of our research, we wish to suggest that in the future rheological parameters in relation to the development of DmA should be regarded as one of good indices of the therapy for diabetes and the development of microangiopathy.

23.6 ABNORMAL RED CELL MEMBRANE FLUIDITY IN ZIEVE'S SYNDROME

K. M. Goebel, R. Schubotz and J. Schneider
Department of Medicine
University of Marburg
Marburg, Germany

To evaluate the effects of ethanol as a hematologic-oncologic toxin and to delineate further the abnormal membrane fluidity in the pathogenesis of hemolytic anemia in alcoholic liver disease, 10 icteric alcoholics were studied on acute phase (group A) and remittent phase (group B) of Zieve's syndrome. Since the peripheral red blood cells (RBC) in patients of group A showed target-and spur-cell deformabilities, aliquots of RBC ghosts were subjected to lipid extraction. A nearly twofold increase of HDL cholesterol and total phospholipids was observed ($P < 0.001$, group A vs group B). Decreased levels of poly-unsaturated fatty acids (FA) with a reciprocal increase of saturated FA were found in RBC ($P < 0.05$, group A vs group B). In addition to the membrane-linked disorder in lipid metabolism, an alcohol-induced vitamin E. deficiency was detected concurrently in the plasma and RBC of group A ($P < 0.001$, group A vs group B). Furthermore, an increased susceptibility to exogenous threat was demonstrable with the aid of hydrogen peroxide, which further implied an intracellular biochemical defect: A twofold reduction of glutathione (GSH) initiated an oxidative degration of cellular sulhydryl (-SH) groups, thus impairing the enzyme kinetics of pyruvate kinase.

Thus, it is conceivable that a linkage of environmental and cellular factors produce a chain reaction: Causing target- and spur-cell formations, vitamin E/PUFA deficiency, abnormal membrane fluidity with an increase of oxidative metabolic disorder, and finally the susceptibility to hemolysis in alcoholic liver disease with Zieve's syndrome.

23.7 FAST DETERMINATION OF WATER MOBILITY IN BLOOD PLASMA. INVESTIGATION OF CLINICAL SIGNIFICANCE.

A. Ganssen*, H. Schmid-Schoenbein**,
H. Malotta**, and R. Schneider**

*Siemens AG UB Med, Erlangen, Germany

**Abt. Physiologie, T. H. Aachen, Germany

The known methods of measuring blood rheologic properties are usually too slow for fast screening of patients under clinical condition.

The correlation between molecular mobility of solvent water molecules in aqueous protein solutions and the nuclear magnetic relaxation rate has been well established. In addition, the closely related dynamics of molecular exchange between solvent water and the water attached to the surface of the protein chains contribute essentially to nuclear magnetic relaxation.

Since nuclear magnetic relaxation rate measurements can be done within seconds and purely electro-magnetically without physical contact to the sample substance, they have been proposed by us as a test method for the microdynamics in biological liquid systems.

The clinical significance of blood plasma spin relaxation rates was therefore tested by us on plasma samples of several hundred patients and test persons with an easy to operate computerized NMR-apparatus.

The data were correlated to fibrinogen content and viscosity as well as to other microrheological properties.

23.8 THE RHEOLOGICAL BEHAVIOR OF THE ABNORMAL PROTEINEMIA DUE TO TEMPERATURE CHANGE AND ITS CLINICAL SIGNIFICANCE

S. Shigehiro
Department of Internal Medicine
Kitasato University School of Medicine
Asamizodai 1, Sagamihara-shi
Kanagawa-ken, Japan 228

Objective: This study was performed in order to understand rheological behavior of the whole blood from healthy persons and patients with protein abnormality in low temperature so that the disease specificity could be identified by measuring blood viscosity in low temperature[1].
Method: The micro cone-plate rotational viscometer (Tokyo Keiki Co.) was used to measure the whole blood (heparinized) viscosity from 6 normal persons and 5 patients with protein abnormality and 4 patients with Raynaud syndrome. The measurement was made at 5 different temperature (5, 10, 20, 30, and 37°C) and at least 4 different rotational speeds (shear rate 7.52-150.45 sec^{-1}). The measured values were plotted on Casson's equation and hematocrit was corrected at 40%. The slope and the intercept of the straight lines were compared.
Results: The square root of yield shear stress ($\tau_y^{1/2}$) of the normal blood increased markedly at low temperature especially below 20°C. The $\tau_y^{1/2}$ of blood from patients with abnormal proteinemia showed increase at low temperature, but did not rise higher than normals. The $\tau_y^{1/2}$ of blood from patients with Raynaud syndrome showed marked increase as shown in Fig. 1. The slope of Casson's equation of the blood from patients with abnormal proteinemia showed very good correlation with the amount of IgM as shown in Fig. 2.
Conclusion: If the hyperviscosity syndrome is devided into 2 groups[2], (the group with high yield shear stress and high slope), it is easier to understand clinical hyperviscosity syndrome. The differences of $\tau_y^{1/2}$ among different diseases are enlarged at low temperature. The microcirculatory disturbance of Raynaud syndrome may have some relation to high yield shear stress of the blood. The correlation between the slope and IgM is better at low temperature. The existence of high IgM can be detected by measuring Casson slope of the blood.

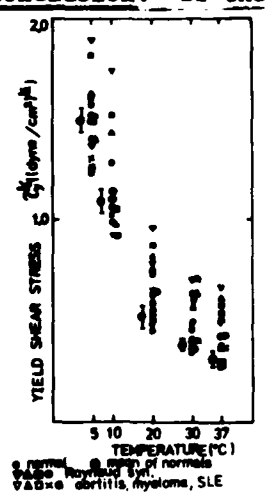

Fig. 1

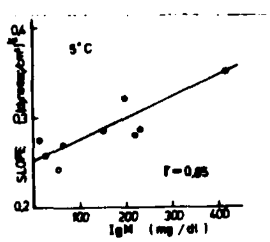

Fig. 2

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24.1 THE CHARACTERISTICS OF SECONDARY FLOW AND TURBULENCE IN A CONE-PLATE APPARATUS*

C. F. Dewey, Jr., S. R. Bussolari, and H. P. Sdougos†
Massachusetts Institute of Technology, Cambridge, MA. 02139

We have measured the wall shear stress, surface streamline direction, and turbulent wall pressure fluctuations in a cone-plate couette flow apparatus. For small angles between the cone and plate (as commonly used in viscometers), the data are correlated using a single parameter $\tilde{R} = (r^2\omega\tan^2\alpha/12\nu)$, where r is the radius from the cone vertex, ω is the angular frequency of cone rotation, α is the angle between the cone and plate, and ν is the kinematic viscosity of the fluid. We observe broad-band turbulence for values of $\tilde{R}$ greater than unity.

In the limit $(\tan^2\alpha) \ll 1$, expansion of the Navier-Stokes equations for small values of the parameter $\tilde{R}$ demonstrates that the azimuthal velocity (v) varies linearly between the cone and plate, and the first correction is of order $\tilde{R}^2$. The radial velocity (u) induced by centrifugal forces is of order $\tilde{R} \cdot v$, and the angle (ϕ) of streamlines near the stationary plate is given by

$$\phi = \lim_{y \to 0} \left[\frac{u}{v}\right] = \tan^{-1}\left[-0.8\tilde{R} + O(\tilde{R}^3)\right]$$

Our experimental values of ϕ agree well with $\tan^{-1}[-0.8\tilde{R}]$ for values of $\tilde{R}$ as large as unity. Shear stresses on the plate, measured using the hot-film method, are increased by secondary flow and are $(\cos\phi)^{-1}$ times as large as in purely azimuthal flow. We find no evidence of significant edge effects on the flow at any radial position between 1/4 and 3/4 of the cone radius, even for values of $\tilde{R}$ sufficiently large that turbulence occurs.

A similar analysis of two counter-rotating cones with a small angle between them has been completed. The radial motion is of order $\tilde{R}\omega r$ and directed inward at the center of the gap and outward on either side of the center. The absolute value of the radial velocity is 200 times larger than that in a cone-plate device with equal included angle.

