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Age Changes in the Human Liver of the Different Races[1]

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The mechanism of the senile changes of the liver has been discussed by many authors, however, there are yet many questions to be clarified. Tauchi and Sato [10] have studied the process of the age changes in Japanese autopsy materials and noted (1) a decrease in number of the hepatic cells, followed by (2) an increase in number of binucleate cells, which was finally replaced by (3) an increase in nuclear volume. In order to make a further study on the mechanism of the senile changes of the liver, comparative studies between Japanese and Caucasian autopsy cases have been made, and some interesting findings are presented here.

Materials and Methods

The livers of 240 Japanese and 214 Caucasian male autopsy cases from 14–96 years of age were used for this study. The subjects had not shown signs of hepatic insufficiency; the liver samples were grossly and microscopically free of changes of cirrhosis, chronic congestion, neoplasm and other pathological conditions. The liver tissue was fixed in 10% formalin from ½–20 h after death, mostly within 8 h. Many paraffin sections of 5 μm in thickness were prepared from each liver tissue and stained with hematoxylin and eosin.

Microphotographic pictures were made from many fields of central and peripheral zones of the hepatic lobules, and 50 (Caucasians) or 100 (Japanese) mononucleate hepatic cells were taken at random from each of the 2 groups (central and peripheral zones). The cells and nuclei were measured along the vertical and horizontal axes, and the square root of the 2 figures was taken as their size. Binucleate hepatic cells were counted among 10,000 hepatic cells which were taken at random from each of the central and peripheral zones in many fields, and the numbers were used as the binucleate cell index for each zone.

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In order to roughly estimate a functional capacity for the organs as a whole the product of the organ weight and the cell number in a given area (176,000 μm^2) in each case was taken as a cell number index for representing a total number of parenchymal cells of the organ.

Results

Mean values of liver weight, size of hepatic cells and their nuclei, binucleate hepatic cell index and of cell number index in each decade are shown in table I and II.

Liver Weight

As shown in table I and II the liver weight decreased with advancement of age. In the Caucasians, the livers in the age groups over 50 years were smaller in weight than the group under 49 years of age, and difference between them was statistically significant, however, after 50 years of age, the decrease with age was not so marked. In the Japanese, the liver weight decreased gradually with advancing age until 60 years of age, and after 70 years of age, the weight sharply decreased with a highly significant difference.

The livers in the Caucasian cases were generally larger in weight than the Japanese. The difference in liver weight between 2 races were statistically highly significant in every age group (tables I, II and III).

Numbers of the Hepatic Cells

The hepatic cells in a given area were decreased with age to some extent in both races as shown in table I and II. Hepatic cell number indices in each case have been plotted in figure 1. These tables and figure clearly show that the estimated cell number also decreased with age. In the Caucasians, it began to decrease earlier than in the Japanese, but gradually decreased in later stage of age. In the Japanese, the decrease with age was more gradual until 70 years of age and thereafter noticed very markedly. In every decade, the hepatic cells were highly significantly larger in number in the Caucasians than in Japanese (table I, II and III).

Binucleate Cell Index

The binucleate cell indices observed in each liver sample have been plotted in figure 2 and 3. In Caucasian cases, binucleate cell index increased with advancing age, reaching maximum value in the 6th

decade, and decreasing thereafter. The difference was significant as shown in table I. In the Japanese, change in the index with age was more conspicuous and the peak was reached about 10 years later. As shown in table II, the differences in the indices were statistically significant either between the groups under 49 years of age and of the 7th decade, or between a group of the 7th decade and of older aged.

Table I. Mean values of liver weights and of micromeasuring data on the hepatic cells of the Caucasians in various age groups

