ON THE FUNDAMENTAL MORPHOLOGY OF THE SENILE CHANGES

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There have been presented very many papers on the problem of senile changes as well as much discussions on the nature of senile changes. However, there are many open questions to be elucidated in the future, too.

The present author has been engaging in the study on some problems concerning clarification of the nature of senile changes and possibilities of management influencing upon those changes.

And, as the introductory thesis, some studies on the senile changes especially of the senile atrophy of parenchym cells have been carried out. Some results together with consideration on them will be presented here.

On the Definition of Senile Changes

At the present time, definition of the senile changes can never be settled precisely, however, it is a fact that a series of the changes go increasing with advancing age have been called as senile changes, though pretty vague and often ambiguous in sense.

If the senility of individual human being ought to be considered a physiological phenomenon in essence, senile changes in the true sense must denote such changes which occur during the long course of life history representing summations of the so-called healthy states in both through the intra- and extrauterine life. In other words, changes which occur based on pathologic life phenomena should not be called as senile changes, even if those changes may happen to appear very frequently in aged people, thus presenting reason why it is impossible to define precisely the senile changes. It tells that so-called healthy conditions are not necessarily considered to be the ideal conditions in maintaining life of human beings; expressed otherwise, so-called healthy conditions are more ideal than pathologic ones but in themselves not ideal ones, either.

Nobody can surely deny whether more ideal conditions for the maintenance of life may be realized this or that way, nor there can be definite conclusion that maintenance of life of human beings get prolonged than now, by far.

All in all, there lie many difficulties to define the senile changes exactly at hand; at present, we must satisfy ourselves with that the senile changes are the changes which occur with advancing age in the course of healthy living conditions, therefore, without any pathologic processes.

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Materials and Methods

Both autopsy cases and experimental animals were used. Examinations were carried out histologically, histochemically and micrometrically in the organs and tissues of 494 autopsy cases, with sex, age and cause of the death as indicated in Table 1-2. Experimental animals were rats exclusively of which specimens of above 2 years of age served as senile subjects and those of about 6 months of age as control. The livers and kidneys of those animals were subjected under various experimental conditions demanded and examined afterwards to histological, histochemical, chemical, micrometrical and electronmicroscopical tests.

TABLE 1. Number of Autopsy Cases

Age	Male	Female	Total
20–29	18	10	28
30–39	28	23	51
40–49	33	16	49
50–59	60	21	81
60–69	65	32	97
70–79	45	64	109
80–89	22	49	71
90–	2	6	8
Total	273	221	494

TABLE 2. Comparison of Autopsy Cases According to Causes of Death

Age	Number of cases	Cancer (%)	Circulatory disease (%)	Others (%)
20–39	79	17(21%)	5(6%)	57(73%)
40–49	49	27(55%)	8(16%)	14(29%)
50–59	81	52(64%)	5(6%)	24(30%)
60–69	97	44(45%)	34(35%)	19(20%)
70–79	109	24(22%)	56(51%)	29(27%)
80–	79	10(12%)	40(50%)	29(38%)
Total	494	174(35%)	148(30%)	172(35%)

1. ON THE CAUSE OF DEATH IN THE AGED

The rate of death from circulatory disease got roughly increased with advancement of age, however, the rate of death of cancer did so before sixth decade, but to get gradually decreased after seventh decade (Table 2).

2. ON THE AGE PATTERN OF ARTERIOSCLEROTIC CHANGES OF THE ORGAN ARTERIES

Arteriosclerosis has been generally considered to increase in grade with advancing age. However, there were found that this tendency toward increase was differing according to various arteries of organs.

In this study, the present author classified the arteries of organs according to their calibers into 3 types, such as middle and small arteries and arteriole.

Generally speaking, arteriosclerosis increased in grade with advancement of age most markedly in artery of the middle caliber, next more markedly in that of the small caliber and lesser markedly in the arteriole. Still, these increase in grade fell different according to the organs.

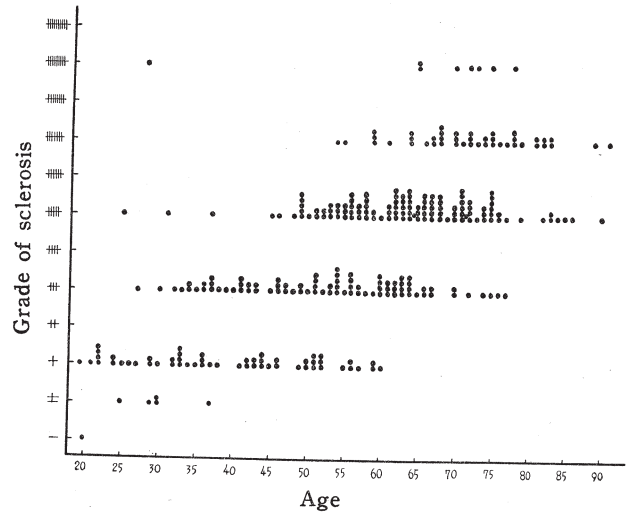

FIG. 1. Change of grade of sclerosis of the arteries of middle caliber in the kidney with advancement of age.

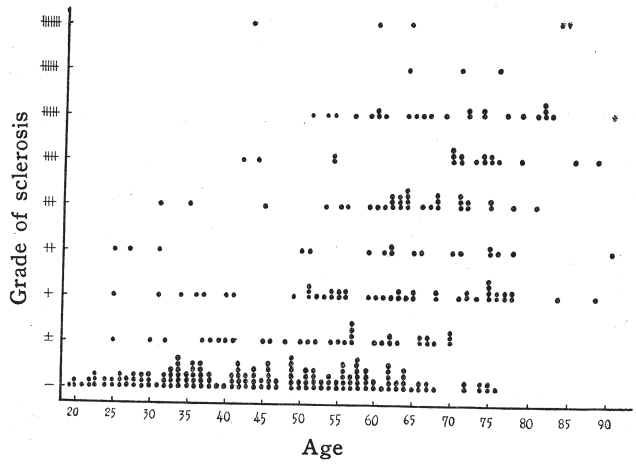

FIG. 2. Change of grade of sclerosis of the arteries of middle caliber in the liver with advancement of age.

The artery of the middle caliber showed a tendency of increase in grade of arteriosclerosis with advancing age most markedly in the kidney (Fig. 1), more markedly in the liver (Fig. 2), spleen (Fig. 3), pancreas (Fig. 4) and thyroid, and lesser markedly in the myocardium (Fig. 5) and uterus. Concerning the small artery, that tendency was proved most markedly in the kidney (Fig. 6) and pancreas (Fig. 7), rather less in the liver (Fig. 8) and spleen

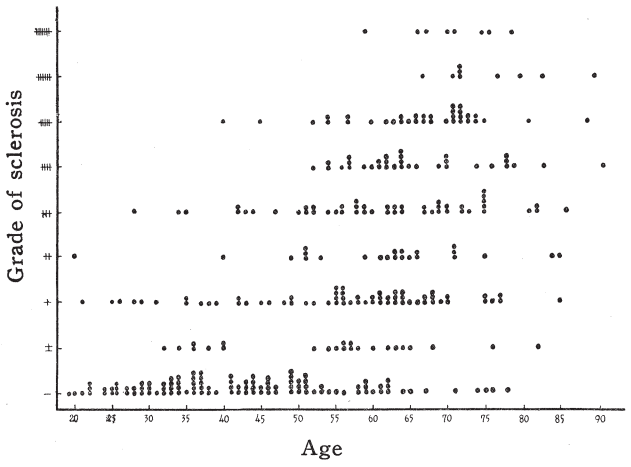

FIG. 3. Change of grade of sclerosis of the arteries of middle caliber in the spleen with advancement of age.

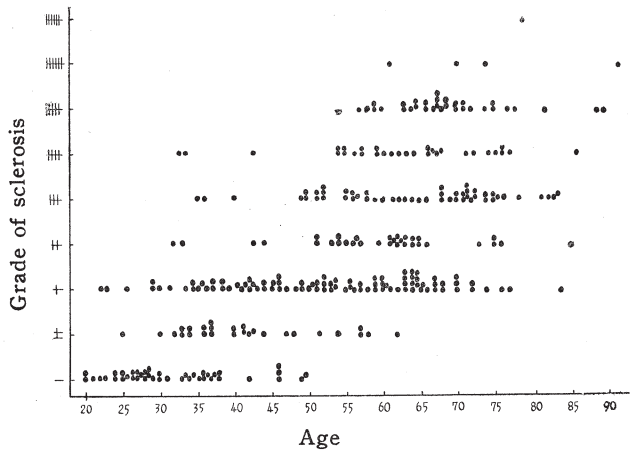

FIG. 4. Change of grade of sclerosis of the arteries of middle caliber in the pancreas with advancement of age.

(Fig. 9), a lesser in the myocardium and uterus, and the least in the thyroid.

The arteriole proved that tendency somewhat markedly in the pancreas (Fig. 10) and myocardium (Fig. 11), rather less in the spleen (Fig. 12) and kidney (Fig. 13), a lesser in the liver (Fig. 14) and uterus, and the least in the thyroid.

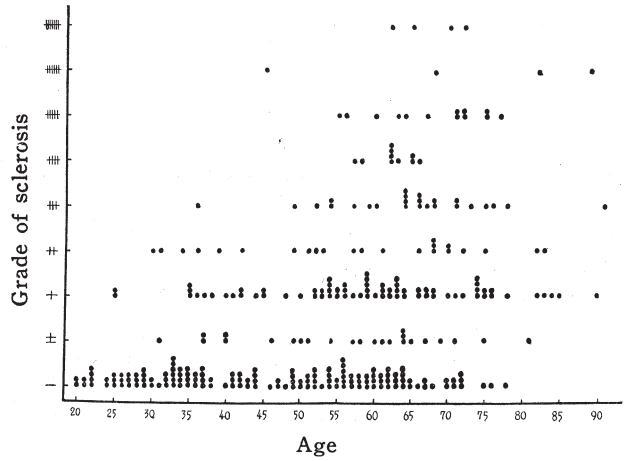

FIG. 5. Change of grade of sclerosis of the arteries of middle caliber in the myocardium with advancement of age.

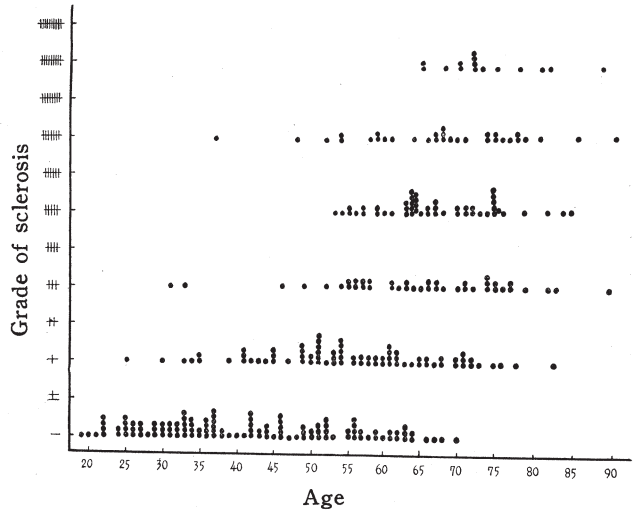

FIG. 6. Change of grade of sclerosis of the arteries of small caliber in the kidney with advancement of age.

In the kidney, sclerosis both of the arteries of middle and small caliber increased in grade with advancing age, while that of the middle artery started to increase from younger age compared with the small artery whose sclerosis started always in older age. The arteriole of the kidney increased in the grade of sclerosis lesser markedly with advancement of age.

In the pancreas, sclerosis of all types of arteries increased markedly in

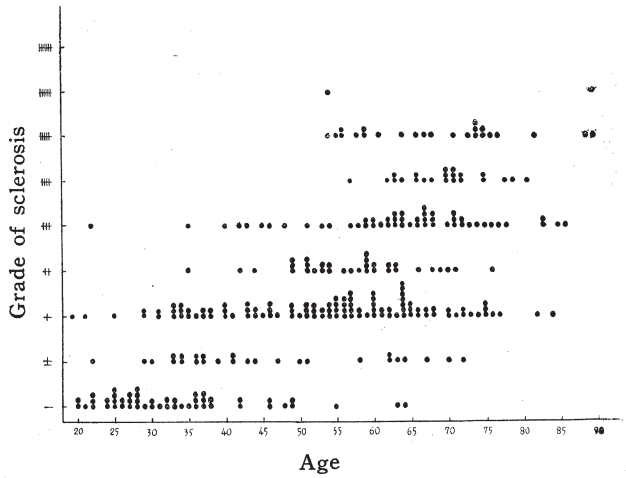

FIG. 7. Change of grade of sclerosis of te arteries of the small caliber in the pancreas with advancement of age.

