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ANALYSIS OF CONSTITUTIONS BY MATHEMATICAL PRINCIPLES
II. THE ANALYSIS OF INTIMAL ARTERIOSCLEROTIC CONSTITUTIONS

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ABSTRACT

Certain aspects of the etiology of the intimal arteriosclerosis were discussed by the development of the mathematical structure of an organism previously proposed.

One school supposed that an essential factor for intimal arteriosclerosis was glycoprotein, but not lipid. The abnormal deposition of glycoprotein into the intima of arteries and the subendotherial space of capillaries might take place only when glycoprotein was excessively synthesized in the liver more than the requirements of an organism. The metabolic tendency mentioned above arises from both elements in set X of genetic factors and in set Y of environmental factors.

It was explained that as for the elements in set Y, there were high fat diet, low protein diet, and pyridoxine deficient diet, while as the elements in set X hereditary deficiencies of hepatic key glycolytic enzymes were considered. A common element in set Z of vital phenomena derived from above mentioned elements, is the use of fatty acids as main source of energy in the liver which, in turn, spares both protein and glucides and scarcely uses glycolytic pathway for energy production.

Although elements in set X always predominate over elements in set Y in intimal arteriosclerosis, the stronger the elements of both set X and set Y have tendencies to suffer from this disease, the shorter the time factor t for onset of this disease will be. Even if all elements in set X are normal, one has to refrain from overeating in older age when he needs less energy and protein per kg body weight per day compared with the younger.

INTRODUCTION

There are numerous empirical knowledge in the field of clinical medicine. Though many investigators have endeavoured to introduce these knowledge in dialectic studies, the attempts have not been fruitful. In the preceding paper[1] a mathematical structure of an organism was proposed, using the theory of

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sets and the development of axiom was adopted into practice for the analysis of the obese-diabetic and the obese-normal constitutions.

In this article the authors intend to discuss certain aspects of the etiology of the intimal arteriosclerosis by further developing the axiom previously proposed.

METHOD

A mathematical structure of an organism is shown in Table 1. Here, the law given to "correspondence f" is of paramount importance. An organism is at least representing itself as having the "fitness" responses to y within certain limits by its x at t *in the physiologic state.* Therefore, the law that an organism would fitly respond to y or its own x within certain limits, is given to correspondence f[1].

TABLE 1. Mathematical structure in an organism

$$z=f(x, y, t) \quad \text{or} \quad (x, y, t) \xrightarrow{f} z$$

fitness

X; the set of genetic factors
x; the element of X
Y; the set of environmental factors
y; the element of Y
Z; the set of vital phenomena
z; the element of Z
t; time factor in aging

This axiom should not be applied *to the pathologic state, i.e.,* vital phenomena with cancer, autoimmunity or *functio laesa* etc. The system of axioms has been developed for the intimal arteriosclerotic constitutions, but not for intimal arteriosclerosis, *a pathologic state.*

RESULTS AND DISCUSSION

(*Development of Axiom*)

The intimal arteriosclerosis is thought to be a subset in set Z of the vital phenomena. The principal changes in this arteriosclerosis are found in the intima of arteries. In the earliest changes, some endothelial cells are enlarged with development of endoplasmic reticulum and closely resemble fibroblasts. These cells are also observed in the subendothelial space, and then myofilamentlike structures appear within the ectoplasm of the intimal cells. Subsequently, some of the intimal fibroblasts differentiate to smooth muscle cells with typical myofilaments. Newly formed collagen and elastica are observed closely around intimal fibroblasts and smooth muscle cells. The transition to

elastica from collagen is noticed[2].

It is well known that this disease is found in the people on high fat diet more often than those on low fat diet. Therefore, it will be proper to discuss the elements in set Y of environmental factors.

Set of Environmental Factors

When the elements in set Y are discussed, it is presumed here that all elements in set X of genetic factors are normal in order to maintain health.

