LIVER AND AGING-1978

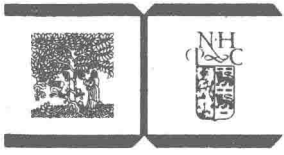
Kenichi Kitani
Editor

LIVER AND AGING – 1978

Proceedings of the Tokyo Symposium "Liver and Aging – 1978" held in Tokyo, Japan on August 27-28, 1978 – a Satellite Symposium of the 11th International Congress of Gerontology.

Editor
KENICHI KITANI

First Laboratory of Clinical Physiology
Tokyo Metropolitan Institute of Gerontology
Itabashi-ku, Tokyo, Japan



1978

ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
AMSTERDAM · NEW YORK · OXFORD

© 1978 Elsevier/North-Holland Biomedical Press

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 permission of the copyright owner.

ISBN: 0-444-80088-3

Published by:

Elsevier/North-Holland Biomedical Press
335 Jan van Galenstraat, PO Box 211
Amsterdam, The Netherlands

Sole distributors for the USA and Canada:

Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Library of Congress Cataloging in Publication Data

Tokyo Symposium "Liver and Aging, 1978", 1978.
Liver and aging, 1978.

Bibliography: p.
Includes index.
1. Liver--Aging--Congresses. 2. Liver cells--Congresses. 3. Liver--Drug effects--Congresses. 4. Aging--Congresses. I. Kitani, Kenichi. II. International Congress of Gerontology, 11th, Tokyo, 1978. III. Title. [DNLM: 1. Liver --Physiology--Congresses. 2. Aging--Congresses. WI702 T646L 1978]
QP185.T64 1978 599'.01'3 78-24443
ISBN 0-444-80088-3

Printed in The Netherlands

PREFACE

Considering the enormous and rapidly expanding information we have on liver functions, morphologies and even their interrelationships, it is surprising how little we know about the liver in relation to the age. While a number of pioneering researchers are working on the effect of aging on the liver, most of biochemists, physiologists or even pharmacologists primarily engaged in liver studies, appear to be too busy with relatively immediate research activities to pursue the relevance of aging to even their own experimental systems.

Clinicians are not an exception to this trend. In today's geriatric practice, the aging of the liver has not received proper attention, doubtless in part, because of the vast reserve capacity of the liver functions. In recent years, clinical pharmacological studies have provided most of the practical information on the clinical relevance of aging to liver functions.

From the limited information available, we are the more intrigued by the diversity and discrepancy among the results reported as age-dependent changes in the liver.

Perhaps, it would be more accurate to say that this lack of data is not so much due to a lack of scientific interest in aging by majority of researchers, but rather to the lack of availability of aged animals. A very minimal estimate is that a healthy 3-year-old rat costs approximately $800. It does not mean, however, that anyone can do experiments on 20 old animals if they have $16,000. The mere availability of old animals, at present, is quite limited in almost every country in the world, and this further confounds the difficulty of repeating and confirming observations. Clinical studies are more difficult from the ethical point of view and are also extremely time-consuming if designed on a longitudinal schedule. Thus, we need to make the best possible use of our information on aging and expend our utmost efforts on careful interpretation.

In view of the above we were very pleased to take the opportunity of having the 11th International Congress of Gerontology in Tokyo to be able to have some 50 participants from 10 different countries in a Tokyo Symposium "Liver and Aging-1978". We are also fortunate in the diversity of the background, which ranges from basic biology to clinical medicine.

It was hoped we would not only out-line what is presently known about the liver

and aging but also that we would plan future work. Furthermore, it is our ambition to promote the recognition of the importance of aging among biomedical scientists in general.

The results of our deliberations are contained in this volume. If it fulfills some of our original purposes, it is due to the efforts of our enthusiastic participants. Though, of course, the results do not uncover all the complexities of the aging liver, we hope that the proceedings are another step toward our objectives.

As the organizer of this Symposium, it is my pleasure to acknowledge my debt to Professor D. Platt who arranged what is to my knowledge the first "Liver and Aging" seminar, the IV International Symposium for Experimental Gerontology at Giessen 1977. Professor Platt demonstrated by his successful meeting the possibilities inherant in international cooperation and encouraged us during the difficult period of organizing the present meeting.