*Sponsored in part by the National Heart, Lung, and Blood Institute.
†Presently at the Institut für Biomedizinische Technik, Zurich, Switzerland.

24.2

THE WALL-SHEAR-STRESS INTENSIFICATION DUE TO PULSATILE BLOOD FLOW

Y. Matunobu
Department of Physics
Keio University
Hiyoshi, Yokohama, Japan

The blood flow in arteries has been widely studied and forms a main theme of the physiological fluid dynamics. In particular detailed knowledge about flow structure in blood vessels seems to be indispensable in relation to the origin of vascular diseases, such as post-stenotic aneurysm and incipient atheroma. It is very likely that the wall shear stress may be intensified extraordinarily by pulsating flow in the stagnation region.

This paper presents some fundamental aspects of the wall-shear-stress intensification due to pulsatile flow in terms of simplified mathematical models. The steady flow impinging perpendicularly on an infinite flat plate is called the Hiemenz flow, for which the Navier-Stokes equation gives an exact solution. This solution can be extended to unsteady cases by linearizing the Navier-Stokes equation. Thus, the unsteady Hiemenz flow is discussed by analytic form of perturbed solutions. Because of the linearity of the equation, a uniform shear flow can be superposed on the unsteady Hiemenz flow to yield an obliquely impinging flow whose stagnation point fluctuates around a mean position.

It is found that when the amplitude is small, the first-order perturbed solution becomes dominant for large frequencies and the wall shear stress at the mean position of the stagnation point is proportional to the square root of the frequency. Since the actual blood flow in large arteries contains high-frequency components near the stagnation region, the above reasoning justifies partly endothelial lesion due to fluid dynamical friction. Further, when the frequency is not large, another perturbed solutions suggest that the wall shear stress undergoes abrupt change when the main flow changes from deceleration to acceleration.

24.3 THE FLUID DYNAMIC EVALUATION OF THE OUTFLOW TRACT STENOSIS IN CARDIAC SURGERY

T. Tsuji, K. Suma, M. Sugawara and Y. Sakurai
Dept. of Cardiovasc. Surg. and Dept. of Surg. Science
Tokyo Women's Medical College, Tokyo, Japan

Resistance coefficient and resistance unit were considered to be more meaningful in evaluating the outflow tract stenosis than the conventionally used indices such as RV/LV or pressure gradient across the stenosis. We studied the resistance values of the stenosis in congenital heart diseases during corrective surgery using pressure transducers and an electromagnetic flowmeter.

Resistance coefficient (λ') was represented as $\Delta P/(F/A)^2$.
Resistance unit (R) was represented as $\Delta P/(F/A)$.

ΔP : peak pressure gradient (mmHg)
F : peak aortic flow measured by an electromagnetic flow-meter using a non-cannulating type flow probe (L/min).
A : body surface area (M^2).

λ', R and ΔP were measured in 27 patients with tetralogy of Fallot (T/F), pulmonary stenosis (PS) or Aortic stenosis (AS) before and after the intracardiac repair during operation. The age of the patients averaged 4.8 ± 1.3 years and the body surface area did 0.7 ± 0.2 M^2 respectively.

The internal diameter of the aortic root averaged 1.5 ± 0.2 cm in 27 patients when the diameter of the flow probe was assumed to be that of the aorta. The mean value of aortic peak flow was 7.5 ± 2.6 L/min. The mean value of the peak Reynolds' number was 2941 (range 1730-4550) in the aortic root. Before the repair of outflow tract stenosis in 12 patients with PS or AS, λ' showed 0.6 ± 0.4, R did 4.4 ± 2.7 and ΔP did 42 ± 24 respectively. After the relief of the stenosis, each index was reduced to the following value. λ' was 0.2 ± 0.1, R, 1.9 ± 1.0 and ΔP, 27 ± 16 respectively. Among those indices, λ' seemed to be most sensitive to the changes of outflow tract stenosis. It revealed that operation was not indicated in the patient with λ' below 0.2 or R below 2.0. After the repair of T/F in 15 patients, λ' averaged 0.4 (0.1-0.7), R did 3.1 (0.7-6.0) and ΔP did 27 (5-60) respectively. The patient with λ' below 0.5 or R below 5.0 showed smooth postoperative course. Heart failure occurred frequently in the patient with those indices of higher values.

As an index of the outflow tract stenosis, ΔP or RV/LV was shown easily fluctuated depending on the cardiac output. However, λ' or R were relatively unchanged in spite of hemodynamic derangements.

24.4

Model Experiment on Genesis of the Korotkoff Sounds

M. Arakawa and Y. Matunobu

Dept. of Physics, Keio University
Hiyoshi, Yokohama, Japan

Since N.S.Korotkov (1905) suggested the auscultatory method in measuring blood pressure, numerous investigations have been reported as to the genesis of the Korotkoff sounds. Although this method is widely accepted in clinical medicine, no physical basis for the sound generation has ever been established.

Here we present some experimental results about the mechanism of sound generation by use of latex tubes and incised blood vessels of dog which are allowed to collapse according to applied external pressures. The tube compliance is much reduced when the transmural (internal minus external) pressure is very high or very low, and extremely increases for intermediate states. Thus the curve of the volume of collapsible tubes against the transmural pressure are characterized by two transition points at which the gradient changes abruptly. Owing to this marked nonlinearity, when a sinusoidal volume fluctuation covers one of the transition points, the output pressure is highly modulated and undergoes steep variation. As a result snapping sounds are produced when an oscillatory flow of water is applied to a collapsing tube.

There is another kind of sounds. When a steady flow is applied to a highly compliant tube, durable sounds may be heard owing to the self-excitation of fluid motion. This fact was reported in detail by Conrad (1969) and Katz et al. (1969). Therefore, it can be concluded that the tube collapsibility plays an essential role in the sound generation and it is possible to explain the mechanism of the Korotkoff sound as well as the change of sound phases over a wide range from systole to diastole in terms of the collapsibility of blood vessels and the stroke volume of blood stream.

24.5 FLOW OF BLOOD THROUGH A CURVED DUCT

V. S. Pratap*, V. L. Shah**, and D. B. Spalding*
*Imperial College, London
**University of Wisconsin-Milwaukee

When a fluid flows through a curved tube, a secondary motion is set up due to centrifugal force. This secondary flow produces higher heat and mass transfer rates. Consequently, coiled tubes are widely used in industrial equipments. The applications of coiled tube in membrane oxgenators, and kidney dialysis devices also appear to be feasible. In addition the flow through a curved tube is encountered in a cardiovascular system. The subject of blood flow through a curved tube is, therefore, of practical significance.

In the present work we have applied the forward marching procedure of Patankar and Spalding (1972) to predict the fully developed flow of blood through a curved tube. The non-Newtonian behavior of blood was expressed through a general form of the Casson's rheological relation.

$$\bar{\bar{\tau}} = \mu_{eff}\, \bar{\bar{\varepsilon}} = \mu_{ref}\, \left(1 + \sqrt{\frac{Y}{\eta}}\right)^2 \bar{\bar{\varepsilon}}$$

Here $\bar{\bar{\tau}}$ and $\bar{\bar{\varepsilon}}$ are the stress and rate of deformation tensors respectively, Y $(= \tau_y\, 2a/\bar{v}_z\, \mu_{ref})$ is the yield number and

$$\eta = \sqrt{\frac{1}{2}\varepsilon_{ij}\,\varepsilon_{ij}} \,/\, (\bar{v}_z/2a)$$ is the dimensionless flow invariant.

The results have been obtained for the yield number Y = 0, 0.2, 0.5. 1 and 10 and for a range of Dean numbers. The computed fully developed friction factor f is shown in Fig. 1. It can be seen that friction factor is a function of yield number and the Dean number.

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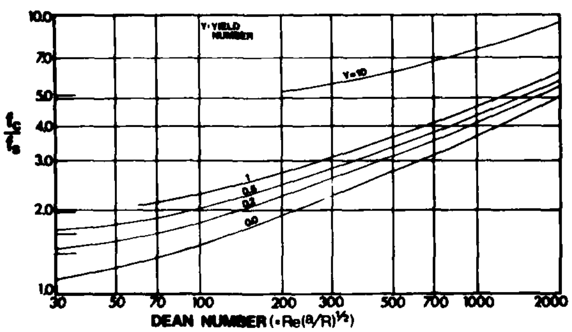

Figure 1. Variation of fully developed friction factor for various yield numbers. f_c and f_s are the curved tube and straight tube values respectively.