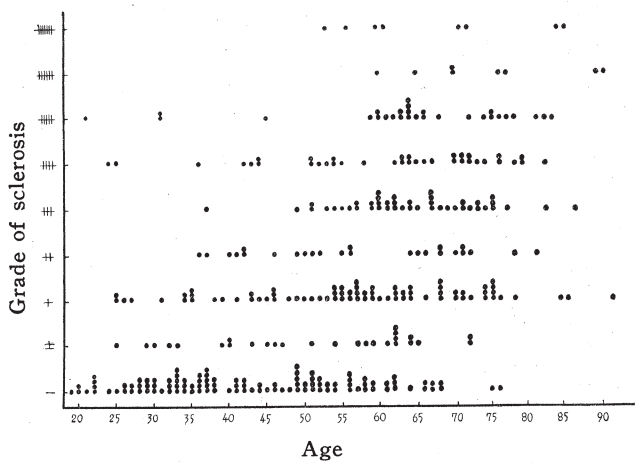

FIG. 8. Change of grade of sclerosis of the arteries of small caliber in the liver with advancement of age.

grade with advanced age in almost same manner. In the spleen, these tendencies were demonstrated generally somewhat less marked, but relatively more marked in artery of the middle caliber and lesser marked in the arteriole. In the liver, those tendencies were generally alike as in the pancreas with some exceptions. In the uterus, there were missed any marked differences concerning the said tendencies, artery of the small caliber making an exception with

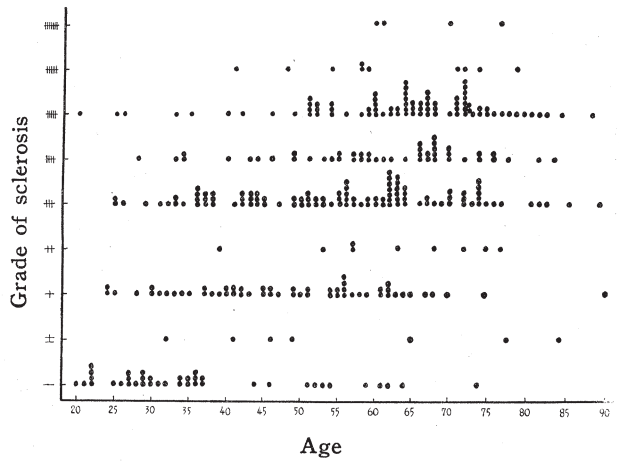

FIG. 9. Changes of grade of sclerosis of the arteries of small caliber in the spleen with advancement of age.

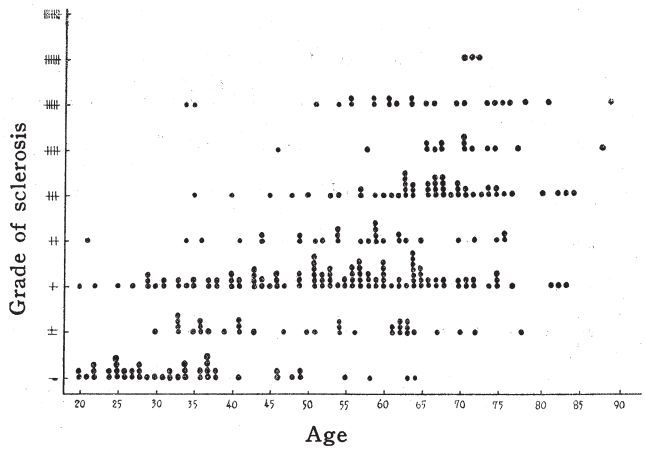

FIG. 10. Change of grade of sclerosis of the arterioles in the pancreas with advancement of age.

relatively marked tendency. In the myocardium, those tendencies were rather more marked in the arteriole than other types of arteries. In the thyroid, those tendencies were more marked in the artery of middle caliber but almost unnoticeable in the smaller artery and arteriole.

And it was beyond questions that these tendencies were generally more

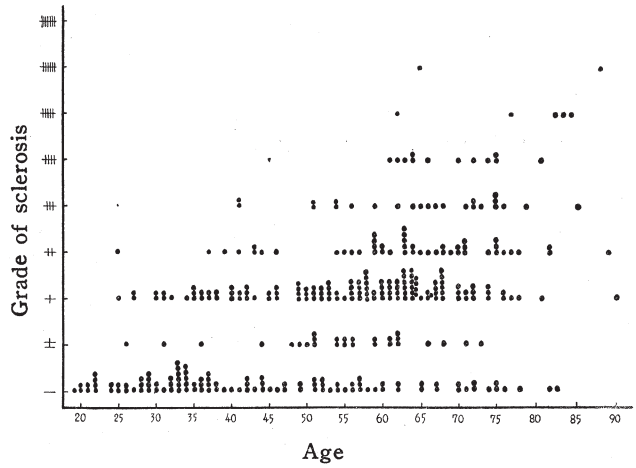

FIG. 11. Change of grade of sclerosis of the arterioles in the myocardium with advancement of age.

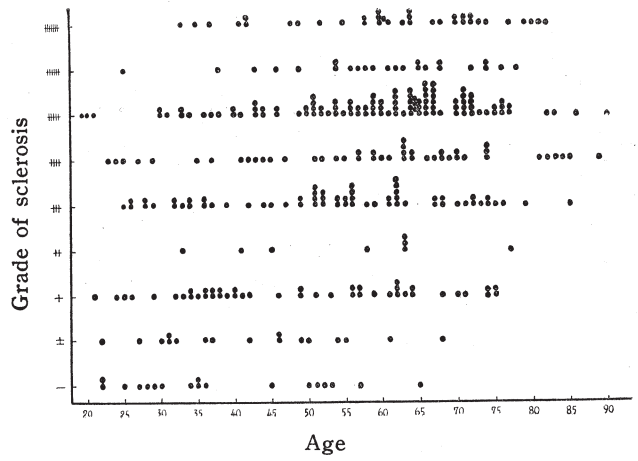

FIG. 12. Change of grade of sclerosis of the arterioles in the spleen with advancement of age.

markedly detected in cases of the circulatory disease than those of the cancer.

Contrasting to the human autopsy cases, there were not recognized any arteriosclerotic changes even in rats of older age as were used by us. At any rate, one thing stands ascertained that there remain many problems to be elucidated concerning the arteriosclerotic changes.

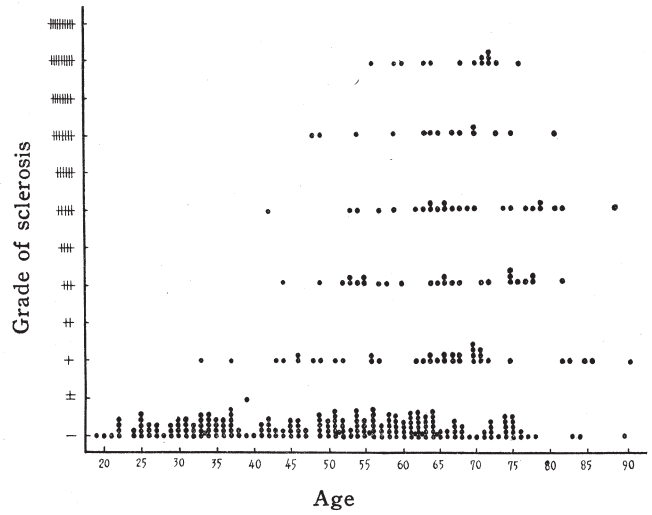

FIG. 13. Change of grade of sclerosis of the arterioles in the kidney with advancement of age.

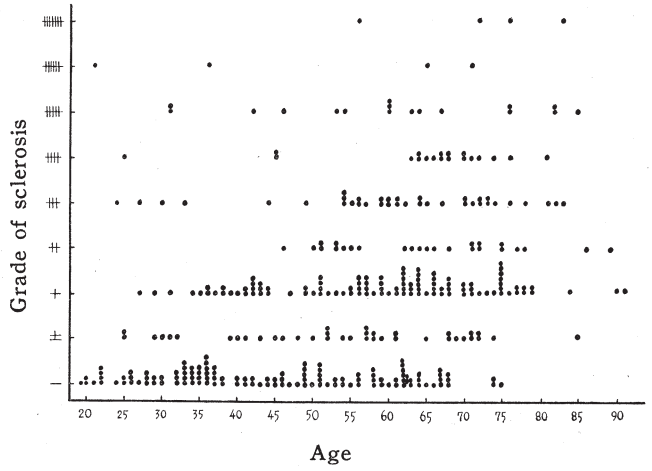

FIG. 14. Change of grade of sclerosis of the arterioles in the liver with advancement of age.

3. ON THE TISSUE FIBROSIS CONSULTING THE AGE

Fibrosis of the interstitium was also considered to be one of the senile changes, however, according to our examination, fibrosis did not get markedly increased in grade with advanced age (Figs. 15, 16).

In the myocardium and myometrium there was found certain increase of fibrotic changes parallel-going with advanced age, but that tendency was never so marked. In the hypophysis, liver, thyroid and adrenal that tendency was less marked and in the spleen, urinary bladder and kidney there was hardly

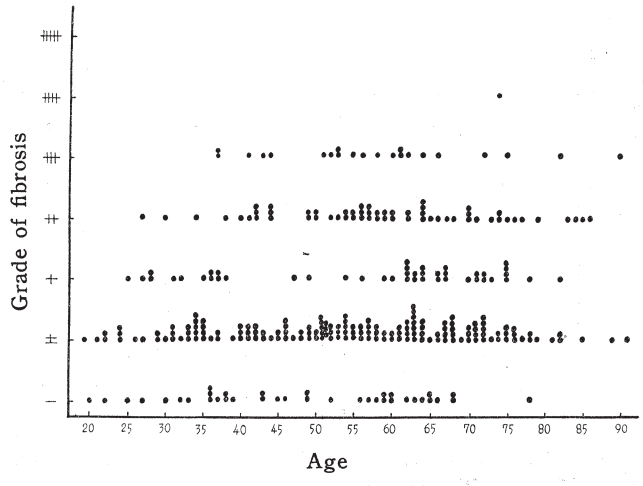

FIG. 15. Relationship between grade of fibrosis of the liver and age.

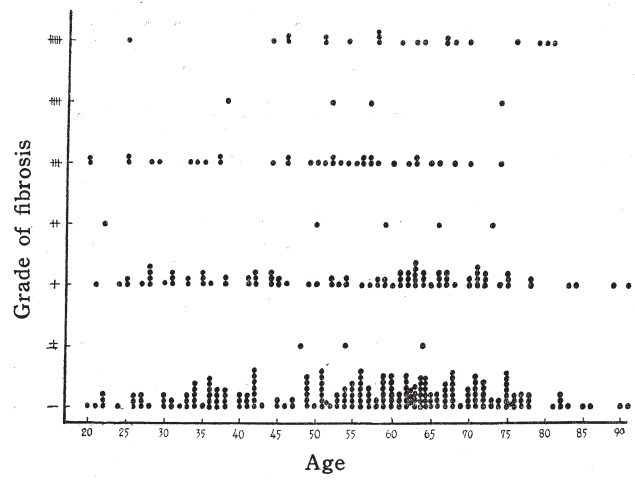

FIG. 16. Relationship between grade of fibrosis of the spleen and age.

noticeable with advancing step of age. As fibrosis is considered to be irreversible change in some degree, the findings that fibrosis went increasing in grade with the age in some organs are reasonable to consider to be due to the pathologic process during the life history of individual rather than due to senility.

4. ON THE LOSS IN WEIGHT OR ATROPHY OF THE ORGANS AND TISSUES WITH ADVANCEMENT OF AGE

a) *On the loss in weight of the organs* (Table 3)

The changes of weight of the important organs were examined according to the age and compared with the results presented by some authors.[21) 22) 27) 30) 31) 52)]

The loss in weight with advancement of age was noticed most markedly in the spleen (Fig. 17) and liver (Fig. 18), more markedly in the pancreas and kidney (Fig. 19), lesser in the uterus, brain (Fig. 20) and testis, and the least in the endocrine organs such as the thyroid (Fig. 21), adrenal (Fig. 22) and hypophysis. The change of weight of the heart according to the age was

TABLE 3. Grade of Loss in Organ Weight with Advancement of Age

1. Spleen	##
2. Liver	##
3. Kidney	#
4. Pancreas	#
5. Brain	+~#
6. Heart	±
7. Uterus	+~#
8. Testis	+
9. Thyroid	±~+
10. Adrenal	±
11. Hypophysis	−~±

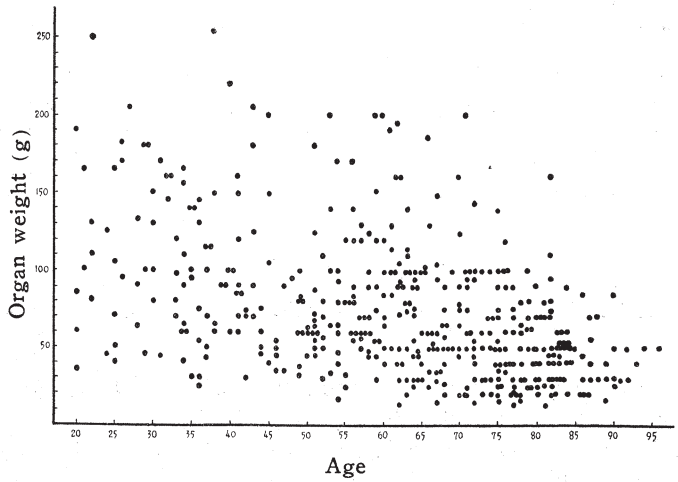

FIG. 17. Relationship between weight of the spleen and age.

rather irregular; in case without circulatory disease, the heart got decreased in weight in some degree with advancement of age.

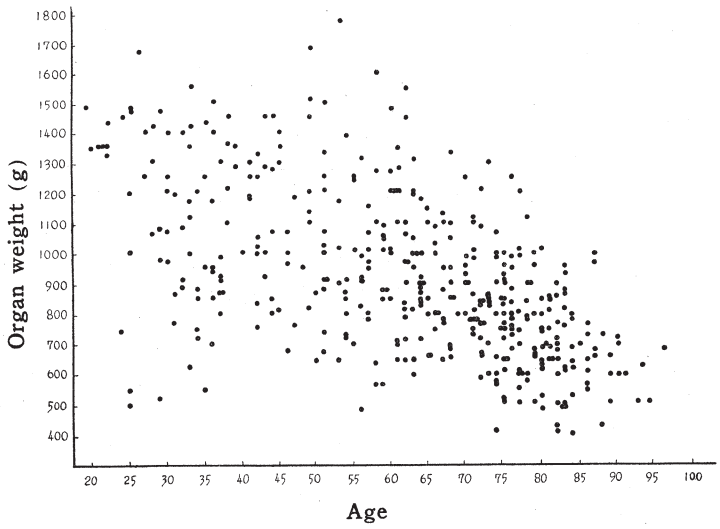

FIG. 18. Relationship between weight of the liver and age.

