

# **PROTEINS OF IRON STORAGE AND TRANSPORT**

**Edited by G. SPIK, J. MONTREUIL,  
R. R. CRICHTON and J. MAZURIER**

083

58-1742/85  
I 61  
1985(7)

# PROTEINS OF IRON STORAGE AND TRANSPORT

Proceedings of the 7th International Conference on Proteins of Iron Metabolism  
held in Villeneuve d'Ascq (France) on 30 June-5 July, 1985

Edited by

**G. SPIK**

**J. MONTREUIL**

**R.R. CRICHTON**

**J. MAZURIER**



1985

**ELSEVIER SCIENCE PUBLISHERS**  
**AMSTERDAM · NEW YORK · OXFORD**

© 1985 Elsevier Science Publishers B.V. (Biomedical Division)

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the publisher, Elsevier Science Publishers B.V., Biomedical Division, P.O. Box 1527, 1000 BM Amsterdam, The Netherlands.

Special regulations for readers in the USA - This publication has been registered with the Copyright Clearance Center Inc. (CCC), 27 Congress Street, Salem, MA 01970, USA. Information can be obtained from the CCC about conditions under which photocopies of parts of this publication may be made in the USA. All other copyright questions, including photocopying outside the USA, should be referred to the copyright owner, Elsevier Science Publishers B.V., unless otherwise specified.

ISBN 0 444 80722 5

*Published by:*

Elsevier Science Publishers B.V. (Biomedical Division)  
P.O. Box 211  
1000 AE Amsterdam  
The Netherlands

*Sole distributors for the USA and Canada:*

Elsevier Science Publishing Company Inc.  
52 Vanderbilt Avenue  
New York, NY 10017  
USA

**Library of Congress Cataloging-in-Publication Data**

**International Conference on Proteins of Iron Metabolism**  
(7th : 1985 : Villeneuve-d'Avesq, France)  
Proteins of iron storage and transport.

**Bibliography: p.**

**Includes index.**

1. Transferrin--Congresses. 2. Ferritin--Congresses.
3. Iron proteins--Congresses. I. Spik, G. (Geneviève)
- II. Title.

QP552.T7I567 1985 612'.3924 85-20603  
ISBN 0-444-80722-5 (U.S.)

Printed in The Netherlands

## PREFACE

Since the First International Conference on the Proteins of Iron Storage and Transport, organised in 1973 by Drs Phil Aisen, Pauline Harrison and Ernie Huehns at the University College in London, the number of participants has more than doubled and the field of iron metabolism has undergone a considerable expansion due to major advances in structure determination, gene cloning and cell receptors.

All of the six previous meetings held in London, Louvain-La-Neuve, New-York, Davos, San Diego and Sapporo marked an important step in the development of the research on Proteins of Iron Storage and Transport, due to the enthusiasm of the participants to share their new results and to exchange ideas.

The VII<sup>th</sup> International Conference on Proteins of Iron Metabolism which was held from the 30<sup>th</sup> of June to the 5<sup>th</sup> of July 1985 in France, on the Campus of the Université des Sciences et Techniques de Lille at Villeneuve d'Ascq, has not failed in this tradition.

206 participants from 22 countries have presented exciting new results in 18 plenary lectures and more than 150 poster communications. Since it is impossible to publish all of the results in this book, we have chosen to give an overview. In particular, the eighteen plenary lectures are included as well as a number of oral communications which have been selected by the chairmen who had, in addition, the heavy responsibility during the round table discussions to summarize the most relevant results presented in the poster sessions. I would like to thank them very warmly.

One of the most pleasant aspects of scientific meetings is to offer an opportunity to honour personalities who have contributed, by their discoveries, to enrich our knowledge of Nature and Life. During the VII<sup>th</sup> International Conference on Proteins of Iron Metabolism we have chosen to honour two pioneers in the field of transferrins : Professor Arthur Schade for his work on conalbumin and siderophilin and Professor Jean Montreuil for his discovery, 25 years ago, of lactotransferrin from human milk. The meeting was dedicated to both of them.

The Conference and satellite events have been achieved thanks to the financial support which has been offered by the Ministère de la Recherche et de la Technologie, the Conseil Régional du Nord/Pas-de-Calais, the Centre National de la Recherche Scientifique, the Institut National de la Recherche Médicale, the Université des Sciences et Techniques de Lille, the City of Lille and by several french and foreign industrial firms. I express my gratitude to all of them for their help.

Financial support is not enough to be able to organized a congress and if we have succeeded, it is thanks to the aid of devoted men and women who have made the stay of the participants as pleasant as possible. With enthusiasm, everyone of the "Laboratoire de Chimie Biologique" contributed to this, and I thank them with all my heart !