24.6 CHAINS OF SPHERES IN POISEUILLE FLOW: THEIR EQUILIBRIUM POSITION, SLIP-VELOCITY AND HYDRODYNAMICALLY INDUCED FORCES A MODEL FOR THE ROULEAUX FORMATION AND PLASMA TRANSPORT

K. Bauckhage
Universitat Bremen; Bereich Produktionstechnik/
Verfahrenstechnik; Acherstrasse/BH; D 2800 Bremen 33; F.R.G.

The mechanism of particle interaction during the formation of chains of spheres in a Poiseuille Flow as well as the chain velocities, equilibrium configurations and particle rotations are studied by further experiments. The suspension has a particle concentration up to a maximum of 10% by volume. The results for the lift forces and transverse velocities of single particles help to quantify the hydrodynamically induced chain forces, the particle concentration distribution, and the fluid transport rates perpendicular to the tube axis. The influence of spin-lag and slip-velocity is also described. These results are compared with our earlier work and also with work by others.

The fluid displacements in the inlet region of the tube and the fluid movement induced by the particle rotation during and after solid-liquid-separations in model suspensions give a good hydrodynamic base for mass transfer calculations to and from the tube walls. The results are discussed with regard to rouleaux formation and transversal plasma transport in blood flow.

24.7 EXPERIMENTAL INVESTIGATIONS ON HYDRODYNAMICALLY AUGMENTED CARBON-DIOXIDE TRANSFER IN FLOWING MODEL SUSPENSIONS

A. Obermayer
Institut fur Thermische Verfahrenstechnik
TU Clausthal 3392 Clausthal-Zellerfeld, West Germany

Hydrodynamical augmentation of mass transfer rates of gases (for instance in the lungs) has been studied by means of an experimental apparatus consisting of a gas permeable membrane tubing in which flows a suspension charged with dissolved carbon dioxide. The rate of permeation from the flowing suspension through the membrane to a gaseous outer atmosphere was measured. Very low solid concentrations of neutrally buoyant spherical particles of three diameter fractions (ye to 100; 150 to 160 and 212 to 250 μm) were used. The rates of molecular transport of the suspensions are different from those of the individual liquid (and dissolved gas). The augmentation of the transport transverse to the main flow direction is induced by the solid-liquid segregation phenomena, well-known in micro-rheology of model suspensions and blood.

The flow in the tubular Silastic membrane of Medical grade silicone rubber of 0.157 cm inner diameter is laminar and steady. Mass transfer rates were measured downstream of the inlet region. Particle to tube diameters were varied from 0.05 to 0.15; tube-REYNOLDS number from 100 to 2,000 and solid concentrations from 0.001 to 0.015 by volume.

The experimental results form the basis for the next paper by HIRSCHMANN and BAUCKHAGE. The investigations will be tended to pulsatile two-phase flow in the future.

24.8 PARTICLE MOVEMENT AND TRANSVERSE FLUID-TRANSPORT-RATE IN A POISEUILLE FLOW OF A SUSPENSION OF LOW CONCENTRATION IN A TUBE WITH MEMBRANEOUS WALL AND THEIR INFLUENCE ON O_2- AND CO_2-MASS TRANSFER AS A MODEL FOR BLOOD FLOW

K. Hirschmann and K. Bauckhage*
*Universitat Bremen
Bereich Produktionstechnik/Verfahrenstechnik
Achterstrasse/BH; D 2800 Bremen 33; F.R.G.

While laminar mass transfer rates of dissolved O_2 and CO_2 from a homogeneous fluid through a tubular membrane can be calculated by means of correlations from GRAETZ/NUSSELT/LEVEQUE, the hydrodynamically caused augmentation of mass transfer rates from a flowing suspension (of spherical particles) to the tubular membrane and from ther to an external gas (and vice versa) has to be explained by the influence of individual particle movements (their very special trajectories) on the fluid transport rates perpendicular to the tube axis.

Based on the experimental results on suspensions of low concentration presented in the preceding articles, the augmentation of O_2 and CO_2 transfer can be quantified and specified mainly as unstationary entrance effects of the fluid and as particle movements during stationary suspension flow. The results will be discussed with regard to mass transfer problems in flowing blood with a special view of O_2- and CO_2-active red cells.

24.9 SENSITIVITY ANALYSIS OF THE PHYSICAL FACTORS AFFECTING FLOW IN A VASCULAR SEGMENT

K. P. Tewari
Biophysics Unit, H. P. Medical College
Simla-171001, India

In computing the flow from the pressure-gradient and studying the pulse wave propagation in the vascular system, number of approximations, pertaining to the arteries and blood which are used in simplifying the equations of the system, are made. In the actual biological system (which is a multivariate system) quantitative values of various parameters vary from point to point as well as during physiological and pathological changes. Therefore, here sensitivity analysis is applied to study and determine the sensitivity of the calculated or computed parameters to the variations in the physical parameters of the system which affect the pulse propagation in an arterial segment.

This analysis shows that the radius of the vessel is the most sensitive element in hemodynamics. The thickness and elasticity of the arterial wall have equal susceptabilities to the wave velocity which affect the transmission of both, the pressure and flow. The viscosity of the blood becomes a sensitive element in the arteriolar level. The viscosity of the wall (viscosity portion of the visco-elasticity of the vessel) is less significance than the thickness and dynamic elasticity to the wave-velocity.

This analysis helps to provide a base for studying the tolerances and specifications of the pulse-wave components which affect the flow of blood in a segment.

24.10 LONG CHAIN POLYMERS: THEIR EFFECT ON PULSATILE BLOOD FLOW IN ELASTIC TUBES

Shmuel Einav* and Menachem Roshu, School of Engineering, Tel Aviv University, Israel.

The effects of long chain polymer, Dextran T 2000, on pulsatile blood flow in elastic tubing have been examined. Pulsatile flow in a recirculating system was produced by a Harvard pulsatile pump (Harvard Apparatus model # 1421). The pump idealizes the pressure time variation in the aorta and reduces the possibility of mechanical destruction of the red blood cells. The stroke volume of the pump was varied continuously between 40 and 100 cycles per minute by increments of 10. Dextran T fractions (Pharmacia Dextran T 2000) polymer, which is prepared for two phase systems, was used. The weight average molecular weight of the Dextran T 2000 is 2,000,000, and its (weight) distribution is narrow and well defined. The Dextran was added to the whole blood in minute concentrations ranging from 100 to 2000 ppm (parts per million). Dextran also has a relatively large degradation time implying that the pressure reading in the in vitro system would not change appreciably with time. Viscoelastic tubing - 3.4, 6 and 9 mm in diameter was used. The tubes were separated by thickness of their wall into three groups: a) 1.6, b) 3.2, and c) 4.8 mm wall thickness and accordingly to a) highly flexible, b) flexible, and c) rigid. In all experiments where the pulse rate of the pump was 70 rpm (revolutions per minute) or higher drag reduction was higher for the more flexible tubing than the rigid one. For pulse rates below 70 rpm, the drag reduction was higher for the rigid tubing. The largest drag reduction was obtained for systole to diastole ratio of S = 30% in the highly flexible tubing, where the polymer concentration and the pulse rate were 100 ppm and 100 rpm respectively. For S = 50% and pulse rate higher than 70 rpm, the drag increased rather than decreased in the rigid tubing. Generally, the reduction in the drag was larger for polymer concentration of P = 1000 ppm than for 100 ppm, but became smaller with increasing polymer concentrations above 1000 ppm. The results clearly demonstrate the potential capabilities of long chain polymers to reduce drag at the vessel wall in both flexible and rigid tubing under pulsatile flow conditions.

* also Visiting Professor, Boston University, Biological Research Center, Boston, MA, U.S.A. (1977 - 1978).