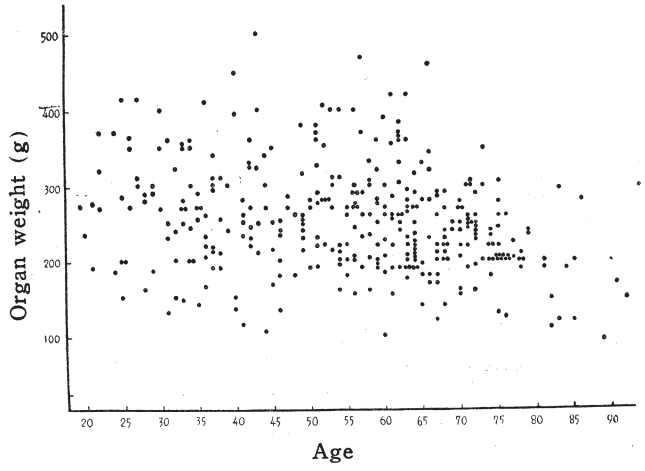

FIG. 19. Relationship between weight of the kidneys and age.

b) Decrease Rate of Number of Parenchym Cells of the Organs (Table 4)

In order to measure the attitude of the parenchym cells, the representant of the organ function morphologically, total number of the parenchym cells of each organ was roughly compared with by ciphers of the organ weight and cell number in a given area of each organ. Number of parenchym cell got

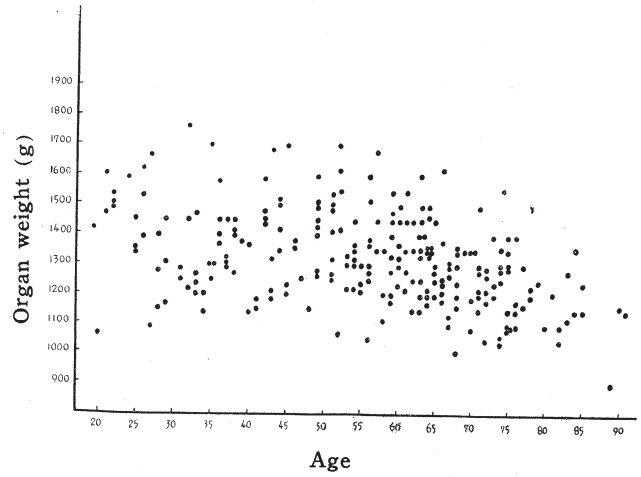

FIG. 20. Relationship between weight of the brain and age.

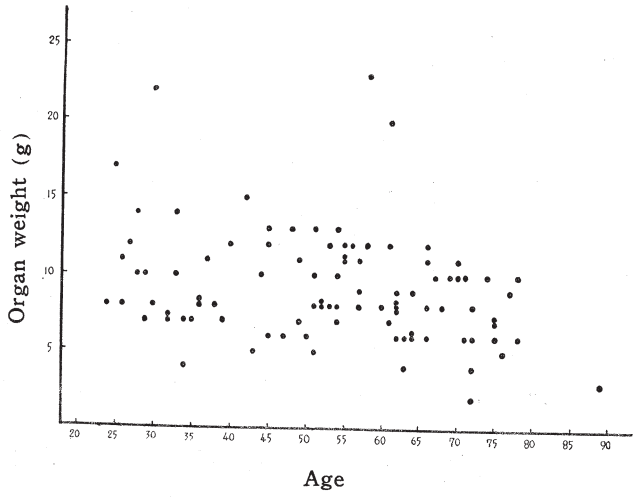

FIG. 21. Relationship between weight of the thyroid and age.

TABLE 4. Grade of Decrease in Cell Number of the Organ Parenchym with advancement of age

1. Spleen	###
2. Liver	###
3. Kidney	## ~ ##
4. Pancreas	##
5. Adrenal	#
6. Thyroid	− ~ ±
7. Hypophysis	±

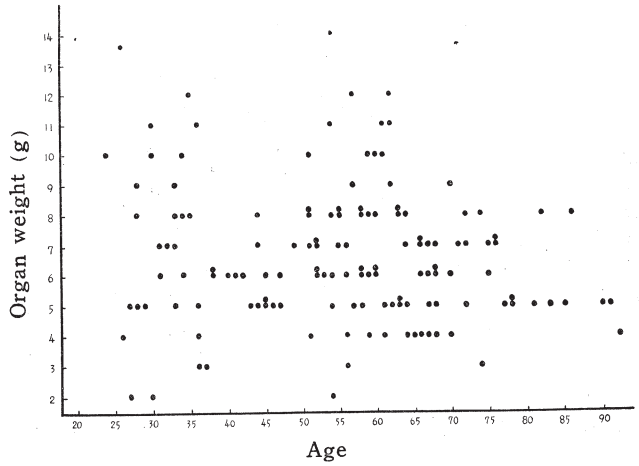

FIG. 22. Relationship between weight of the adrenal and age.

decreased with advancement of age most markedly in the spleen and liver (Fig. 23), more markedly in the kidney and pancreas, and much lesser in the adrenal, hypophysis and thyroid.

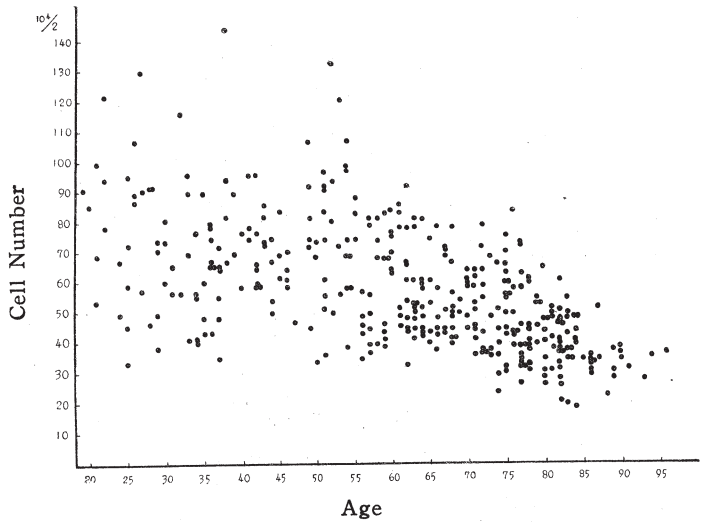

FIG. 23. Relationship between age and cell number of the liver (represented by ciphers of the organ weight and cell number in a given area),

5. SIGNIFICANCE OF ARTERIOSCLEROSIS AND FIBROSIS OF THE ORGANS IN CONNECTION WITH LOSS IN WEIGHT OR DECREASE IN NUMBER OF PARENCHYM CELLS

a) On the relationship between grade of arteriosclerosis of organ arteries and the degree of decrease in number of parenchym cells as well as loss in weight of each organ

This relationship was compared in individual organ, with degree of arteriosclerosis represented by that of arteries of the middle caliber of each organ, as the grade of sclerosis parallel-going with advancement of age was most remarkable compared with other arteries. The degree of numerical loss of parenchym cell went roughly parallel to the grade of arteriosclerosis in the kidney (Fig. 24). But, in the spleen (Fig. 25), liver (Fig. 26) and thyroid etc., this parallelism could be found only in a trace or not at all. Of all things in the ages above 60 years this parallelism was more markedly shown in the kidney (Fig. 27) between the grade of arteriosclerosis and that of loss in parenchym cells while it was missed in the spleen, liver and thyroid.[22] In other words, arteriosclerosis of organ arteries and loss in the organ weight were considered to mean an accidental complication in the spleen, liver and thyroid in the light of the age; on the contrary, in the kidney these factors proceeded related in grade intimately with the aspect of age.

It is noteworthy that the kidney arteries fell increasing in grade all the earlier ages in sclerosis than loss in organ weight.

From above mentioned facts, arteriosclerosis of the kidney arteries seemed to play an important part of parenchym loss of the kidney. Namely, the senile loss of the kidney parenhym was considered to be due to arteriosclerosis in

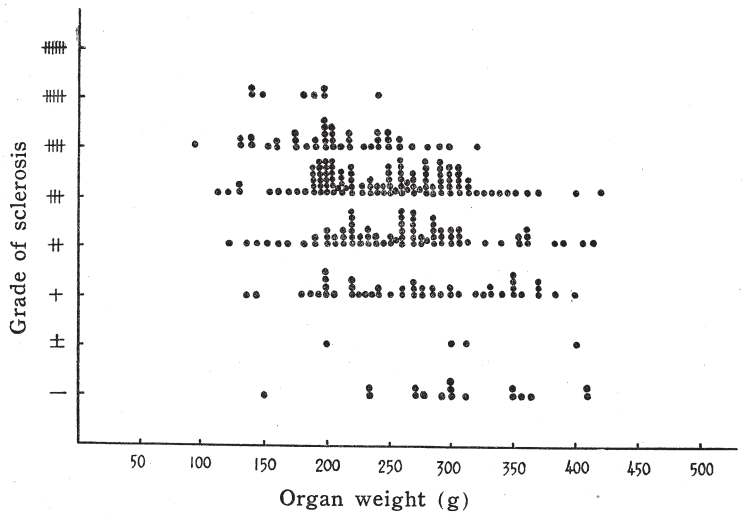

FIG. 24. Relationship between grade of sclerosis of arteries of middle caliber in the kidney and weight of the kidneys.

the organ on the one hand, though it has also been noticed on the other hand that there were found some senile-atrophied kidneys without severe arterio-sclerosis of the organ arteries.[45) 53)]

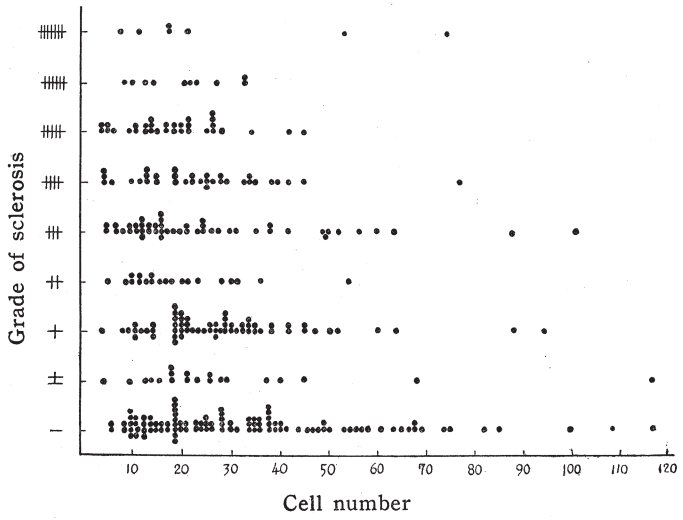

FIG. 25. Relationship between grade of sclerosis of arteries of middle caliber in the spleen and number of splenocytes (represented by ciphers of the organ weight and cell number in a given area).

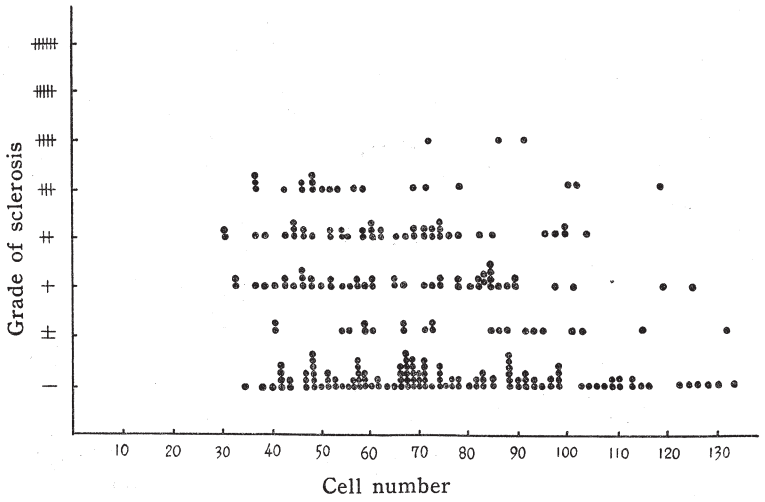

FIG. 26. Relationship between grade of sclerosis of arteries of middle caliber in the liver and number of liver cells (represented by ciphers of the organ weight and cell number in a given area).

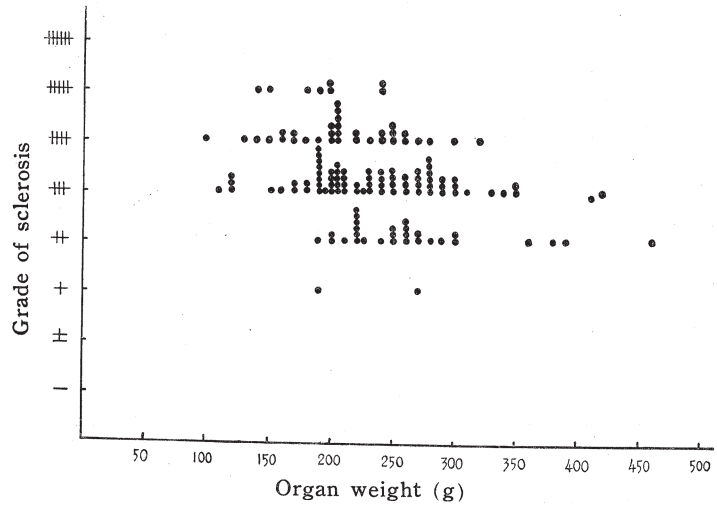

FIG. 27. Relationship between grade of sclerosis of arteries of middle caliber in the kidney and weight of the kidneys (in case of aged above 60 years).

b) On the relationship between the degree of fibrosis and the degree of parenchym loss of individual organ

Regarding this relationship, there was noticed a few parallelism between the said changes in the spleen (Fig. 28), only a few parallelism in the kidney (Fig. 29) and liver (Fig. 30), but no parallelism in the myocardium and thyroid.