May I express my particular gratitude to the Members of the Organizing Committee for their constant and efficient help : Jean Montreuil, Robert R. Crichton, Joël Mazurier and André Verbert.

The meeting was placed under the shadow of the belfry of the North of France and under the sign of iron. I hope that the forged friendships which are the basis to link scientific connections will be solid and durable as iron itself!

Geneviève SPIK

## LIST OF CONFERENCE PARTICIPANTS

AISEN P., A. Einstein College of Medicine, NEW YORK, U.S.A.  
 ALFREY C., The Methodist Hospital, HOUSTON, U.S.A.  
 ALVAREZ X., University of Glasgow, GLASGOW, UNITED KINGDOM  
 ANDREWS S., University of Sheffield, SHEFFIELD, UNITED KINGDOM  
 APPEL H., Kernforschungszentrum Gmbh, KARLSRUHE, W. GERMANY  
 AROSIO P., University of Milano, MILANO, ITALY  
 AWAI M., Okayama University Medical School, OKAYAMA, JAPAN  
 BACON B., Cleveland Metropolitan General Hospital, CLEVELAND, U.S.A.  
 BAKKEREN D., Erasmus Universitat, ROTTERDAM, THE NETHERLANDS  
 BARON C., Faculté des Sciences Mirande, DIJON, FRANCE  
 BATES G., Texas A&M University, COLLEGE STATION, U.S.A.  
 BAUMINGER E., Racah Institute of Physics, JERUSALEM, ISRAEL  
 BEAUMONT C., Hopital Louis Mourier, COLOMBES, FRANCE  
 BEZKOROVAINY A., St Luke's Medical Center, CHICAGO, U.S.A.  
 BIRGEGARD G., University Hospital, UPPSALA, SWEDEN  
 BOTHWELL T., University of the Witwatersrand, JOHANNESBURG, SOUTH AFRICA  
 BOTTOMLEY S., University of Oklahoma, OKLAHOMA CITY, U.S.A.  
 BOUREL M., Hopital Pontchaillou, RENNES, FRANCE  
 BOWMAN B., Texas Health Science Center, SAN ANTONIO, U.S.A.  
 BRECHOT C., Institut Pasteur, PARIS, FRANCE  
 BRIDGES K., Howard Hughes Medical Institute, BOSTON, U.S.A.  
 BROCK J., University of Glasgow, GLASGOW, UNITED KINGDOM  
 BROSSARD C., Laboratoires Cassenne, OSNY, FRANCE  
 BROWN E., Washington University School of Medicine, SAINT-LOUIS, U.S.A.  
 BROWN J., Oncogen, SEATTLE, U.S.A.  
 BROWN-MASON A., University of Vermont, BURLINGTON, U.S.A.  
 BROXMEYER H., Indiana University, INDIANAPOLIS, U.S.A.  
 BRUVIER C., Laboratoires Cassenne, OSNY, FRANCE  
 BURET J.-P., Laboratoires Cassenne, OSNY, FRANCE  
 CAZZOLA M., University of Pavia, PAVIA, ITALY  
 CHAN Y., The Chinese University, HONG-KONG, HONG-KONG  
 CHASTEEN N. D., University of New Hampshire, DURHAM, U.S.A.  
 CHIANCONE E., University 'La Sapienza', ROMA, ITALY  
 CLETON M., Pathological Institute Rou, UTRECHT, THE NETHERLANDS  
 COHEN G., Institut Pasteur, PARIS, FRANCE  
 COOK J., University of Kansas, KANSAS CITY, U.S.A.  
 CÔRNELIS P., Unité de Médecine Expérimentale, BRUXELLES, BELGIUM  
 CRICHTON R., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 DALLMAN P., University of California, SAN FRANCISCO, U.S.A.  
 DEUGNIER Y., Hopital Pontchaillou, RENNES, FRANCE  
 DOOLEY J., Royal Free Hospital School of Medicine, LONDON, UNITED KINGDOM  
 DORNER M., Medizinische Universitäts-Klinik, HEIDELBERG, W. GERMANY  
 DRYSDALE J., Tufts Medical School, BOSTON, U.S.A.  
 DYCK J.-L., ORSTOM, LOME, TOGO  
 EGYED A., National Institute of Haematology, BUDAPEST, HUNGARY  
 EVANS R., Guy's Hospital Medical School, LONDON, UNITED KINGDOM  
 FARGION S., University of Milan, MILAN, ITALY  
 FEENEY R., University of California, DAVIS, U.S.A.  
 FIGARELLA C., Unité de Recherches de Pathologie Digestive, MARSEILLE, FRANCE  
 FINKELSTEIN M., University of Missouri-Columbia, COLUMBIA, U.S.A.  
 FINKELSTEIN R., University of Missouri-Columbia, COLUMBIA, U.S.A.  
 FLANAGAN P., University of Western Ontario, ONTARIO, CANADA  
 FLETCHER J., City Hospital, NOTTINGHAM, UNITED KINGDOM  
 FOUCRIER J., Université de Paris, BOBIGNY, FRANCE  
 FRANCOIS C., S. A. Oléofina, BRUSSELS, BELGIUM