Age in years / Subjects (No. of cases)	Under 49	50-59	60-69	70-79	Above 80
Weight of the liver (g) (214)	1814.1±47.00 CV (18.86%)	1566.2±57.15 (21.89%)	1479.5±54.57 (25.53%)	1487.8±46.10 (20.54%)	1410.1±53.93 (21.93%)
	P<0.005, NS, NS, NS; P<0.001, NS, NS; P<0.001, NS; P<0.001				
Numbers of hepatic cells in a given area $(176{,}000\,\mu m)^2$ (109)	548.9±11.14 CV (9.07%)	515.6±15.17 (12.12%)	490.3±12.03 (13.20%)	474.2±14.77 (14.92%)	449.0±13.11 (13.05%)
	NS, NS, NS, NS; P<0.005, NS, P<0.01; P<0.001, P<0.005; P<0.001				
Hepatic cell number index (109)	91.50±4.94 CV (24.14%)	78.24±4.69 (24.72%)	74.17±4.30 (31.32%)	70.35±4.37 (29.82%)	65.25±4.47 (27.00%)
	NS, NS, NS, NS; P<0.05, NS, NS; P<0.005, P<0.05; P<0.001				
Binucleate cell index: Central zone (109)	591.8±39.03 CV (29.47%)	705.5±35.39 (23.20%)	635.0±32.26 (27.73%)	575.5±40.46 (24.73%)	564.6±20.01 (23.84%)
	NS, NS, NS, NS; NS, NS; P<0.05; NS, P<0.005; NS				
Binucleate cell index: Peripheral zone (109)	544.3±33.84 CV (27.81%)	633.1±35.65 (20.65%)	580.9±29.89 (27.39%)	534.3±40.46 (33.78%)	522.3±27.84 (15.86%)
	NS, NS, NS, NS; NS, NS; P<0.05; NS, P<0.05; NS				

Table I (continued)

Age in years / Subjects (No. of cases)	Under 49	50-59	60-69	70-79	Above 80
Size of hepatic cells[1] µm: Central zone (109)	14.76±0.048 CV (8.49%)	15.28±0.046 (7.71%)	15.31±0.036 (8.28%)	15.34±0.048 (8.87%)	15.50±0.064 (10.18%)
	P<0.05, NS, NS, NS; P<0.05, NS, NS; P<0.05, NS; P<0.05				
Size of hepatic cells[1] µm: Peripheral zone (109)	14.88±0.050 CV (8.97%)	15.27±0.054 (7.98%)	15.31±0.042 (8.30%)	15.27±0.054 (9.27%)	15.54±0.061 (9.89%)
	NS, NS, NS, NS; NS, NS; NS; P<0.05				
Size of hepatic cell nuclei[1] µm: Central zone (109)	6.56±0.022 CV (8.85%)	6.59±0.024 (8.51%)	6.76±0.020 (9.48%)	6.77±0.020 (8.48%)	6.88±0.025 (9.90%)
	NS, NS, NS, NS; NS, NS; NS; P<0.05				
Size of hepatic cell nuclei[1] µm: Peripheral zone (109)	6.52±0.022 CV (9.16%)	6.60±0.023 (8.34%)	6.77±0.022 (9.82%)	6.89±0.026 (9.49%)	6.86±0.025 (10.41%)
	NS, NS, NS, NS; P<0.05, NS, NS; P<0.01, NS; P<0.005				

[1] Square root of value of areas.

CV = coefficient of variation = $\frac{\text{standard deviation}}{\text{mean}} \times 100$.

The difference in the changing pattern between 2 races was highly significant as shown in table III.

Size of Hepatic Cells and Their Nuclei

As shown in tables I, II and III, hepatic cells and their nuclei are generally larger in size in the Caucasians than in the Japanese.

In both races, there is noted no distinct difference in the mean values of size of the hepatic cells among various age groups, with few exceptions. However, the hepatic cell nuclei show a tendency to

increase in size with age, and this tendency showed to be more marked in the Japanese.

Arteriosclerotic Changes

The grade of sclerotic changes of the intrahepatic arteries was classified into 5 groups, and the grading of each case has been plotted

Table II. Mean values of liver weights and of micromeasuring data on the hepatic cells of the Japanese in various age groups