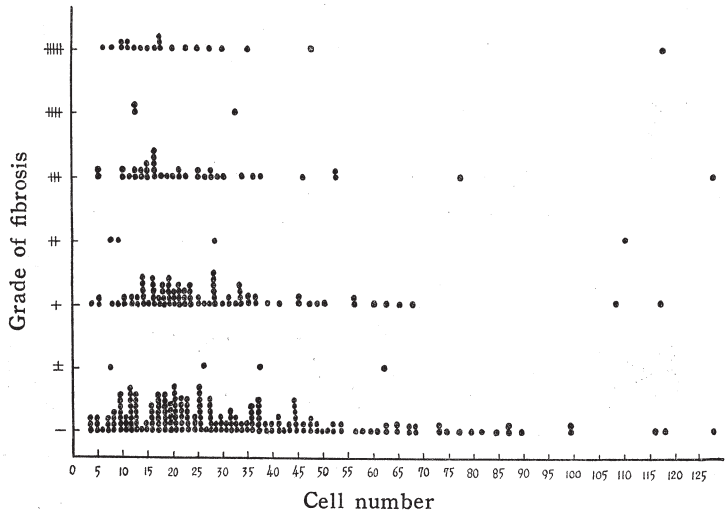

FIG. 28. Relationship between grade of fibrosis and cell number of splenocyt in the spleen (represented by ciphers of the organ weight and cell number in a given area).

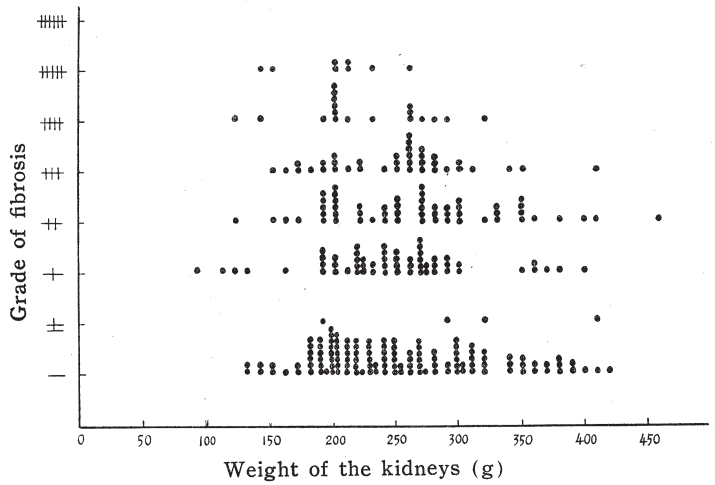

FIG. 29. Relationship between grade of perivascular fibrosis and organ weight in the kidney.

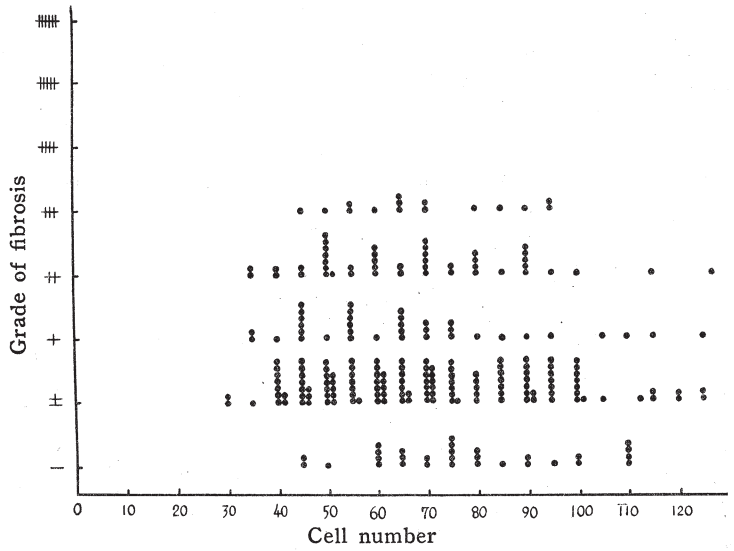

FIG. 30. Relationship between grade of fibrosis in the liver and number of liver cells (represented by ciphers of the organ weight and cell number in a given area).

6. ON THE SIGNIFICANCE OF CHANGES OF THE ENDOCRINE ORGANS REGARDING THE SENILE CHANGES OF OTHER ORGANS AND TISSUES

Changes of the endocrine organs were considered to play an important part for the senility by many authors.[27) 34) 36) 52) 54) 56)] Nevertheless, our examination

did not reveal any findings that the loss in weight and decrease in the number of parenchym cell of the endocrine organs were all the akin with those of other organs and tissues. The changes in finer structures of the endocrine organs were undeniable by the present study, still they well play little important part for explanation for the cause of senility after all.

7. ON THE SENILE CHANGES OF ORGAN PARENCHYM CELLS WITH SPECIAL REFERENCE OF SENILE DECREASE IN NUMBER OF THEM

From the above mentioned findings, the positive causal factors for the senile loss of organ parenchym can hardly be ascertained morphologically excepting in the kidney, the latter losing in its parenchym through senile sclerosis of organ arteries.

(*i*) *Changes in volume of parenchym cells of the organs according to age*

In some organs, the cut area of parenchym cells were measured micrometrically in histological specimens under consideration of age factor. At first, number of parenchym cells in a given area were calculated in various organs always under control of age factor, as the results are presented here. In the parenchymatous organs numbers of parenchym cells in a given area are considered to be reverse proportional to the cell volume generally. In the liver (Fig. 31), the number of liver cells in a given area went decreased to a certain degree with advanced age. In the adrenal, this tendency was recognized though in a slighter degree in zona reticularis and fasciculata but hardly recognizable in zona glomerulosa.[21] In the muscle layer of the stomach, this tendency was also noticed in a slighter degree but none in the muscle layer of the urinary bladder, in the hypophysis and epidermis altogether. Exocrine cells of the pancreas (Fig. 32) showed little change in number rela-

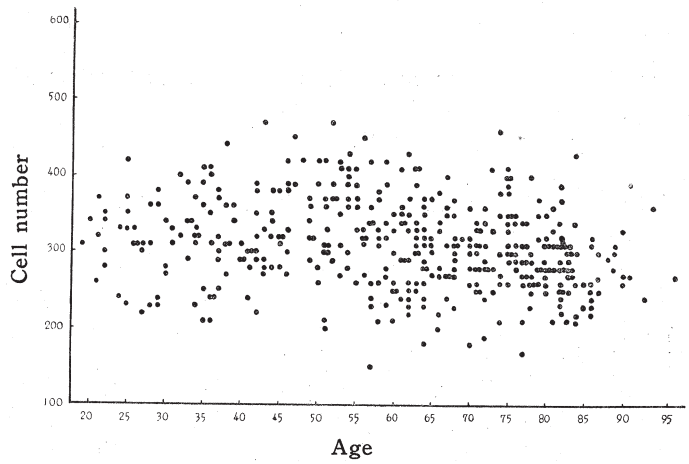

FIG. 31. Relationship between number of the liver cell in a given area and age.

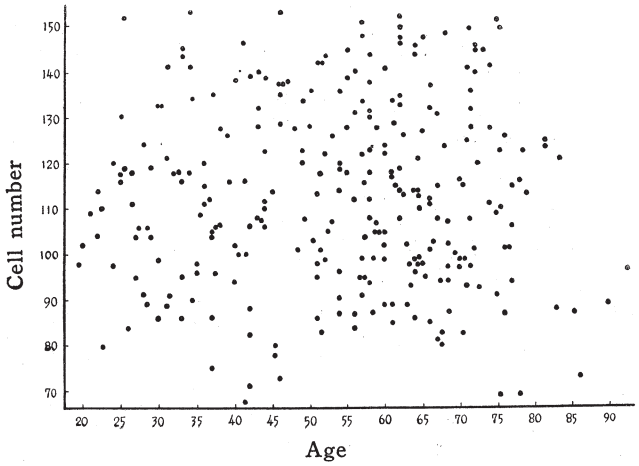

FIG. 32. Relationship between number of the exocrine cells of the pancreas in a given area and age.

tion in a given area controlled by the age factor, but there was surely a decrease in number of the acini in a given area accompanied by an increase in cell number in a given acinus definitely controlled by advancing senility. An increase of number of the follicle in a given area of the thyroid accompanied by a decrease in cell number in a given follicle was also noticed going hand in hand with advancement of age.[22] These controversial findings between the pancreas and thyroid must afford a matter of interest to be discussed furthermore.

Generally speaking, the parenchym cells did not only decrease in number but often increased in their volume with advancement of age, this being especially the case in the liver.

(*ii*) *Comparative studies between senile and non-senile atrophy of the liver*

Histological and micrometrical investigations have been performed in the liver which markedly lost their weight due to senility and to malnutrition, respectively.

Details of the results on this problem have been reported by the present author and his co-workers.[40] A summary will be presented here.

The non-senile atrophy of the liver was considered to be brought about mainly due to decrease in the cell volume, unlike the cases of senile atrophy considered mainly due to a decrease in cell number despite of the co-existent increase in the cell volume.

But in senile-atrophied liver, there was sometimes noticed decrease in the liver cell volume. However, this finding shall to have to thank its forthcoming to the cell atrophy resulting from malnutrition or congestion there, the conditions likely to occur more frequently in the senile case than in the non-senile one.

(*iii*) *Comparative studies between the senile and non-senile atrophy of the kidney, and between the senile kidney without loss in weight and without arteriosclerotic changes consulted with the control one*

From the above, senile atrophy of the kidney was considered, on the one hand, to be due to sclerosis of arteries of the organ, and, on the other hand, histological and micrometrical investigations have been performed compared with the cases of atrophy caused by malnutrition and of simple senile atrophy without marked arteriosclerosis in the organ. In the kidney of the former case, there was found atrophy of individual cells of the glomerular tuft and of the convoluted tubuli; on the contrary, there was found decrease in number and increase in volume of those cells in the latter case.

Micrometrical examinations have been also made of senile kidney without loss in weight and lacking of arteriosclerotic changes comparing with the control kidney. These examinations revealed plainly that the senile kidney showed decrease in number and increase in volume of parenchym cells of the organ.

In other words, the senile atrophy of the kidney was considered, on the one hand, to be due to arteriosclerosis in the organ, but on the other hand, essentially to be due to a decrease in number of parenchym cells accompanied by an increase in volume to a certain degree.

The details of these findings noticed in this paragraph have been reported previously by the present author and his co-workers.[45)53)]

(*iv*) *On the senile atrophy of the uterus*

Details of this subject have been reported by the co-worker of the present author.[16)] Here they will be summarized as follows.

In the uterus, muscle cells of the myometrium and glandular cells of the endometrium gave a decrease in number with advancing age, and it is interesting that decrease in volume of parenchym cells was markedly found in such stages extending for several years following the period of menopause as well as in the cases standing above 70 years of age. And as a noticeable finding, this decrease in volume of the uterine parenchym cells was much more marked than in the other organs.

(*v*) *On the difference among patterns of resting liver tissue and of regenerative process of the remaining liver tissue after partial hepatectomy judged from the age factor in rats*

a) *Histological, histochemical and biochemical observations*

Regenerative process of remaining liver tissue after partial hepatectomy about 60 per cent was examined histologically, histochemically and chemically.

In the control group of about 6 month old rats, the mitotic figures of the liver cells were most frequently detected with steep curve about 30–36 hours after operation, but in the senile group about 24 month old, appearance of the mitotic figures was much delayed and curve of increase ran lesser steep, while duration of appearance of mitosis was again delayed than in the control group. To be exact, contents of RNA in cytoplasm and nucleoles in the liver cells, and pictures of mitochondria there were changed, closely related with the

changes of the pattern of appearance of mitotic figures, thus indicating for some contrast between the patterns to the control and senile cases.

In the senile case, both cells and their nuclei were much larger and more irregular in sizes among neighbouring cells and nuclei than in the control specimen even in the resting stage, but in the regenerating process of the senile group, they became much more larger and far much irregular in sizes among neighbouring cells and nuclei than in the resting stage. In other words, there were noticeable that the liver cells of the senile group look decreased in ability of regeneration, showing increase in the volume of cells and nuclei and in the grade of irregularity in size.

Binuclear liver cells were found more often in senile case than control, even in the resting stage, and in the postoperative regenerative period these cells got increased in number both in senile and control cases with steep curve after operation, the maximum value in number being reached 24 hours after operation, gradually to get decreased numerically and to reach the value of the resting stage at 120 hours after operation. And these tendencies of increase in binuclear cell number were far more markedly noticed in senile case than in control.

Some biochemical studies have also been performed in the regenerating liver tissue above mentioned. In the senile case, relative ribonuclease activity of the tissue showed a lower value in the course of regeneration; in base analysis of RNA there were noticed the changes in value regarding content of cytosin, urasil and adenin in the same manner as in control but guanin content did not suffer change during the course of regeneration contrasted with the control case where guanin content went increased markedly in the course of regeneation.

Details of these findings noticed in this paragraph have been previously reported by the present author and his co-workers.[47) 50) 55)]

b) Enzyme-morphological observations

Regarding to the enzymatic activities in various organs of senile animals, some papers have been presented by some authors[4) 13) 26) 33) 58)] who examined chemically tissue-homogenates.

However, enzyme-histochemical studies on senility has not still been found in our survey of literature, thus, enzyme-histochemical investigations on some enzymatic activities in the liver cells have been performed comparing between senile rats and control ones.

Details of this subject will be reported by a co-woker of the present author. Here will be presented a summary of them.

There were used the method of Wachstein et Meisel for succinic dehydrogenase, that of Graeff for cytochrome-c-oxidase and that of Takamatsu for alkaline phosphatase, respectively.