FUNK F., Lab. f. anorg. Chemie, ZURICH, SWITZERLAND  
 GALENT A., Société Diététique Gallia, LEVALLOIS PERRET, FRANCE  
 GARRATT R., Guy's Hospital Medical School, LONDON, UNITED KINGDOM  
 GAUTHIER Y., Cent. de Rech. du Serv. de Santé des Armées, LYON, FRANCE  
 GAUTREAU C., Institut de Pathologie Moléculaire, PARIS, FRANCE  
 GIANNI L., Istituto Nazionale Tumori, MILANO, ITALY  
 GIMPEL J., State University Hospital, UTRECHT, THE NETHERLANDS  
 GLASS J., Beth Israel Hospital, BOSTON, U.S.A.  
 GRABER S., University of Vermont, BURLINGTON, U.S.A.  
 GRADY R.W., Cornell University, NEW YORK, U.S.A.  
 GRISARU S., Hebrew University, JERUSALEM, ISRAEL  
 HALLIDAY J., University of Queensland, BRISBANE, AUSTRALIA  
 HANOTTE O., Université de l'Etat, MONS, BELGIUM  
 HANSEN C., Ges. f. Strahlen und Umweltforschung, FRANKFURT/MAIN, W. GERMANY  
 HANTKE K., Lehrst. Mikrobiol. II, TUBINGEN, W. GERMANY  
 HARRISON P., University of Sheffield, SHEFFIELD, UNITED KINGDOM  
 HAURANI F., Thomas Jefferson University, PARIS, FRANCE  
 HERSHKO C., Shaare Zedek Medical Centre, JERUSALEM, ISRAEL  
 HOEPELMAN I., University Hospital, UTRECHT, THE NETHERLANDS  
 HSUAN J., Bristol University, BRISTOL, UNITED KINGDOM  
 HUEBERS H., University of Washington, SEATTLE, U.S.A.  
 IANCU T., Carmel Hospital, HAIFA, ISRAEL  
 JACOBS A., University of Wales, CARDIFF, UNITED KINGDOM  
 JIN Y., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 JOLIVET C., Laboratoires Cassenne, OSNY, FRANCE  
 JONES R., Rockefeller University, NEW YORK, U.S.A.  
 JOSHI J., University of Tennessee, KNOXVILLE, U.S.A.  
 JULIEN D., Laboratoires Cassenne, PARIS, FRANCE  
 KALTWASSER J., Universität Frankfurt, FRANKFURT/MAIN, W. GERMANY  
 KARIYONE S., Fukushima Medical College, FUKUSHIMA-SHI, JAPAN  
 KELLERSHOHN C., Faculté de Médecine Necker, PARIS, FRANCE  
 KEUNG W.M., The Chinese University, HONG-KONG, HONG-KONG  
 KLAUSNER R., National Institute of Health, BETHESDA, U.S.A.  
 KOHGO Y., Medical College, SAPPORO, JAPAN  
 KONIJN A., The Hebrew University, JERUSALEM, ISRAEL  
 KUHN L., Swiss Cancer Research Institute, EPALINGES, SWITZERLAND  
 LAMBERT M., Université Libre de Bruxelles, BRUXELLES, BELGIUM  
 LEGER D., Université de Lille, VILLENEUVE D'ASCQ, FRANCE  
 LEROY M., Hopital Saint Louis, PARIS, FRANCE  
 LESCOAT G., Hopital Pontchaillou, RENNES, FRANCE  
 LESUISSE E., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 LINDER M., California State University, FULLERTON, U.S.A.  
 LINK G., Shaare Zedek Medical Centre, JERUSALEM, ISRAEL  
 LISTOWSKY I., A. Einstein College of Medicine, NEW YORK, U.S.A.  
 LOH T., The Chinese University, HONG-KONG, HONG-KONG  
 LONGUEVILLE A., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 LONNERDAL B., University of California, DAVIS, U.S.A.  
 LOUACHE F., Cent. Hosp. Univ. H. Mondor, CRETEIL, FRANCE  
 LYNCH S., University of Kansas, KANSAS CITY, U.S.A.  
 MAC ARDLE H., University of Western Australia, NEDLANDS, AUSTRALIA  
 MAC LAREN G., Case Western Reserve University, CLEVELAND, U.S.A.  
 MACK U., University of Queensland, BRISBANE, AUSTRALIA  
 MARTIN MATEO M., Facultad de Ciencias, VALLAOLID, SPAIN  
 MARTINEZ-MEDELLIN J., Lady Davis Institute, MONTREAL, CANADA  
 MARX J., University Hospital, UTRECHT, THE NETHERLANDS  
 MASSEVER W., New Jersey Medical School, NEWARK, U.S.A.  
 MATTIA E., National Institute of Health, BETHESDA, U.S.A.