25.1

BIAXIAL MEMBRANE INFLATION TECHNIQUES FOR IDENTIFICATION OF CONSTITUTIVE EQUATIONS AND FAILURE CRITERIA FOR SOFT BIOLOGICAL TISSUES

J. W. Melvin*, A. S. Wineman**, and N. M. Alem
*Highway Safety Research Unit
**Applied Mechanics & Engineering Sci.
The University of Michigan
Ann Arbor, Michigan 48109

The results of a cooperative research program to develop experimental and analytical techniques aimed at studying the constitutive equations and failure criteria for membranous soft biological tissues are presented. The main objective of the program was to be able to produce data on the material response of such tissues under dynamic loading (time to failure ~ 10 msec.) using simple test techniques. The three major features of the method are; (1) a simple membrane inflation technique is used to obtain a biaxial state in the tissue, (2) Direct Linear Transformation (DLT) methods are used to obtain accurate photometric data on material deformations using low cost equipment, (3) material identification procedures are used to determine the constitutive properties of the tissue.

The test configuration consists of an initially plane clamped circular membrane loaded by lateral pressure on one side. This configuration virtually eliminates grip failures and allows easy labeling of material particles and measurement of their current coordinates. A single camera and two angled mirrors are used to provide complete three-dimensional data on the inflated membrane in each photograph (35 mm for quasi-static tests and high speed 16 mm for dynamic tests). The resulting three views are each treated as a separate "camera" and are all calibrated using a precisely machined and marked metal hemisphere as a control field. Eleven DLT coefficients are calculated for each view from the calibration data. Without correcting for lens distortion, reconstructed points have been found to be located within an average error of 0.15 mm over the field of view which covers 40 mm.

The identification procedure consists of (1) solving the boundary value problem for the experimental configuration for any reasonable constitutive equation in order to predict the coordinates of specific particles during deformation, (2) representing the material response functions in the constitutive equation in terms of undetermined parameters; and (3) adjusting these parameters so as to minimize the error between measured and predicted coordinates. Since the inflated membrane is subjected to nonhomogeneous deformation it may be regarded as an assemblage of an infinite number of local homogeneous deformation states. Thus, if the coordinates of particles from the entire specimen are used, the minimization procedure is essentially selecting material parameters to fit data to an infinite number of simultaneous homogeneous deformation test states.

25.2 RHEOLOGY OF BIOMEMBRANES

by D. Bourgoin, M. Joly, D. Robaglia and W. Shankland
Département de Biophysique et de Biomathématiques
Faculté de Médecine, Université Paris 6.
91, Bd de l'Hôpital 75634 Paris Cedex 13

Our aim is to deduce the rheological parameters of biomembranes such as erythrocyte ghosts from the stress response of their very concentrated suspensions to various mechanical strains.

This study has been carried out on a Weissenberg rheogoniometer over a range of shear rate extending from 10^{-3} to 10 sec^{-1} under steady motion or sinusoidal motion (1).

These suspensions have been examined for different degrees of hydration and their rheological properties are compared to those of lecithin-water mixtures in the lamellar phase.

An analogous rheological behaviour is found for both systems ie : irreversible thixotropy in the low range of shear, followed by a steady flow, shear thickening at higher rate of shear.

An attempt to corrolate the microscopic rheological and structural properties to the macroscopic ones is given.

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25.3 BIOMECHANICS OF THE UTERINE CERVIX

R. M. Little
Department of Biomechanics
Michigan State University
East Lansing, Michigan 48824

The human cervix has received attention by only a limited number of investigators examining its ability ot undergo extreme dilation in labor. Prior to 1947, the cervix was believed to be basically muscular and the extremes from non-pregnant to full dilation during labor and then its return to its initial state were explained by muscular action. D.N. Danforth[1] initiated twenty years of search on the cervix by showing that it is predominantly fibrous connective tissue consisting primarily of collagen fibers and ground substance. This is very different from the uterine corpus which is smooth muscle.

The non-pregnant cervix has its collagen in dense, tightly woven bundles of interlacing fibers. There is negligible amounts of elastin and the reticulin fibers appear as short segments irregularly dispersed. This tissue has physical properties very similar to tendon permitting only limited deformations. During pregnancy the tissue changes such that there are clear spaces between the bundles and the percent of collagen is reduced. Danforth[2] initially felt that this "loosening" of the tissue was due to interstitial edema. Careful fturue studies showed that the change in water content was small and that the changes in the cervix were due to the decrease in the percent of collagen and extreme changes in the biochemistry of the ground substance. Changes in the properties of the connective tissue are not only observed in the cervix but in skin, blood vessels, ligaments and tendons during pregnancy. Establishment of biorheological information about both the non-pregnant and pregnant cervix represents an important area of research in connective tissue biomechanics.

The cervix is modeled by a quasi-linear viscoelastic equation, as suggested by Y. C. Fung, using the particular form developed by Haut and Little[3] for collagen. The finite element analysis by Rice and Yang[4] indicates that the cervix may be treated as a ring shaped membrane. Experimental studies are suggested to determine the necessary material parameters.

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254 THE STUDY OF SURFACE AND INTERFACIAL KINETICS OF BIOPOLYMERS USING A NORMALIZED RESONANCE OSCILLATORY SURFACE RHEOMETER

B. Warburton
Department of Pharmaceutics
The School of Pharmacy
University of London
29/39 Brunswick Square
London, WC1N 1AX, UK.

Introduction

Over the past few years a very sensitive oscillatory surface rheometer has been developed[1, 2] to monitor the surface elasticity and surface viscosity of solution of biopolymers both at the aqueous-air interface and the aqueous-oil interface. A novel feature of the technique is that the relatively large amplitude of oscillation available at or near to resonance can be made available over a wide frequency range by means of electronic feedback circuits which effectively cause the combination of instrument and sample to behave in a manner resembling resonance, irrespective of the operating frequency.

Present Work

By an extension of von Smoluchovski's aerosol coagulation kinetics and the application of ideal rubber elasticity theory [3] it has been found possible to predict the rate of increase of the real part of the dynamic surface shear modulus, G^1, as a function of time, t, for a wide range of biopolymers including soluble collagen, acacia senegal, and bovine serum albumen. The theory predicts that a plot of $1/G^1$ versus $1/t$ must be linear for a single molecular species but that the slope of such a plot will be a function of the surface concentration (and surface pH, in the case of polyelectrolytes).

Conclusion

These findings are confirmed and the implications are that a relatively simple mathematical model can be put forward to explain the physical behaviour of biopolymers on the surface of cell membranes. This has important indications for research in areas dependent on such phenomena e.g. cell to cell adhesion, immunological response and membrane potential.

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The author acknowledges the generous travel and subsistence grant from the Royal Society, 6 Carlton House Terrace, London and the Wellcome Trust, 1 Park Square West, London.

25.5 MATERIAL PROPERTIES OF THE LIVING HUMAN CORNEA

William P. Graebel, Bruce E. Cohan, and Andrew C. Pearch

Department of Applied Mechanics and Engineering Science
College of Engineering, The University of Michigan
Ann Arbor, Michigan 48109

A method and results are presented for obtaining for the first time material properties values of the cornea in the living human eye.

Knowledge of corneal material properties may provide insight into alterations in corneal shape produced in the growth process (the development of the adult shape, including abnormalities such as near-sightedness and astigmatism), by disease and trauma (keratoconus, corneal dystrophies, and chemical burns), and by the effects of surgery (astigmatism produced by suture placement and tension).

Previous measurements of corneal material properties have been in vitro and have usually involved strip testing. The indication from these strip tests is that the cornea has an exponential stress-strain curve. However, the validity of the results is subject to criticism because of the necessarily small size of the specimen and because of its nonuniform thickness, which varies by a factor of more than two over its length, causing nonuniform stress and strain. Because water balance and shape cannot be maintained in isolated cornea in a manner which models satisfactorily the in vivo condition, further doubt is cast on in vitro results.