Age in years / Subjects (No. of cases)	Under 49	50-59	60-69	70-79	Above 80
Weight of the liver (g) (231)	1194.2±35.96 CV (24.81%)	1072.2±62.07 (37.51%)	1004.9±32.59 (23.61%)	886.6±26.40 (19.06%)	771.8±38.53 (25.91%)
	NS, P<0.001, P<0.001	NS, P<0.01, P<0.01	P<0.01, P<0.05, P<0.001	P<0.001, P<0.001	P<0.001
Number of hepatic cells in a given area (176,000 μm²) (185)	525.9±12.45 CV (18.61%)	537.1±21.00 (22.79%)	526.8±16.84 (20.71%)	501.4±19.69 (21.83%)	424.2±14.06 (13.26%)
	NS, NS, NS	NS, NS, P<0.05	NS, P<0.001	NS	P<0.001
Hepatic cell number index (185)	58.80±2.47 CV (33.08%)	55.20±2.78 (29.37%)	53.12±2.14 (26.09%)	45.81±2.04 (24.73%)	32.94±2.03 (24.65%)
	NS, NS, P<0.001	NS, P<0.01, P<0.001	P<0.05, P<0.001	P<0.001	P<0.001
Binucleate cell index: Central zone (64)	531.4±96.81 CV (51.20%)	732.7±51.33 (41.20%)	735.7±51.33 (26.00%)	570.5±47.41 (37.15%)	456.1±52.28 (41.38%)
	NS, P<0.05, NS	NS, P<0.05, P<0.005	NS, P<0.05	NS	P<0.05
Binucleate cell index: Peripheral zone (64)	413.7±59.00 CV (40.21%)	494.4±55.20 (33.50%)	619.0±53.95 (32.60%)	536.0±41.35 (34.49%)	398.4±49.96 (45.14%)
	NS, P<0.05, NS	NS, NS, P<0.05	NS, P<0.01	NS	NS

Table II (continued)

Age in years / Subjects (No. of cases)	Under 49	50-59	60-69	70-79	Above 80
Size of hepatic cells[1] μm: Central zone (39)	13.12±0.062 CV (11.68%)	12.30±0.066 (15.29%)	12.50±0.058 (11.41%)	12.60±0.118 (15.00%)	12.58±0.078 (14.72%)
	P<0.005				
	There is no significant difference between other each age group.				
Size of hepatic cells[1] μm: Peripheral zone (39)	13.32±0.096 CV (10.33%)	12.97±0.138 (13.00%)	12.77±0.079 (15.02%)	13.70±0.154 (12.81%)	12.83±0.131 (11.06%)
	There is no significant difference between each age group.				
Size of hepatic cell nuclei[1] μm: Central zone (39)	5.80±0.026 CV (12.00%)	5.68±0.028 (12.87%)	5.87±0.027 (10.67%)	6.02±0.035 (10.85%)	6.57±0.045 (14.88%)
	NS, NS, NS, P<0.05	NS, NS, P<0.01	NS	P<0.005	P<0.05
Size of hepatic cell nuclei[1] μm: Peripheral zone (39)	5.54±0.058 CV (10.33%)	5.85±0.055 (17.78%)	6.06±0.033 (13.33%)	6.34±0.038 (14.87%)	6.68±0.061 (18.67%)
	NS, NS, NS, NS	NS, NS	NS	P<0.05	P<0.05

[1] Square root of value of areas.

CV = coefficient of variation = $\frac{\text{standard deviation}}{\text{mean}} \times 100$.

in figure 4. As shown in figure 4, arteriosclerotic changes increase in grade with age in the Japanese, but in the Caucasians there was not noted any distinct relation between grade of sclerosis and age.

Discussion

TAUCHI and MORIKAWA [8] and TAUCHI [9] reported that an important characteristic of senile change of the liver was a decrease in number of the parenchymal cells. TAUCHI [9] also considered that a decrease in number of parenchymal cells in senility may be due to an extracellular fluid factor, so-called inhibitory factor for cell division, derived from each cell, and suggested that production of the inhibitory

Table III. Difference between 2 races (Caucasians and Japanese) by analysis of variance (methods of weighted square means)

Subjects (No. of cases) (Caucasians)	(Japanese)		Average changes with age	Average differences between races[2]	Difference between 2 races changing from one age group to another
Weight of the liver					
(214)	(231)		P<0.001	P<0.001 (+565.6 g)	NS
Number of liver cells in a given area (176,000 μm^2)			P<0.001	NS (−50.90)	NS
(109)	(185)				
Hepatic cell number index			P<0.001	P<0.001	NS
(109)	(185)				
Binucleate cell index		Central zone	P<0.001	NS (+9.6)	NS
(per 10,000 cells)		Peripheral zone	P<0.005	P<0.01 (+70.8)	P<0.001
(109)	(64)				
Size of hepatic cells[1]		Central zone	NS	P<0.001 (+6.54 μm)	NS
(109)	(39)	Peripheral zone	NS	P<0.001 (+2.14 μm)	NS
Size of hepatic cell nuclei[1]		Central zone	P<0.001	P<0.001 (+0.72 μm)	NS
(109)	(39)	Peripheral zone	P<0.001	P<0.001 (+0.63 μm)	NS

