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CONTENTS

LIST OF ABBREVIATIONS.....	5
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INTRODUCTION.....	8
--------------------------	----------

CHAPTER 1.

FEATURES OF LIPID METABOLISM IN DIABETES MELLITUS AND

ISCHEMIC HEART DISEASE	10
-------------------------------------	-----------

1.1. Metabolic Reaction of Lipoproteins and Hormones in a Healthy Person's Organism.....	10
1.2. Syndrome X (Hyperinsulinemia, Insulin Resistance)	30
1.2.1. Pathogenetic Mechanisms of Syndrome X Development	31
1.2.2. Syndrome X and Its Clinical Manifestations.....	38
1.2.3. Obesity and the Syndrome X	45
1.2.4. Syndrome X and Heart Pathology.....	58
1.3. Pathophysiological Relation between Obesity, Diabetes Mellitus, and Ischemic Heart Disease	71
1.4. Disorders of Lipid Metabolism in Ischemic Heart Disease Patients.....	93
1.5. Lipid Metabolism Disorders in Diabetes Mellitus Patients	114
1.6. Conclusion.....	136

CHAPTER 2.

DISORDERS IN THE HEMOSTASIS SYSTEM AND CHANGES IN THE

RHEOLOGICAL PROPERTIES OF THE BLOOD IN ISCHEMIC HEART

DISEASE AND DIABETES MELLITUS PATIENTS	141
---	------------

2.1. Hemostasis System and Rheological Properties of the Blood in Healthy Persons.....	141
2.1.1. Vessel Wall as a Regulator of the Functional State of the Hemostasis System.....	141
2.1.2. Rheological Properties of the Blood in Healthy Persons	155
2.2. Hemostasis System and Rheological Properties of the Blood in Ischemic Heart Disease Patients	162
2.2.1. Rheological Properties of the Blood in Ischemic Heart Disease.....	163
2.2.2. Hemostasis System in Ischemic Heart Disease	170
2.3. Hemostasis System and Rheological Properties of the Blood in Diabetes Mellitus Patients	192
2.3.1. Injury of a Vessel Wall in Diabetes Mellitus	192
2.3.2. Rheological Properties of the Blood in Diabetes Mellitus	197
2.3.3. Thrombocyte-Vessel Unit of Hemostasis in Diabetes Mellitus.....	206

2.4. Correction of Blood Coagulating System in Ischemic Heart Disease and Diabetes Mellitus Patients	222
2.5. Conclusion.....	240
CHAPTER 3.	
DIABETES MELLITUS AND ISCHEMIC HEART DISEASE.....	242
3.1. Pathophysiological Fundamentals of Development of Cardiac Insufficiency in Diabetes Mellitus Patients	243
3.2. Energy Metabolism in Diabetes Mellitus.....	248
3.3. Lesion of Myocardium in Diabetes Mellitus	270
3.4. Conclusion.....	286
CONCLUSION.....	290
BIBLIOGRAPHY	295
INDEX.....	326

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
ADP	Adenosine diphosphate
AI	Atherogenic index
AP	Arterial pressure
Apo-A (B, C)	Apolipoprotein A (B, C)
AT	Antithrombin
ATP	Adenosine triphosphate
BWI	Body weight index
BPM	Beats per minute
CA	Catecholamines
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CI	Clearance
CL	Cardiolipin
CM	Chylomicrons
CNS	Central nervous system
CRLV	Contraction rate of left ventricle
CS	Cholesterol
CSE	Cholesterol esters
DIC	Disseminated intravascular coagulation (syndrome)
DLP	Dyslipoproteinemia
DM	Diabetes mellitus
DNA	Desoxyribonucleic acid
DOPA	Dihydroxyphenylalanine
DPR	Duration of plasma recalcification
DT	Diet-dependent thermogenesis
EDD	End diastolic distance
EDV	End diastolic volume
EEI	Energy expenditure index
EF	Ejection factor
ESD	End systolic distance
ESV	End systolic volume
F	Fibrinogen
FAB	Fibrinolytic activity of blood

FC	Free cholesterol
FFA	Free fatty acids
FPOL	Free-radical peroxide oxidation of lipids
GC	Glucocorticoids
GHDLP	Glycosylized high density lipoproteins
HDLP	High density lipoproteins
HL	Hyperlipacidemia
HMG	3-hydroxy-3-methyl glutaryl
HSL	Hormonosensitive lipase
Ht	Hematocrit
HTG	Hypertriglyceridemia
IDL	Intermediate density lipoproteins
IHD	Ischemic heart disease
IIDM	Insulin-independent diabetes mellitus
IRI	Immunoreactive insulin
LA	Lactic acid
LAT	Lecithin acyl transferase
LCAT	Lecithin cholesterol-acyl transferase
LDLP	Low density lipoproteins
LP	Lipoprotein
LPC	Lysophosphatidylcholine
LPL	Lipoproteinlipase
MOC	Maximum oxygen concentration
NA	Noradrenaline
NADP, NADPH ₂	Oxidized and reduced forms of nicotinamide adenine dinucleotide phosphate (coenzyme II)
NEFA	Nonesterified fatty acids
NMOC	Normal maximum oxygen consumption
PC	Phosphatidylcholine
pct	Pulse coefficient
PEA	Phosphatidylethanolamine
PG	Prostaglandin
PL	Phospholipids
PPh	Plasmapheresis
PRA	Pyruvic acid
PrC	Prostacyclin

PS	Phosphatidylserine
PUFA	Polyunsaturated fatty acids
RNA	Ribonucleic acid
RRLV	Relaxation rate of left ventricle
SFMC	Soluble fibrin-monomer complexes
SM	Sphingomyelin
SNS	Sympathetic nervous system
STH	Somatotropic hormone
TAF	Thrombocyte activation factor
TF	Thrombocyte factor
TG	Triglycerides
TP	Total phospholipides
TPH	Tolerance of plasma to heparin
TPR	Total peripheral resistance
TSH	Thyroid-stimulating hormone
TX	Thromboxan
V_{cr}	Rate of circular shortening of the myocardium fiber
VLDLP	Very low density lipoproteins

INTRODUCTION

Obesity develops when the energy received with food exceeds its expenditure. There is no doubt that obesity is a genetically determined process and may be inherited. Lipid tissue is a highly active link in metabolism and functions under conditions of a constant exchange with its other participants. In high caloric diet lipogenesis exceeds lipolysis resulting in an increased triglyceride accumulation in adipocytes. Obesity leads to metabolic and humoral changes that may be completely reversible when the body weight returns to its previous "ideal" level. Clinicians noted long ago that diabetes mellitus (DM) develops more often in obese persons with disturbed carbohydrate and lipid metabolism.

Patients with obesity have been revealed to have an increased appetite, hyperinsulinism, and high activity of the cortical suprarenal hormones. Metabolic disturbances appear when obesity is combined with hyperinsulinism and a disturbed tolerance to glucose and hyperglycemia. These metabolic disturbances cause DM to develop. Lipid tissue metabolism and insulin secretion are closely related to the activity of the autonomous nervous system. Catecholamines are its most important link. Lipolysis in the lipid tissue and the level of free lipid acids are controlled by adrenaline and noradrenaline.

Hypertriglyceridemia and insulin resistance are close companions. Persons with hypertriglyceridemia have a low level of glucose utilization by tissues. It was also shown experimentally that VLDLP decrease glucose utilization by tissues and stimulate insulin secretion provoking hyperinsulinemia. The high level of latter stimulates the synthesis of triglycerides that are part of VLDLP and thus *circulus virtuosus* is closed. The intensification of glucogenesis in obesity stimulates hyperglycemia and hyperinsulinemia. In DM the transformation of carbohydrates into fats is an insulin dependent process and takes place in lipid tissue. In these patients, lipoproteinlipase plays an important role in all lipid metabolic transformations, as the lipid acids supply of cells depends on this substance. The circulating lipid acids perform fat synthesis from glucose in DM patients. Lipid acids reach the lipid depots as a triacylglycerol component of lipoproteins and chylomicrons. The hyperlipidemia in DM depends on the severity of the disease, the nature of its decompensation, and the level of hypertriglyceridemia. The blood level of free lipid acids generally increases in all DM patients, especially in the ketose state.

Insulin promotes glucose penetration into the lipocytes, enhances its transformation into glycerophosphate and lipid acids. It not only augments the synthesis, but also diminishes fat dissociation and lipid acid liberation from the lipid tissue. The disturbed carbohydrate metabolism in DM patients involves suppression of liver carbohydrate oxidation

and intensification of lipid oxidation. The increased synthesis of hepatic carnitine in DM patients intensifies lipid acid oxidation.

CHAPTER 1.

FEATURES OF LIPID METABOLISM IN DIABETES MELLITUS AND ISCHEMIC HEART DISEASE

1.1. Metabolic Reaction of Lipoproteins and Hormones in a Healthy Person's Organism

Clinical studies of recent years revealed that the main risk factors of IHD and atherosclerosis are disorders of LP metabolism – dyslipoproteinemia (DLP), arterial hypertension, smoking, obesity, DM. Disorder of LP metabolism is almost always a component of IHD and atherosclerosis. The most severe manifestation of hyperlipidemia – a growth in the level of total cholesterol in the blood plasma, i.e. hypercholesterolemia – is widely known. A growth in the content of total cholesterol to above 225 mg/dl drastically increases the probability of the development of atherosclerosis. If the level of total cholesterol is 275 mg/dl and more, atherosclerosis appears still more rapidly [30, 51, 77, 189, 267, 301, 537].

In clinical observations, the pathogenesis of IHD is considered from the viewpoints of the atherogenic effect of DLP, i.e. the qualitative and quantitative disturbances of the level of blood components such as cholesterol, triglycerides, apoproteins, that are transported in the blood in the composition of LP of a very low density (VLDLP), low density (LDLP), and high density (HDLP). Lipoproteins form the structure basis of all the biological membranes of the cells of the blood and endothelium. A considerable part of them forms in the liver and in the walls of the small intestine. The LP are the main transportation form of lipids in an organism.

Structurally, LP are an association of lipids and proteins in various proportions. In the rate of settling in ultracentrifuging, they are divided into five main classes: (i) chylomicrons (CM) – they contain 2% of protein and 98% of lipids (mainly TG up to 90%); under normal conditions no CM are contained in the blood plasma when food is not being taken, (ii) VLDLP – 10% of protein and 90% of lipids (mainly TG); (iii) lipoproteins of an intermediate density (IDL) – they are intermediate between VLDLP and LDLP in their physicochemical composition, (iv) LDLP contain 25% of protein and 75% of lipids (mainly cholesterol esters), and (v) HDLP – about 50% of protein and 50% of lipids (phospholipids form about 30%, TG and free cholesterol – 70%). Apoproteins are the protein component of LP.

The main functional role of chylomicrons is the transportation of triglycerides. They form in the walls of the small intestine and then along the lymph tracts get into a lymphatic duct and the blood. They are not atherogenic because they cannot penetrate into an artery wall owing to the large particle size [107, 167, 176, 292].

The VLDLP mainly synthesized in the liver and to a smaller extent in the wall of the small intestine are a significant atherogenic factor. They are the main transportation form of endogenous triglycerides. They are atherogenic, because owing to the smaller particle size (in comparison with that of the chylomicrons), they penetrate more readily into an artery wall and may remain in it. Moreover, in the hydrolysis of triglycerides they first transform into IDLP – remnant fine particles that can also penetrate with the blood into an arterial wall [33, 74, 302, 347, 351, 377].