What is stored in the cellulofibrous intima? This is mainly collagen, a most important component in the animal connective tissue, comprising about one-third of body protein[3]. High fat diet makes a person use fatty acids as a main source of energy in the liver to maintain his blood sugar, and then carbohydrate and protein tend to be stored in his body. The connective tissue consists mainly of ground substance containing soluble glycoproteins in addition to well known mucopolysaccharide constituents, and of the fibrous proteins-reticulin and collagen-which are also glycoproteins. The plasma lipid may not cause the earliest changes of intimal thickening[4]. In atherosclerotic lesions of human aorta, fibrosis in the upper layer of intima and loosening with lytic changes of collagen fibrills due to the infiltration of plasma lipid into the lower part of the intima are seen. Similar atherosclerotic lesion is experimentally produced in acrylic resin-invested carotid artery of the rabbit fed on cholesterol. Without intimal fibrosis, however, the lesion resembling to human atherosclerosis is not seen despite excess of lipid deposition in the intima. Therefore, Ooyama[2] stressed that atherosclerosis is produced by infiltration of lipid from plasma into the collagenous fiber of fairly advanced intimal fibrosis which appeared at the end stage of cellulofibrous thickening.

Arteriosclerotic lesions in pyridoxine deficient monkeys resemble, in the distribution and histological characteristics, with those encountered in a person[4][5] (Table 2 and Fig. 1). Early changes do not appear to contain any appreciable quantity of lipid, but lipid has been demonstrated in more advanced lesions. Mushett *et al.*[6] found that the addition of 2% cholesterol to a pyridoxine deficient diet did not cause accumulation of lipids in the arteriosclerotic lesions.

What is an essential factor for intimal thickening? Let us presume that it is glycoprotein, but not lipid[7], and evaluate whether this hypothesis is proper for the axiom proposed in the previous paper or not.

It is well known that diffuse intimal thickening in the human aorta appears with physiologic growth. It is of fitness for animal to store glycoprotein in the large and median arteries where the obstruction of vessels does not occur normally and glycoprotein can easily shift out of arterial wall into blood at need. Shin[8], one of the co-workers, reported that the trypsinized bovine thyroid cells in tissue culture exhibited such a striking changes that they were not

TABLE 2. Intimal arteriosclerosis in pyridoxine-deficient monkeys

No.	Sex.	Experi. Periods. (months)	Serum Cho-lesterol. (mg/dl)	A/G	Abdominal Aorta.	Iliac Art.	Coronary Art.	Renal Art.	Splenic Art.	Basilar Art.	Cerebral Art.
				Pyridoxine-deficient monkeys							
1	male	10			+	+	+	−	+	−	−
2	female	12	342	0.39	+	+	+	+	+	−	−
3	male	14	202	0.68	+	+	+	+	+	+	+
4	male	15	252	0.67	+	+	+	+	+	−	+
				Control monkeys							
1	male	12	215	1.09	−	−	−	−	−	−	−
2	female	15			−	−	−	−	−	−	−
3	female	15	272	0.91	−	−	−	−	−	−	−

+: Intimal arteriosclerotic lesions are observed.
−: Arterial walls are normal.

distinguished from fibroblast in fine structure. These cells were connected together with terminal bar and, therefore, fibroblastic alteration took place in the follicular cells cultured *in vitro* (Fig. 2). The inhibition of expression of cell differentiation *in vitro* is seen when cells are grown without chicken embryo extract but at high cell densities, at which they may get insufficient amounts of proper nutrients[9] or when cells are grown with the high-molecular weight fraction of chicken embryo extract[10]. Though cells *in vitro* need not act as organ cells, they must be alive. Cells *in vitro* change into cells like fibroblasts and produce collagenous fiber, and this fact means a nitrogen assimilation in animal kingdom. In need of nitrogen or carbohydrate in body, collagen is easily dissolved there[11] and will be utilized.