In the control cases, activities of both succinic dehydrogenase and cytochrome-c-oxidase were generally recognized only a little in the central portion of the lobules and markedly in the peripheral; in the senile case, however, the area which showed the said activity markedly was noticed to have a tendency

to be limited toward the periphery of the lobules.

In the control cases, alkaline phosphatase activity of liver cells was markedly recognized in the peripheral portion of the lobules and not at all in the central; but in the senile cases, even in the central portion there was sometimes noticed the said activity besides in peripheral.

These enzyme-morphological findings are considered to coincide with the results obtained by some authors who examined chemically organ homogenates. But, biological significances of the above mentioned findings upon the senility remain to be discussed in future.

Studies on the regenerating liver after partial hepatectomy are now carried on by co-workers of the present author, and details of them will be presented in future.

c) Electron microscopic observation

There are many discussions[5) 9) 15) 23) 24) 28) 35)] about the biological significance of cell organelles, setting a series of questions to be solved in the future. Here will be presented a brief summary of the results obtained by the present author and his co-workers.

In resting liver cells of senile rats, mitochondriae were smaller in relative number, somewhat decreased in density and spherical in shape. "Microbodies" or "cytosomes", characterized by their uniformly dense content plus excentrically located nucleoid in the body, were found in abundance. The rough surfaced endoplasmic reticulums had a tendency to form larger lumina, as compared with those of thin, parallel arrays in normal liver cell. The smooth surfaced endoplasmic reticulums were also noticeable in areas of the cytoplasm described as regions of glycogen depot scatteringly and along the margin of the cells, but never so richly.

Liver cells of senile and control rats along the course of regeneration were observed 5, 8, 12, 16, 20, 24, 30, 36, 48, 60 and 96 hours after partial hepatectomy.

In the control livers: Cytoplasms were occupied by large number of swollen mitochondria much more increased in density of basophilia, and the rough surfaced endoplasmic reticulum became vesicular from 5 to 12 hours onward of hepatectomy. From 16 to 24 hours, these two organelles are grouped together in dense masses at the juxtanuclear areas and the cell periphery, while "microbodies" grew abundant in number. Accumulations of lipids started around 12 hours, reached the highest level to return to normal level around 48 hours or so after hepatectomy. Generally speaking, the cell changes following partial hepatectomy came back to normal, for the most part, 48 hours or so.

In the aging rat livers, "microbodies" were also numerous but maintained their numbers for a long period. Swollen mitochondria and vesicular formation of rough surfaced endoplasmic reticulums were seen for a longer time thereafter. The smooth surfaced profiles, forming the clumps of smooth vesicles, appeared more frequently than under the regenerating process of the control livers, while glycogen areas were found somewhat less frequently in those of aging livers. A picture of exhaustion of lipid was abundantly noticed on several occasions 24 hours or so in the cytoplasms of regenerating liver of senile rats,

forming something like a splashed mark caused by indian ink always to be enclosed by one-layered smooth membrane. Generally speaking, the cell changes of senile rat livers regenerated following partial hepatectomy were much more prolonged for longer time.

There was recognized that some characteristic findings seen in resting senile liver cells were similar to some pictures noticed in regenerating control liver cells.

Details of these findings noticed in this paragraph will be presented by co-workers of the present author in future.

(*vi*) *On the age difference in the patterns of compensatory hypertrophy of the remaining kidney tissue after unilateral nephrectomy in rats*

Details on this subject have been previously reported by the present author and his co-workers.[32) 45) 46)] A summary of the report will be presented here.

Nuclei of the glomerular tufts kept on to increase gradually in number in the course of hypertrophy after the operation both in the senile and control cases; however, in senile case the glomeruli increased in size more markedly than control, suggesting that a tendency of hypertrophy of glomerular cells was more marked in the senile case than the control. In the control cases, epithelial cells of convoluted tubuli increased in volume and number during several days after the operation, thereafter to get increased remarkably and mainly in number; in the senile cases, on the contrary, the epithelial cells of the convoluted tubuli increased only in the volume during the course of hypertrophy after the operation, while they turned somewhat to increase in number along several days after operation.

In other words, hypertrophy of the remaining kidney tissues subsequent to unilateral nephrectomy was resulted mainly through increase in the number of parenchym cells in case of the control specimen, but substantially through increase in the volume of the same in the senile case. Thus, there has been ratified lowering of ability of pathologic regenerative proliferation of the parenchymal kidney cells in senility.

(*vii*) *On the age difference among the patterns of compensatory hypertrophy of the human kidney*

Histological and micrometrical studies have been made on process of the compensatory hypertrophy of the remaining side of kidney after unilateral nephrectomy in cases of some renal diseases in various ages. Details of this study have been previously reported by the present author and his co-workers.[45) 46) 53)] A summary of the report will be presented here.

Cells of the glomerular tufts and of convoluted tubuli increased mainly in number in the hypertrophied kidney of younger people, but in older case they increased mainly in volume. In other words, hypertrophy of the kidney of younger people was mainly due to an increase in number of the parenchym cells, on the contrary, that of the kidney of elder people was mainly due to an increase in cell volume. In these cases, the age of patients when the operation took place was considered to play an important part on the process of hypertrophy.

(*viii*) *On decrease in number of parenchym cells signifying the senile change*

From above mentioned findings, there will be noticed as an important basic picture of senility the decrease in number of parenchym cells.

Regarding the numerical decrease of the parenchym cells, there were some reports on the senile nature in number of some ganglien cells such as Purkinje's cells and others,[2)3)] however, there were only a few reports on that of parenchym cells of the other organs.

a) *On the dark cells*

The present author and his co-workers examined so-called dark cells histologically and histochemically in the liver, kidney, intestine and cancer tissue.[39)41)42)44)]

Concerning the dark cells, the author may put emphases on the following points: 1) they manifest feature of condensation and dehydration of cytoplasm, 2) they represent stages more or less transitory from sol to gel condition of cytoplasm and 3) there is also testifiable a marked lowering of electric charge in the findings of isoelectric point of the plasm. From the above mentioned findings associated with other facts, some of the dark cells are to be taken for morphological appearance of parenchym cells representing spontaneous senile decay of cytoplasm just assumable as a colloid.

And pattern of appearance of dark cells in each organ was examined thoroughly, and the parenchym cells were considered to disappear probably after passing through a picture of dark cells even under the physiological condition, where the parenchym cells belonged to so-called "postmitotics" of Cowdry *et al.* under passing of eventual regeneration. In other words, decrease in number of parenchym cell in senility was considered to be due to lowering of regenerative ability of the said cells.

b) *On the process of regenerative proliferation of parenchym cells as well as on differentiation and proliferation of the cells with special references to so-called "inhibitory factor"*

A fit example of the cells which vigorously proliferate under physiological condition is that of embryonic tissue, that under pathologic condition that of cancerous and regenerative tissues.

At any rate, there is commonly recognized that proliferative power of the cells stands reversely proportional to their differentiation grade generally. Regarding the promotion and inhibition of cell proliferation there have been much discussion, for instance, through examination of some of parenchym cells, cancer cells etc.

A working hypothesis on the cell proliferation and cell differentiation was proposed some time ago by the present author[48)] from his results obtained experimentally. It will be introduced with some surveys on literatures[8)10)11)12)25)38)] as follows:

1. In the process of mitotic proliferation of various kinds of the cultured cells, there were found under some conditions hardly any differences between cancer cells and ordinary non-cancerous cells, and also little differences were found under mitosis-promoting condition between ordidnary cells originating

from older and younger individuals all the alike.

2. In the tissue culture mitosis was found only in the periphery of the cell-crowd.

3. Decrease in amount of the serum protein of the host must have worked stimulative upon the mitosis of the liver cells.

4. Partial hepatectomy worked likely stimulative upon the mitotic activity of the liver cells.

5. Transplantaion of the endocrine organs proved pretty successful in lowering of function of each organ of the host.

6. It worked on some patterns of regenerative proliferation subsequent to the partial loss of the tissue just accentuating.

From the above, a working hypothesis was proposed by the present author as follows:

Inhibitory factors for cell division seems to be put out, possibly the usage of the word "secreted" may be rather fitted, into tissue fluid from the cells. These factors are principally specific for each kind of cells which produced these factors, though the factors must be assumably a lesser selective in effect. Now, these factors shall act highly probably upon the cells by the way of the tissue fluid or the blood circulation. Some papers[20)51)57)] reported that a homogenate of organs works stimulating upon promotion of the cell mitosis of each organ; in this case of accentuation, therefore, so-called "inhibitory factors" inhered in each organ must have been inactivated by such homogenate in this or that way.

Secretion of these factors from the cell ought theoretically to stand in an intimate relation with differentiation of each cell, which was considered to become higher with advancement of maturity grade and necessarily with the senility grade of the cell. In other words, the cell is thus considered to become matured after each cell division: the secretion grade of the inhibitory factors related with the cell differentiation seems now to get raised with advanced maturity. As there prevail here differences in the differentiation grade among various cell sorts, in the same manner and in turn, there prevail once more differences in amount of secretion of the inhibitory factors as a necessary issue of the matter.

In any case, tissue cells may get raised in their differentiation grade with advancement of cell maturity and cell senility, and this raising is reasonably asserting for promotion of cell secretion of the inhibitory factors into the tissue fluid. This deliverance of the inhibitory factors shall now result in decrease of number of the tissue cells as tangible expression of the tissue senilitas as mentioned above.

c) On the irregularity in cellular and nuclear size among neighbouring parenchym cells and on the appearance of binuclear cells

The irregularity in size among neighbouring cells went generally parallel with that of their nuclei, but it was more clearly seen in the latter in general than in the former. The degree of the irregularity among neighbouring nuclei also ran parallel with that of appearance of giant nuclei in each organ.

In this paper, the degree of irregularity in size of the nuclei among neighbouring cells was compared with according to age.

In the epidermis, in irregularity in size of nuclei among neighbouring basal cells there was not found any differences in degree according to age, on the contrary, the degree of said irregularity in case of the prickle cells grew somewhat higher with advancing age (Figs. 33, 34). In the adrenal, irregularity in size of nuclei among neighbouring parenchym cells went generally increased

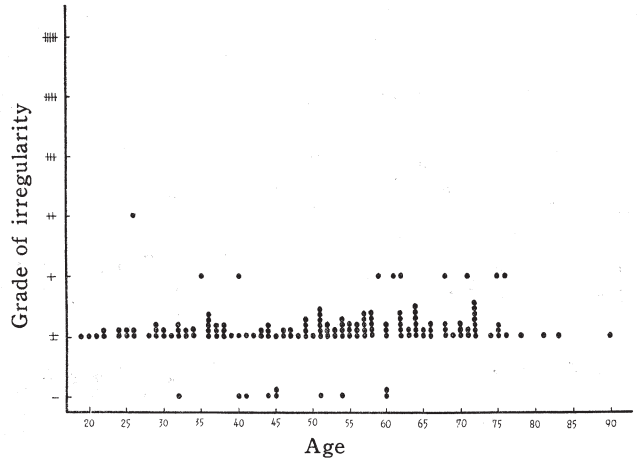

FIG. 33. Change of grade of irregularity in size of nuclei among neighbouring cells in basal layer of the epidermis with advancement of age.

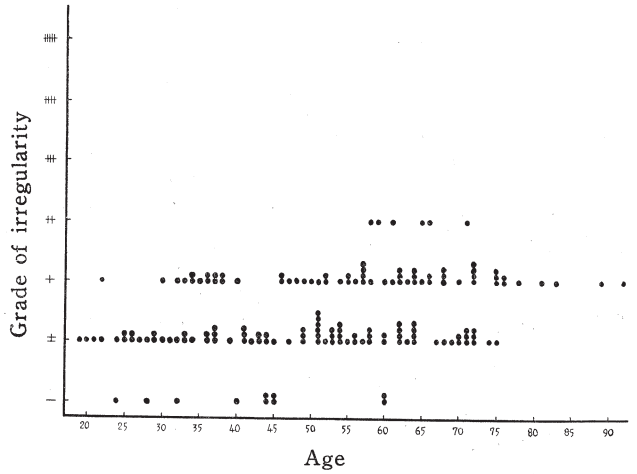

FIG. 34. Change of grade of irregularity in size of nuclei among neighbouring cells in prickle cell layer of the epidermis with advancement of age.

in grade with advancement of age (Fig. 35). This tendency was most marked in zona reticularis, more marked in zona fasciculata, and less marked in zona glomerulosa. In the pancreas, irregularity in size of nuclei among neighbouring exocrine cells increased in only a few degree with advancing age (Fig. 36),