Last, but not least, I would like to express my sincere gratitude to Dr. C.F.A. van Bezooijen for his continuous help before, during and even after the Symposium.

Kenichi Kitani
Tokyo
September, 1978

此为试读,需要完整PDF请访问: www.ertongbook.com

ACKNOWLEDGEMENTS

The Organizing Committee gratefully acknowledges

COMMEMORATIVE ASSOCIATION FOR THE
JAPAN WORLD EXPOSITION (1970)

for its generous financial support for the symposium
and this publication.

We also gratefully acknowledge the assistance of

TOKYO METROPOLITAN INSTITUTE OF GERONTOLOGY

and

INTERNATIONAL MEDICAL FOUNDATION OF JAPAN

who served as cosponsoring organizations.

CONTENTS

Preface V

Acknowledgements VII

SESSION 1 - MORPHOMETRY AND PATHOLOGY

Hepatic cells of the aged
H. Tauchi and T. Sato 3

A quantitative morphological evaluation of hepatocytes in young, mature and senescent Fischer 344 male rats
D.L. Schmucker 21

Strain and age-associated pathology of the rat liver
C.F. Hollander and J.D. Burek 39

SESSION 2 - ALTERATION OF ENZYMES

Search for alterations of three enzymes with a different turnover rate in the liver of senescent rats
F. Schapira, A. Weber, C. Guillouzo and J.C. Dreyfus 47

Methionine sulfoxide reductase: A novel protective enzyme in liver and its potentially significant role in aging
U. Reiss and D. Gershon 55

Alterations in the NAD-linked and NADP-linked isocitrate dehydrogenase of the liver of aging rats
S.N. Singh and R.N. Singh Yadav 65

SESSION 3 - NUCLEAR PROTEINS

Microfluorimetric studies on the DNA-protein interactions in rat liver cells
I. Zs.-Nagy, S. Damjanovich and S. Papp 79

Comparative study on the polyploidization of hepatocytes of mouse and fish during ageing
A. Shima, N. Egami and T. Sugahara 93

Nucleosome properties of aged livers
G. Yagil and F. Shimron 103

SESSION 4 - PHYSIOLOGY AND CLINICAL MEDICINE

Changes in kinetics of exogenous dyes in the ageing process
V. Skaunic, P. Hůlek and J. Martínková 115

A comparison of age-related changes in bromsulfophthalein metabolism of the liver and isolated hepatocytes
C.F.A. van Bezooijen and D.L. Knook 131

Hepatic metabolism of sulfobromophthalein (BSP) and indocyanine green (ICG) in aging rats
K. Kitani, S. Kanai and R. Miura 145

Aging and gross anatomical alterations of the liver
K. Okuda, F. Nomura, H. Okuda and Y. Shimokawa 159

SESSION 5 - CHOLESTEROL AND BILE SALTS METABOLISM

Aging and hepatic cholesterol metabolism : Initial changes of cellular components concerning cholesterol metabolism in rat livers by aging
N. Takeuchi, M. Koga, H. Kukita, K. Uchida and Y. Yamamura 177

Age-related changes in cholesterol metabolism
J.A. Story and D. Kritchevsky 193

Biosynthesis of bile acids
E.H. Mosbach, B.I. Cohen and R.M. Graham 203

Effect of age on bile acid metabolism in rat
K. Uchida, M. Kadowaki, Y. Nomura, M. Nagatsu and N. Takeuchi 223

SESSION 6 - ENZYMES AND ENZYME REGULATIONS

Lysosomes in Kupffer cells isolated from young and old rats
D.L. Knook and E. Ch. Sleyster 241

Induction of isoenzymes of alanine aminotransferase and tyrosine aminotransferase of the liver of the rat as a function of age
M.S. Kanungo, S.K. Patnaik and B.K. Ratha 253

Impairment of neural regulation of liver enzymes in aged animals
T. Shimazu 263

Regulation of hormone levels and activities during aging
R.C. Adelman, T.L. Klug, M.F. Obenrader and A. Kitahara 277