MAZURIER J., Université de Lille, VILLENEUVE D'ASCQ, FRANCE  
 MENOZZI F., Université de l'Etat, MONS, BELGIUM  
 MILLER A., Université de l'Etat, MONS, BELGIUM  
 MIYAZAKI T., Hokkaido University, SAPPORO, JAPAN  
 MOGUILLEVSKY N., Int. Inst. of Cell. and Molec. Pathol., BRUXELLES, BELGIUM  
 MONTREUIL J., Université de Lille, VILLENEUVE D'ASCQ, FRANCE  
 MORGAN E., University of Western Australia, NEDLANDS, AUSTRALIA  
 MOSTERT L., University of Rotterdam, ROTTERDAM, THE NETHERLANDS  
 MULLER A., Hausmann Laboratories Inc., SAINT GALLEN, SWITZERLAND  
 MUNRO H., Department of Agriculture, BOSTON, U.S.A.  
 NEMET K., Nat. Inst. of Haematol. and Blood Transfusion, BUDAPEST, HUNGARY  
 NEUWIRT J., Inst. of Hematol. and Blood Transfusion, PRAGUE, CZECHOSLOVAKIA  
 NIEUWENHUIS M., Rijksuniversiteit, UTRECHT, THE NETHERLANDS  
 NOYES W., University of Florida, GAINESVILLE, U.S.A.  
 NUNEZ M., University of Chile, SANTIAGO, CHILE  
 O'CONNELL M., MRC Clinical Research Center, HARROW, UNITED KINGDOM  
 OKADA S., Faculty of Medicine, KYOTO, JAPAN  
 OSTERLOH K., MRC Clinical Research Center, HARROW, UNITED KINGDOM  
 PATTANAPANYASAT K., University of Wales, CARDIFF, UNITED KINGDOM  
 PECHINOT D., Université de Paris, BOBIGNY, FRANCE  
 PENHALLOW R., University of Vermont, BURLINGTON, U.S.A.  
 PERRIN P., Laboratoires Sopharga, PUTEAUX, FRANCE  
 PETER H.H., Ciba-Geigy Ltd, BASEL, SWITZERLAND  
 PETERS T., MRC Clinical Research Center, HARROW, UNITED KINGDOM  
 PLANAS-BOHNE F., Kernforschungszentrum, KARLSRUHE, W. GERMANY  
 POLLACK S., A. Einstein College of Medicine, NEW YORK, U.S.A.  
 PONKA P., Mc Gill University, MONTREAL, CANADA  
 PORTER J., University College, LONDON, UNITED KINGDOM  
 POWELL L.W., University of Queensland, BRISBANE, AUSTRALIA  
 RAGUZZI F., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 RAMSAY W., University of Edinburgh, EDINBURGH, UNITED KINGDOM  
 RAYMOND K., University of California, BERKELEY, U.S.A.  
 REGOECZI E., Mc Master University, HAMILTON, CANADA  
 RIBADEAU DUMAS B., Inst. Nat. Recherche Agronomique, JOUY-EN-JOSAS, FRANCE  
 RICE L., Baylor College of Medicine, HOUSTON, U.S.A.  
 RIMBERT J.-N., Faculté de Médecine Necker, PARIS, FRANCE  
 ROBERTS S., Kings College Hospital, LONDON, UNITED KINGDOM  
 ROESER H., University of Queensland, BRISBANE, AUSTRALIA  
 ROLAND F., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 ROSE T., Oncogen, SEATTLE, U.S.A.  
 ROTH P., Ges. f. Strahlen, FRANKFURT/MAIN, W. GERMANY  
 RUMMEL W., Inst. für Pharmakol. und Toxikol., HOMBURG/SAAR, W. GERMANY  
 RYMER J.-C., Hopital Henri Mondor, CRETEIL, FRANCE  
 SALSER W.A., University of California, LOS ANGELES, U.S.A.  
 SALTMAN P., University of California, LA JOLLA, U.S.A.  
 SATAKE K., Science University, TOKYO, JAPAN  
 SAWATZKI G., University of Ulm, ULM, W. GERMANY  
 SCHADE A., ALBUQUERQUE, U.S.A.  
 SCHAEFFER E., Institut Pasteur, PARIS, FRANCE  
 SCHNEIDER C., Eur. Molec. Biol. Lab., HEIDELBERG, W. GERMANY  
 SCHNEIDER W., Lab. f. anorg. Chemie, ZURICH, SWITZERLAND  
 SCHUMANN K., Universität München, MÜNCHEN, W. GERMANY  
 SELIGMAN P.A., University of Colorado, DENVER, U.S.A.  
 SHINJO S., Nippon Medical School, TOKYO, JAPAN  
 SIBILLE J.-C., Université Catholique, LOUVAIN-LA-NEUVE, BELGIUM  
 SIMON M., Hopital Sud Clinique Medicale B, RENNES, FRANCE  
 SIMPSON R., MRC Clinical Research Centre, HARROW, UNITED KINGDOM