The present technique applies small known loads within the physiologic range to the cornea of normal human subjects by means of a modified applanation tonometer. Corneal shape is calculated from photographs, obtained before and during loading, of a pattern projected onto the surface of the cornea. Corneal thickness is calculated from photographs of the interference fringes generated from the reflection of coherent light by the posterior and anterior surfaces of the cornea. Knowledge of pointwise corneal thickness, undeformed and deformed shape, and applied load are brought together in a finite element program to determine the material properties. The initial model assumes that the cornea is incompressible, isotropic, and linearly elastic within the loading range. Results for the material properties are presented.

25.6 MECHANICAL STRESSES AND PIEZOELECTRICITY OF DENTAL TISSUES

R. Ogolnik*, B. Picard*, and D. Geiger**
Laboratoire de Biomecanique et de Physiologie
Faculte de Chirurgie Dentaire-Universite Paris VII
5 rue Garanciere-75006 Paris

**Laboratoire de Biorheologie et d'Hydrodynamique Physiologique
Universite Paris VII-2 Place Jussieu, 75005 Paris

The presence of the teeth influence to a large extent the biomechanics of the calcified tissues, not only at the level of the mouth, but in the whole skull and face (1,2). Our objective here is to study the biomechanics of the dental tissues themselves.

Dental tissues subjected to in vitro compression or flexion exhibits piezo-electric phenomenon. This allows one to assess the biomechanics of the dental tissue (3,4,6).

The comparative importance of these charges at the level of the enamel, the amelodentine junction, the dentine and the pulp region, on sections of teeth cut parallel to their vertical axis and submitted to compression strains, led us to suppose that the piezo-electric phenomenon is all the more marked when the organic ground substance, consisting mainly of collagen, is itself larger (Fig. 1) (5). To confirm this phenomenon, we submitted the same dental tissues to extraction of the organic element. The piezo-electric phenomenon is then reduced. (Fig. 2).

If it would be possible to find a link between the piezo-electricity and the local pH, it suggests that an occlusal imbalance, producing abnormal stresses, and consequently abnormal electric charges and local pH, may be an etiological factor in caries, by way of the piezo-electric activity of the dental tissues.

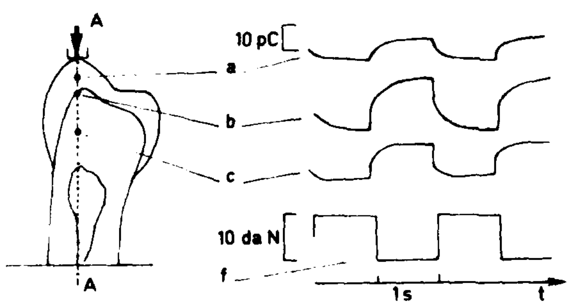

Fig. 1-Response to a compression strain.

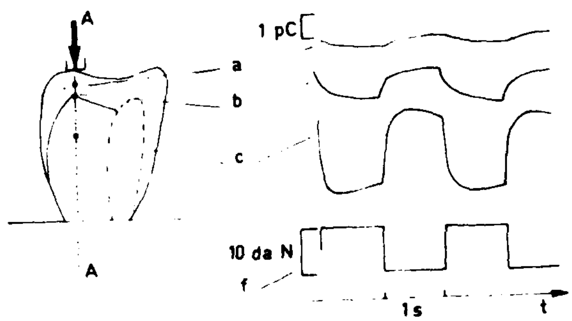

Fig. 2-Response of an organic-less Tooth.

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25.7 INFLUENCE OF FREEZE-DRYING AND GAMA STERILIZATION ON THE MECHANICAL PROPERTIES OF HUMAN DURA MATER GRAFTS

N. Petrov
Institute of Mechanics and Biomechanics
kv. Geo Milev bl. 8, POB 373
Sofia-1113, Bulgaria

St. Mechkarsky
Tissue Bank to the Pirogov Institute for Urgent Medical Aid
Sofia, Bulgaria

Subject of study is the influence of freeze-drying and gama sterilization on the mechanical properties of human dura mater grafts. It is shown that after freeze-drying the stress-strain curve and the ultimate values of the stress and strain do not change considerably. On the contrary, after gama sterilization of freeze-drying grafts great change of their mechanical properties is observed. For example, the ultimate stress decreases more than twice.

The conclusions are based on the results obtained at the experimental study of 474 samples from 30 donors.

26.1

THE HISTORY OF THE MEASUREMENT OF THE VISCOSITY OF HUMAN BLOOD SERUM AND PLASMA IN RELATION TO DISEASE

John Harkness
Department of Clinical Pathology
Musgrove Park Hospital
Taunton, England

The history of the estimation of the viscosity of human blood serum and plasma can be divided into three main phases. Each phase contains a different geographical distribution of interest, a different design of viscometer and a different objective for the measurement.

The first phase, beginning around 1900, was characterized by the use of the Hess single-limb straight capillary viscometer, mainly in Germany, and the object of the viscosity measurement was to derive the A/G ratio of the serum protein. It was realised that the serum viscosity values of normal people fell within a restricted range, that in patients in the early stage of acute disease the serum viscosity showed no marked changes and that it was significantly increased in chronic diseases such as tuberculosis, syphilis and malignancy. It was also known that this serum viscosity increase reflected a rise in the serum globulin. A widely-used method for the estimation of the serum albumin and globulin, and of the A/G ratio, was based on a combination of the serum specific gravity and serum viscosity.

The second phase began in the 1940s following the original papers of Whittington. Most of this work was carried out in England and the instrument was the Ostwald U-tube viscometer or its modifications. The object was to correlate the increase in the plasma viscosity with the clinical assessment of the severity of the disease. Because of the retention of fibrinogen in the plasma (as compared to serum) and the early changes in this plasma protein fraction, it was shown that the plasma viscosity test could be used in both acute and chronic conditions. Many papers pointed out the superiority of the plasma viscosity over the ESR as a clinical pathology test. Because of the inconvenience of the equipment and the time-consuming technique, this phase was virtually at an end by 1955.

The third phase began in 1963 with the commercial production (Coulter Electronics Ltd.) of a semi-automated capillary viscometer, designed by Harkness to overcome the criticisms of earlier instruments and methods. The estimation of the plasma viscosity was established as a clinical pathology test throughout the world. It is progressively displacing the ESR test.

The next phase, in the future, will require a fully-automated system by which a whole-blood sample is presented to an instrument and the plasma viscosity is printed out, in the same time scale (= 40 seconds) as a blood count by the Coulter S or its equivalent. We have available the extremely rapid viscometer (based on a new principle); a method for the automated separation of the plasma has not yet been developed.

26.2 CHANGES IN THE OXYGEN PRESSURE OF HUMAN MUSCLE TISSUE BY VARIATIONS OF THE FLOW PROPERTIES OF BLOOD

A. M. Ehrly and W. Schroeder
Div. of Angiology, Dept. of Internal Medicine and
Div. of Applied Physiology, Dept. of Physiology
Univ. Med. School Frankfurt, West Germany

Although flow properties of human blood can be easily varied *in vitro*, only a few methods are known to do so *in vivo* (hemodilution, reduction of fibrinogen concentration, improvement of erythrocyte deformability). Extravivum measurements, however, cannot give reliable information about the *in vivo* effects. Therefore we compared the rheological in-vitro-parameters (blood and plasma viscosity, erythrocyte deformability, erythrocyte aggregation) with the results of tissue oxygen pressure measurements from the human tibialis anterior muscle using membrane-coated micro-pt-electrodes (for methodelogical details see 1, 2).

In patients with arterial occlusions (intermittent claudication) variations of rheological parameters were performed by a) reduction of fibrinogen concentration b) improvement of red cell deformability and c) by varying the hematocrit.

Reduction in fibrinogen concentration by subcutaneous injection of Arwin (Ancrod) decreases blood and plasma viscosity and leads to a marked reduction in red cell aggregation, while the red cell deformability remains unchanged (3). At the same time the muscle tissue pO_2 increases significantly ($p < 0,005$).

After the i.v. injection of 200 mg Pentoxifyllin, red cell deformability (as measured by filtration through 8 µm-Millipore-filters) increases ($p < 0,05$ for about 1-2 hours. Muscle-pO_2 increases temporarily as well ($p < 0,0001$) (4).