The LDLP, whose main function is the transportation of cholesterol into the peripheral cells, are the richest in it; their particles are still smaller, owing to which the LDLP readily penetrate into a cell and can be deposited in it. They form mainly in the hydrolysis of TG-containing VLDLP with the participation of the enzyme lipoproteinlipase (LPL). In healthy persons, two thirds of the plasma cholesterol is contained in the LDLP. Of all the classes of LP, the most atherogenic are LDLP.

In recent years, great significance is being attached to HDLP (in particular, alpha-LP), which are divided in turn into two subclasses: HDLP₂ and HDLP₃ differing in their average hydrated density, magnitude of the particles, physicochemical composition, and functions. The main function of the LP of this class is the transport of cholesterol and phospholipids (PL) from a cell. The HDLP are synthesized in the liver and small intestine [116, 148, 270, 333, 423].

The work of the LP transportation system is determined in many ways by the function of the apolipoproteins, which create the pathophysiological basis of development (or inhibition) of atherosclerosis of the coronary arteries. By forming soluble complexes with the lipids owing to which the latter are readily transported by the blood, they activate individual reactions of lipid metabolism and participate in a reaction with the specific receptors of a cell, ensuring the capture of LP particles from the cells.

The apolipoproteins B (apo-B) are the main protein component of LDLP, VLDLP, and chylomicrons. The catabolism of apo-B-LP occurs in the peripheral tissues. By combining with receptors on the surface membrane of the cells, the apo-B-LP are transported into the cells, where the hydrolysis reactions proceed.

A growth in the level of apo-B-LP is generally attended by the transportation of more cholesterol into the tissues and membranes of the cells.

The main part of apo-A-1 is in the HDLP; an important role in the catabolism of apo-A-1 is played by parenchymal cells of the liver. Some authors discovered a relation between the LPL level in the blood and the apo-A-1 concentration. Forming the main part of the protein component of the HDLP, the apo-A-1 accepts and transports cholesterol into the liver and accordingly ensures its catabolism.

As already indicated, metabolism of the plasma LP regulates the content of the specific apo-LP, the main ones of which are apo-A-1, apo-A-2, apo-A-4, and apo-B. Moreover, there are also minor apo, namely apo-E, apo-C-1, apo-C-2, and apo-C-3. From the standpoints of functional biochemistry, the apo-LP play the role of specific enzymes or cofactors [58, 88, 116, 234, 453, 567].

The apo-E/apo-A-1 ratio is an important criterion of the atherogenic properties of healthy persons and of patients with IHD. The atherogenic index (AI) determines the relation between the intensity of transporting cholesterol to the tissues and the rate of its removal from the cells. The AI is calculated from the content of the total cholesterol C_{tot} and that of the HDLP C_{hdlp} :

$$\frac{C_{tot} - C_{hdlp}}{C_{hdlp}}$$

The functional reaction of the apolipoproteins with the tissue elements ensures a system of transportation of the lipids in an organism and facilitates the formation of atherosclerotic changes in the vessels. The directed transfers of apolipoproteins between the lipoproteins of different classes during fasting or taking food, performing physical exercise, and taking various metabolic drugs determine in every person the individual nature of the physiological relations of lipid metabolism.

When speaking of apo-A-1 (the main protein of HDLP), we cannot fail to consider briefly the antiatherogenic role of HDLP.

It was shown in clinical and experimental studies that the antiatherogenic function of HDLP is achieved as a result of the acception by them of unesterified cholesterol from the membranes of the smooth muscle and endothelial cells of the vessels, and also from the VLDLP and chylomicrons in the hydrolysis of their triglycerides in the blood plasma. The biochemical transformation of unesterified cholesterol into the esterified material proceeds with the participation of the enzyme lecithin acyl transferase (LAT). The product of a reaction catalyzed by LAT – esterified cholesterol – forms only on the surface of HDLP particles containing apo-A-1 in a complex with apo-D and LAT [490, 515, 617].

The particles of HDLP₂ transfer cholesterol esters into the liver, where the cholesterol transforms into bile acids that are excreted from the organism. The system of with-

drawing cholesterol from tissues in a healthy organism achieved by HDLP consists of several units, each of which performs a strictly definite function: (i) the protein-lipid structure of the surface monolayer ensures the building into it of unesterified cholesterol, (ii) the enzyme system conducts a reaction catalyzed by LAT with its activator apo-A-1 and inhibitor apo-A-2, (iii) the system of nonenzymatic directed transportation of cholesterol esters includes lipid-carrying proteins.

This self-regulating system under physiological conditions performs an antiatherogenic function autonomously. The degree of activity of the entire system is determined in many ways by the activity of the LAT and the intensity of removing the product of the reaction it catalyzes (esterified cholesterol) from the surface of the HDLP particles. When the rate of this reaction is higher, the inflow to the fine spherical particles of HDLP of the unesterified cholesterol from both the LP enriched in TG (chylomicrons and VLDLP) and the cell membranes is more active.

The development of the atherosclerotic process in IHD patients is affected by the ratio of the intensities of two nonenzymatic processes of transportation of cholesterol esters, namely, in the composition of HDLP₂ into the liver (for the removal of cholesterol from an organism), and in the composition of VLDLP and LDLP into the smooth muscle and endothelial cells of a vessel wall [115, 203, 282, 288].

In view of the fact that the nature of lipid metabolism in every person is an integrative quantity depending both on genetic and environmental factors (the nature of feeding, physical activity, level of hormonal regulation, age, etc.), we studied 37 healthy men from 20 to 51 years old (23 from 20 to 29 years old, 6 from 30 to 39, and of 8 from 40 to 51). All of them were mental workers: students and instructors of a medical institute (22), scientific workers (7), physicians and engineers (8). None of them had arterial hypertension, endocrine disorders, obesity, diseases of the liver or kidneys, or took drugs during the investigation period. To exclude IHD, all of them were examined with the aid of instrumental and laboratory methods. No indications of disturbance of coronary blood circulation or other lesions of the myocardium were discovered on the ECG at rest. When making tests with a physical load according to the conventional scheme, all of the examined persons revealed the retaining of a high physical workability. The individual power of the threshold load varied from 900 to 1320 kgm/min (on an average 1040 ± 42 kgm/min). No indications of ischemia of the myocardium, disorders of the rhythm and conductance (according to the results of the ECG), appearance of other symptoms requiring the stopping of the physical load in veloergometry was discovered in any of the persons tested. When collecting anamnesis for excluding IHD, we used J. Rose's standard questionnaire.

**Table 1. Distribution of Healthy Persons with
Consideration of the IHD Risk Factors.**

Group	Age, years	BWl	Smokers, % of total number in group	Inherited predisposition, % of total number in group
1-я	26	23	75	25
2-я	34	26	71	71

The content of cholesterol, triglycerides, and HDLP cholesterol was determined by the chemical method in an analyzer AA-11 of the Tekhnikon firm, and the content of apo-A-1 and apo-B by the method of quantitative rocket immunoelectrophoresis with the use of antisera at the Center of prophylactic medicine.

To reveal the group with atherogenic DLP, we used the criteria proposed by the European society for atherosclerosis. We included in this group persons in whom the content of cholesterol on an empty stomach was over 200 mg/dl, of TG over 200 mg/dl, and of HDLP cholesterol under 35 mg/dl. Simultaneously with determination of the lipid parameters, we measured the level of the hormones insulin and cortisole.

Group 1 (persons with normal lipid parameters of the LP spectrum, i.e. a content of cholesterol under 200 mg/dl, of TG under 200 mg/dl, and of HDLP cholesterol over 35 mg/dl) included 20 persons (54%), group 2 (persons with atherogenic disorders, i.e. with an increased content of cholesterol or triglycerides, or with a reduced level of alpha cholesterol) included 17 persons (46%). Apart from the differences in the background parameters (cholesterol, TG, HDLP cholesterol), in group 2 persons the content of LDLP cholesterol, the level of apo-B-1, and the ratio apo-B/apo-A-1 were higher. The differences in the content of HDLP cholesterol and apo-A-1 in these two groups are not authentic.

In connection with the fact that in the anamnesis of the healthy persons of both groups there were no diseases capable of causing secondary DLP, we singled out the factors that cause dyslipidemia in them. They were as follows:

- (1) an excess body mass with a body weight index (BWl) over 25;
- (2) regular smoking;
- (3) hypodynamia (when working sitting down over 50% of the working time);
- (4) an inherited predisposition (in persons whose parents suffered from cardiovascular diseases such as IHD, hypertension, insultus).

When analyzing these factors, we found that men of group 2 (with DLP) were older, had a higher body weight index, and most of them had an inherited predisposition to

Fig. 1. Content of Lipids, Apoproteins, and Hormones in Blood of Healthy Persons.

IHD and hypodynamia. The number of smokers was about the same in both groups (Table 1).

Consequently, the differences in the lipid parameters in the two groups may be due either to hereditary factors or to a difference in age, body weight, mode of life, where the main role is played by improper feeding and hypodynamia.

When comparing the parameters of lipid metabolism in healthy persons of groups 1 and 2, we noted clear distinctions, namely, the cholesterol level in group 1 was 166 mg/dl, and in group 2 it was 260 mg/dl (Fig. 1).

What is such a difference in the cholesterol level due to?

Whether or not an excess of cholesterol in the food causes the appearance of "atherogenic factors" still remains a puzzle. In experiments involving the creation of hypercholesterolemia, we can increase the cholesterol content in the cells, but must remember that it is distributed unevenly in a human organism: 7% of the cholesterol is in the transportation form in the composition of the LP circulating in the blood, while 93% of it is in the cells. Normally homeostasis is maintained between these two forms of cholesterol. The latter gets into a liver cell in the composition of LDLP owing to the presence of LDLP receptors. Confirmation of the fact that the amount and activity of these LDLP receptors is regulated automatically by the level of the cholesterol in the blood is very interesting. Atherosclerosis is incurred most frequently when mismatching of the regulatory processes of exchange between the LP in the plasma and the cholesterol in the cells occurs in an organism. The function of the key regulators in matching is played by the LDLP receptors whose molecular defects in atherosclerosis associated with hereditary factors play the leading role. A strategic direction in studying atherosclerosis is the studying of the bioregulators responsible for the redistribution of the cholesterol flows between the blood and wall of a vessel. This is a promising direction when developing methods of therapeutic action on atherosclerosis.

With a growth in the total cholesterol content in the blood and a change in the rate of the forward and reverse transportation thereof into the tissues of the organs of the cardiovascular system, a multitude of adaptive changes appears. An important role here is played by activation of the peroxide oxidation of the lipids in the cells and tissues, consequently, the addition of antioxidants for diminishing side effects on various enzyme systems, including membrane ATPases, lowers the damaging effect in an atherosclerotic process [77, 99, 126, 519].