SKIKNE B., University of Kansas, KANSAS CITY, U.S.A.  
SKIKNE M., University of Kansas, KANSAS CITY, U.S.A.  
SMETS P., Laboratoires Cassenne, OSNY, FRANCE  
SMITH A., Louisiana State University, NEW ORLEANS, U.S.A.  
SOROKIN L., University of Western Australia, NEDLANDS, AUSTRALIA  
SPIK C., Université de Lille, VILLENEUVE D'ASQ, FRANCE  
SRAI S., Royal Free Hospital, HAMPSTEAD, UNITED KINGDOM  
STEIN B., Stanford University School of Medicine, STANFORD, U.S.A.  
SUSSMAN H., Stanford University School of Medicine, STANFORD, U.S.A.  
SWEENEY G., Mc Master University, HAMILTON, CANADA  
TAKAMI M., Meiji Institute of Health Science, NARUDA, JAPAN  
TANGERAS A., University of Bergen, BERGEN, NORWAY  
TAVILL A., Case Western Reserve University, CLEVELAND, U.S.A.  
TESTA U., Instituto Superiore di Sanita, ROMA, ITALY  
THEIL E., North Carolina State University, RALEIGH, U.S.A.  
THEN G., Universitat Karlsruhe, KARLSRUHE, W. GERMANY  
THIES W., Kernforschungszentrum Gmbh, KARLSRUHE, W. GERMANY  
THORSTENSEN K., University of Trondheim, TRONDHEIM, NORWAY  
TREFFRY A., University of Sheffield, SHEFFIELD, UNITED KINGDOM  
TRINDER D., University of Western Australia, NEDLANDS, AUSTRALIA  
TSUNOO H., Meiji University of Health Science, NARUDA, JAPAN  
TUIL D., Cent. Hosp. Univ. Cochin, PARIS, FRANCE  
URUSHIZAKI I., Medical College, SAPPORO, JAPAN  
VALENTI P., Università 'La Sapienza', ROMA, ITALY  
VAN ASBECK B., University Hospital, UTRECH, THE NETHERLANDS  
VAN EYK H., Fac. Der Geneeskunde, ROTTERDAM, THE NETHERLANDS  
VISCA P., Facoltà di Medicina e Chirurgia, ROME, ITALY  
VOGEL W., Kings College Hospital, LONDON, UNITED KINGDOM  
VOSBECK K., Ciba-Geigy Ltd, BASEL, SWITZERLAND  
WAGSTAFF M., University of Wales, CARDIFF, UNITED KINGDOM  
WERNER E., Ges. f. Strahlen und Umweltforschung, FRANKFURT/MAIN, W. GERMANY  
WILLIAMS J., University of Bristol, BRISTOL, UNITED KINGDOM  
WOLLENBERG P., Inst. fur Pharmakol. und Toxikol., HOMBURG/SARRE, W.GERMANY  
WONG C., National University, SINGAPORE, REPUBLIC OF SINGAPORE  
WORWOOD M., University of Wales, CARDIFF, UNITED KINGDOM  
YAMAMURA T., Science University, TOKYO, JAPAN  
ZAK O., A. Einstein College of Medicine, NEW YORK, U.S.A.  
ZUYDERHOUDT F., Academic Medical Centre, AMSTERDAM, THE NETHERLANDS



# CONTENTS

Preface	V
List of conference participants	VII

## STRUCTURE AND FUNCTION OF TRANSFERRINS

A.L. SCHADE	
Conalbumin and siderophilin as iron-binding proteins: a review of their discovery	3
J. WILLIAMS	
The structure of transferrins	13
J. MONTREUIL, J. MAZURIER, D. LEGRAND and G. SPIK	
Human lactotransferrin : structure and function	25
J.P. BROWN, T.M. ROSE and G.D. PLOWMAN	
Human melanoma antigen p97, a membrane-associated transferrin homologue	39
G. SPIK, B. CODDEVILLE, D. LEGRAND, J. MAZURIER, D. LEGER, M. GOAVEC and J. MONTREUIL	
A comparative study of the primary structure of glycans from various sero-, lacto- and ovotransferrins. Role of human lactotransferrin glycans	47
T. YAMAMURA, H. IKEDA, K. NAKAZATO, M. TAKIMURA and K. SATAKE	
Cooperativity between the N and C domains of ovotransferrin observed on iron binding and thermal denaturation	53
R. GARRATT, P. LINDLEY, R. EVANS and S. HASNAIN	
Transferrin: a study of the iron binding sites using extended X-ray absorption fine structure	57
O. ZAK and P. AISEN	
Iron is not randomly distributed between the binding sites of circulating human transferrin	61