[1] Square root of value of areas.
[2] The unweighted average difference between the 2 races (Caucasian − Japanese).

factor was increased with cellular differentiation associated with cellular maturation. There was essentially no difference between the Japanese and the Caucasians in the aging process as far as a loss of parenchymal cells is concerned. TAUCHI and SATO [10] examined the liver in Japanese autopsy cases of different ages and noted that in the course of the aging process the decrease in number of hepatic cells was followed by binuclearity of the cells, which was later replaced by an increase in volume of the nuclei (polyploidization).

In the present study, both in the Japanese and Caucasians, the changing process of behavior of the hepatic cells with age was noticed to be essentially similar as previously reported by TAUCHI and SATO [10].

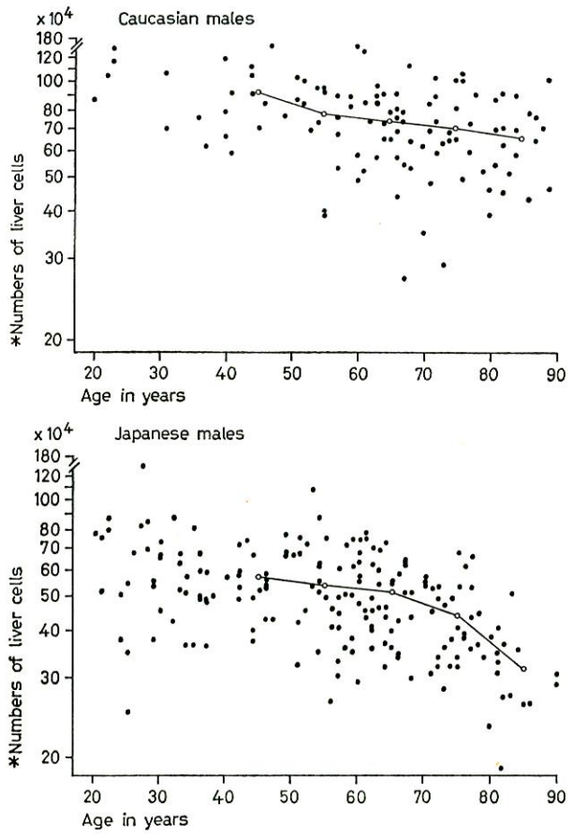

Fig. 1. Changes with age in cell number index of the liver. —○— Mean values in each decade.

However, there have been noticed some interesting differences between the two races in the changing pattern of the hepatic cells with age. The present study revealed that the decrease in liver weight and in number of hepatic cells appeared to begin earlier in the Caucasians, but in the later stage of age the decrease was more marked in the Japanese, and that the decrease in liver weight and in number of the hepatic cells in the old aged was more pronounced in the Japanese.

The binucleate hepatic cell index generally increased in value with age, reaching the highest value in the 6th decade in the Caucasians, in the 7th in the Japanese respectively, and decreased thereafter.

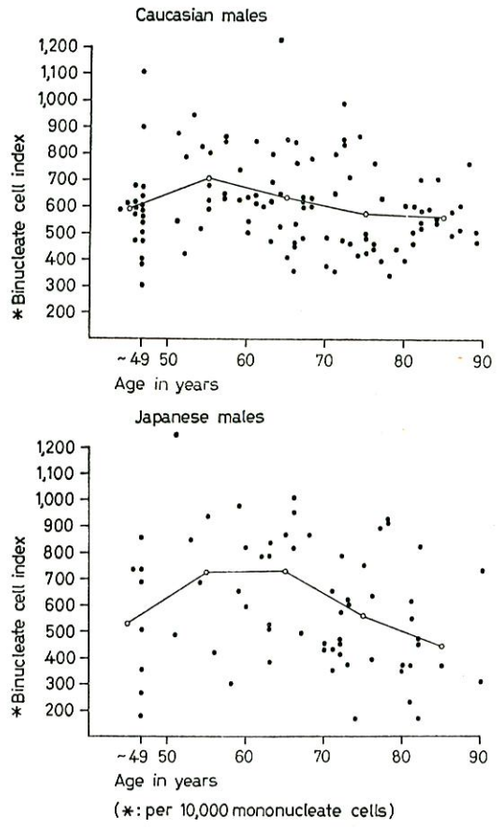

Fig. 2. Changes with age in binucleate hepatic cell index (central zone of the lobule). —○— Mean values in each decade.