An important matter in cholesterol metabolism is the presence of specific protein receptors for LDLP on the surface of membranes of endothelial and smooth muscle cells. With the aid of these receptors, the lipoprotein particles enter the lysosomes for decomposition. A biochemical reaction in the lysosomes yields unesterified cholesterol that has a multilateral effect on a cell. In particular, it suppresses the key enzyme hydroxymethylglutaryl-CoA-reductase regulating the rate of cholesterol biosynthesis. The functional activity of the receptors on the membranes of the endothelial and smooth muscle cells ensures the capture of LDLP by a cell, thus retaining the normal level of the LP. It is exactly

the functional activity of an endothelial cell with an increased receptor-dependent capture of LDLP that creates conditions for the prevention of atherosclerosis. Prolonged hyperlipidemia disturbs the physicochemical characteristics of the endothelial membranes with the subsequent change of both the receptor apparatus and the enzymatic properties of the cells. After this, the excess of cholesterol in the blood causes damaging of the endothelial cells and the rapid development of atheromatous plaques [169, 347, 444, 454, 515].

When analyzing such an important parameter of lipid metabolism as the triglyceride content in the blood of persons of both groups, we noted the following distinctions: in group 1 it is 70 mg/dl, and in group 2 – 109 mg/dl. In the physiological studies it was found that the level of the triglycerides is closely related to the activity of LPL in the blood.

Triglycerides are a form of accumulating and carrying energy in an organism, and a large amount of them is constantly carried between individual organs. This exchange is carried out with the aid of such specific transportation forms as chylomicrons and VLDLP, and also in the form of the products of hydrolysis of TG, FFA, and glycerol [315, 316, 376, 425, 489].

The energy needed for an organism (90%) is ensured by the free fatty acids (FFA), which have a very high rate of metabolism. Notwithstanding intense metabolism, the content of the FFA in the serum is very insignificant. After a fat food load, the major part of the FFA forms from the food fats along the way of their transformation into chylomicrons. Under the influence of the lipase of the fat tissue, the TG of a fat depot decomposes into glycerol and fatty acids (FA) that are used for the resynthesis of the triglycerides or enter the blood.

Many clinicians give special significance to the level of the HDLP cholesterol. A drop in this parameter is an unfavorable prognostic feature. We can see from Fig. 1 that if in group 1 the HDLP level was 52.0 mg/dl, in group 2 it was 45.0 mg/dl. The apo-A-1 content is almost the same: 139.0 mg/dl in group 1 and 142.0 in group 2.

A higher apo-B level is a very important indication of dyslipoproteinemia in healthy persons of group 2. If in group 1 it is 100.0 mg/dl, in group 2 it is 163.0. Accordingly, the parameter apo-B/apo-A-1 in group 1 is 0.72 and in group 2 it is 1.17. Generally in IHD, this parameter is greater than unity.

Our investigations showed that in persons of group 2 the level of HDLP lowers, and the content of apo-B grows. This suggests the following conclusion: first of all, in persons of group 2, the removal of cholesterol from the tissues into the liver (performed by the HDLP) is disturbed. The increased level of apo-B in the studied persons of group 2

also facilitates the development of atherosclerotic changes [234, 302, 310, 342, 347, 425, 625].

The apo-B/apo-A-1 ratio determines the relation between the intensity of transportation of cholesterol into the tissues and the rate of its removal from the cells. A growth in the level of apo-B-LP is generally attended by the increased transportation of cholesterol into the tissues and membranes of the cells.

Major significance in regulating lipid metabolism in an organism is attached to the state of hormonal regulation, especially to the activity of insulin, cortisol, the adrenocorticotrophic hormone (ACTH), and the somatotrophic hormone (STH). Most investigators consider that insulin plays a special role here.

Many clinicians note the relation between the insulin content in the blood and the level of triglycerides. In some patients, this can be explained by obesity, which is attended by hypertriglyceridemia, in others obesity is absent, but they have resistance to insulin.

LPL is discovered chiefly in adipose tissue and the skeletal muscles, where it is bound to glycosaminoglycans. There is also a liver lipase that is not sensitive to inhibitors and activators. Both lipases participate in the catabolism of VLDLP and chylomicrons, i.e. lipoproteins rich in triglycerides.

It was proved that LPL is synthesized under the influence of insulin, while when there is a lack of the latter there is a deficiency of this enzyme. In DM, when there is a lack of insulin, the level of LPL drops, and a large amount of lipoproteins rich in triglycerides accumulate in the blood (diabetic lipemia) [420, 423, 424, 469, 474, 547].

When comparing the background level of hormones in persons of the two groups, we revealed a difference in the insulin level. If in persons of group 1 its value was 5.2 $\mu\text{U/ml}$, in these of group 2 it was 10.9 $\mu\text{U/ml}$. The content of cortisol and ACTH differed insignificantly: in group 1 persons the cortisol level was 18.6 mg/dl and of ACTH was 15.0 pg/ml, in group 2 the relevant figures were 16.1 mg/dl and 25.8 pg/ml.

How ACTH affects lipid metabolism (in particular cholesterol) remains to be clarified. When ACTH is administered, some authors noted a growth in the cholesterol level, while others did not. When ACTH was administered to animals, the content of free fatty acids and total fatty acids increased. This allows us to conclude that the level of triglycerides associated with the metabolism of the FFA grows. Klimov [291] considers that a growth in the level of FFA accelerates the synthesis of atherogenic lipoproteins.

Apart from comparing the numerical parameters, of great importance is an analysis of the relations between the parameters of the lipids and hormones. A glance at Table 2 reveals that in healthy persons of group 1 (without DLP), there is a positive correlation between the content of cholesterol and triglycerides, cholesterol and apo-B, cholesterol

Table 2. Coefficient of Correlation between Content of Lipids and Hormones in the Blood of Healthy Persons of Groups 1 and 2.

Parameters	Coefficient of correlation			
	CS	TG	HDLP CS	Apo-B
TG	<u>0.7720*</u> 0.6152*			
Apo-B	<u>0.7244*</u> 0.7029*	<u>0.6448</u> 0.9427		
Apo-B/Apo-A-1	<u>0.7814*</u> 0.7029*	<u>0.5708</u> 0.7790	<u>-0.2415</u> -0.8311	
Cortisol	<u>0.5361</u> 0.8726*	<u>0.8209*</u> 0.7545*	-	<u>0.4948</u> 0.7307*

* The results are authentic.

The numerator gives the coefficient for group 1, the denominator – for group 2.

and the apo-B/apo-A-1 ratio. The correlation of the level of cholesterol and apo-B, cholesterol and apo-B/apo-A-1 also remained in force for persons of group 2. However, correlations were established in group 2 that are absent in group 1, namely, a positive correlation of the level of triglycerides and apo-B, and of triglycerides and apo-B/apo-A-1, a negative correlation of the HDLP cholesterol and apo-B/apo-A-1, and a positive correlation of the content of cholesterol and cortisole, apo-B and cortisole, apo-B and ACTH. Some of these relations are also typical of IHD. This indicates changes in persons of group 2 in the normally proceeding physiological processes and the appearance of disorders of lipoprotein and hormone metabolism that in their direction are identical to the changes discovered in patients with IHD.

Our results confirm the opinion of many clinicians that DLP is a significant risk factor in the development of IHD. Here great significance is attached to functional disintegration of the hormonal systems, which is an important link in the pathogenesis of IHD. In most cases, however, samples for analysis were taken in the persons being investigated on an empty stomach. However, after each taking of food (especially with a high content of saturated fats), temporary lipemia develops that may cause atherogenic shifts in the lipid transportation system of the plasma. This is why clinical studies appeared in recent years in which a fat load was used to study the metabolism of lipoproteins [68, 89, 116, 186, 237, 270, 385, 449].

A lipid load is the best physiological test for determining the functional possibilities of the metabolic activities of an organism. Fat loads are quite popular under clinical con-

ditions. They vary in composition, but do not differ noticeably in their energy value and average about 1300 kcal (or 5443 kJ). All investigators noted an increase in the triglyceride level in the blood plasma in from two to six hours after a fat load. After eight or nine hours, the level returned to normal. The lipolytic activity of the blood plasma also increased in from three to six hours, while in five or six hours the content of nonesterified fatty acids (NEFA) in the plasma increased. Most clinicians find that with a lipid load, the level of triglycerides in the plasma changes the most obviously. It depends both on the amount of fat eaten and on the capture of triglycerides by extraliver tissues. Very contradictory data were obtained when determining the cholesterol level after a fat load: some authors noted only an insignificant increase of it, while others found no differences in the cholesterol amount.

When investigating 28 healthy volunteers after a lipid load, we found a negative relation between the initial triglyceride level and the content of HDLP₂ particles in the plasma. Accordingly, after a single fat load (sweet cream) in persons with a low HDLP₂ level in the plasma, a more pronounced triglyceridemic response was registered in 2, 4, 6, and 8 hours, which may be one of the factors affecting the development of atherosclerosis.

However, when using a fat load, we studied only the biochemical parameters of the lipoprotein spectrum and how pronounced the changes in the lipoproteins are in response to a fat load. A number of questions remain a puzzle: how does the atherogenic effect of food manifest itself, how can one explain the differences in the reaction of the parameters of the lipid transportation system of the plasma to a fat load in healthy persons and in patients with IHD, and is it possible to detect early atherogenic disorders?

Studying of the pathogenetic mechanisms of development of atherogenic shifts in the lipid transportation system of the plasma after taking fat food makes it possible to substantiate clinically the principles of correcting the metabolic processes of the lipid and hormonal units for the prophylaxis of IHD.

A fat load was applied according to the procedure used by J.R.Patsch (1983) [the taking during five minutes of 20% sweet cream on the basis of 130 g of fat per 2 m² of the body's surface area (660 g on an average) and 50 g of white bread]. The total energy value of the proposed breakfast was 1300 kcal, and the cholesterol content was 420 mg.

From clinical standpoints, we posed the following tasks:

- (1) studying the dynamics of the parameters of the plasma lipid transportation system in healthy persons during a day after a fat load;
- (2) studying the reactions of the hypophyseal-adrenal and vagoinsular systems in healthy persons at different times after a lipid load.

Fig. 2. Influence of Lipid Load on Content of Lipids and Apoproteins in Blood of Healthy Persons.

To solve these problems, we conducted the following biochemical investigations: determination of the content of total cholesterol, triglycerides, HDLP cholesterol, LDLP cholesterol, the concentration of apo-A-1 and apo-B, the part of the subfractions HDLP₂ in the total HDLP fraction and the part of the subfractions HDLP₃ in the HDLP fraction, and also the dynamics of the hormonal profile of the plasma (content of insulin, cortisol, ACTH, and STH).

The results indicate (Fig. 2) that the cholesterol level with a lipid load does not virtually change in healthy persons of both group 1 and group 2. The background value of the cholesterol in healthy persons of group 1 was 167 mg/dl, in three hours after the load it was 161 mg/dl, in six hours it was 164 mg/dl, in nine hours it was 171 mg/dl, and in 24

hours it was 160 mg/dl. There was also no dynamics in group 2: 259, 249, 245, 274, and 233 mg/dl.

The dynamics of the triglyceride level in response to a lipid load is more pronounced. In group 1 persons, the background value of the TG was 70 mg/dl, in three hours it grew to 138 mg/dl, in six hours to 172 mg/dl, in nine hours to 41 mg/dl, and in 24 h to 62 mg/dl. It is very important to note the obvious drop in the TG level after nine hours.