## STRUCTURE AND FUNCTION OF FERRITINS

P.M. HARRISON, J.L. WHITE, J.M.A. SMITH, G.W. FARRANTS, G.C., FORD, D.W. RICE, J.M. ADDISON and A. TREFFRY	
Comparative aspects of ferritin structure, metal-binding and immunochemistry	67
E.C. THEIL, D.E. SAYERS and C.C.Y. YANG	
Properties of an Fe(III)-apoferritin complex and models for the polynuclear iron core studied by X-ray absorption spectroscopy (EXAFS and XANES)	81
J.G. WARDESKA, B.J. VIGLIONE and N.D. CHASTEEN	
The effect of pH on the binding of metal ions to apoferritin	85
J.M. ADDISON, A. TREFFRY and P.M. HARRISON	
Peptide specific antibodies for immunochemical and functional studies on ferritin	89

- J.G. JOSHI, S. GOODMAN, V.V. DESHPANDE and D.J. PRICE  
Ferritin, a multifunctional molecule

93

# CELLULAR IRON METABOLISM AND IRON-BINDING PROTEINS-CELL INTERACTIONS

- R.R. CRICHTON

Intracellular iron metabolism

99

- R.D. KLAUSNER, J.B. HARFORD, K. RAO, E. MATTIA, A.M. WEISSMAN,  
T. ROUAULT, G. ASHWELL and J. VAN RENSWOUDE

Molecular aspects of the regulation of cellular iron metabolism

111

- P.A. SELIGMAN and C.R. CHITAMBAR

Effect of different transferrin-metal forms on both cellular iron metabolism and proliferation

123

- E. BAKER, H.J. McARDLE and E.H. MORGAN

Transferrin-cell interactions : studies with erythroid, placental and hepatic cells

131

- H.H. SUSSMAN, B.S. STEIN and L. TSAVALER

Studies of the transferrin receptor in human cell lines

143

- Y. KOHGO, Y. NIITSU, T. NISHISATO, Y. URUSHIZAKI, H. KONDO,  
M. FUKUSHIMA, N. TSUSHIMA and I. URUSHIZAKI

Transferrin receptors of tumor cells - potential tools for diagnosis and treatment of malignancies

155

- L.M. NECKERS, S. BAUER, R. McGLENNEN, J.B. TREPEL, K. RAO and  
W.C. GREENE

Calcium regulation of transferrin receptor expression in normal and malignant T cells: evidence for a transcriptional control point subsequent to interleukin-2 receptor activation

171

- C.G.D. MORLEY, L. SOLBERG and A. BEZKOROVAINY

The removal of iron from transferrin by isolated plasma membranes of rat hepatocytes

175

- J. FOUQUIER, D. PECHINOT, M.T. CHALUMEAU and G. FELDMANN

Investigation of transferrin secretion at single hepatocyte level using the reverse hemolytic plaque test

179

- J. GLASS and I. PINTO

Kinetics of  $^{59}\text{Fe}$  uptake by K562 cells

183

- K.R. BRIDGES and N. SHAKLAI

Dynamic relationship between surface and internal transferrin receptors in K562 cells

187

- B.S. STEIN and H.H. SUSSMAN

Characterization of the endocytosis and recycling of the human transferrin receptor in K562 cells; evidence for two receptor recycling pathways and ligand-independent endocytosis

191

H.I. McARDLE, B.J. BOWEN and E.H. MORGAN Phenylglyoxal inhibits receptor mediated endocytosis and stimulates non-receptor mediated endocytosis in cultured rat placental cells	195
N. MOGUILEVSKY, P.J. COURTOY and P.L. MASSON Study of lactoferrin-binding sites at the surface of blood monocytes	199
U. MACK, E.L. STOREY, L.W. POWELL and J.W. HALLIDAY Characterization of the binding of ferritin to the rat hepatic ferritin receptor	203