How or where is glycoprotein deposited in intima? The usual sugar constituents of glycoproteins are the amino sugars, glucosamine and galactosamine, presenting themselves in their N-acetyl form; the neutral sugars, mannose, galactose, and fucose; and the N-acetyl or N-glycolyl form of neuraminic acid, the acid ninecarbon amino sugar whose derivatives are collectively known as the sialic acids. Certain generalizations about the structure of glycoproteins can be made at this point and certain concepts of structure can be proposed, especially for orosomucoid and fetuin[7]. The glycoproteins in the biological membrane also should have such a structure as seen in plasma glycoproteins. Sialic acids are fairly strong acid and show considerable magnitude of negative charges on the membrane. If glycoproteins, especially orosomucoid, agglutinate on the basement membrane of endothelial cells in excess, then the membrane will not be able to function sufficiently. As Ooyama's observation[2], therefore, some endothelial cells multiply and resemble fibroblasts in the earliest changes of intimal arteriosclerosis. Subsequently, some of these cells appear in sub-

endothelial space and form connective tissue into which excess of glycoproteins on the basement membrane moves. It is observed that a nitrogen assimilation in animal is cleverly carried out. Plasma glycoproteins tend to be deposited on the places where blood does not stream laminally. This fact is recognized on hydrodynamics as well as clinically. However, it is likely that the deposition of glycoproteins to intima takes place only when glycoproteins are excessively produced in the liver than the requirements of an organism. It has been shown that liver is a mammalian tissue active in glycoprotein synthesis, being primarily responsible for the production of a large number of glycoproteins present in serum[12].

How does physiologic phenomenon change to pathologic? The behavior of mesenchymal cells in phylogeny needs to be understood. Mesenchymal cells had no choice but to inherit the fundamental model of responses of a protozoan, and this fact results in the vital phenomena that mesenchymal response happens to come gradually pathologic. If a person always continues to have a metabolic environment which increases glycoproteins in his body, the blindness in respect to the organ function of mesenchymal cells phylogenically determined will continue to store collagen. Consequently, mesenchymal cells will alter the function of the organ, because they are devoid of their own considerations for differentiated organ[13]. It is not infrequent that abnormally functioning mesenchymal cells result in termination of the host as cirrhosis of liver or contracted kidney.

What of set Y do increase collagen? There are many elements, for example-high fat diet[14], low protein diet[15], and pyridoxine deficient diet[4)5] etc. A common feature of these diets is to use fatty acids as main energy source in the liver, which has in turn sparing action for protein and glucides, thus utilizing less of glycolytic pathway for energy production.

Renal glomerular alterations have often been observed in patients with chronic liver disease of varying etiologies. Sakaguchi *et al.*[16] reported that rats administered carbon tetrachloride or ethionine developed progressive glomerular changes, consisting of fusion of epithelial foot processes, subendothelial and mesangium deposits of amorphous and of granular material, thickening of the basement membrane, and increase in mesangial matrix; and that the structure of these lesions was similar to those of human glomerulosclerosis associated with hepatic disease. It is supposed that the glycolytic pathway of the liver cells of these rats administered carbon tetrachloride or ethionine was injured by these chemicals and that these liver cells utilized fatty acids as main energy source.

It is known that the common feature mentioned above is produced by the interchanges of elements in set Y of environmental factors.

Set of Genetic Factors

Discussing the genetic factor set X, presume all elements in set Y of en-

vironmental factors to be in an ideal state in order to maintain health. Even if all elements in set *Y* are kept within normal limits, a person with hereditary deficiency in hepatic glycolytic pathway—that is, diabetic or obese person[1], will tend to use fatty acids as main energy source in his liver and to have a sparing action for protein and glucides as far as he has hyperinsulinemia, but also insulin resistance in future.

Bencosme *et al.*[17] reported that the lesions of the capillaries in diabetic patient consisted of thickened and laminated basement membrane, while the endothelium and pericyte seemed to be normal. The thickened membrane was composed of concentric bands of different electron density and fine collagen fibers were present in clearer zone. Surrounding the basement membrane of the endothelium, usually there is a space containing loose collagenous fibrils and some adventitious cells. In the capillary from diabetic patients, the space is occupied by thickened basement membrane. Since changes in the basement membrane of the capillary have been observed very early following the onset of the diabetes, it is likely that the initiation of thickening in the basement membrane coincides with the onset of the metabolic disturbances. It is known that endothelium of smaller vessels does not multiply like that of the medium or the larger vessels, and that the endothelium of smaller vessels does not usually obstruct their lumen. The distinctions between responses by the smaller versus the larger vessels to the depos tions of glycoproteins indicate the fitness of the organism.