In analyzing the TG content after a lipid load in healthy persons of group 2, we found considerable differences: the background level was 109 mg/dl, in three hours it increased to 258 mg/dl, in six hours to 299 mg/dl, in nine hours it was 133 mg/dl, and in 24 h it was 101 mg/dl. These results show that in healthy persons of group 2 there is no phase of lowering of the TG level in nine hours to below the background levels, and a sharper growth in three and six hours is noted.

How can we explain these changes in persons of group 2? Doubtlessly, by the activity of the lipolytic enzymes [126, 343, 376, 424, 519].

VLDLP form mainly in the liver and ensure the transportation of endogenic triglycerides. The rate of formation of the VLDLP depends on the flow of FFA entering the liver and grows with a carbohydrate diet, when the synthesis of the FFA in the liver increases. As a result of lipolysis, the VLDLP transform into HDLP. The latter are the lipoproteins that transport the cholesterol. Unlike the VLDLP, the LDLP contain less triglycerides, but apo-B is a component of them.

The dynamics of the apo-B level is the next important parameter of development of dyslipoproteinemia in response to a lipid load. In group 1 of healthy persons, the apo-B content is insignificant (100 mg/dl), in three hours after a lipid load it remained at the same level, in six hours it dropped to 86 mg/dl, in nine hours it was 96 mg/dl and in 24 h it was 98 mg/dl. In group 2, the background level of apo-B was quite high (163 mg/dl), it remained at the same level in three hours, lowered moderately to 151 mg/dl in six hours, was restored in nine hours – 161 mg/dl, and in 24 h was 159 mg/dl [64, 183, 250, 330, 373, 519].

The ratios apo-B/apo-A-I in healthy persons of groups 1 and 2 differed accordingly. If in group 1 this ratio was less than unity, the background parameter was 0.72, in three hours it was 0.67, in six hours it was 0.55, in nine hours it was 0.63, and in 24 h it was 0.71, then in group 2 the background parameter was increased considerably to 1.17, in three hours it was 1.22, in six hours it was 1.05, in nine hours it was 1.07, and in 24 h it was 1.20.

An increased level of apo-B (especially an increase in the ratio apo-B/apo-A-I) is a criterion of atherogenesis both in healthy persons and in patients with IHD.

The ratio characterizes the intensity of transportation of cholesterol into the tissues or out of them.

A growth in the level of apo-B and especially of the ratio apo-B/apo-A-1 indicates the increased transportation of cholesterol into tissues and the membranes of cells. The liver triglyceridelipase is the enzyme affecting the apo-B-LP transformation.

In recent years, both clinicians and biochemists have been attaching major significance in the regulation of lipid metabolism, especially under conditions of fasting or taking fat food, to NEFA and consider them to be regulators of the content of both triglycerides and apo-B in the blood [444, 493, 500, 561].

When comparing the dynamics of the level of the antiatherogenic factors of lipid metabolism (HDL cholesterol, apo-A-1), we noted the clear distinction in healthy persons of groups 1 and 2 under a lipid load (see Fig. 2). It follows from the results that the background level of HDL cholesterol in group 1 is higher (52 mg/dl) than in group 2 (45 mg/dl). In response to the lipid load in healthy persons of group 1, the background value of the HDL cholesterol remained virtually constant; in three hours it was 51 mg/dl, in six it was 53 mg/dl, in nine it was 53 mg/dl, and in 24 hours it was 46 mg/dl. In healthy persons of group 2 the relevant figures were 43 mg/dl in three hours, 41 mg/dl in six hours, 45 mg/dl in nine hours, and 46 mg/dl in 24 hours. It is very important to note the growth in the apo-A-1 level in healthy persons of group 1: the background was 139 mg/dl, the value in three, six, nine, and 24 hours were 152, 159, 153, and 139 mg/dl, respectively. Such a positive dynamics was not noted in healthy persons of group 2: the background was 142 mg/dl, and the values in three, six, nine, and 24 hours were 137, 148, 156, and 133 mg/dl, respectively.

Thus, if the second group of healthy persons with dyslipidemia was distinguished by higher background parameters of the total cholesterol triglycerides, apo-B, a higher ratio apo-B/apo-A-1 and a higher fraction of HDL_{3B}, then in three hours after a fat load the level of apo-A-1 increased authentically on an average by $14 \pm 6\%$, while in individual persons the deviations reached 47%, i.e. were within the limits of the physiological norm. In six hours after a lipid load, the level of HDL cholesterol lowered only in persons of group 2 with dyslipidemia ($p < 0.05$). As regards the subfractions HDL_{2B} and HDL_{3B}, their background value differs in both groups. If in group 1 the fraction of HDL_{2B} is 33.4%, in group 2 it dropped to 25%. The level of HDL_{3B}, conversely, in group 1 is 21%, and in group 2 is 28% (the difference is authentic). Under the influence of a lipid load, these parameters did not practically change: in group 1 the fraction of HDL_{2B} in 3 h was 34%, and in group 2 it was 23%. The value of HDL₃ in group 1 persons in three hours was 22%, and in group 2 was 31%. There is strict correlation here between the fraction of

HDLP_{2B} and the triglyceride level in the plasma. when the value of HDLP_{2B} is lower, the TG level in the plasma is higher and, accordingly, the activity of lipoproteinlipolysis is lower. In healthy persons of both groups, there is no negative correlation between the background level of the triglycerides and the fraction of the HDLP_{2B}.

It was shown in biochemical investigations that in the lipoproteinlipolysis of particles enriched in triglycerides, part of the cholesterol of their surface layer detaches and passes over into the composition of the HDLP. After a lipid load, the coefficients of negative correlation of the parameters of the triglycerides and HDLP_{2B} cholesterol in group 2 reached significant values. This indicates the preservation and increase in the activity of the lipoproteinlipolysis in the intensification of the flowing off of cholesterol from the chylomicrons onto HDLP particles with the formation of large particles of HDLP_{2B} that transport the cholesterol into the liver. It was noted that an increase in the triglyceride content in the nucleus of the HDLP_{2B} particles in persons with hypertriglyceridemia makes such particles a convenient substrate for the liver triglyceridelipase also having phospholipase activity. After the hydrolysis of the phospholipase and triglycerides in the HDLP_{2B} fraction, the latter diminish in size without losing cholesterol, however, and return into the blood flow in the form of HDLP_{3B}. All this contributes to lowering of the functional activity and disturbance of the antiatherogenic properties of HDLP [272, 342, 376, 604, 621].

Part of the apo-A-1 has an intestinal origin: 70% of the apo-A-1 formed after the fat load enters the blood flow with the chylomicrons and immediately passes from the latter to the HDLP. If a growth in the apo-A-1 level in healthy persons in three hours after a lipid load plays, as it were, a "protective" antiatherogenic role in the utilization of fats after food lipemia, the absence of such a reaction presumes damaging of this protective mechanism. Lowering of the apo-A-1 level in healthy persons with dyslipidemia indicates disorder in the system of removal of cholesterol from the peripheral tissues as a result of damage to the cascade of reactions of cholesterol capture by the high density lipoproteins.

What are the differences in the metabolism of lipoproteins in persons of groups 1 and 2 associated with?

Doubtlessly, an important role is played by genetic factors of the predomination of the "functional unit of switching over" nervous or humoral regulation. Some clinicians attempt to find the initial links of the pathogenesis of atherosclerosis in just this "switching over" of the neurogenic influences to humoral ones.

An important factor in the humoral metabolism in cells is the free endogenic heparin of the blood. It is considered biochemically as an activator of the enzyme LPL. Under conditions of stress with pronounced tension of the neurogenic structures, a considerable discharge of endogenic heparin is noted in healthy persons. It prevents thrombogenesis

and the development of atheromatous changes in the vessels. An absolutely different picture is observed in atherosclerosis and DM. Under the influence of factors of the environment and internal medium, and also of genetic risk factors, in patients with atherosclerosis disintegration of the hormonal systems appears. It is manifest in polymorphism and disconnection of the functions of individual units, namely, a change in the reactions of an organism to a load (emotional, physical, lipid), disturbance of the sensitivity of the receptor apparatus, and distortion of the metabolic reactions of an organism [173, 214, 239, 273, 288].

The above facts suggest that the adaptational reorganization of the endocrine and metabolic status of a person in the direction of disadaptation is an integrative process and includes first of all an increase in the sympathico-adrenal and glucocorticoid activity and also the corresponding changes in the activity of carbohydrate and lipid metabolism (Fig. 3).

Hyperinsulinemia, hyperlipidemia, and hyperglycemia are important links in disadaptation. These metabolic disorders cause diseases such as IHD, hypertension, DM, and obesity.

Of major significance in the progress of metabolic disintegration of an organism (the development of dyslipidemia) is the level of physical activity of a person and his or her professional activities, especially in middle or old age because a physical load increases the expenditure of energy resources. Here the weight of the body lowers, the reserves in the fat depots diminish, the nature of distribution of the fat changes, and the inclusion of lipids into the striated muscles grows. Under a physical load, the metabolism of the adipose tissue alters: the lipolytic activity grows, the sensitivity to hormones increases, and the liability of reesterification of the NEFA diminishes [74, 101, 148, 155, 212].

Clinical studies showed that the NEFA can be mobilized in physical activity in two ways, namely, spontaneously (lipolysis not blocked by the beta blocking agents) and with the aid of adrenergic lipolysis. Under a physical load, special importance is attached to adrenergic lipolysis. At rest, the physiological influence of the sympathetic nervous system on the regulation of fat metabolism is insignificant. Under conditions of physical activity, sympathetic stimulation of the receptors facilitates the additional discharge of the FFA from lipocytes (adipocytes). Physical load is just what increases the mobilization, oxidation, and recirculation of the FFA. If in a healthy person at rest the free fatty acids are mainly (80%) spent on the processes of synthesis of triglycerides, phospholipids, and cholesterol, with physical activity the proportion changes – not 20%, but 80% (depending on the intensity of the physical load) is spent on the oxidizing processes. To date, the pathogenesis of this switching over of the processes of oxidizing FA under conditions of

physical activity was established only partly. In most clinical and experimental studies, the main significance is attached to the increased oxygenation of the muscles and accordingly to the increased oxidation of the FFA.

What hormonal systems react to a lipid load and what are their dynamics?

Lipolysis in adipose tissue is an integrative process combining both the energy requirements of an organism and the metabolism of lipids. The hydrolysis of triglycerides yields glycerol and NEFA. Special significance is attached to the level of the NEFA concentration in the blood that regulates cell metabolism, in particular in the tissues of the cardiovascular system. The synthesis of ATP, the absorption of oxygen and the utilization of glucose in the smooth muscle cells of the vessels and heart depend on the content of NEFA and triglycerides in the blood, and the contracting properties of the indicated tissues depend on these features. Catecholamines, ACTH, STH, and TSH are the main hormonal stimulants of lipolysis. Insulin has an antilipolytic effect. It increases the transportation of glucose into a cell, and since glucose is an important component for the synthesis of triglycerides, the antilipolytic effect of insulin is partly associated with a growth in the reesterification of the NEFA. Under the influence of insulin, the level of cAMP in the lipocytes lowers, while the content of cGMP in them grows [310, 489, 551, 556, 622, 628].