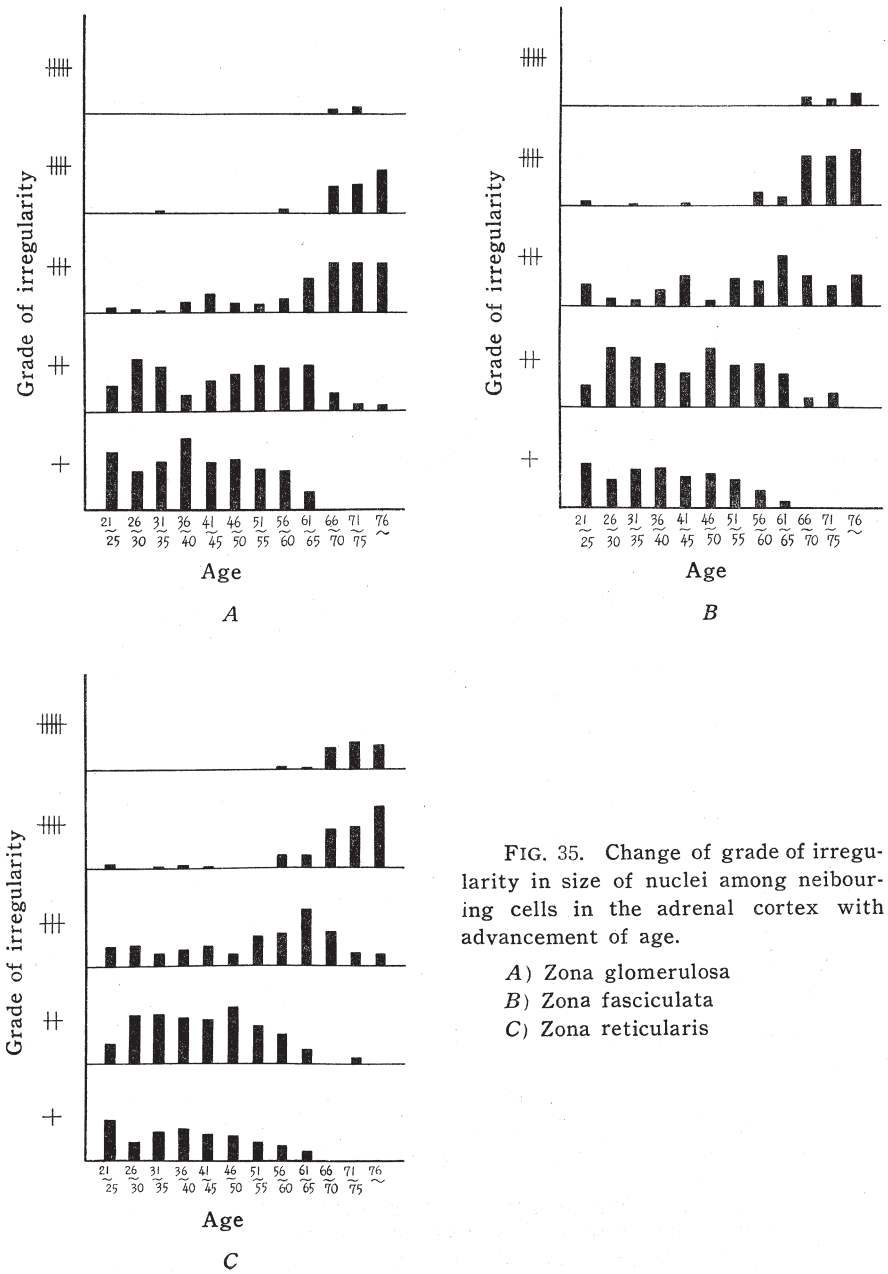

FIG. 35. Change of grade of irregularity in size of nuclei among neibouring cells in the adrenal cortex with advancement of age.

A) Zona glomerulosa
B) Zona fasciculata
C) Zona reticularis

but on the contrary, in the liver, that irregularity among neighbouring liver cells increased in grade very markedly with advancing age (Fig. 37). In this case, it was noticeable that the said irregularity was not so marked in case of very old people such as above 90 years of age.

Patterns of appearance of binuclear liver cells were also compared with according to age (Fig. 38).

Generally speaking, binuclear liver cells increased in number with advance-

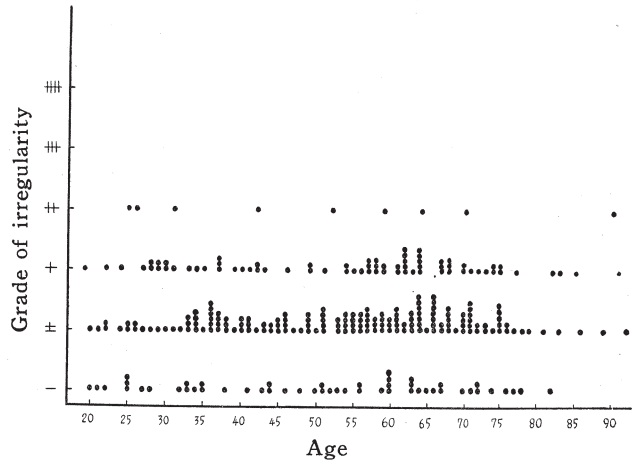

FIG. 36. Change of grade of irregularity in size of nuclei of the exocrine cells of the pancreas among neighbouring cells with advancement of age.

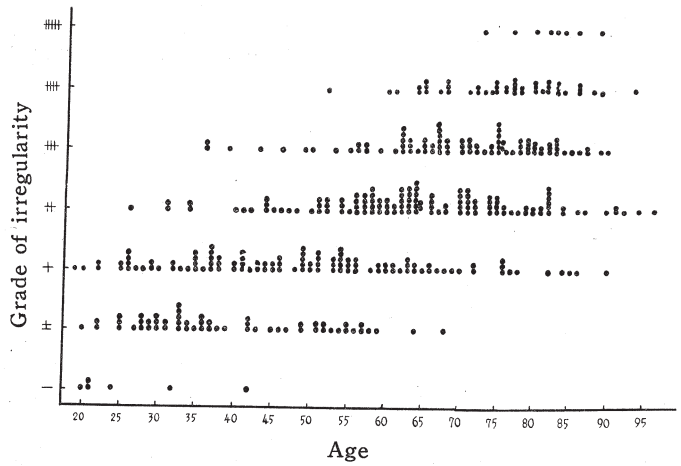

FIG. 37. Change of grade of irregularity in size of nuclei among neighbouring cells of the liver in the periphery of the lobulus with advancement of age.

ment of age, but in case of older people above 75 years of age these cells were found rather decreasing in number with advancing age. This tendency was marked in case of the liver made of non-atrophic liver cells, but in case of the liver made out of atrophied liver cells this tendency was not clearly ascertained.

From the above, the tendency that the nuclei of parenchym cells became more irregular among neighbouring cells with advancement of age, was considered to be more marked in the cells which were considered to be more differentiated and of lower potentiality to proliferation.

The findings above mentioned in case of the adrenal may support the so-called escalator theory. And the findings in the liver and pancreas may as-

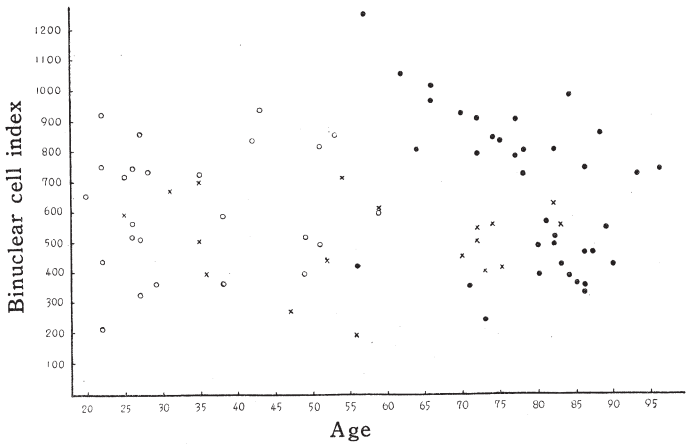

FIG. 38. Relationship between appearance of binuclear cells in the liver and age (periphery of the lobulus).
○ Control case
× Case of non-senile atrophied liver
● Case of senile atrophied liver with hypertrophied liver cells

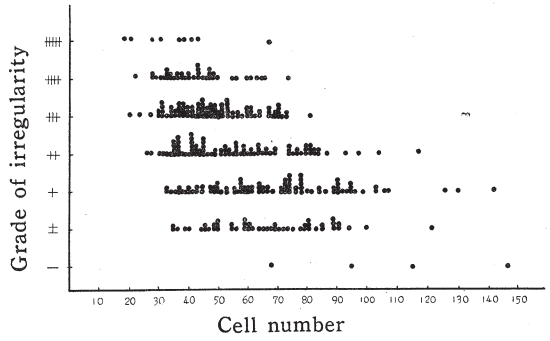

FIG. 39. Relationship between grade of irregularity in size of nuclei among neighbouring cells of the liver in the periphery of the lobulus and cell number of the liver (represented by ciphers of the organ weight and cell number in a given area).

certain that the liver cells are considered to be more differentiated than the pancreatic cells, and this coincides with the facts that generally there are found mitotic figures in some degree in the pancreas in good contrast to the liver where mitotic figures are very rare.

Clara[6] also discussed in his paper on the binuclear and giant nuclear liver cells.

At any rate, the nuclear irregularity among neighbouring cells, giant-nuclearity and binuclearity of cells are considered to be of active state of cells setting a limit to the condition where cell division starts to be inhibited, and also rendering it well considerable to induce their irregularity intimately related with hypertrophy of cells (Fig. 39). Thus, there may be proposed an important biological problem connecting the whole with the phenomenon of polyploidy and cellular hypertrophy. And even in the liver cells which were considered to be highly differentiated, the irregularity in size among neighbouring cells became lesser in degree in highly senile case such as above 90 years of age, whereby appearance of binuclear liver cells went decreased in number in case of above 75 years of age.

From these findings, the said active state of cells toward cell divison was considered to become decreased in case of very high age and also it may be reasonable to consider that binuclearity of the cells may constitute a feature of much more active state than irregularity in size of nuclei among neighbouring cells. In other words, decrease in cell number with advancement of age was considered to be due to an increase in the grade of cellular differentiation following cellular maturity, but in very high aged case that decrease in cell number was considered to be, beside the increase in the grade of cellular differentiation, due to lesser active state of cells themselves favouring cell division.

(*ix*) *On some experiments on retardation in growth of rats*

McCay and others[14)18)19)] reported that the life span of animals may be prolonged under influence of retardation of the growth. The present author and his co-workers have examined histologically and micrometrically on some organs and tissues of rats which were retarded in their growth by restriction of diets, comparing with rats experimentally led to starve. Details of this study have been previously reported;[17)] some themes out of a summary of them will be presented here. In this study, there presented two groups of experimental rats and control rat group; the first group was retarded in their growth by restriction in quantum of diets, the second was that of absolute starvation after a period fed with standard diet, the control group standing under the standard diet feeding. The experiments were carried on to keep animals of equally aged in the same body weight between the two experimental groups. In this case, the liver kept on its weights roughly almost equal between two experimental groups, thereby the size of liver cells of the first group remained almost equal to those of the control group, but those of the second group were far smaller in size than those of the control group.

In other words, in case of retardation in growth through restriction in

quantum of diets, the liver cells did not decrease in size and weight of the liver was of course less than the control of equal aged and this less value in weight was considered to be due to smaller number of the cells, and the latter status was considered in its turn to be due to retardation of proliferation of liver cells in the course of the growth.

Morphological picture of mitochondria and RNA content in the cytoplasm of the liver cells went changed closely related with their sizes. Namely, there were noticed clearly some differences of mitochondrial picture and RNA content of the liver cells between two experimental groups, and there were found only a few differences between the first and control groups.

In other words, if retardation of growth causes the prolongation of life span, the senile change was considered to be delayed, expressed in extension of period of cell proliferation; in turn, this extension of the proliferative period was again considered to occur by virtue of the delay of formation of so-called "inhibitory factor" closely related with a factor leading to cell differentiation. Lastly, how this factor mentioned lastly has to be manifested in this way certainly thanks its issue to the delay in the activity of mitotic factor of the cells as the outcome of lower cell nutrition there.

Summary

There are many problems, at present, on the essential nature of senile change of the parenchym cells. Whether the lowering of proliferative potency of the parenchym cells in senility may be due to extracellular fluid factor or not is unsettled yet. Extracellular tissue fluid is considered to be closely related with the living cells of the individual in material exchange functionally.

And so far an attempt to discuss whether the essential cause of senility may be found in tissue fluid or in the cells themselves may be a matter of little significance in clarifying the kernel problem of senile change.

And a key to solve the problem seems to be hidden in search of the biological phenomena, such as maturation, proliferation and cell differentiation.

In any case, decrease in number of and a mild increase in volume of the parenchym cells may be considered to prepare a phenomenon pretty essential for senility problem. This phenomenon may certainly be considered due to a lowering of potentiality for the physiological regeneration in senility, and that lowering seems to be closely related with the cellular differentiation, whose level gets always higher along the course of cellular maturation as mentioned above. In other words, cellular maturation brings about increase in degree of the cellular differentiation, and closely related with this increase there starts now increase in the grade of secretion of so-called "inhibitory factors for cell division", which cause decrease in number of the parenchym cells everywhere. Thus, there results the senility.

For the decrease in number of the cells, besides, in case of very high aged, lesser active state of cells themselves disfavouring cell division could not be denied.

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EXPLANATION OF PLATES

Figures (1–18) are histological pictures stained with *H-E*, Figures (19–22) are electron microscopic pictures.

FIG. 1. Human control liver (S. N. 932, 27 year old male, liver weight 2090 g). ×200.

FIG. 2. Atrophied human liver due to malnutrition (S. A. 93, 22 year old male, liver weight 850 g). ×200.
Smaller in size of liver cells.

FIGS. 3, 4, and 5 Human senile liver. ×200.
Fig. 3 (S. Y. 2255, 77 year old female, liver weight 810 g).
Larger in size of liver cells especially of their nuclei and irregularity in size among neighbouring nuclei.
Fig. 4 (S. Y. 2155, 83 year old female, liver weight 760 g).
Larger in size of liver cells.
Fig. 5 (S. Y. 2320, 84 year old female, liver weight 410 g).
Larger in size of liver cells especially of their nuclei and irregularity in size among neighbouring nuclei.

FIG. 6. Human control kidney (S. N. 800, 37 year old male, weight of kidneys 295 g). ×140.

FIG. 7. Atrophied human kidney due to malnutrition (S. N. 528, 35 year old female, weight of kidneys 140 g). ×140.
Smaller in size of tubular epithelium and glomerulus.

FIGS. 8 and 9. Senile simple atrophied human kidney. ×140.
Fig. 8 (S. N. 745, 77 year old male, weight of kidneys 203 g).
Fig. 9 (S. N. 371, 71 year old female, weight of kidneys 260 g).
Somewhat larger in size of tubular epithelium and smaller in number of cells of glomerular tuft.

FIG. 10. Human control kidney (S. N. 800, 37 year old male, weight of kidneys 295 g). ×200.