The baleful effect of diabetes in promoting atherosclerosis of the coronary and other arteries is disclosed by the aspects of acute myocardial infarction in diabetic patients that differ from the experience generally observed in non-diabetic persons. Namely, nondiabetic males usually predominate over females by 2 to 5 against 1 until the sixth or seventh decade, whereas in the presence of diabetes, women either equal or outnumber men at every age[18].

Let us consider the sexual difference in the incidence of intimal arteriosclerosis in nondiabetic persons. Tomkins *et al.*[19] showed that estrogenic steroids have an influence upon molecular conformation of glutamate dehydrogenase. Estrogen makes glutamate dehydrogenase inactive and makes alanine dehydrogenase active. It is clear that glutamate dehydrogenase is a key enzyme responsible for urea synthesis. Alanine dehydrogenase synthesizes alanine from NH_3, pyruvic acid and reduced nicotinamide-adenine dinucleotide. The inactivation of glutamate dehydrogenase and the activation of alanine dehydrogenase show nitrogen assimilation by estrogen when intake of protein is insufficient in females. Ito *et al.*[20] studied the histological changes of the mouse thymus of the both sexes during involution and regeneration following administration of cortisol and reported that the thymus of females recovered faster in structure as well as in weight. It is understood that estrogen regulates nitrogen assimilation in such condition as gestation[21] and that a woman must

not overeat protein in order to keep her feminine beauty. Estrus needs more nucleic acid, protein and collagen etc. in females than in males. There are other utilizations of nitrogen in females compared with in males, resulting in difference in accumulation of the cellulofibrous materials into intima between the both sexes.

Diabetic patients tend to suffer from infections by pyogenic bacteria and from diabetic retinopathy[22], because neutrophil leukocytes and cells in retina have Crabtree effect[23] rather than Pasteur effect, and so the higher blood sugar goes up and the longer it continues, the worse the functions of these cells will become.

Time Factor in Aging

Though elements in set X of genetic factors always predominate over elements in set Y of environmental factors in intimal arteriosclerosis, when the elements in both sets of X and Y have stronger tendencies to suffer from this disease, the time factor t will become shorter for an onset of this disease[18].

Even if all elements in set Y are kept in an ideal state in order to maintain health, a person with hereditary deficiency in hepatic glycolytic pathway —for example, namely a person with diabetic or obese constitution, will tend to suffer from intimal arteriosclerosis in future. However, hypersecretion of insulin increases the net synthesis of hepatic key glycolytic enzymes and compensates for their hereditary deficiency at the time t when he has own fitness and is healthy. Therefore, it is natural that the appearance of the intimal arteriosclerosis is more frequently noted at middle or old age.

Furthermore, even if all elements in set X are normal, one has to refrain from overeating in older age when he needs less energy and protein per Kg body weight per unit time compared with the younger.

CONCLUSION

"Specialization and Synthesis in Medicine" had been stressed by Katsunuma, the president of the 17th General Assembly of the Japan Medical Congress. It is important that numerous empirical knowledge in the field of clinical medicine is arranged under new light and synthesized with mathematical concept. Although it is clear that an abstract theory has nothing concrete, the more abstract a theory is, the more it has possibilities of being widely applicable to many cases.

In this paper it has been demonstrated, by citing some knowledge about intimal arteriosclerosis, that the abstract theory of sets presents an excellent approach for solving difficult problems in medicine.

It is supposed that an essential factor for intimal arteriosclerosis is glycoprotein, but not lipid. The deposition of glycoprotein onto intima will take place only when glycoprotein is excessively synthesized in the liver exceeding

the requirements of an organism. The metabolic tendencies mentioned above come from both elements in set X of genetic factors and in set Y of environmental factors.

It is shown that on one hand there are high fat diet, low protein diet, pyridoxine deficient diet, and intake of such a chemical as carbon tetrachloride or ethionine as the elements in set Y, and on the other hand hereditary deficiencies of hepatic key glycolytic enzymes as the elements in set X. A common feature in set Z of vital phenomena represented by these elements is to use fatty acids mainly as an energy source in the liver, which has in turn sparing action for protein and glucides, scarcely using glycolytic pathway. Though elements in set X always predominate over elements in set Y in intimal arteriosclerosis, when there are stronger tendencies of the elements in both sets X and Y to suffer from this disease, the time factor t becomes shorter resulting this disease to be manifest sooner.