Investigations (Fig. 3) showed that the background level of insulin in both groups of healthy persons is different – it was 5.2 $\mu\text{U/ml}$ in group 1 and 10.9 $\mu\text{U/ml}$ in group 2, i.e. moderate hyperinsulinemia was observed with dyslipidemia.

What is the influence of insulin on lipid metabolism?

The liver and adipose tissue are the main targets of the action of insulin for regulating fat metabolism in an organism. Biochemical investigations showed that an increase in the insulin level in the blood plasma stimulates the synthesis of fatty acids in the liver. This effect is ensured by the following mechanisms:

(1) insulin can have a direct stimulating effect on acetyl-CoA-carboxylase – the key enzyme of liposynthesis;

(2) diminishing of the supply of FFA (under the influence of insulin) eliminates their inhibiting effect on acetyl-CoA-carboxylase;

(3) since insulin stimulates the utilization of glucose along the pentose path, the amount of reduced NADP grows; it is the required hydrogen donor for many stages of fatty acid synthesis;

(4) the growth in the flow of glycolysis substrates in the Krebs cycle occurring under the influence of insulin increases the level of citrate that also stimulates acetyl-CoA-

Fig. 3. Adaptational Reorganization of the Endocrine-Metabolic Status of a Person.

carboxylase. The fatty acids synthesized in the liver are then transported (in the composition of VLDLP) into adipose tissue where they accumulate in the form of triglycerides.

Insulin stimulates LPL – an enzyme synthesized in the lipocytes and acting on the surface of the endothelial cells of capillaries penetrating into adipose tissue. This accelerates the adsorption by the fat cells of the triglycerides circulating in the blood that form from endogenic or exogenic sources [120, 210, 292, 333, 365, 421].

Fig. 4. Influence of Lipid Load on Hormone Level in Blood of Healthy Persons.

When studying the dynamics of the insulin content in the blood plasma under a lipid load, we noted that in persons of group 1 the insulin level increased moderately – it was 10.8 $\mu\text{U/ml}$ in three hours and 11.6 $\mu\text{U/ml}$ in six hours. After nine hours, the insulin level in group 1 persons returned to the background parameters (5.0 $\mu\text{U/ml}$). A different picture was noted in healthy persons of group 2 (with dyslipidemia). The background insulin value of 10.9 $\mu\text{U/ml}$ in three hours increased to 15.6, in six it was 16.6, in nine it was 15.9, and in 24 hours it was 13.2 $\mu\text{U/ml}$. Consequently, the moderately increased insulin content in group 2 persons became still greater after three hours and remained at a high level during 24 h (see Fig. 4).

The main effects of the action of insulin on adipose tissue include a growth in the penetration of glucose into the lipocytes, an increase in glycolysis (especially of the pentose cycle), a growth in the biosynthesis of fatty acids, and also their esterification to triglycerides. Regardless of these effects, insulin is a powerful inhibitor of hormonosensitive lipase (HSL) that catalyzes the hydrolysis of the accumulated triglycerides and the release of fatty acids (i.e. lipolysis). The anticatalytic influence of insulin can be detected at very low concentrations of the hormone (about 0.1 $\mu\text{U/ml}$). Such an insulin level is much lower than the value needed for stimulating the penetration of glucose into a lipocyte. Moreover, the greater part of the glucose absorbed by the fat cells under the influence of insulin is used in the formation of alpha-glycerophosphate needed for the esterification of the fatty acids and the synthesis of triglycerides [382, 435, 469, 490, 563, 586].

As a whole, the adipose tissue is characterized by a considerable sensitivity to the action of insulin, and it is 10 times more sensitive to this hormone than muscle tissue.

In obesity, a typical disorder is a growth in the insulin concentration in the blood serum, i.e. the appearance of hyperinsulinemia. To date, the existence of basic and glucose-stimulated hyperinsulinemia in obesity is doubtless and is confirmed by numerous experimental and clinical studies.

What is the pathophysiology of hyperinsulinemia and dyslipidemia?

Under conditions of a surplus of insulin, the following occurs in an organism: (i) activation of LPL, (ii) a growth in the absorption of free fatty acids from VLDLP (contained in the blood), (iii) stimulation of lipogenesis, (iv) an increase in the transportation of glucose, (v) acceleration of the transformation of glucoso-6-phosphate along all the metabolic paths (oxidation to CO_2 , synthesis of fatty acids, and oxidation by the pentosophosphate path), and (vi) the formation of a large amount of alpha-glycerophosphate needed for the synthesis of triglycerides. At the same time, the hydrolysis of triglycerides with the aid of hormonosensitive lipase is greatly inhibited by insulin.

Fat cells as their size grows become resistant to insulin. A drop in the number of receptors to insulin per cell is found in them (and also in hepatocytes and myocytes). When the body weight lowers because of limited food consumption, the fat cells again become sensitive to insulin, and the number of its receptors grows in all tissues [301, 358, 365, 435, 493, 584, 620].

Consequently, insulin facilitates the formation of a "store" of fat in a lipocyte, but when the stores are greater, its further accumulation proceeds more slowly. The appearance of insulin resistance in this situation is thus a physiologically protective reaction that prevents further obesity.

The accumulation of triglycerides in the fat cells is attended by a tendency of a growth in the level of the FFA in the blood, which ensures the supply of a large amount of substrates to the liver for the synthesis of VLDLP.

Consequently, a lipid load clearly demonstrates the adequate hormonal provision of lipoproteinlipolysis and catabolism of lipoproteins. The increase in the insulin concentration during the maximum lipemia (in three and six hours after a lipid load) lowered the decomposition of endogenic triglycerides in the fat depots and increased catabolism of the newly formed VLDLP, IDLP, and HDLP₂.

Do other hormones participate in these processes of lipid metabolism?

Of special interest is studying of the dynamics of the content of the somatotropic hormone (STH). The background level of it in both groups of healthy persons was practically the same (0.72 ng/ml in group 1 and 0.69 ng/ml in group 2). However, under the in-

fluence of a lipid load, the dynamics of the level of this hormone in the blood differed in the two groups. In group 1, the STH level was 1.06 ng/ml in three hours, 1.32 in six, 0.58 in nine, and 0.82 ng/ml in 24 hours. The dynamics was less pronounced in group 2, namely, 0.98, 0.90, 0.67, and 0.74 ng/ml in three, six, nine, and 24 hours, respectively.

The STH has a pronounced anabolic effect on protein metabolism (it increases the synthesis of protein, DNA, RNA), and also an insulin-like effect on fat metabolism (the content of NEFA in the blood grows). The functional activity of the STH is regulated by the hypothalamus.

Consequently, investigation of the metabolism of lipoproteins and the hormonal profile in healthy persons of both groups points to a broad range of lipid and hormonal parameters. As already indicated, in the formation of the groups (with normal parameters of the lipids and atherogenic disorders), we found that in persons of group 2 with atherogenic DLP (cholesterol over 200 mg/dl, triglycerides over 200 mg/dl, HDLP cholesterol under 35 mg/dl), disintegrative processes appear, evidently as a result of genetic or environmental factors, or both. They lead to disturbances of both the metabolism of lipoproteins and the hormonal status. The presence in group 2 of correlations between the lipid and hormonal parameters (similar to those for the group of IHD patients) makes this group (with DLP) a sort of intermediate one between healthy persons and IHD patients.

Studying of the influence of the lipid load on the lipid and hormonal status of persons of both groups showed that the dynamics of parameters such as the content of triglycerides, HDLP cholesterol, apo-A-I and apo-B/apo-A-I is more pronounced in persons of group 2 (a growth in the atherogenic shifts of the lipoprotein system). Here a delay in the return of the content of triglycerides and IRI to the initial level was noted (in 24 h after the taking of a lipid load).

Consequently, the application of a lipid load makes it possible to detect latent shifts in the lipoprotein system in healthy persons of group 2 (with DLP) in comparison with group 1 (normal lipid and hormonal spectra), namely, the absence of an increase in the content of apo-A-I and a growth in the level of HDLP_{3B} in three hours and a drop in the level of HDLP cholesterol by the sixth hour after a fat load.

1.2. Syndrome X (Hyperinsulinemia, Insulin Resistance)

Active studying of the pathogenesis of cardiovascular diseases allowed investigators to single out the special role of metabolic disorders. Individual aspects of the problem are continuing to receive attention by both cardiologists and endocrinologists.

The exceedingly pronounced interaction of all the risk factors of cardiovascular diseases, hyperinsulinemia or insulin resistance, or both, made it possible to interpret this

state more likely as a syndrome than as a set of individual factors. In other words, a definite metabolic set of symptoms underlying the pathogenesis of many metabolic diseases was singled out. Reaven proposed to call them syndrome X [406, 417, 475, 477].

Hypertension, obesity, disturbance of tolerance to glucose, and dyslipidemia are the main risk factors of cardiovascular diseases. Currently, another factor was added to them – chronic hyperinsulinemia. A special, leading role is assigned to this factor in the formation of a metabolic syndrome leading in most cases to the development of cardiovascular diseases.

Syndrome X is thus a pathogenetic combined state of metabolism in which hyperinsulinemia may precede (in time) IHD, DM, and, consequently, coronary sclerosis and disorder of carbohydrate metabolism [110, 166, 225].

1.2.1. Pathogenetic Mechanisms of Syndrome X Development

Syndrome X described by Reaven [474, 475] is based on the following disorders: resistance to insulin in the introduction of glucose, disturbance of the tolerance to glucose, a growth in the content of VLDLP, hyperinsulinemia, lowering of the HDLP level, and hypertension. The author succeeded in combining the known risk factors of cardiovascular diseases and single out especially the significance of insulin resistance, although the relation between the indicated factors and their role in the appearance of cardiovascular diseases was discussed previously.

The influence of the environment, prolonged action of nonspecific factors, and a change in the function of the internal organs activate the adaptive mechanisms in an organism (see Fig. 3) [222, 289, 301, 327, 476].

Reorganization of the metabolic processes is one of the main conditions for maintaining homeostasis under the effect of nonspecific factors. Here the mechanisms of regulation of the carbohydrate and lipid metabolism are switched on especially actively. Metabolic reorganization reflects the state of the hormonal and mediator units in the process of adaptation to the new level of functioning. The adaptation reorganization of the endocrine and metabolic status is manifest in activation of carbohydrate and lipid metabolism on the background of an increase in the glucocorticoid and sympathico-adrenal activity.

Many investigators are interested in matters of the control of the metabolism and functional activity of cells, and determination of the molecular mechanisms of the intracellular reaction to hormones (their concentration in the blood). In recent years, most scientists acknowledge that hormones are the regulators and integrators of metabolism in organs and tissues. To understand the essence of metabolism, it is very important to study

Obesity and Diabetes Mellitus

Fig. 5. Central Nervous System and Carbohydrate Metabolism.

the mechanisms of the reception and transformation of hormonal signals fed to the receptor apparatus of a cell [280, 330, 368, 472, 620].