#### ROLE OF IRON-BINDING PROTEINS IN MYELOPOIESIS

H.E. BROXMEYER, L. LU, D.C. BICKNELL, G.W. SLEDGE, D. WILLIAMS, W.G. DIPPOLD, G. HANGOC, W. McGUIRE, T. COATES and S. COOPER The interacting roles of lactoferrin, transferrin and acidic isoferritins in the regulation of myelopoiesis <i>in vitro</i> and <i>in vivo</i>	209
M. CAZZOLA, L. DEZZA, W. PIACIBELLO, P. AROSIO and M. AGLIETTA Studies on the suppressive effect of acidic isoferritins on <i>in vitro</i> human myelopoiesis	221
G.B. SALA, M. WORWOOD and A. JACOBS The effect of isoferritins on granulopoiesis	225

#### BACTERIAL IRON METABOLISM: SIDEROPHORES AND ANTIBACTERIAL ACTIVITIES OF TRANSFERRINS

K. HANTKE Iron transport in bacteria	231
P. VALENTI, P. VISCA, M. NICOLETTI, G. ANTONINI and N. ORSI Synthesis of siderophores by <i>E. coli</i> strains in the presence of lactoferrin-Zn	245
M. BOESMAN-FINKELSTEIN, C.V. SCIORTINO and R.A. FINKELSTEIN Iron-related antimicrobial activities of human milk	251

#### MOLECULAR ASPECTS OF IRON ABSORPTION

H.A. HUEBERS and C.A. FINCH Molecular aspects of iron absorption and its control	263
L.A. DAVIDSON and B. LÖNNERDAL Isolation and characterization of monkey milk lactoferrin and identification of a specific brush border receptor	275
S.K.S. SRAI, E.S. DEBNAM, M. BOSS and O. EPSTEIN The ontogeny of duodenal iron absorption in the guinea pig: clues to the aetiology of idiopathic haemochromatosis	279

#### IRON OVERLOAD AND IRON DEFICIENCY

C. HERSHKO, G. LINK, A. PINSON, S. GRISARU, S. SAREL and R.W. GRADY Iron overload and chelation therapy	285
------------------------------------------------------------------------------------------------------------	-----

## XIV

H.H. PETER	
Industrial aspects of iron chelators: pharmaceutical applications	293
I. ERNI, N. OSWALD, H.W. RICH and W. SCHNEIDER	
The chemistry relevant to oral iron preparations	305
A. LONGUEVILLE and R.R. CRICHTON	
An animal model of hepatic iron overload	309
B.R. BACON, G.M. BRITTENHAM, C.H. PARK and A.S. TAVILL	
Hepatic mitochondrial and microsomal function in experimental chronic iron overload	313
E.R. BAUMINGER, G. LINK, A. PINSON and C. HERSHKO	
Mössbauer studies of heart cell cultures	317
S.W. PETERS, B.M. JONES, A. JACOBS and M. WAGSTAF	
"Free iron" and lipid peroxidation in the plasma of patients with iron overload	321
S.A. HENDERSON, P.R. DALLMAN and G.A. BROOKS	
Glucose turnover and oxidation are increased in iron deficiency	325

### MOLECULAR BIOLOGY OF FERRITIN, TRANSFERRIN AND TRANSFERRIN RECEPTOR GENES

H.N. MUNRO, E.A. LEIBOLD, J.K. VASS, N. AZIZ, J. ROGERS, M. MURRAY and K. WHITE	
Ferritin gene structure and expression	331
J. DRYSDALE, S.K. JAIN, D. BOYD, K.I. BARRETT, C. VECOLI, D.M. BELCHER, C. BEAUMONT, M. WORWOOD, R. LEBO, J. MCGILL and J. CRAMPTON	
Human ferritins: genes and proteins	343
S. TERAOKA, P. CONCANNON, C.C. CHOU, M. FULLER, S. CHADA, A. WONG, J. WRIGHT, S. KANIA, C. SNYDER, J. HWA, R. DAVIS, R. NELSON, A. THOMAS and W. SALSER	
Gene regulation during myeloid differentiation: characterization of novel ferritin genes and reintroduction of their clones into a cell line that differentiates <i>in vitro</i>	349
J.B. LUM, F. YANG and B.H. BOWMAN	
Molecular biology of the human transferrin gene	357
E. SCHAEFFER, I. PARK, G.N. COHEN and M.M. ZAKIN	
Organization of the human serum transferrin gene	361
F. LOUACHE, U. TESTA, M. TITEUX and H. ROCHANT	
Expression of transferrin receptors and intracellular ferritin during differentiation of two human leukemic cell lines HL-60 and U 937	365
L.C. KÜHN	
Human transferrin receptor expressed from a transfected cDNA is functional in murine cells	369

### SUMMATION

R.E. FEENEY	373
Author index	379

# **STRUCTURE AND FUNCTION OF TRANSFERRINS**



Conalbumin and Siderophilin as Iron-binding Proteins :  
A Review of Their Discovery