With advancing age, the hepatic cell nuclei showed a tendency to increase in size, and the tendency seemed to be more marked in the Japanese.

From the above, it is considered to be reasonable that the senile change begins a little earlier in Caucasians but it progresses more markedly in the Japanese.

These differences between the two races may be considered to be due to differences in genetic factors and/or in environmental conditions. The present study revealed that in the Caucasians the liver was larger

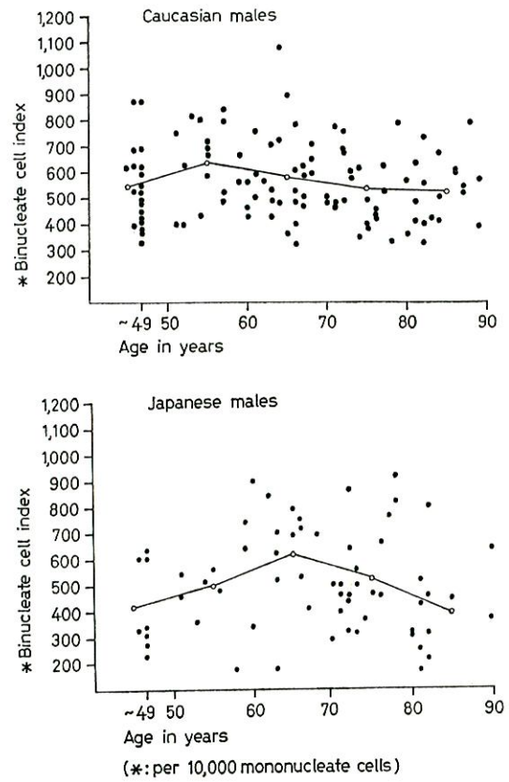

Fig. 3. Changes with age in binucleate hepatic cell index (peripheral zone of the lobule). —○— Mean values in each decade.

in weight and the hepatic cells were larger in size and number in every age group.

There are some papers on the differences in the organ weight, number and size of the parenchymal cells according to differences of species [1, 7]. However, there has been found no report on the differences in liver weight and in number and size of hepatic cells between the native Japanese and Caucasians in the USA.

BARROWS and ROEDER [2], WINICK and NOBLE [12] and WIDDOWSON and MCCANCE [11] from their experimental study, concluded that in animals fed by low protein diet, their growth was retarded and their

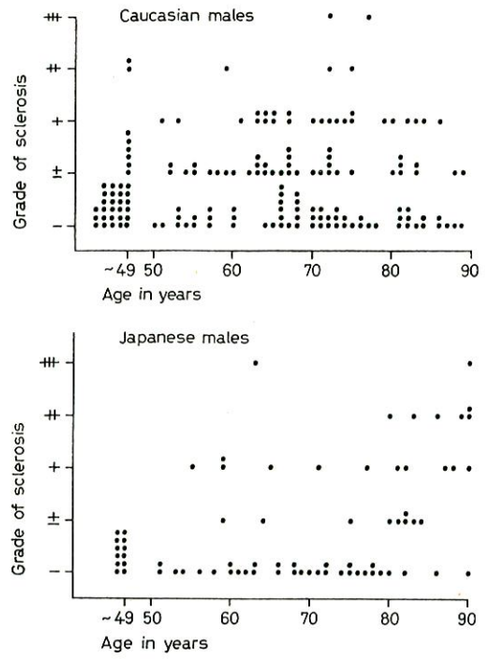

Fig. 4. Changes with age in arteriosclerosis in the liver.

body and organ weights were smaller in value. The nutritional condition seemed, to be an important factor for the difference noticed between 2 races. On the influence of nutritional conditions upon length of the life span, there have been several papers [3, 4, 6]. MCCAY *et al.* [6] reported that a retardation of the growth of rats by restricted diet resulted in prolongation of their life span.