SESSION 7 - PHARMACOKINETICS 1 : EXPERIMENTAL ASPECTS

Hepatic microsomal drug metabolizing enzymes in aged rats - History and future problems
R. Kato 287

Barbiturate pharmacokinetics in ageing tolerant and non-tolerant mice
I.S. Pardon and T.W.G. Jones 301

Development of hepatic excretory function in the newborn rat
C.D. Klaassen 313

Age dependent changes in blood supply of the liver and in the biliary excretion of eosine in rats
F. Varga and E. Fischer 327

SESSION 8 - PHARMACOKINETICS 2 : CLINICAL ASPECTS

Studies of drug disposition in the elderly using model compounds
R.E. Vestal, A.J.J. Wood, R.A. Branch, G.R. Wilkinson and D.G. Shand 343

Drugs in the elderly : Pharmacokinetics and effects of some metabolised drugs
K. O'Malley, B. Cusack, J. Kelly and I.H. Stevenson 359

Hepatic elimination of drugs in the elderly
U. Klotz and G.R. Wilkinson 367

List of participants 383

Author index 387

SESSION 1
MORPHOMETRY AND PATHOLOGY
Chairman: C.F. Hollander

此为试读,需要完整PDF请访问: www.ertongbook.com

© 1978 Elsevier/North-Holland Biomedical Press
Liver and Aging – 1978, K. Kitani editor.

HEPATIC CELLS OF THE AGED

HISASHI TAUCHI and TSUNEKO SATO
Department of Pathology, Aichi Medical University and Department of Clinical Pathology, Aichi Cancer Center Hospital, Aichi Prefecture, Japan.

There have been many studies on the problems of senile changes and much discussions on the nature of age changes. However, there are many questions to be clarified in the future. Tauchi and his co-workers have been studying for many years on the age change of organs and tissues at the cellular and subcellular levels, using human materials and experimental animals. Some of the results obtained by them will be presented together with consideration especially on the age changes of the liver.

FUNDAMENTAL MORPHOLOGY OF THE SENILE CHANGES OF THE LIVER

The autopsy findings generally accepted as senile changes are sclerosis of the vessels, fibrosis and regressive changes such as atrophy, degeneration and pigment deposition. Arteriosclerosis and fibrosis of the organs are important signs of senility in the human beings, however, they are not considered to be the senile changes in the strict sense. One of the most important points in the fundamental morphology of senile changes of the liver is an atrophy or a decrease in weight, which is considered not necessarily due to sclerosis of organ arteries and fibrosis[1].

In this paper, the senile atrophy of the liver will be discussed at the cellular and subcellular level with special reference to the correlation between morphology and function.

AGE CHANGES OF THE LIVER AT A CELLULAR LEVEL

In case of malnutrition, decrease in volume of hepatic cells is usually more marked than decrease in weight of the liver, while in senile atrophy of the liver, the hepatic cells are frequently increased in volume, and variability in size of the cells is noted, with rather constant or even larger mean volume with advancement of age. From above, atrophy of the liver in senility is due to decrease in number of the hepatic cells in contrast to the case of malnutrition, where the atrophy is due to decrease in their volume[1,2] (Fig. 1).