FIG. 11. Senile human kidney without loss in weight (S. N. 797, 83 year old female, weight of kidneys 295 g). ×200.
Larger in size of nuclei of tubular epithelium.

FIG. 12. Hypertrophied kidney of control rat 45 days after unilateral nephrectomy. ×140.

FIG. 13. Hypertrophied kidney of senile rat 45 days after unilateral nephrectomy. ×140.
Larger in size of tubular epithelium and of glomerulus with loss in number of the cells.

FIG. 14. Hypertrophied human kidney after unilateral nephrectomy in younger aged (S. N. 356, 24 year old). ×140.

FIG. 15. Hypertrophied human kidney after unilateral nephrectomy in older aged (S. N. 2772, 63 year old male). ×140.
Larger in size of tubular epithelium and glomerulus with loss in number of the cells.

FIG. 16. Control liver of 4 month old rat (body weight 173 g liver weight 6.8 g).

FIG. 17. Liver of 4 month old rat in case of retarded growth by restricted diet (body weight 115 g liver weight 4.8 g).
Almost same in size of liver cells as control.

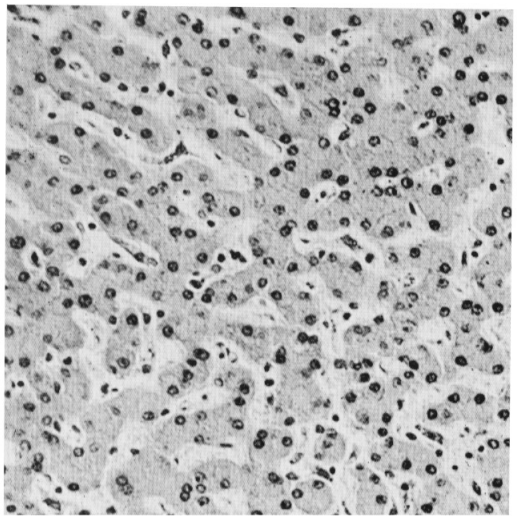
FIG. 18. Liver of 4 month old rat absolutely starved for last several days (body weight 120 g. liver weight 4.2 g).

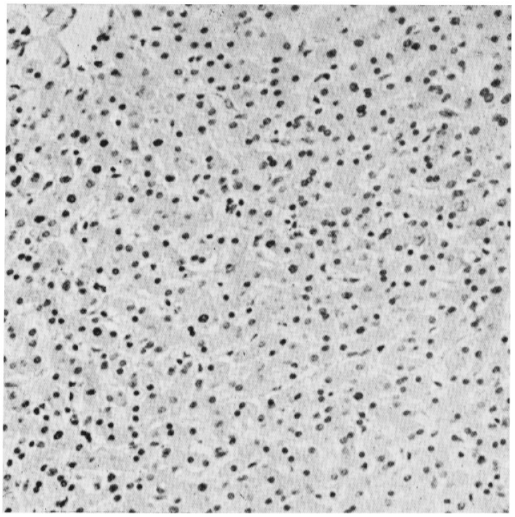
FIG. 19. Senile rat liver in resting stage; larger in number of microbodies (mb), rough surfaced endoplasmic reticulum (rer) with wider lumina and swollen mitochondria. M: mitochondria, ly: lysosome.

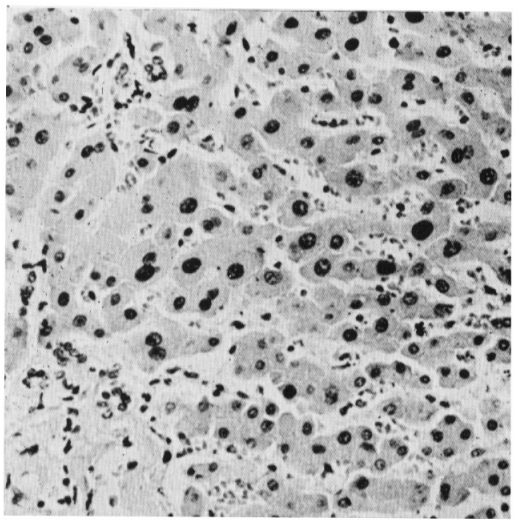
FIG. 20. Senile rat liver in resting stage; a clump of rough surfaced endoplasmic reticulum and glycogen area and larger in number of microbodies.
G: golgi complex, gl: glycogen area, gu: glycogen unit

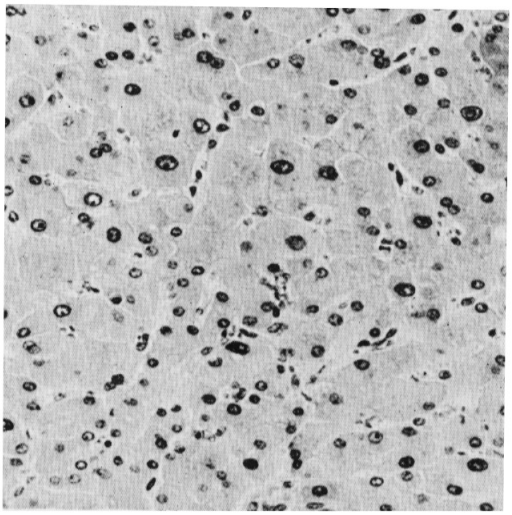
FIG. 21. Senile rat liver 12 hours after partial hepatectomy; mitochondria crowded together, closely associated with endoplasmic reticulum.

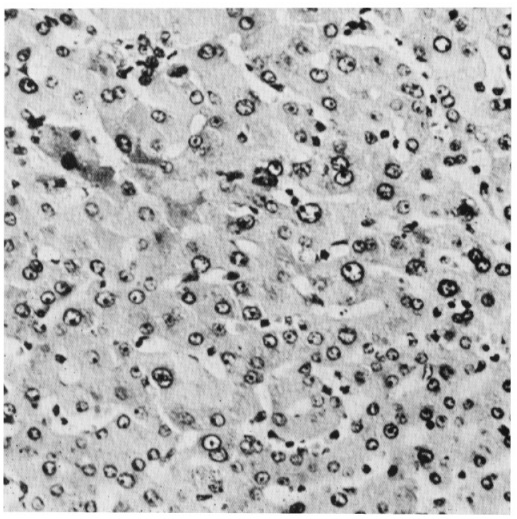
FIG. 22. Senile rat liver 24 hours after partial hepatectomy; a picture of exhaustion of lipid (lip) and vesicular endoplasmic reticulum (rer).