Preliminary experiments show that muscle tissue pO_2 is also influenced by changes in the hematocrit (hemodilution with Rheomacrodex, washed red cell transfusion).

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26.3 FUNDAMENTAL MECHANISMS CONTROLLING HEMORHEOLOGY

Herbert L. Davis
Departments of Surgery and Biochemistry
University of Nebraska College of Medicine, Omaha 68105

In the study of human stress and disease many parameters must be assayed to establish their contributions to causes and effects. In the past 25 years much evidence demonstrates that hypercoagulability is the major common factor in disease and death. It is relevant to impaired blood distribution (especially in the microcirculation), aggregation of platelets, leucocytes, erythrocytes (with resultant DIC), pathological manifestations of cardiovascular disease, cancer, infections, diabetes, shock, etc., and to concomitant alterations in the form and function of living proteins of nerves, membranes, and enzymes. Hypercoagulability is a major factor also in the hyperviscosity of stress and disease.

Many papers demonstrate that fibrinogen is the key plasma component which determines coagulability and viscosity of plasma and blood. Fibrinogen continues to circulate normally as long as there exists a sufficient excess of negative charges and of hydration (bound water) on all its polar sites. The action of thrombin in splitting off two strongly negative fragments lowers the charge to spontaneous polymerization producing a gel. Other procoagulants include (a) cationics to lower the negative charge and the hydration, and (b) dehydrant surfactants to displace bound water from positive sites and thus to lower the hydrophilic character. Low to moderate amounts of representatives of these two classes lower clot times, but high concentrations retard and prevent coagulation (irregular series). Anticoagulants have the opposite effects and include (c) anionics (heparin) and (d) hydrants to increase or protect the hydration of fibrinogen. Procoagulants cooperate to form gels in minimum times, and then in excess precipitate fibrinogen.

Many papers report elevated viscosity of blood in clinical situations now recognized as associated with hypercoagulability. Disseminated intravascular coagulation (DIC) is now recognized in a wide variety of stress and disease states. Low-dose intrafat heparin represents a significant advance in the prevention and reversal of lethal degrees of thromboembolic episodes. The plasma gel and the blood clot represent the end stages of both hypercoagulability and hyperviscosity. In vivo there are many stages of disorder between the normal flowing blood and the increasing viscosity that ends with vascular occlusion. Therapeutic control of the charge and hydration on fibrinogen will solve many problems.

26.4 RED BLOOD CELL AGING AS A MODEL TO INFLUENCE PHARMACOLOGICALLY THE RED CELL DEFORMABILITY

H.-G. Grigoleit, H. Leonhardt*, R. Schroer**, F. Lehrach**
Hoechst AG, 6230 Frankfurt/M-80, Germany
*Klinikum Steglitz der Freien Universitat, Berlin
**Hoechst AG, Werk Albert, Wiesbaden

Red blood cells (RBC) from freshly shed blood develop a considerable decrease in deformability during short time storage (< 3 hrs). This highly reproducible phenomenon, proven by a filtration technique (1) with 5 μm filters encouraged us to use it to evaluate possible influences of pharmacological agents on red cell deformability (RCD). The flow rate (FR, ml/min) of whole blood through the filter is considered to be a measure of the mean RCD of a RBC population. In 3 series of experiments we investigated the effect of pentoxifylline (P, 10 and 20 μg/ml), theophylline (T, 96.6 μg/ml) and prednisolone (PR, 20 μg/ml) as well as of penbutolol (PE, 0.5 and 2.0 μg/ml) on RCD in this model. In each experiment blood (100 ml) from 10 healthy donors was divided into 3 aliquots (A). A1 served as a control, to A2 and A3 the a.m. compounds were added. FR measurements (4-6 filtrations/sample/time) were done at times 0, 45', 90' and 180' after adding the compounds. The data were evaluated by non-parametric statistics - P increased FR dose dependent ($p < 0.05$). T and PR do not differ statistically from control, though T slightly increases, PR slightly decreases FR. PE (2.0 μg), a beta-blocking agent, increases FR ($p < 0.05$; 0'). For P the influence on RCD is known (2, 3). T, a methylxanthine derivative as P is probably due to a different chemical structure ineffective. The nature of the RCD increasing effect of P might be related to an elevation of RC-ATP (4, 5). SEM revealed that P does not influence RC surface. The effects of the other compounds can not be explained at the moment. The model used seems to be sensitive enough as a screening system.

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26.5 THE BEHAVIOR OF DIFFERENT TYPES OF MATERIALS IN THE DYNAMIC PHYSIOLOGICAL ENVIRONMENT

Stephen D. Bruck, Ph.D.
Stephen D. Bruck Associates, Inc.
One Central Plaza Building, Suite 10 NE
11300 Rockville Pike
Rockville, Maryland 20852

Hemorheological considerations are often ignored when assessing the blood compatibility of biomaterials. Most synthetic materials when in contact with blood almost instantaneously adsorb some plasma proteins, water, and small inorganic ions, influenced not only by various surface properties of the substrate but also by conditions of flow. The initial rapid reaction subsequently gives rise to slower, time-dependent phenomena, including desorption and/or enzymatic modifications of the adsorbed proteins. Materials not compatible with blood cause the polymerization of fibrinogen to fibrin, activate platelets and in association with cellular elements, lead to thrombosis. Flow conditions affect the composition of thrombus: under low shear forces, so-called red thrombus forms composed mainly of fibrin and enmeshed red cells, while under high shear forces, so-called white thrombus forms that is composed chiefly of fibrin and enmeshed platelets. Fibrinolysis *in vivo* mitigates these reactions, possibly causing the dissolution of small thrombi and in such cases some materials may become "blood tolerable." It should be pointed out that adsorption is accompanied by absorption and both affect the ultimate biological and physical performance of polymeric materials. Hemorheological events are markedly influenced by the types of biomaterials, such as smooth-surfaced materials (rigid as well as elastomeric), gels, cell-cultured scaffold structures, and rough-surfaced "flocks" composed of individual tiny (25 x 250 μm) polyester fibrils which protrude in the blood flow path. In contrast to the former systems, the latter forces the deposition of a fibrinogen/cellular coagulum often inaccurately referred to as a "neointima" or "pseudo-neointima" as the blood-contacting interface. The deposition of this layer is dependent on time, species, blood-flow, and device configuration. Furthermore, the build-up is uneven, difficult to control, and continues to a thickness of 500-600 μm that greatly exceeds the height of the "flock." The nourishment of this layer is entirely diffusion-controlled from the blood. Fragmentation of the coagulum/cellular matrix and detachment of individual fibrils have been reported under flexing conditions. Synthetic smooth-surfaced, deformable gels that approximate the modulus of elasticity of the endothelium, as well as endothelial cell-cultured scaffold structures with their active secretory processes, matching elastic moduli and hydrodynamic properties, are useful not only for prosthetic applications but importantly also as models for the study and prevention of atherosclerosis and related diseases.

26.6 EVALUATION OF BLOOD MICROFILTER PERFORMANCE

Cherry H. Tamblyn, Robert J. Knox, Frank J. Nordt,
G.V.F. Seaman, Roy L. Swank, and C.F. Zukoski IV
Department of Neurology
University of Oregon Health Sciences Center
Portland, Oregon 97201, USA

An effective blood microfilter must ensure adequate delivery of stored blood or blood components while removing microaggregates and debris without traumatization of any blood components or addition of foreign particulate matter from the filter itself. A variety of blood microfilters are available commercially and it is therefore desirable to monitor both their relative and absolute efficacy. However, the quantitation of the performance characteristics of blood microfilters poses several problems. Blood is not an ideal test fluid since some of its properties vary both from donor to donor and also in the same donor at different times. Even the characteristics of the same specimen of blood change over a period of time. However any other test fluid or system would have to be qualified in some way against blood to ensure that the measured parameters of any test are reliable indicators of the way a blood microfilter will "clean up" blood. Two promising methods of assessing the removal of blood microaggregates or other particulates from stored blood by microfilters, namely electronic particle size distribution analysis and screen filtration pressure (SFP) measurements, were compared. Microaggregate counts and size distributions have been difficult to quantitate because of a marked decrease in microaggregate counts during the time required to repeat the procedure. This problem has now been largely eliminated by the use of a red cell lysing solution containing a low concentration of glutaraldehyde which permits destruction of the red cells but yet stabilizes the microaggregate counts. As a consequence it has been possible to make a quantitative comparison with the screen filtration pressure method. The correlation between the SFP values obtained with 20 x 20, 30 x 30, and 40 x 40 μm screens and the number of microaggregates measured electronically has been examined for outdated blood bank blood. Samples containing different relative concentrations of microaggregates were prepared by mixing various proportions of repeatedly filtered (clean) blood and unfiltered blood. It has been shown that the SFP values are linearly related to the relative quantity of filtrable material, provided that the screen is not largely clogged. A linear relationship was also observed between the relative quantity of microaggregates and the electronic counts per ml. The simplicity and reproducibility of the SFP procedure offer advantages over electronic particle size distribution analysis for the evaluation of the performance of blood microfilters. It has been shown also that the commercially available blood microfilters do not release significant quantities of non-biological particles or fibers into the blood during filtration.