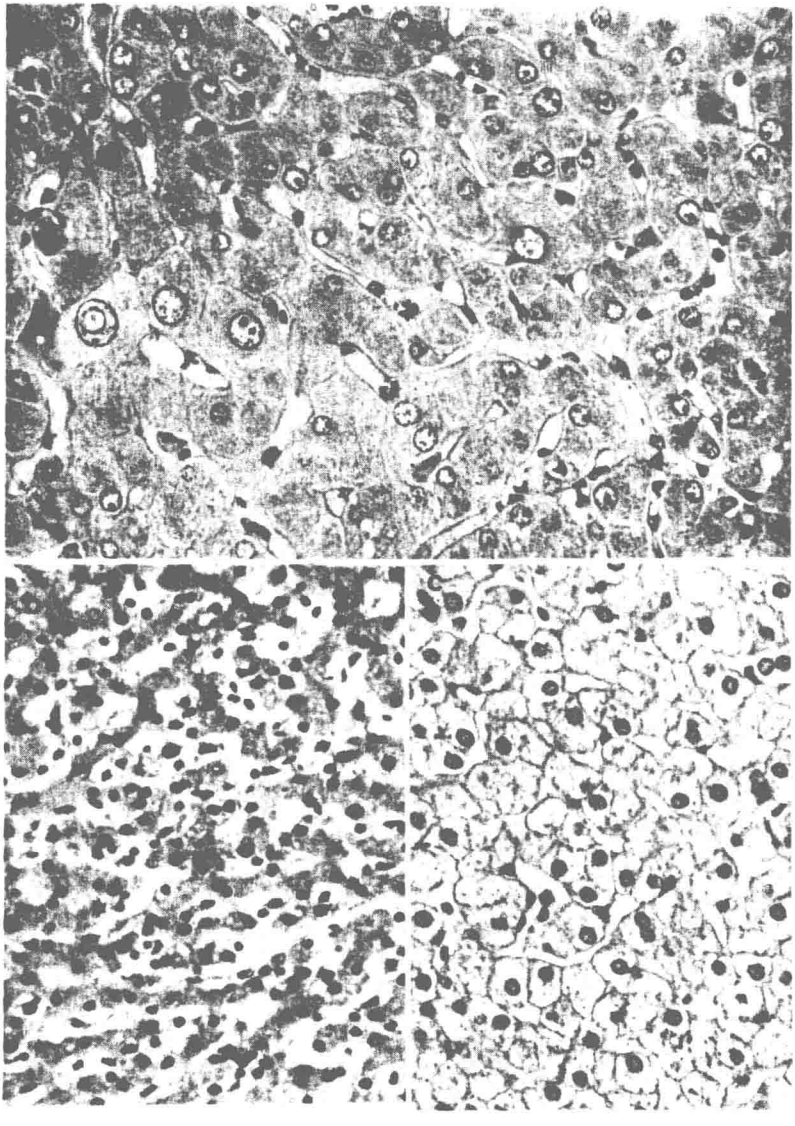


Fig. 1. Histological pictures of the human liver (× 350)
a. atrophic liver in senility (84 year old female)
b. atrophic liver in malnutrition (22 year old male)
c. normal liver (21 year old male)

In the Japanese autopsy cases, the number of hepatic cells begins to decrease in the sixth decade, decrease significantly in the eighth decade and markedly thereafter. On the other hand, binucleate hepatic cells increase in number with advancing age, reaching the maximum value in the seventh decade, and decreasing thereafter. However, hepatic cell nuclei show an increase in size in the age groups above 70 years, in which the irregularity in nuclear size was also marked. In other word, in the course of aging process, the decrease in number of hepatic cells is accompanied by binuclearity of the cells, which is later replaced by increase in volume of the nuclei (polyploidization)[3] (Fig. 9).

We examined histologically and histochemically the so-called dark cells of the hepatic tissues, and placed emphasis on the following points[4] (Fig. 2); the so-called dark cells were considered to manifest features of condensation and dehydration of cytoplasm, to represent a stage more or less transitory from sol to gel condition of cytoplasm, and to be in a condition of a marked lowering of electric charge of the plasm. From the above mentioned findings associated with other facts, some of the dark cells should be a picture of spontaneous senile decay of hepatic parenchymal cells. So the hepatic parenchymal cells are considered to disappear after passing through a picture of dark cells even under the physiological condition, in which the hepatic cells physiologically regenerate to maintain a constant number of cells. In other words, decrease in number of hepatic cells in senility is considered to be due to lowering of regenerative ability of the cells and/or to increasing loss of the cells.

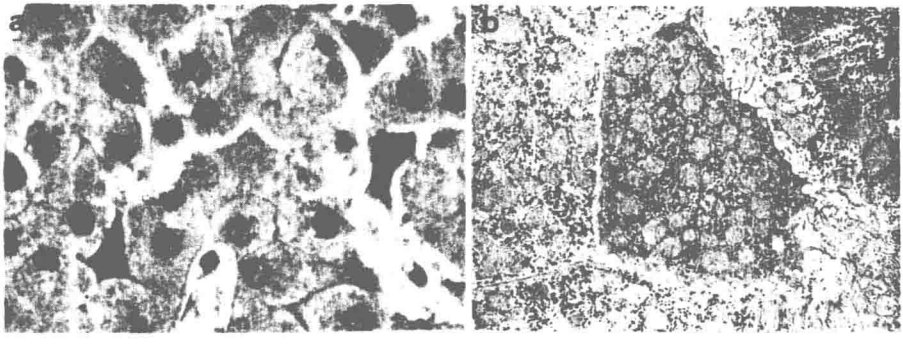


Fig. 2. So-called dark cells in the hepatic tissue
a. light microscopy b. electron microscopy