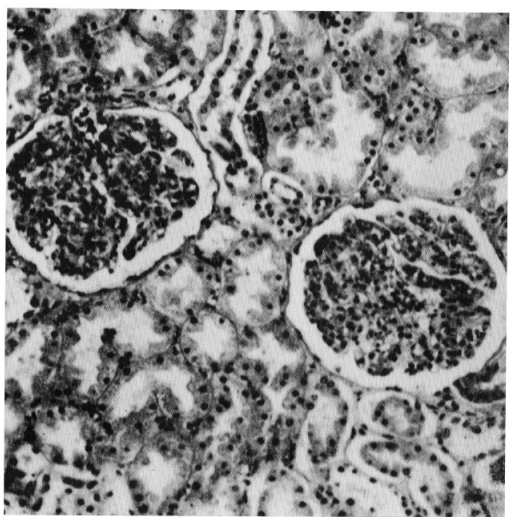


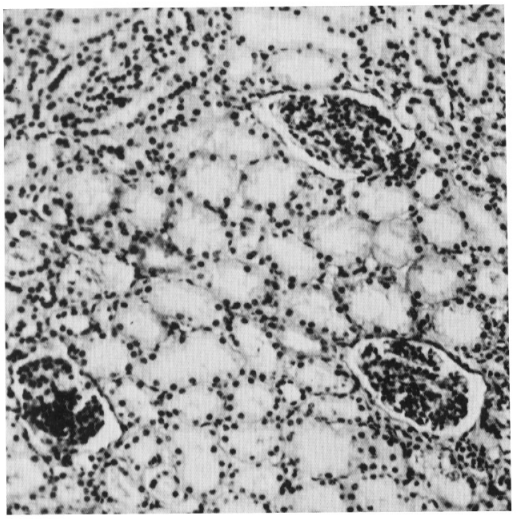


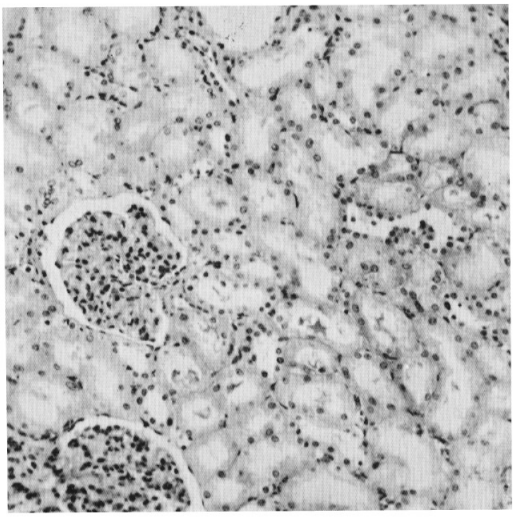


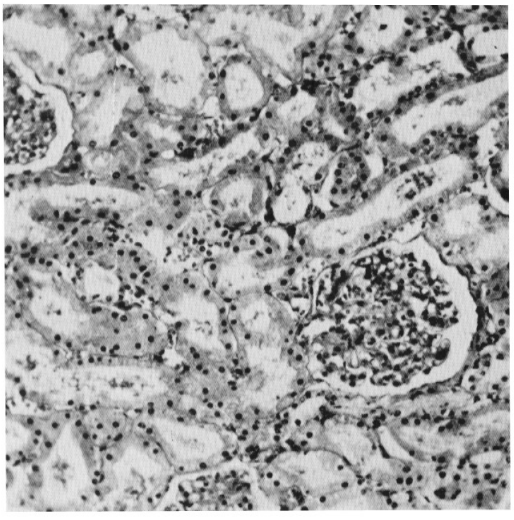


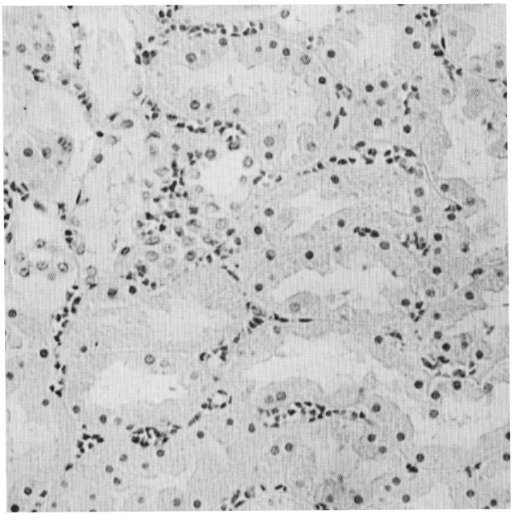


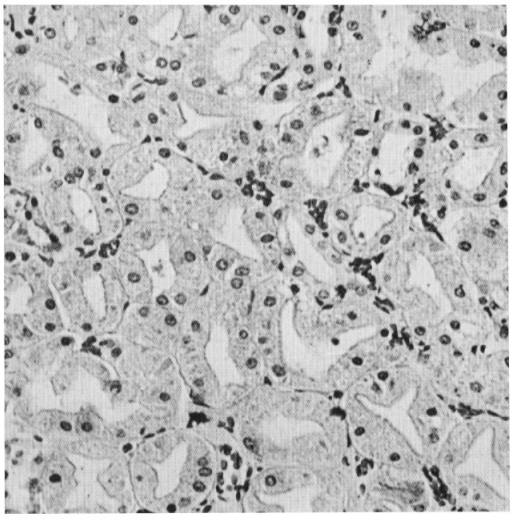


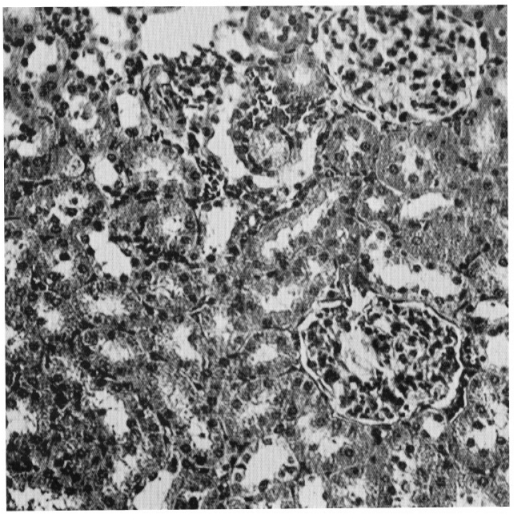


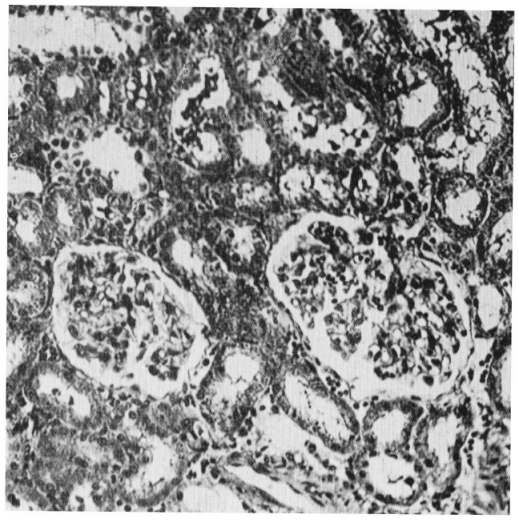


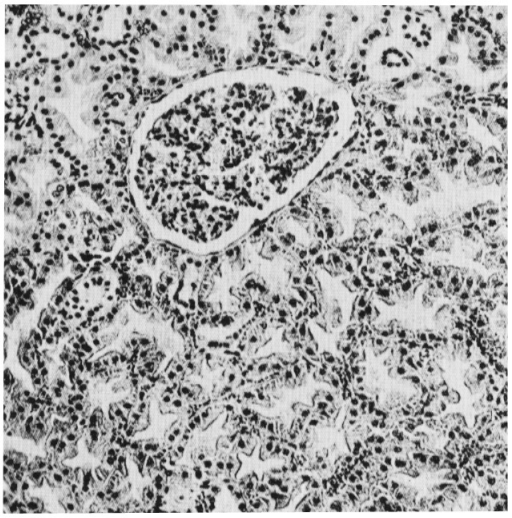


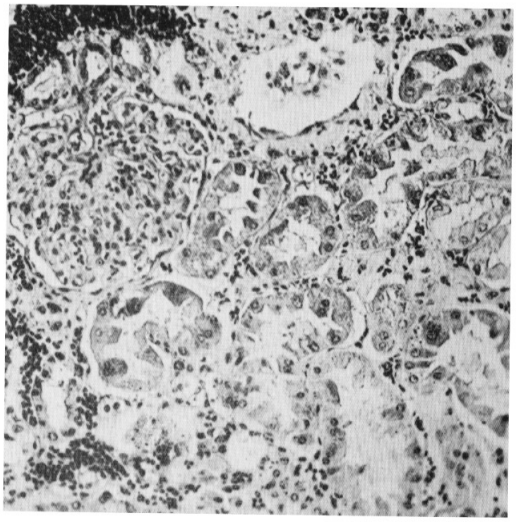


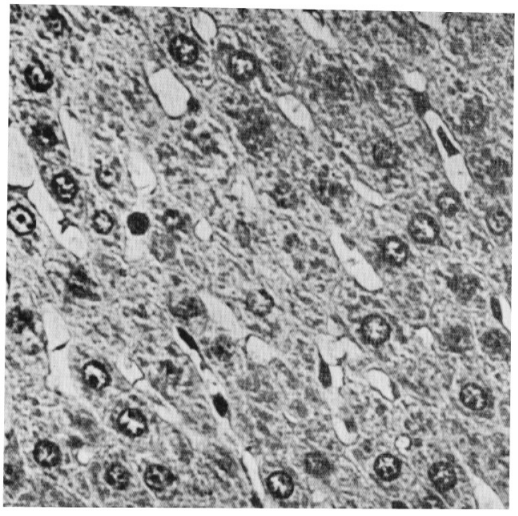


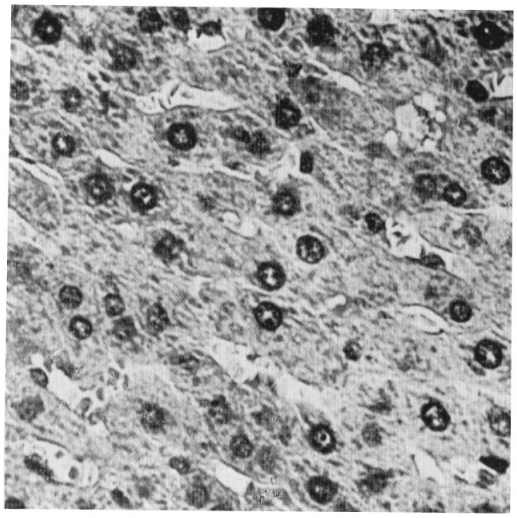


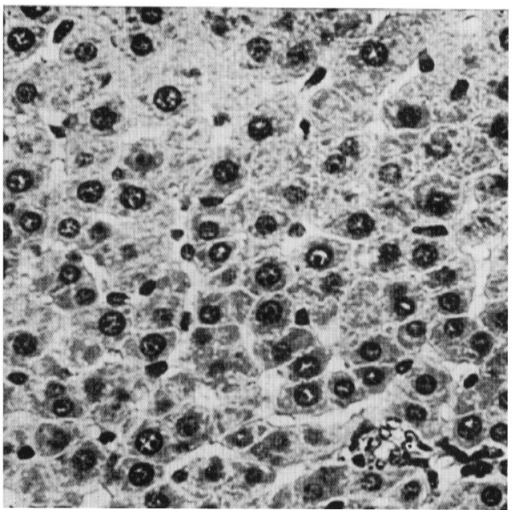


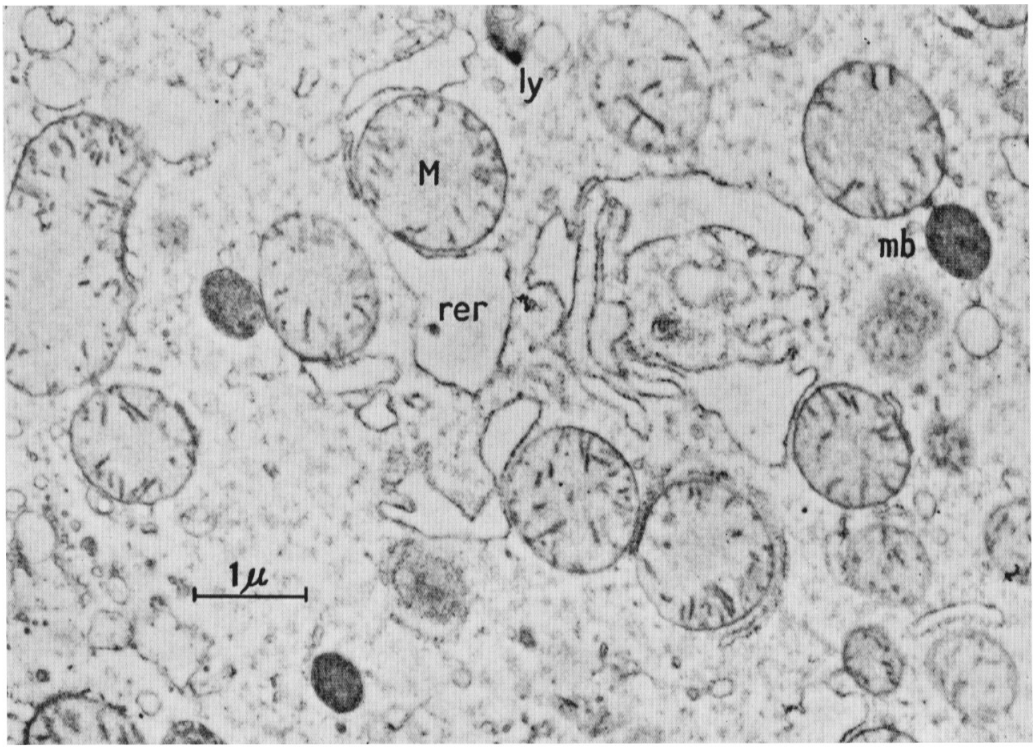








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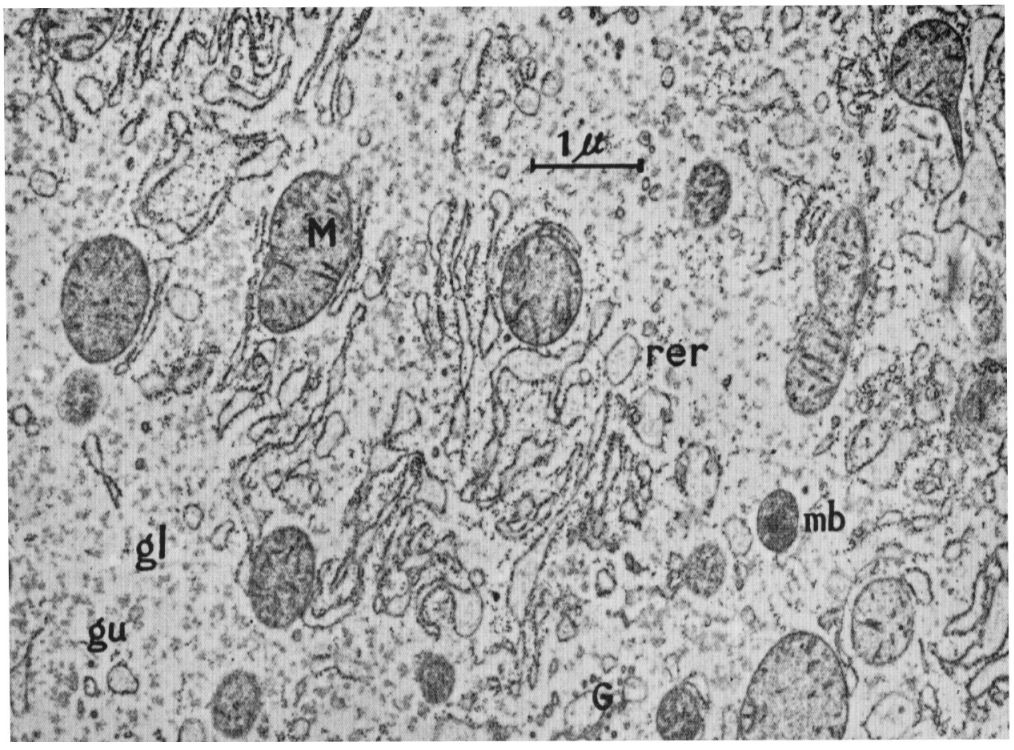
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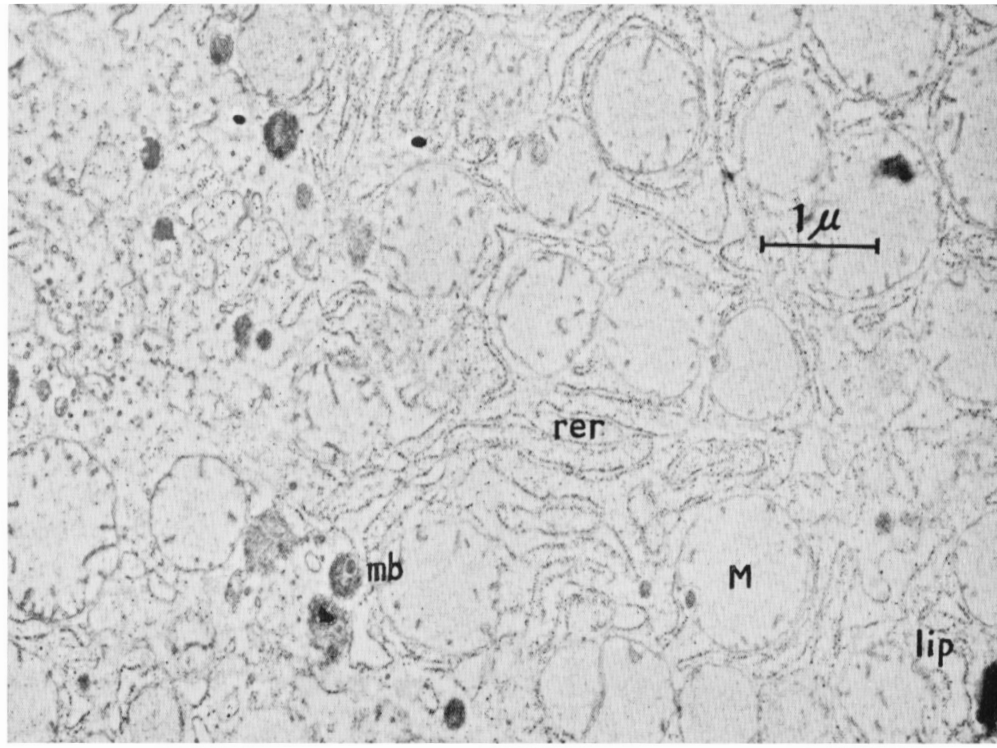
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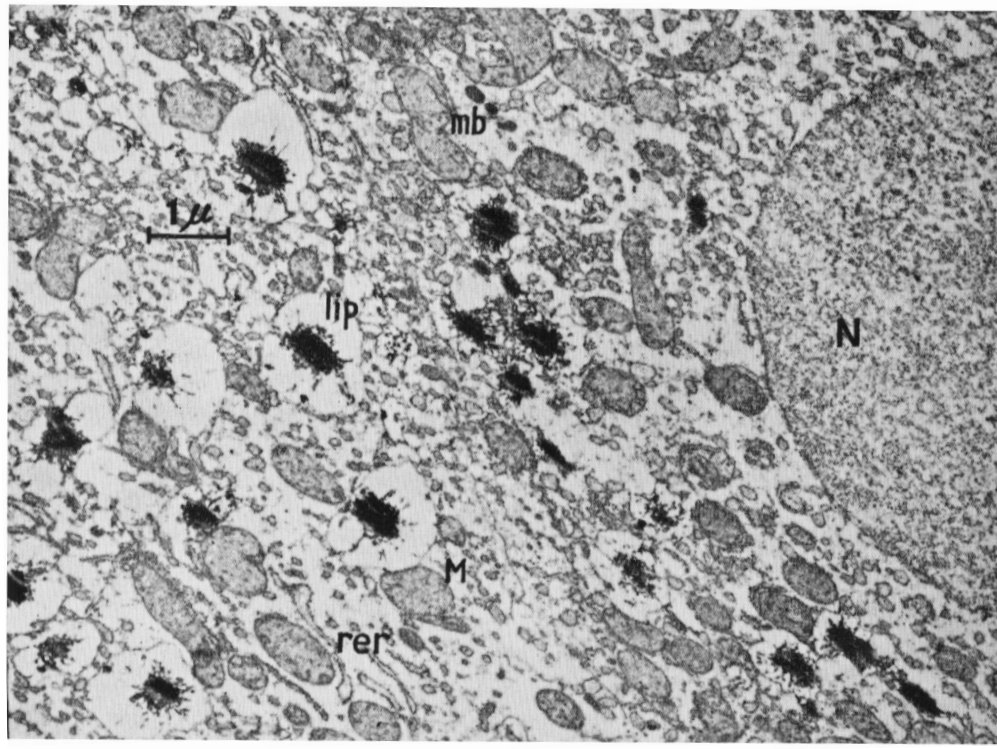
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