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EXPLANATION OF FIGURES

Er: Rough-surfaced endoplasmic reticulum
Gol: Golgi apparatus
Is: Intercellular space
M: Mitochondrion
N: Nucleus
Col: Colloid
tb: Terminal bar
mvl: Microvilli
av: Apical vesicle
cd: Colloid droplet
G: Intracellular granule
L: Lipid droplet
F: Fibrilar structure

FIG. 1. Histological appearance of arteriosclerotic lesions in pyridoxine-deficient monkeys.
A: Cellulofibrous thickening of intima of an iliac artery in the monkey on the control diet for 6 months as recovery experiment, after 12 months of the pyridoxine-deficient stadium; van Gieson stain. Magnification: ×500.
B: Early intimal fibrous plaque on the wall of the coronary artery branch. Pyridoxine deficiency, 10 months; hematoxylin and eosin stain. ×500.
C: Intimal fibrosis in small branches of the splenic artery in the monkey on the control diet for 4 months as recovery experiment, after 12 months of the pyridoxine-deficient stadium; van Gieson stain. ×500.

FIG. 2. Electron micrograph of follicular cells in bovine thyroid and of those cultured *in vitro*.
A: Follicular cells in bovine thyroid. A number of relatively short microvilli are projecting into the colloid. Below them there is a zone containing small vesicle of different contents. A number of droplets, varying in size and density, are present. ×15,000.
B: Electron micrograph of a cell cultured for one day. The same granule as in normal follicular cells is found. The endoplasmic reticulum is developed in the form of small vesicles and tubules. ×20,000.
C: A cell cultured for 7 days. Microvilli are still present and the cells are connected together with convoluted intercellular space and terminal bar. The basement membrane is missing and the cell surface is smooth. Many fibrilar structures are recognized at that part. ×15,000.
D: A cell cultured for 14 days. Short microvilli and terminal bar are still recognized. The endoplasmic reticulum shows tubular profiles. ×56,000.