Tauchi previously proposed that the lowering of regenerative ability of the cells may be due to inhibitory factors for cell division[1]. The inhibitory factors seem to be put out, possibly the usage of the word " secreted " may be rather fitted, into tissue fluid from the cells, and are principally specific for the same kind of cells which produce these factors. Secretion of these factors from the cell ought theoretically to stand in an intimate relation with differentiation of each cell, which is considered to become higher with advancement of maturity grade and necessarily with the senility grade of the cell. As mentioned before, the hepatic cells of the aged are frequently larger in volume and considered to be in a hyperfunctioning state compensating the cell loss.

Our histochemical study revealed that the hepatic cells of the aged are not in the state of degeneration or malnutrition but rather in active state[5,6]. At any rate the binuclearity and increase in volume of nuclei, polyploidization of the hepatic cells, as mentioned before, are considered to be some expressions of an active state of cells in conditions where cell division is inhibited.

Succinic dehydrogenase (SDH) activity of the hepatic cells was not decreased, but rather increased especially in the binucleate and giant nucleate cells[5] (Fig. 3). The hepatic cells of the aged, which are considered to be in an active state, may have more limited reserve power, and more readily exhausted to become the above mentioned dark cells, which are noticed more frequently in the aged[4,6].

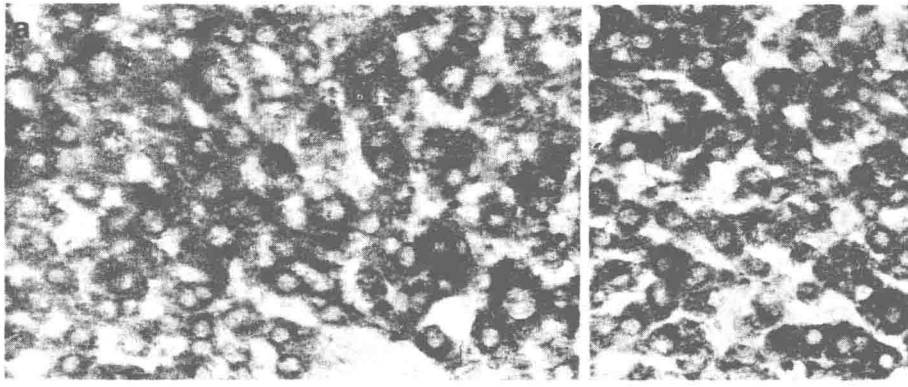


Fig. 3. Histochemical demonstration of SDH activity in the rat liver
a. old (24 months old) b. young adult (6 months old)

AGE CHANGES OF THE HEPATIC CELLS AT A SUBCELLULAR LEVEL

Our ultramicromeasuring studies have shown that the mitochondria were fewer in number and larger in volume in old rats and mice[7,8,9]. Mitochondria of the human hepatic cells of the aged are also decreased in number and increased in average value of the area and circumference[10] (Fig. 4). The number of mitochondria is significantly decreased with age after 60 years, but their