A major role in metabolic processes in an organism is played by hormonal regulation, which is realized depending on the supply of a hormone to the tissues and the sensitivity of the latter to its effect. The efficiency of the action of a hormone on an organ depends on the sensitivity of the cell receptors, which for some hormones are on a cell mem-

brane, for others – in the cytoplasm, and for still others – in a cell nucleus. These receptors are responsible for the hormonal action on the metabolism in a cell, the change in the activity of enzymes, and the synthesis of protein structures. A disturbance in the adaptive-trophic and modulating effect of hormones in diseases such as DM and IHD causes disintegration of the regulator and adaptive mechanisms in the activity of the cardiovascular system and carbohydrate metabolism in an organism. In a number of experiments, a correlation was noted between the amount of circulating hormone in the blood: and the concentration of receptors in the tissues. In experimentally induced DM, a drop in the level of the circulating insulin is attended by a growth in the number of receptors specifically binding insulin in the target tissues [301, 345, 421, 439].

Under the action of nonspecific factors (see Fig. 3), a healthy organism reacts by an increase in the sympathico-adrenal and glucocorticoid activity, and also by pronounced activation of carbohydrate and lipid metabolism. However, the prolonged action of various nonspecific factors (emotional stress, hypoxia, a physical load, etc.) produces disadaptation of the regulator mechanisms and the appearance of a metabolic syndrome whose main fragments are hyperinsulinemia, hyperlipoproteinemia, hyperglycemia, obesity, and hypertension. All these metabolic disorders lead to the development of diseases such as IHD, insulin-independent diabetes mellitus (IIDM), hypertension, and syndrome X [110, 405, 439].

In the pathogenesis of metabolic diseases, a special role belongs to the harmful consequences of the prolonged increased content of circulating insulin. The hypothesis was advanced of central regulation of the endocrine part of the pancreas. For instance, in an experiment a hypothalamic factor was separated of a polypeptide nature that affects the secretion of insulin. When obesity was studied in an experiment with animals, hyperinsulinemia was found to be preceded by hyperphagia (Fig. 5).

The insulin resistance syndrome includes IIDM, obesity, hyperinsulinemia, dyslipidemia, and hypertension (Fig. 6). The syndrome of insulin resistance is a marker of the syndrome X. Numerous clinical studies showed that the resistance to the insulin-stimulated capture of glucose may be one of the etiological links of IIDM, arterial hypertension, and IHD. It was shown that obesity is always associated with hyperinsulinemia and insulin resistance. Patients generally note a lowered physical activity, they smoke and overeat. Hyperinsulinemia in combination with insulin resistance leads to disturbance of lipid metabolism (Fig. 7). Factors of dyslipidemia such as an increased content of VLDLP and LDLP and lowering of the level of HDLP facilitate the development of IHD. Another aspect of the manifestation of hyperinsulinemia consists in the increased reabsorption of sodium ions, the pronounced activity of the sympathetic nervous system (SNS), an in-

Obesity and Diabetes Mellitus

Fig. 6. Disturbance of Insulin Metabolism.

creased level of angiotensin II, and a natural growth of the arterial pressure [32, 111, 273, 345].

In obesity, an increased content of endogenic opioides both in the CNS and in the pancreas is significant in the appearance of hyperinsulinemia. Their stimulating effect on the secretion of insulin was also established.

Studying of the interaction of insulin, the CNS, and various neuropeptides revealed new aspects of the activity of insulin and the ways of its action on the CNS, insulin recep-

Fig. 7. Syndrome of Insulin Resistance.

tors were discovered on the membrane of nerve cells, and the suppression by them of the delivery of noradrenaline to the neurons was established. Insulin participates in the metabolism of the neuromediators because the content of the latter in DM patients lowers, while in the compensation of DM their level is restored. Therefore, insulin has a modulating effect on the state of the neuromediator systems [368, 472, 516, 555, 616].

Insulin is an anabolic hormone facilitating the utilization of glucose and the biosynthesis of glycogen, lipids, and proteins.

The metabolic transformations of glucose follow several paths:

- (1) The transformation of glucose into glucoso-6-phosphate with subsequent re-synthesis into glucose;
- (2) transformation of glucose into glycogen;
- (3) transformation of glucose into pyruvic acid, lactic, then into oxalic-acetic acid and further into acetyl-Co-A;
- (4) participation of glucose in a pentose cycle, transformation of glucose into ATP (the cycle of tricarboxylic acids, or the Krebs cycle);
- (5) transformation of glucose (glycolysis or the Embden path) via the key compound – acetyl-Co-A, and then the synthesis of lipids (cholesterol, fatty acids, and ketone bodies).

Substantial changes occur in the metabolism of lipids with a lack of insulin in DM patients. First of all, lipolysis in adipose tissue increases and accordingly the amount of FFA in the blood grows. The supply of the FFA into the liver increases, where the synthesis of triglycerides, the formation of cholesterol and ketone bodies grow [96, 285, 294, 567, 573]. The reason is that the increased amount of FFA does not have time to be oxidized in the Krebs cycle, and in DM patients with a lack of insulin, the content in the blood of FFA, triglycerides, cholesterol, beta-hydroxybutyric, acetoacetic acids, and acetone increases. This results in decompensation of DM [280, 358, 397, 432, 551, 601].

It was noted that in a healthy person, an increased glucose level (its excess in the blood) inhibits the secretion of contrainsular hormones and preserves the homeostasis of insulin in the blood. A paradoxical reaction was revealed in patients with hyperinsulinemia, namely, the introduction of glucose did not inhibit, but stimulated the secretion of contrainsular hormones. The increased secretion of insulin antagonists is an important factor in the development of insulin resistance and is often observed in many diseases [120, 131, 153, 176, 271, 318].

The antagonists of insulin include glucocorticoids (GC), STH, and hormones of the thyroid gland that cause hyperinsulinemia in various ways. Special importance in this process is attached to glucocorticosteroids that increase glycogenesis, promote the development of hyperglycemia leading to hyperinsulinemia, and also lower the affinity of the receptors for insulin. On the one hand, STH increases the secretion of insulin by stimulating the insular apparatus of the pancreas, while on the other, insulin in physiological doses stimulates the secretion of prolactin by the hypophysis. Experiments showed that when human insulin acts for five days on a culture of hypophysis tumor cells, the secretion of prolactin increased by 30% both in the control culture and in the tumor cells.

Consequently, hyperinsulinemia may be a result of dysfunctioning of the hypothalamus-hypophyseal system, and pronounced chronic hyperinsulinemia enhances it [313, 321, 328, 399, 472, 541].

Chronic endogenic hyperinsulinemia, apart from disturbances of the function of the hypothalamus-hypophyseal system, is maintained in an organism by a number of other factors.

The biochemical adaptation of an organism to the effect of extremal factors is thus closely related to the reactivity of the endocrine system, and also to the sensitivity to insulin. The performance of muscular work by an organism depends on the change in the content of glucose and insulin. Experiments with animals showed the hypoglycemic effect when insulin is introduced to be more pronounced in physically well trained animals than

in untrained ones. Therefore, the sensitivity of the cAMP receptors to insulin in trained animals is much higher.

The experimental studying of the biochemical transformations of insulin in an organism of trained and untrained animals revealed that in the former the sensitivity of the tissues to insulin does indeed grow, but simultaneously the rate of inactivation of this hormone in the blood grows, i.e. it reacts very rapidly with cAMP and is then decomposed in the organism [83, 109, 199, 314, 358, 597].

Every biological homeostatic system is characterized by a multitude of contours that ensure various forms of hierarchic regulation with a differing fraction of the autonomous nature of functioning at different levels of the complicated dynamic system.

The homeostasis of glucose is maintained with a constant reaction of insulin and glucagon. The direct effect of these hormones is realized via cAMP.

An important principle of glucose homeostasis is the stable activity of the insular apparatus. On the one hand, fluctuations of the glucose level in the blood both excite and inhibit the insular apparatus of the pancreas, while on the other hand they stimulate the functioning of the adrenal glands and hypophysis. It is exactly hypoglycemia that is a powerful factor in activating the function of the adrenal glands with the discharge of catecholamines and contrainsular hormones.

It was shown in a number of experiments that even without regulation by the hypophysis and adrenal glands, the liver is an important regulating factor (ensuring a constant glucose level in the blood) that maintains the homeostasis of glucose in an organism [316, 384, 559, 574].

Clinical observations showed that chronic hepatitis and hepatic cirrhosis are characterized by pronounced dystrophic, necrobiological and necrotic processes in its parenchyma that lead to the replacement of the main part of its functional elements with connecting tissue. Such a liver extracts less insulin from the blood of the vena porta as a result of lowering of the specific binding. The latter is the only factor causing the degradation of insulin. This is why the development of hyperinsulinemia with lesion of the liver can be explained primarily by the lowering of the degradation of this hormone. The relation between lesion of the liver and hyperinsulinemia, and also insulin resistance may be due to the following factors [77, 137, 148, 271, 301, 365]:

- (1) a drop in the number of functionally active cell elements in the liver;
- (2) lowering of the glycogen-forming function of the liver (accordingly a high level of glycemia after taking food and a drop in the tolerance to glucose);
- (3) diminishing of the volume of the liver parenchyma (this results in hyperinsulinemia);

(4) a growth in the secretion of insulin in response to pronounced glycemia after the taking of food.

1.2.2. Syndrome X and Its Clinical Manifestations

Syndrome X is based on metabolic disorders that can be revealed only in laboratory studies. Clinical symptomatology forms in time, i.e. well known metabolic diseases, namely, hypertension, atherosclerosis, and obesity.

DM, arterial hypertension, and hypercholesterolemia are undoubted risk factors of cardiovascular diseases, while according to Modan *et al.*, hyperinsulinemia is the main element combining obesity, DM, and arterial hypertension.

Major prospective investigations conducted recently by Haffner *et al.* [225] and devoted to the observation for many years of persons with metabolic disorders revealed that hyperinsulinemia is what can predetermine other metabolic disturbances that are risk factors in the appearance of cardiovascular diseases. They proposed using the term "insulin resistance syndrome" instead of metabolic syndrome (syndrome X) [32, 58, 70, 431, 460, 558].

We revised somewhat and supplemented the scheme proposed by DeFronzo [111]. Insulin resistance was shown to precede atherosclerosis, dyslipidemia, and hypertension (see Fig. 6). It is apparently expedient to note the influence of insulin resistance on the development of obesity and DM. According to Reaven, only the active function of beta cells normalizes carbohydrate metabolism in insulin resistance, i.e. the latter is a state of relative insulin insufficiency when hyperglycemia (or disturbance of the tolerance to glucose) is combined with a high insulin level in the blood (hyperinsulinemia). At the same time, when such patients are stimulated with glucose, an increased sensitivity of the insular apparatus of the pancreas is noted. Lowering of the sensitivity of tissues to insulin is the pathogenetic basis of this relative insulin insufficiency. Insulin resistance of the tissue is what leads to compensatory hyperinsulinemia. The variant of the formation of relative insulin insufficiency into absolute insufficiency is quite possible, when the compensating possibilities of the beta cells of the pancreas are exhausted [302, 303, 476, 542, 558, 595].

The reason for the development of insulin resistance still remains to be established completely. One can think of the existence of many mechanisms leading to the development of relative insulin insufficiency. They include (i) a change in the chemical structure of the insulin, (ii) disturbance of the transformation of proinsulin into insulin, (iii) the increased secretion of insulin antagonists into the blood (as noted previously), and (iv) the formation of antibodies to insulin or disorder of the function of the insulin receptors.

There are currently little proofs of the disturbance of the chemical structure of insulin, and also of the change in the transformation of proinsulin into insulin.