LECOMPTE [5] reported that aging process of the human race was accelerated by environmental condition especially by chronic malnutrition. The native Japanese people were considered to be more inbred than the Caucasians in USA. However, coefficient of variation in size of the hepatic cells and their nuclei was generally larger in value in the Japanese than in the Caucasians; therefore, the individual variation is considered to be higher in grade in the former.

From the above, in the differences in the process of senile change between two races, the environmental conditions, especially nutrition may play a more important role than the genetic factor.

In the organism, the senile change has been believed to begin after maturation. An earlier appearance of the aging process in the Caucasians was thought to be due to earlier maturation by better nutritional conditions. It may be also considered that the poorer nutritional conditions in the Japanese aged accelerate the reduction of parenchymal cells by reduced ability of physiological regeneration of parenchymal cells.

Summary

As the characteristic of senile change of the human liver, decreases in weight and in the number of hepatic parenchymal cells and changes in the number of binucleate hepatic cells were determined. However, there have been noticed some differences in the process of senile change between the native Japanese and Caucasians in USA. The senile change seemed to begin earlier in the Caucasians, but progress more markedly in the Japanese. Some discussions have been made on the difference between the 2 races.

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Book Reviews – Buchbesprechungen – Livres nouveaux

E. W. BUSSE and F. C. JEFFERS (ed.): **Proceedings of Seminars 1965–1969.** Duke University Council on Aging and Human Development. Duke University, Med. Center, Durham, N. C. 1969. 330 p. $ 7.50.

These 28 lectures were given during 5 years in Duke University's Center for the study of aging, and cover many sides of mainly medical, psychological and social human aging. Also some other territories, such as asthma and obesity are discussed. Red.

Homeostatic regulators. Ciba Foundation Symp. Churchill, London 1969. 327 p.

Readers of this book should start on page 303 where the members of this Ciba Symposium in a final discussion confessed their embarassment at calling 'homeostasis' all the 'regulations' or rather 'reactions' which they described with interesting examples. Homeostasis is an accepted physiological definition of the state of the 'milieu interieur'. If we extend it to all that is said here, genetics, immunology, etc. we find ourselves in the situation of 'anthropology' which, 20 years ago, was a well-defined science of human cultures and then became a science which discusses everything from skin colour to food habits, and from customs, to anatomy and pathology of the human race.

Inspite of this, the volume contains much interesting material, as in the paper of JOHNS, who gives an admirable review on histones and their interaction with DNA for gene-control. The role of bacteriophages (F. GROSS), or thromboplastic tumor material (O'MEARA), and immunity reactions, as regular or accidental ways to keep normality of the body, are all valuable facts. They are 'regulations', as are cell growth regulations *in vitro* (STOKER) or in the intestinal or skin epithelium (SUBAK-SHAPER), where 'contact' or 'tension' or 'metabolites' or 'chalons' act. But what about the determination and differentiation which forms our face to look like that of our parent and is certainly not a homeostatic regulation. *F.V.*

W. DOBERAUER, A. HITTMAIR, R. NISSEN und F. H. SCHULZ: **Handbuch der praktischen Geriatrie,** Band 3. Enke, Stuttgart 1969 (siehe auch Gerontologia *12:* 123 [1966] und *15:* 64 [1969]). XII + 659 p., 169 fig., 57 Tab. DM 140.–.

Der dritte Band des Handbuchs der praktischen Geriatrie enthält auf 660 Seiten ausführliche Kapitel über dringliche Chirurgie im Alter, elektive Chirurgie, Neuro-Chirurgie, Kieferchirurgie und Unfallchirurgie im Senium. Kapitel wie kleine geratrische Chirurgie, chirurgische Infektionen, Vor- und Nachbehandlung, physiologische und metabolische Probleme und Anästhesiologie scheinen sich oft zu überdecken. Die Kapitel über Hals-, Nasen-, Ohren-, Augen-, Haut- und gynäkologische Krankheiten im Alter bilden die letzten 200 Seiten. Ein Schlusswort von Prof. HITTMAIR und ein ausführliches Sachregister von 20 Seiten für alle drei Bände beenden den Band. *F. V.*