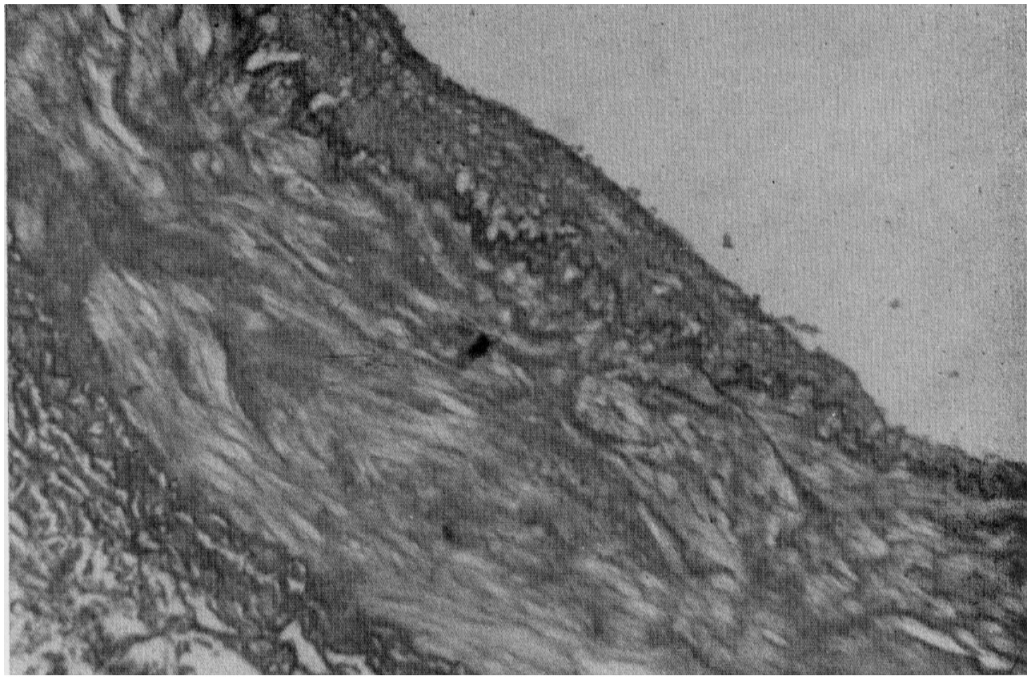

FIG. 1 A

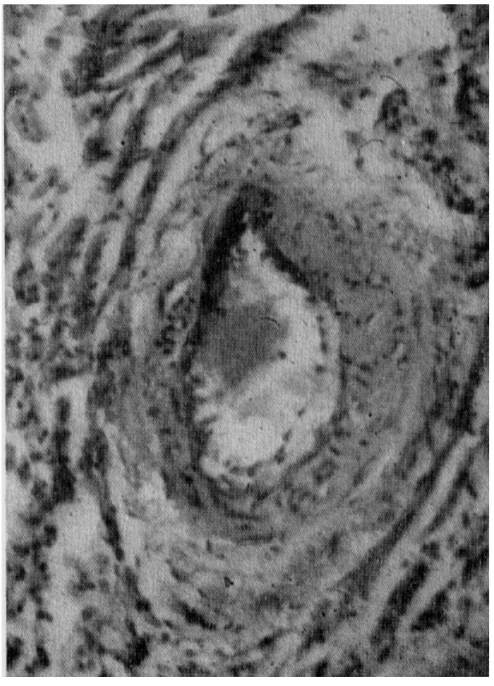

FIG. 1 B