Arthur L. Schade

Appropriate to the opening of this "Conference on the Proteins of Iron Metabolism", an historical review of the original investigations leading to the elucidation of what biochemically constitutes the iron-binding factors of hen's egg white and of human plasma has been requested by interested well-wishers. I am pleased to comply. References are appended (1-30). To introduce this tale of scientific adventure, I offer you an extract of a letter that Horace Walpole of England wrote to his friend Horace Mann on January 28, 1754 :

"I once read a silly fairy tale, called "The Three Princes of Serendip" : as their highnesses travelled, they were always making discoveries by accidents and sagacity, of things they were not in quest of : for instance, one of them discovered that a mule blind of the right eye had travelled the same road lately, because the grass was eaten only on the left side, where it was worse than on the right -- now do you understand "serendipity" ? One of the most remarkable instances of this "accidental sagacity" (for you must observe that "no" discovery of a thing you "are" looking for, comes under this description) was that my Lord Shafsbury, etc." (1).

From this letter, "serendipity" and its derivatives became accepted, if at times misused, words of the English vocabulary. In what follows, I trust that Walpole would approve the use of "serendipity" to describe our discovery of a protein whose property of iron chelation under physiological conditions has stimulated many significant biological and biochemical studies.

During the past World War we were engaged in an effort, among others, to serve the Medical Corps of the U.S. Army in the production of a polyvalent bacteriophage preparation effective against Shigella

dysentaria as well as against a variety of paradysentery strains (2, 3, 4). Individual bacteriophage lysates were evaluated for potency by the recording of effective lysis of a succession of ten-fold dilutions of a test lysate in a standard culture of its specific bacterial host grown in nutrient broth for 24 to 48 hours incubation at 37°C. When we had succeeded in the production of an effective polyvalent combined lysate, the Army suggested that it be made available in a dry form suitable for pill administration as a prophylactic to military personnel in dysentery-threatening areas. Lyophilization of the individual and combined lysates resulted in some losses of viral activity of the lysates, but the loss was particularly severe in the lysates active against Sh. Dysenteriae. To protect the latter phages from the effects of dessiccation, a great variety of additives were tested, including hen's egg white (5). For such tests, a control series of original lysate dilutions without egg white or other additives were run against the water-reconstituted lyophilized "protected" lysates. With egg white as additive and Sh. dysenteriae as test bacterium, we noted, after 48 hours incubation, that the customary secondary growth of the organism following initial lysis as seen in the control series did not appear in the first tubes of the duplicated dilution series where the concentration of egg white was the highest. Further investigation showed that a comparable amount of egg white, raw or lyophilized, added to nutrient broth inhibited the primary growth of this bacterium. Titrations run in the absence of phage with various concentrations of egg white proved that the inhibition of growth depended upon the amount of egg white added to the inoculated medium and not to the number of active bacterial viruses.

The problem presented by the five results simply stated was : Why did 0.02 ml of fresh egg white when added to 1 ml of 1 % meat broth plus 0.5 % peptone at pH 7.2 inhibit the growth of  $2-20 \times 10^5$  Sh.



dysenteriae organisms for 24 hours at 37°C ? Serial dilutions of transfers from inhibited cultures to egg-white-free broth showed that failure to grow was not due to death of the cells. This result made lysozyme an unlikely culprit for the observed bacteriostasis. Avidin, a known constituent of egg white and complexer of biotin, was ruled out as the inhibitory factor when additions of twice the egg white concentration of avidin to the growth medium failed to prevent normal bacterial development. Conversely, additions of biotin in amounts double that estimated to be bound by the avidin in egg white failed to overcome the growth inhibition. We observed that the inhibitory effect of egg white resisted dialysis ; was active following incubation at 60°C for one hour, but was destroyed after one hour at 70°C ; and was salt-precipitable. The immediate indications were that the active agent was a protein.

Attempts to reverse the growth inhibition of Sh. dysenteriae by egg white were successful by additions to the nutrient broth of yeast extract, corn steep liquor, or meat extract in relatively large amounts. Ten recognized growth factors in yeast extract were tested singly and in combination. None were effective in abolishing the bacteriostasis. When yeast extract was ashed and the ash dissolved in hydrochloric acid, its addition in graded amounts following neutralization resulted in good bacterial growth in the inoculated egg white-nutrient broth. Of 31 elements tested, iron alone, both ferrous and ferric, overcame the growth inhibition. By the use of all-or-none growth measurements, we determined that 1 ml of egg white could make 15-20 micrograms unavailable to Sh. dysenteriae. Investigating the effect of pH on the dializability of iron from egg white-iron saline mixtures, we observed a close relationship between increasing acidity on the lability of the iron from the egg white-iron complex and the failing inhi-