A major role in the appearance of insulin resistance is played by the state of the receptors and the mechanisms of the postreceptor effect of insulin. Moreover, as already noted, stimulation by glucose increases the sensitivity of the beta cells of the pancreas [314, 358, 515, 574, 584].

Insulin resistance is often accompanied not only by hyperinsulinemia, but also by disturbance of the tolerance to glucose and by basal glycemia. Overstressing of the function of the pancreas beta cells results in their exhaustion, and absolute insulin insufficiency appears.

Relative insulin insufficiency is characterized by improper carbohydrate metabolism, and it also leads to a change in lipid metabolism.

Insulin has a powerful antilipolytic effect. It stimulates lipogenesis processes and acts like an antagonist of hormones ensuring lipolysis. Insulin increases the permeability of the plasmatic membranes of the lipocytes and ensures the delivery of glucose into adipose tissue.

Insulin plays a quite important role in the genesis of dyslipidemia. It is one of the main factors regulating fat metabolism and facilitating lipogenesis. The inverse relation between the content of HDLP in the blood and insulinemia was indicated previously. In persons with increased HDLP content in the plasma, hyperinsulinemia is a lower risk factor of cardiovascular diseases. A growth in the insulin content in the plasma increases the synthesis of VLDLP leading to the development of hypertriglyceridemia, i.e. hyperinsulinemia or insulin resistance or both combine with the atherogenic nature of the blood plasma [56, 91, 238, 267, 302, 313, 345].

Triglycerides play an important role in the regulation of insulin sensitivity. We found that in healthy persons the concentration of insulin and level of the free fatty acids correlate negatively with the metabolism of triglycerides, i.e. there is a relation between the decomposition of the latter and the resistance of an organism to insulin. A growth in the concentration of the FFA in the plasma in obesity facilitates the development of insulin resistance.

Recent experimental studies showed that brief hyperlipidemia stimulates, and prolonged hyperlipidemia inhibits the glucose-stimulated secretion of insulin. The inhibition is specific only for glucose and evidently associated with the oxidation of the FFA and also with the reduced oxidation of glucose. All these changes occur both under normal conditions and in hyperglycemia [253, 264, 281, 330].

Thus, when the triglyceride content in the blood plasma grows, redistribution of the assimilation in an organism of the main energy substrates – glucose and lipids – occurs, and the content of insulin in the plasma therefore depends on the state of the energy balance and initial level of these substrates in the plasma.

Insulin resistance was shown to have a metabolic nature with an accompanying growth in the FFA level in the plasma, i.e. substrate competition plays a role in the mechanism of its development. When fat is introduced, insulin does not alter the glucose oxidation process. Redistribution of the assimilation of the glucose in a cell occurs. According to Thorburn *et al.* [573], both hyperinsulinemia and hyperglycemia stimulate the assimilation of glucose and increase the intracellular metabolism of glucose at the expense of the increase in its accessibility as an energy substrate. However, insulin also regulates the oxidation of glucose by suppression of the formation of FFA and the metabolism of fats.

Nevertheless, with the maximum suppression of the formation of FFA and the oxidation of fats, the paths of intracellular metabolism of glucose are determined to a greater extent by the rate of absorption of glucose than by the level of insulin [120, 280, 341, 358, 431, 576].

Lowering of the rate of intracellular oxidation of glucose in IIDM (without obesity) occurs independently of lowering of the rate of glucose utilization by the tissues and of the intracellular absorption of fat.

The activity of the glycolysis enzymes also depends on the level of the free fatty acids in the blood. Randle's glucose-fatty acid cycle coordinates biochemically the reaction of glucose and fatty acids. For example, in fasting, when the content of glucose in the blood diminishes, fatty acids are mobilized from the adipose tissue because of a growth in lipolysis. As a result, the concentration of the FFA in the blood grows together with their oxidation in the muscles.

It was shown in experiments that the FFA block glycolysis in the stages of its regulation. There is an inversely proportional relation between the level of FFA in the blood and the activity of hexokinase. Moreover, the FFA inhibit the oxidation of pyruvate in the Krebs cycle and simultaneously increase the production of glucose in the liver, activate the pentosophosphate path of glucose metabolism.

There are thus a number of factors regulating individual units of carbohydrate metabolism. However, the chief role in this process undoubtedly belongs to insulin [137, 310, 449, 472, 498, 601].

Consequently, we can note (see Figs. 5-7) that the formation of an insulin resistance syndrome is an integrative process including both genetically determined defects of metabolism (carbohydrate and lipid metabolism) and acquired pathological syndromes

(obesity and hyperinsulinemia). An important result of these metabolic disorders is the growth in the content of VLDLP and LDLP in the blood, and also the drop in the level of HDLP. These disorders of lipid metabolism cause the development of IHD, atherosclerotic changes in the vessels of the brain and lower extremities. Hyperinsulinemia leads to disturbance of the resorption of sodium ions, an increase in the activity of the sympathetic nervous system, and to development of hypertension. Hypertrophy of the smooth muscle cells of the arteries is a morphological manifestation of these metabolic disorders [49, 75, 87, 133, 271, 284, 314].

Considering the great significance of insulin resistance in the formation of syndrome X, we studied the sensitivity to insulin of 10 healthy persons and 15 youths with obesity of a hypothalamic and hypophyseal genesis. To appraise the state of the insulin resistance, we ran a test with insulin that was introduced in a dose of 0.15 units per kg of body weight. The insulin test reveals most vividly the sensitivity of receptors to insulin and disorders of carbohydrate metabolism. It was proved biochemically that glucose is a very important regulating factor of physiological homeostasis. In different organs and tissues, glucose is transported by various biochemical structures. For example, in adipose tissue, the transportation of glucose is associated with two glycoproteins. In the brain, apart from transmembrane cell transportation, there is a system of stereospecific vectors through the capillaries of the hematoencephalic barrier that carry glucose from the blood into the tissues. In human erythrocytes, the vector of glucose is a protein with a molecular weight of 55,000 and a high lipid and carbohydrate content. Numerous biochemical studies revealed that the rate of glucose transportation correlates without fail with its intracellular metabolism. The level of the latter is determined by the amount of glucose oxidized to CO_2 and by the biosynthesis of lipids in isolated lipocytes [96, 111, 131, 153, 213, 258].

After the introduction of insulin in healthy persons, a physiological drop in the glucose level in the blood plasma was noted from 4.88 mmol/l (background) to 2.04 mmol/l in 30 min. The glucose level gradually increased to 3.6 mmol/l (in 60 min), and after 120 min returned to its initial level (4.6 mmol/l). A similar reaction proceeds in erythrocytes: the background amount of glucose was 3.4 mmol/l; in 30 min after the introduction of insulin, the glucose level dropped to 1.55 mmol/l; in 60 min it increased to 2.4, and in 120 min returned to the background figures of 3.5 mmol/l (Fig. 8).

An absolutely different picture was observed in the obesity patients, namely, a background value of 5.1 mmol/l of glucose in the blood plasma and 3.6 in the erythrocytes. After the introduction of insulin, the glucose level did not practically lower. In 30 min, the glucose content in the plasma diminished to 4.5 mmol/l, and in the erythrocytes to 3.1. In 60 min, the glucose level in the plasma increased to 4.8, and in erythrocytes to 3.4;

Fig. 8. Change in Glucose Content in the Blood When Conducting an Insulin Test in Patients with Obesity.

in 120 min it returned to the initial values – 5.26 mmol/l in the plasma and 3.7 in the erythrocytes.

The results indicate disturbance of carbohydrate metabolism in the obesity patients and the development of the insulin resistance syndrome in patients with a dysfunction of lipid metabolism. Hyperinsulinemia undoubtedly plays an important role in these pathological shifts.

Currently, numerous experimental and clinical data confirmed the influence of hyperinsulinemia on the development of atherosclerosis of the coronary vessels.

Most authors consider hyperinsulinemia to be another independent risk factor like hypercholesterolemia and arterial hypertension. When studying the pathophysiological fundamentals of hyperinsulinemia, our goal was to see whether hyperinsulinemia is associated with ischemia of the tissues in atherosclerosis or with disorder in the permeability of the pancreas arteries. Clinical and experimental investigations showed that there is no relation between lesion of the pancreas arteries and hyperinsulinemia. The latter is a precursor of the development of IHD, and not a secondary factor. This reasoning is based on numerous studies in populations with a varying frequency of atherosclerosis development. During many years of observations of patients with a high insulin level in the blood, it was shown that IHD develops in them much more frequently than in persons not having such a level, and that an increased basal level of insulin makes it possible to predict the development of IHD in the future. The course of atherosclerosis and the degree of manifestation of

Fig. 9. Change in Glucose and Insulin Content in the Blood when Conducting an Insulin Test in Patients with IHD.

IHD symptoms depend to a considerable extent on the increased content of insulin in the blood plasma [289, 305, 400, 437, 469, 495, 547].

Hyperinsulinemia plays a very important role in the development of syndrome X. This is confirmed by a number of investigations in which it was shown that the biochemical adaptation of an organism to the effect of external extremal factors is closely related to the reactivity of the endocrine system of an organism, including its sensitivity to insulin.

When comparing these experimental results with clinical data on the diagnosis of disorders of insulin metabolism in IHD patients, we determined the sensitivity to insulin of the glucose in the blood plasma in erythrocytes in healthy persons and IHD patients. The

insulin test, which determines the sensitivity of glucose to the action of insulin, is the most successful model. We ran it with 52 healthy persons and 31 IHD patients. First we determined the initial level of glucose and insulin in the blood plasma and in the erythrocytes, and then measured these parameters in 30, 60, and 120 min after the introduction of insulin (Fig. 9). In healthy persons, the introduction of insulin caused a clear physiological change in the glucose level. The background level of glucose in the blood plasma was 4.82 mmol/l, in the erythrocytes was 3.78, the initial insulin concentration in the blood plasma was 14.5, and in the erythrocytes was 146.8 $\mu\text{U}/\text{ml}$. In 30 min after the introduction of insulin, hypoglycemia appeared in the plasma (3.05 mmol/l) and in the erythrocytes (2.09 mmol/l). The insulin level in plasma grew to 41.0 $\mu\text{U}/\text{ml}$, and in the erythrocytes to 226.0 $\mu\text{U}/\text{ml}$. In 60 min, the hypoglycemia diminished – the glucose content in the blood plasma increased to 3.9 mmol/l, and in the erythrocytes to 3.1. The insulin level in the plasma increased somewhat (up to 53.3 $\mu\text{U}/\text{ml}$), and lowered in the erythrocytes (to 203.4 $\mu\text{U}/\text{ml}$). In 120 min. all the parameters approached the background values.

In the IHD patients who were given the insulin test, the background values of the glucose and insulin increased. The glucose level in the blood plasma was 5.13 mmol/l, and in the erythrocytes was 3.56 mmol/l. The hyperinsulinism syndrome was very pronounced: the level of insulin in the blood plasma increased to 22.6 $\mu\text{U}/\text{ml}$ (in healthy persons it was 14.5 $\mu\text{U}/\text{ml}$), and in the erythrocytes to 182.9 (in healthy persons it was 146.8 $\mu\text{U}/\text{ml}$).

What are these changes associated with?