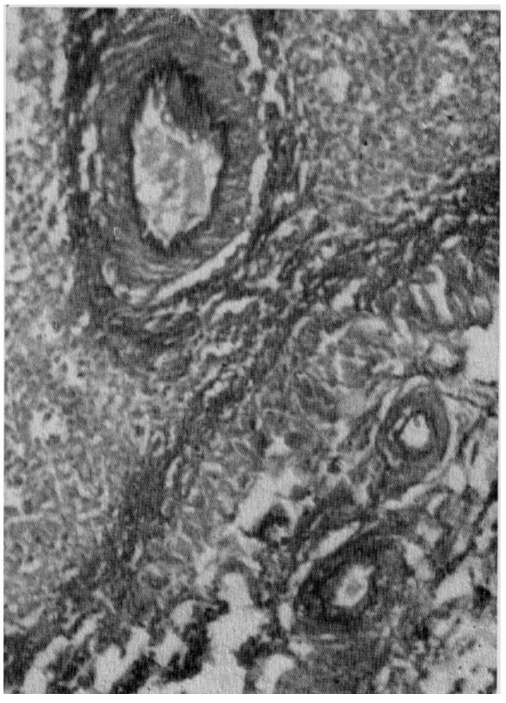

FIG. 1 C

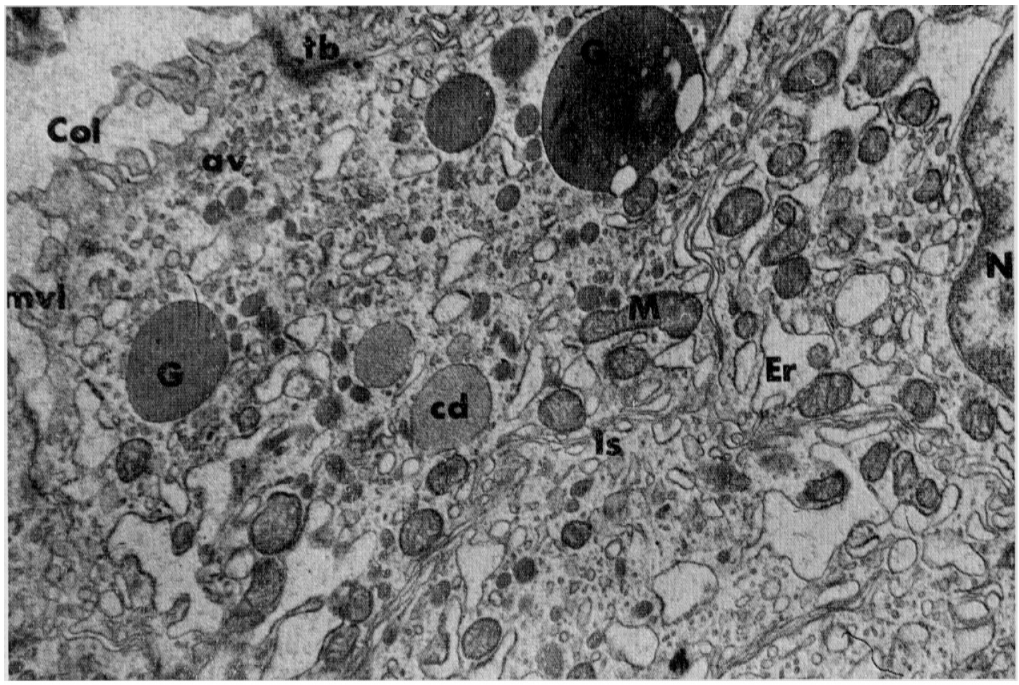

FIG. 2 A

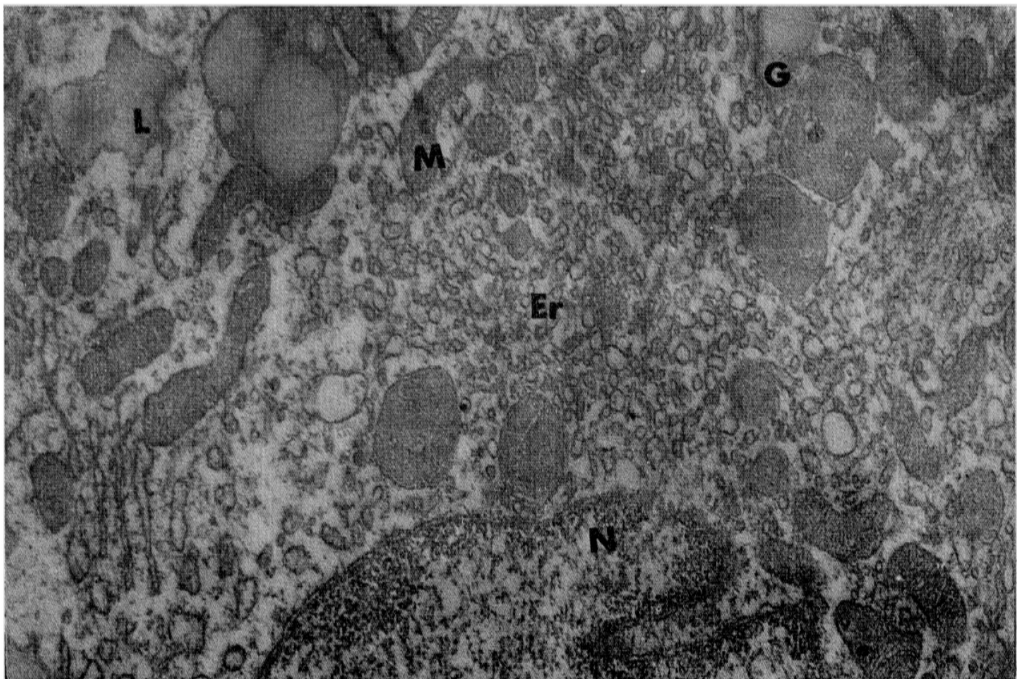