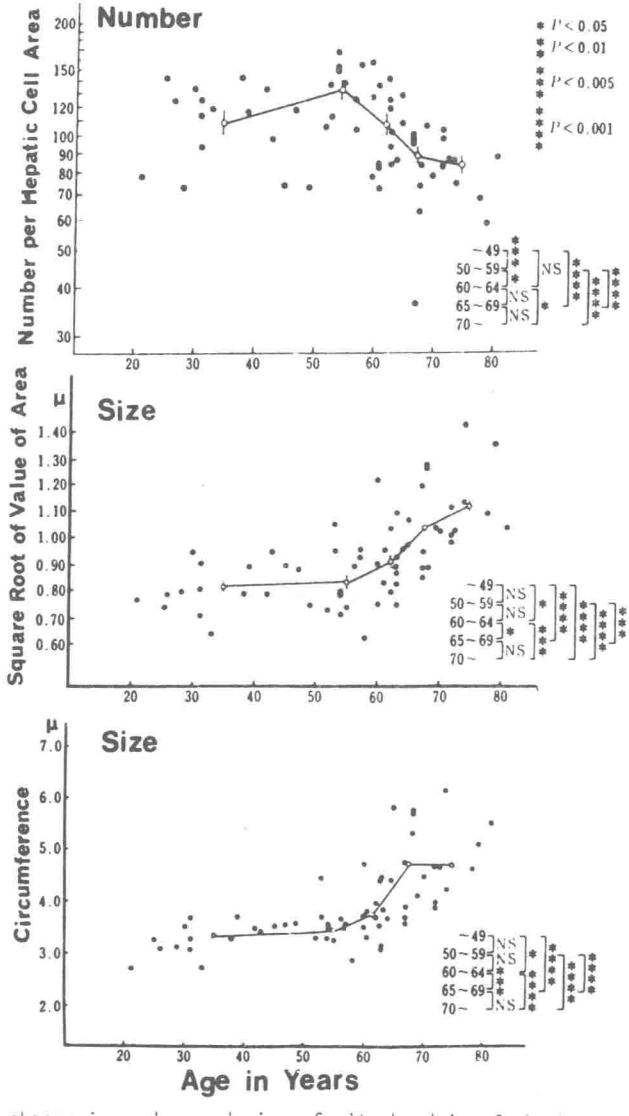


Fig. 4. Age change in number and size of mitochondria of the human hepatic cells

size is not significantly increased for another five years, and increases significantly after 65 years of age. Total mitochondrial area per hepatic cell area (areal ratio of mitochondria to hepatic cell cytoplasm) (Fig. 5) also increases according to age, but it slightly decreases in the period between 60 and 65 years of age, where the cristae of the majority of the mitochondria are ultramicrometrically observed to be more compactly arranged than in the cases under 49 years of age. Although the total mitochondrial area per

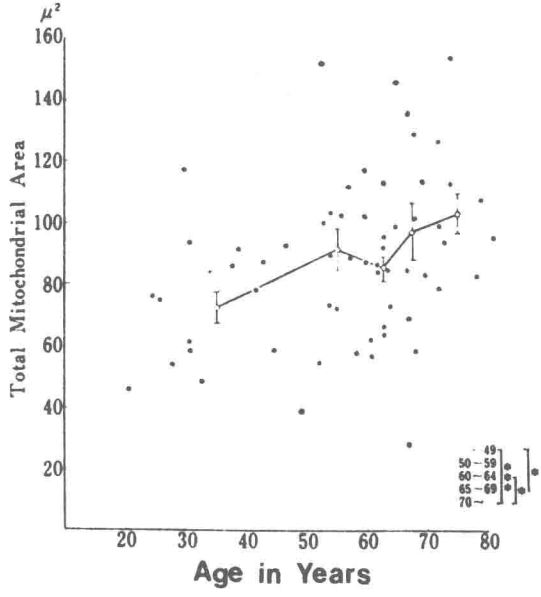


Fig. 5. Age change in total mitochondrial area per hepatic cell area

hepatic cell area is the largest in the groups above 70 years of age, the mitochondrial cristae are noted to be rather thinly distributed compared with the cases in the preceding decade[11]. The majority of the enlarged mitochondria in the aged show no degenerative signs (Fig. 6). The hepatic cells of the aged generally show no significant decrease in activity of SDH and of cytochrome-C-oxidase.

From above, it is proposed that the mitochondria in the hepatic cells of the aged are hypertrophied in order to function more actively in compensation for the decrease in their number. From the fact before mentioned on the correlation between mitochondrial size and their cristae according to age, the hypertrophy of the mitochondria to compensate a decrease in their number in the aging process seems to start with an increase of the cristae which precedes the actual increase in size[11].

此为试读,需要完整PDF请访问: www.ertongbook.com