26.7

EFFECTS OF EXERCISE AND CONDITIONING ON PROPERTIES OF RED BLOOD CELLS SIGNIFICANT FOR BLOOD FLOW. R.E. Lovlin, L.S. Sewchand, J. S. Beck and S. Rowlands. Division of Medical Biophysics, Faculty of Medicine, The University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

In an effort to determine the effects of exercise and conditioning on the erythrocyte (RBC) membrane, we have shown an increase in membrane phospholipid with training and a greater deformability of athletes' erythrocytes as indicated by the pressure required to force them through a small glass capillary tube. The cellular volume of the erythrocytes from male athletes was found to be larger than that of sedentary subjects (males) but there was no significant difference between the membrane areas. Since an increased volume-to-area ratio is expected to result in a decrease in deformability of RBC from trained subjects, we conclude that the measured increase in deformability reflects some change in the membrane with exercise. This change, whether chemical or otherwise, results in a greater fluidity of the RBC membrane.

In addition to the above findings, we have also observed a linear relation between cell volume and cell count as determined on a Coulter Counter (Model Z). Anyone with a relatively large cell count was found to have cells of small volume and the converse is also true. This linear relationship holds true not only for trained mountain climbers and cyclists but also for a large population ($\sim$ 200) of supposedly untrained subjects. This finding is still being investigated.

These observations may contribute to understanding organ effects of exercise and training that depend on differences in blood flow.

Supported by the Medical Research Council of Canada.

26.8 LOWER PLASMA VISCOSITY OF JOGGERS VS. NON-JOGGERS

Stanley E. Charm and Harold Paz
Tufts University School of Medicine
Boston, Massachusetts 02111
George S. Kurland
Beth Israel Hospital
Harvard Medical School
Boston, Massachusetts 02115

The plasma viscosity of joggers (running at least 14 miles per week for at least a year) is significantly lower than non-joggers who are apparently healthy. The difference between the means is 6% with some joggers having plasma viscosities 15% lower. The reason for the lower viscosity among joggers appears to be associated with lower gamma globulin concentrations in their plasmas. However, there was no significant difference in whole blood viscosities between these two groups due to variations in hematocrit and possibly red cell flexibility.

High density lipids were significantly higher among joggers than non-joggers as would be expected from previous reports appearing in the literature.

Equations modeling flow in small arterioles and capillaries indicate that pressure drop through these vessels should be directly proportional to plasma viscosity. Since most of the energy loss for flow occurs through these vessels, it is concluded that joggers should require less energy to maintain circulation than non-joggers, other factors being equal.

Viscosity data were measured using a Wells-Brookfield cone and plate viscometer (RVT) and calculated using the Casson equation.

27.1

CONTRIBUTION TO THE STUDY OF BLOOD FLOW USING LOW FREQUENCY SPECTRAL ANALYSIS OF DOPPLER ULTRASONIC WAVES. APPLICATION TO A PULSED MODEL

J. C. Vera, M. Lefort and J. F. Stoltz
Groupe d'Hemorheologie - Centre Regional de Transfusion - Brabois - 54500 Vandoeuvre-les-Nancy - France, et LEMTA - Ecole des Mines - 54000 Nancy - France

The ultrasonic debitmetry by Doppler effect is of great interest in hemodynamics; however, it appears to be limited by the l w precision of the results, and by the difficulty of deducing the velocity or the other characteristics of the flow, even in the case of relative measures. In Fact, the signal obtained from the transducer results from several targets (the red blood cells), contained in the measuring volume. The Doppler signal obtained after translation of frequencies, includes a great quantity of information which concern not only the characteristics of the flow, but also that of the transducer and the ultrasonic field.

The experimental study carried out concerns the spectral analysis at low frequencies, in real time, of the Doppler signal. This study has been realized on a hydrodynamic model which allows to simulate a pulsatile flow through a cylindric, and viscoelastic tube. The fluid used has a viscosity very close to that of the blood (0.04 St) and contains particles of starch in suspension.

The amplitude spectra of the Doppler signals give access to informations from which characteristics parameters of flow can be derived (parameter of Womersley, Instantaneous Reynolds numbers).

From that model, we have studied several flows at different Reynolds' numbers: (Re = 2210, 2650, 3200 and 3540) and different frequencies corresponding to the physiologic field (0.9 Hz to 1.2 Hz).

The results obtained show the originality of this technic of analysis which permits to improve the precision of the ultrasonic flowmeter and to foresee new developments of their applications.

27.2

STUDYING THE FORMATION OF RED BLOOD CELL AGGREGATES USING AN ULTRASONIC RESONATING TECHNIQUE

D. Cathignol*, C. Fourcade*, M. Heitz**
J. C. Vera** and J. F. Stoltz**

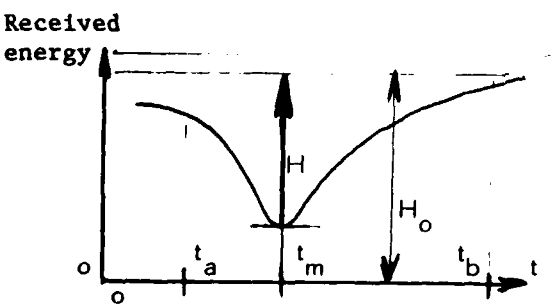
*Centre d'Etude et de Technologie Appliquees a la Clinique
SCR2-INSERM, 18 avenue du doyen Lepine-69500 Bron -France

**Groupe d'Hemorheologie
Centre Regional de Transfusion et d'Hematologie
Brabois - 54500 Vandoeuvre-les-Nancy, France

An ultrasonic technique which follows the formation of aggregating particles in a liquid is described. The instrument used has been specially adapted to study red blood cell aggregates during sedimentation.

When a particle was placed in an ultrasonic field it behaves like a diffusing object provided its size was relatively inferior to the wavelength used. However, if the particle size was progressively increased a critical or resonating stage was reached in which the ultrasonic energy was completely absorbed. This resonating phenomena was observed during blood sedimentation. A correlation was observed between operating frequency and aggreated particle size.

The ultrasonic frequency on the utilized instrument could be altered from 1 to 25 MHz. The ultrasonic waves after having crossed the blood sample are reflected and gathered by the same transducer. The registered transmitted energy during sedimentation varied as indicated in the figure shown below:



The characteristic curve parameters are:

t_a :appearance of absorption peak

t_m :time corresponding to the minimum received energy

H_o :end of absorption peak

$\frac{H}{H_o}$:absorption percentage

This study was carried out at 5 MHz and was performed on blood of healthy donors. A hematocrit of between 20 to 60% was used either in plasma or in the presence of either albumin, dextran 40 or fibrinogen. The results for 10 samples taken from one blood sample with a hematocrit of 20% were as follow: t_m = 627 (27s); t_b = 807s (= 40,5s); $\frac{H}{H}$ = 0,98 (= 0,0026)

Similar mean values were obtained for 30 different blood samples indicating the validity of this technique to follow the formation of red blood cell aggregation or of other blood constituents.