FIG. 2 B

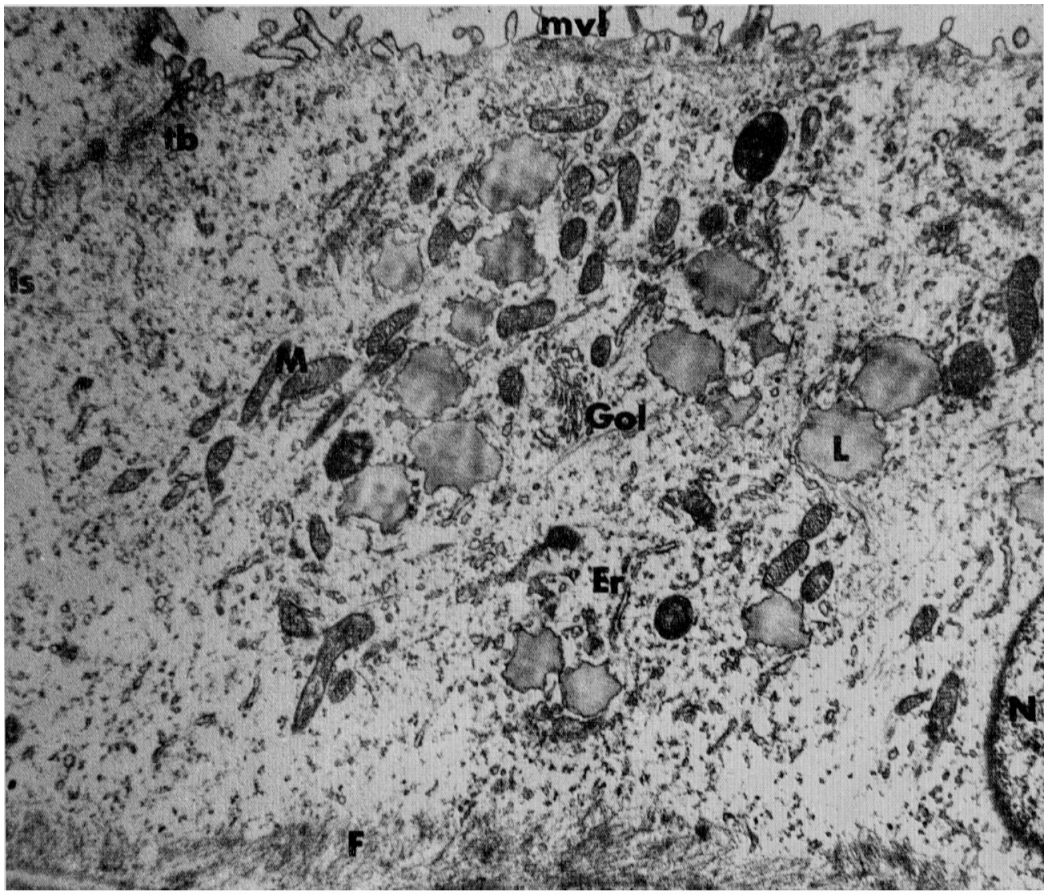

FIG. 2 C

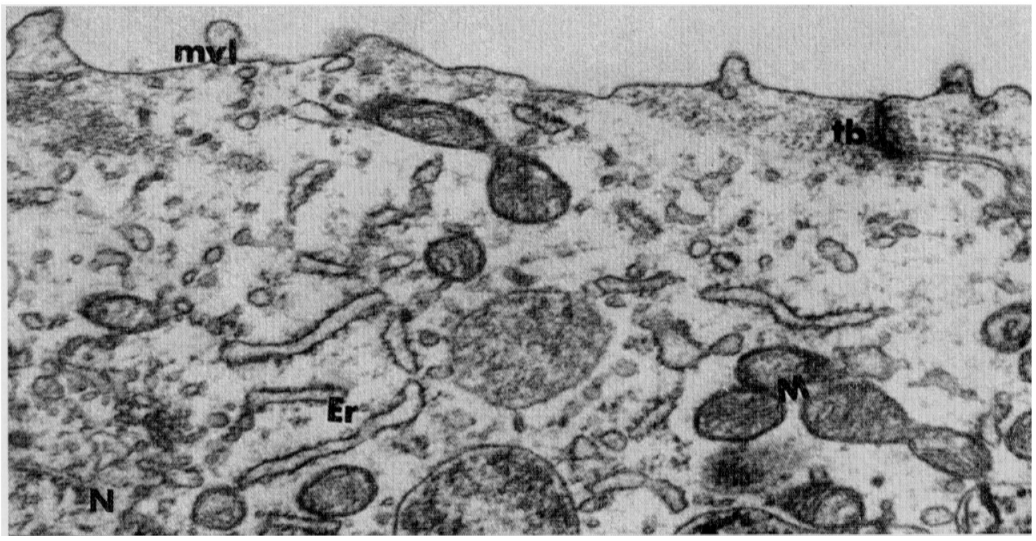

FIG. 2 D