ACKNOWLEDGEMENT: Grant DGRST No 77 71 930

27.3 ULTRASONIC VELOCITY MEASUREMENTS AND PHASE TRANSITIONS IN LIPOSOME SUSPENSIONS

Akio SAKANISHI
Department of Physics, Faculty of Science
University of Tokyo, Tokyo, Japan

In order to elucidate the mechanical effects of existing states of lipid constitutions and phase transitions in biological membrane (1), we have measured the ultrasonic velocity in dilute suspensions of lipid vesicles, liposomes, including phospholipids and cholesterol as a model system of membrane with varying the temperature.

An ultrasonic velocimeter was constructed by means of an improved sing-around method, in which reflection type twin cells were used. One of the cells contained a suspension of liposome and the other only a medium; each cell had a single transducer of electrostrictive ceramics of lead titanate and zirconate at the resonant frequency of 3 MHz. This ceramics transmitted the sound wave in a sample through an electric pulse generator and received the wave reflected by a block end of brass to trigger the next pulse. Periods of the pulses were measured with an electric period counter in seven digits. The accuracy of the sound velocity was 5 ppm, since the difference of velocity between suspension and medium was obtained directly (2).

Phospholipids were beef brain sphingomyelin (SM), and synthetic dimyristoyl (DMPC) and dipalmitoyl (DPPC) phosphatidylcholines. Suspensions of lipids were sonicated under nitrogen gas in a medium of 150 mM NaCl with potassium phosphate buffer at pH 7.0. Nonsonicated liposomes of DPPC were also prepared by the use of a vortex mixer only. Cholesterol was added to DPPC and sonicated in suspensions.

The difference of the ultrasonic velocity ΔV between liposome suspensions and the medium decreases monotonously with increasing the temperature from ca. 0°C to 60°C except the transition region. In a case of SM an abrupt change of ΔV broadly occurs in the temperature range of 35° to 44°C, which corresponds to the transition of beef brain SM. For DMPC and DPPC a sharp minimum of ΔV is observed at the temperature T_C of 24°C and 42°C respectively. For unsonicated DPPC we have a deep and discontinuous depression of ΔV at the lower side of T_C and a similar behavior to sonicated DPPC in the higher temperature than T_C. Addition of cholesterol to DPPC liposome brings to smearing out of the sharp minimum at 42°C; ΔV decreases in the lower and increases in the higher temperature range than 30°C with increasing the cholesterol.

These anomalous temperature dependence of ΔV demonstrate the gel to liquid crystalline phase transitions of phospholipids and are concerned with critical fluctuation.

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27.4 THE MICRORHEOLOGY OF COLLOIDAL DISPERSIONS: SOME BIOLOGICAL APPLICATIONS

K. Takamura, H.L. Goldsmith and S.G. Mason
Department of Chemistry, McGill University, Montreal, Canada

A series of investigations from this laboratory have reported on the effects of shear on the flow behavior of charged colloidal-size spheres in aqueous suspension. In these systems, translational and rotational Brownian motion affect the particle motions and electrostatic and dispersion forces significantly alter interactions between spheres (1). Hydrodynamic theory predicts that, at a given shear rate G, the period of rotation T of a doublet of rigid spheres depends on the separation distance h between sphere surfaces and on the ability of the spheres to rotate relative to each other. The dimensionless period of rotation TG is significantly higher for freely rotating than for rigidly connected spheres. Using a traveling microtube apparatus for tracking particles in Poiseuille flow (2), this theory was applied to latex sols in a detailed study of two-body collisions between 2.6 μm dia. spheres and the rotations of the formed doublets. Measurements of the mean TG over 100 rotations in a population of spheres in KCl solution demonstrated the existence of doublets of freely rotating spheres in the secondary energy minimum having h between 15 and 17 nm. In the presence of a cationic polyelectrolyte, however, the measured TG for 80% of doublets was lower, corresponding to that of rigidly connected spheres showing that flocculation by polymer-bridge formation had occurred.

The trajectories of colliding latex spheres were also studied in the presence of polyelectrolyte and some unexpectedly long-range interactions over 2 to 5 μm were noted. These resulted in sphere capture and the formation of non-separating doublets, in some of which $h > 2$ μm. Doublets having similarly large h were observed in the presence of γ-globulin (purified human Cohn fraction 2). From the measured TG of these aggregates and the observed increase in TG with increasing G, it was concluded that the spheres were linked by a flexible bridge of aggregated immunoglobulin molecules. In most doublets, the length h of the bridge < 1 μm, although a few particles had much higher h.

We believe that the above approach to the investigation of latex sphere interactions may prove to be of value in immunological studies. The measured TG and its dependence on shear rate yields information on whether the molecular bridge between spheres is rigid or flexible, and from measurements of G at doublet break-up, it is possible to calculate the force of attraction between the spheres.

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27.5 THE VISCOSITY OF NORMAL AND PATHOLOGICAL SYNOVIAL FLUID

I. Anadere[+], H. Chmiel[+], and W. Laschner[++]

[+]Institut fur Grenzflachen-und Bioverfahrenstechnik
Eierstrasse 46, 7000 Stuttgart 1, Federal Republic of Germany

[++]Abteilung fur orthopadische Rheumatologie
Klinik fur Orthopadie und Unfallchirurgie Dr. Baumann e.V.
Alexanderstrasse 5-7a
7000 Stuttgart 1, Federal Republic of Germany

The role of the synovial fluid as a lubricant to prevent friction and wear of cartilage in joints is indisputable. Apart from that it acts as a shock absorber to store mechanical energy which can add up to several times of body weight as a result of impact loading, Synovial fluid shows both viscous and elastic flow properties, i.e. it can store and dissipate energy, a property which is characteristic of viscoelastic fluids. The existence of a hyaluronic acid-protein complex is responsible for the viscoelastic properties of normal synovial fluid. This biopolymer with a molecular weight of a million or more shows high viscous properties in low shear rates, but which lead to decrease of viscoelasticity due to uncoiling of the polymer chains and their orientation to stress direction at higher shear rates. Pathological synovial fluids however, exhibit a decrease in viscoelasticity due to either increased production of the fluid and/or due to depolymerisation of glycosaminoglycan chains and thus a resulting decrease in molecular weight. The rheological properties of hyaluronic acid and synovial fluid (normal and pathological) were measured both under conditions of oscillating sinosoidal flow and steady flow for a large range of shear rates. A new oscillating capillary rheometer was used for the determination of the viscoelasticity and a rotating viscometer of Couette type for the steady flow properties. Other physical and biochemical measurements were performed like the determination of the intrinsic viscosity, molecular weight and concentration of hyaluronic acid etc. The results for normal and pathological fluids (rheumatoid, degenerative and traumatic) will be presented and discussed in relation to their diagnostic and preventive aspects for joint diseases.

27.6 · THE VISCOSITY OF THE URINE FROM CATHETERIZED PATIENTS PROBLEMS AND POSSIBILITIES

U. Parkhede, A. Norberg, and B. Norberg
Department of Internal Medicine
University Hospital of Lund
S-221 85 Lund, Sweden

The urine of patients with indwelling catheters is invaded with bacteria within a week, mainly via the mucus layer between the catheter and the urethra. The bacterial growth produces a cloudy foul-smelling urine, catheter blockage and uring leakage between the catheter and the urethra.

The aim of the present study was to evaluate the effect of methenamine hippurate treatment on urinary infection in patients with indwelling catheters. It seemed reasonable to assume, that urine viscosity reflects urine changes due to bacterial growth. Since the physical properties of the voided catheter urine are altered continuously by bacterial growth and leukocyte disintegration, freshly voided urine was measured by capillary viscosimetry at room temperature at the ward.

During treatment with methenamine hippurate, there was a tendency towards reduction of urine viscosity. In contrast, catheter life was doubled. It is concluded, that the catheter itself provided the most adequate measure of methenamine hippurate effects on urine flow properties of clinical significance (1, 2).

REFERENCES

1. A. NORBERG, et al, Acta Soc. Med. Suec. 86:584 1977.
2. B. NORBERG, et al, Acta Soc. Med. Suec. 86:584 1977.

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