Many clinicians consider that in IHD a relative insulin insufficiency is often noted with an increase in the glucose level in the blood and with hyperinsulinemia.

Insulin increases the consumption of oxygen in the cells of the internal membrane of vessels, and its local hypoxia is possible with a subsequent increase in the lipid content in it. Of major significance is the presence in IHD patients of insulin resistance, the increased discharge of glucocorticoids being one of its causes.

Clinicians proved the stimulating influence of glucose on the secretion of insulin.

What is the pathophysiological mechanism of this stimulation?

Two theories appeared to answer this question, namely, the glucoreceptor and the metabolic ones. The first theory postulates that glucose binds with the specific membrane receptors of the beta cells which send information to the mechanisms releasing insulin. The adherents of the second theory consider that insulin is stimulated not by glucose itself, but by its direct and more remote metabolites [87, 113, 205, 280, 301, 358, 596].

A major role in the mechanism of the stimulating effect of glucose on insulin secretion is given to cAMP. Experiments showed that substances stimulating or inhibiting the decomposition of cAMP correspondingly inhibit or stimulate insulin secretion. The

cAMP activates proteinkinase – an enzyme catalyzing the phosphorylation of definite function proteins. The results of endocrinological studies indicate that STH stimulates the secretion of insulin and has a certain influence on biosynthesis [145, 157, 223, 259, 269, 324].

There was an opinion that hormones enter a cell by diffusion. Recent studies showed the intracellular penetration of hormones to be a very involved biological process, and an equality sign cannot be placed between the concentration of the hormone in the blood and the efficiency of its biological effect.

Analysis of the change in the glucose and insulin content in the blood of IHD patients after the introduction of insulin showed substantial differences between these parameters in healthy and ailing persons and also the presence of insulin resistance in patients with syndrome X and IHD. If in healthy persons in 120 min the background level of glucose is restored, in IHD patients in 60 min it increased, while in 120 min the glucose content authentically exceeded the background level, being 5.56 mmol/l. The hyperinsulinemia syndrome stood out very clearly in IHD patients: in the plasma in 30 min the insulin level increased from 22.6 to 48.3 $\mu\text{U/ml}$, and in the erythrocytes from 182.9 to 330.0 $\mu\text{U/ml}$. In 60 and 120 min. these quantities gradually became smaller, but a trend to hyperinsulinemia and insulin resistance (inhibited hypoglycemia) was preserved.

The close relation between hyperinsulinemia and the development of atherosclerosis was proved morphologically. It was established in experiments on animals that the artery wall is a tissue very sensitive to insulin. It was noted that insulin ensures proliferation of the cells in the smooth muscles of arteries, and also increases the synthesis of lipids. Experiments with isolated arteries showed insulin to stimulate the growth of a culture of fibroblasts [447, 469, 491, 505].

1.2.3. Obesity and the Syndrome X

The disturbance of fat metabolism – obesity – is another important metabolic disorder that stimulates the development of syndrome X. Its incidence is based on involved mechanisms leading to a change in lipid metabolism.

Clinicians noted long ago that DM is encountered most frequently in persons with obesity, and the metabolism of carbohydrates and fats is disturbed in them. Biochemists showed adipose tissue to be the main object in which insulin transforms carbohydrates into fats [51, 75, 87, 115, 128, 171].

How does this occur?

Major importance is attached to hereditary factors in the development of obesity (in particular, an increased amount of fat cells and a changed nature of the hypothalamic

function is transmitted from generation to generation), and also to disturbance of processes of tissue metabolism. Clinical studies of obesity patients showed the presence of hypertrophy of fat cells, their inadequate metabolic adaptation with lowered oxidation in the Krebs cycle, a lower activity of the lipolytic enzymes, and an increased content of the atherogenic fractions of the blood. Biochemical investigation of the blood of obesity patients indicated an increased content of lactate, pyruvate, and betaglycerophosphatedehydrogenase. The clinical relation between obesity and the development of DM is of special importance. Most scientists consider that 60% of DM patients also suffer from obesity. Generally in about 50% of obesity patients, a disturbed tolerance to carbohydrates is determined. We must stress that the presence of hyperinsulinism and also disturbance of the secretion and deposition of insulin are noted in obesity patients.

The pathophysiological interpretation of the increased insulin level in obesity consists in that most clinicians associate it with the resistance to the effect of endogenous insulin, an increase in the volume of the fat cells, and disturbance of metabolism (e.g. lipid metabolism), and also with a growth in the content of uric acid [38, 472, 561, 585, 596, 604]. We must note improper fat metabolism in obesity patients, in particular a growth in the level of NEFA. A biochemical relation was established between a growth in the level of NEFA and the insulin content. It is considered that an increased amount of NEFA inhibits the stimulating influence of insulin on the assimilation of glucose by tissues, and this results in the development of a state of hyperinsulinism. Simultaneously, an increased glucocorticoid activity of the adrenal cortex is noted in obesity patients.

Hyperinsulinemia with a view to its influence on lipid metabolism may enhance the course of cardiovascular diseases.

To prove the relation between obesity and hyperinsulinemia, we studied the tolerance to glucose of 10 healthy persons and 35 youths with obesity (Table 3). The average values of the anthropometric parameters in the group of obesity patients was height – 178.4 cm, body weight – 99.03 kg, and body surface area 2.17 m².

Clinically, the obesity patients exhibited first of all an increased appetite, emotional instability, irritation, disturbance of sleep, fatigue, pains in the joints and muscles, thirst. Auscultation of the heart showed tonelessness. Moreover, an increased arterial pressure was established.

The obesity patients were divided into two groups depending on the degree of obesity. Group 1 included 15 patients (BWI=25.0–30.0) and group 2 included 20 (BWI=30.1–35.0). There was a clear difference in the groups in the insulin content after the introduction of glucose. Pronounced hyperinsulinemia was noted in the obesity patients. If in healthy persons the background value of the insulin was 5.3 µU/ml, in obesity group 1 it

Table 3. Results of Test for Tolerance to Glucose in Obesity Patients.

Group	Glucose, mmol/l			IRI, μ U/ml		
	background	in 1 h	in 2 h	background	in 1 h	in 2 h
Control	3.7 $\pm$ 0.4	6.8 $\pm$ 0.6 ^a	3.9 $\pm$ 0.3 ^b	5.3 $\pm$ 0.7	14.2 $\pm$ 3.8 ^a	4.8 $\pm$ 0.5 ^b
1 st	3.9 $\pm$ 0.3	6.6 $\pm$ 0.4 ^a	4.4 $\pm$ 0.6 ^b	15.5 $\pm$ 3.6 ^c	53.5 $\pm$ 8.4 ^{a,c}	36.0 $\pm$ 8.6 ^{a,c}
2 nd	4.0 $\pm$ 0.3	6.3 $\pm$ 0.5 ^a	4.1 $\pm$ 0.3 ^b	16.9 $\pm$ 1.5 ^c	91.8 $\pm$ 11.4 ^{a,c,d}	59.7 $\pm$ 16.3 ^c

The difference of the parameters is authentic:

^a at the given time and before the load;

^b at the given time and in one hour after the load;

^c in the given and control groups;

^d in the given group and in group 1.

was 15.5 and in group 2 – 16.9 μ U/ml. After a glucose load, the insulin content increased, namely, in healthy persons to 14.2 μ U/ml, in group 1 patients to 53.7 and in group 2 to 91.8 μ U/ml. A slow drop in the insulin level was noted in two hours after the introduction of glucose. If in the healthy persons it returned to the normal value (4.8 μ U/ml), in group 1 patients it was 36.0 μ U/ml (the background was 15.5) and in group 2 it was 69.7 (the background was 16.9 μ U/ml).

These comparisons show that hyperinsulinemia and obesity are mutually related metabolic disorders in obesity patients.

Experimental results obtained by Stout indicate that chronic hyperinsulinemia leads to the development of systemic atherosclerosis because of the proliferation of the smooth muscle and connecting tissue membranes of an artery wall stimulated by insulin.

It is shown that if glucose is perfused as a substrate in combination with insulin, the greatest amount of triglycerides are synthesized in an artery wall. We already noted that insulin increases the consumption of oxygen in the intima cells of human vessels. This, in turn, leads to development of the rigidity of the intima, narrowing of the lumen of an artery and arterioles over a considerable length, a growth in the total peripheral resistance, and to development of hypertension with subsequent hypertrophy of the myocardium. Cardiovascular pathology forms in this way, and one of its pathogenetic units is hyperinsulinemia or insulin resistance, or both, enhanced by DLP. Hyperinsulinemia and disturbance of the tolerance to glucose may be attended by the development of DM that affects adversely the course of cardiovascular diseases. Their prophylaxis requires early diagnosis of metabolic disorders [97, 111, 145, 166, 222, 243].

Consequently, metabolic disorders closely related to hyperinsulinemia underlie syndrome X whose inheritance is doubtless, while its pathogenetic mechanisms lead to the development of clinical symptomatology of many metabolic diseases.

The metabolism of adipose tissue and the secretion of insulin are closely related to the vegetative nervous system. The hypothalamic structures and adipose tissue are the points of their contact. Catecholamines are a very important regulator unit in the metabolism of adipose tissue. The FFA content in the blood is regulated by adrenaline and noradrenaline, which via the beta-1-adrenergic receptors stimulate lipolysis in the adipose tissue. The influence of catecholamines is very important. Through the system of cAMP they activate the hormonesensitive lipase that catalyzes triglycerides to free fatty acids and glycerol [237, 248, 281, 328, 396, 524].

The lipolytic effect of the catecholamines is achieved because of their simultaneous inhibition of insulin secretion via the alpha-adrenoreceptors.

Adipose tissue is one of the largest target tissues for catecholamines in an organism whose innervation is represented exclusively by adrenergic endings. The central vegetative centers and adrenal glands regulating the content of neuromediators and hormones play a substantial role in maintaining the FFA level in the blood.

The interaction of insulin and the sympathetic nervous system at the level of the hypothalamic structures is based on their possibilities of affecting diet-dependent thermogenesis (DT). Fasting suppresses, while the taking of carbohydrate or fat food stimulates the activity of the central structures of the SNS owing to the metabolism of glucose in the intermediate region of the hypothalamus (the ventromedial nucleus) promoted by insulin. The taking of carbohydrates and the growth in the content of glucose and insulin boost the metabolism of glucose in the nuclei of the hypothalamus. This results in deactivation of the inhibitor path connecting the ventromedial nucleus of the intermediate region of the hypothalamus to the central sympathetic structures increasing sympathetic activity [19, 237, 534, 567, 616].

Under conditions of the normal sensitivity of tissues to insulin, the growth in the activity of the SNS increases DT and thus helps retaining the energy balance withstanding the storage of a surplus amount of energy in the form of fat and helping its liberation in the form of heat.

We can assume that obesity develops when consuming a surplus amount of food combined with disturbance of DT. We already indicated that with an excessive body weight, insulin resistance appears as a sort of protective mechanism preventing its further increase. Under conditions of insulin resistance, the SNS as a means of restoring energy equilibrium cannot be stimulated normally by insulin. The physiological price of such a compensating mechanism is the increasing hyperinsulinemia and stimulation of the SNS, which subsequently facilitate the development of arterial hypertension [328, 400, 436, 447, 469, 488].

To verify our assumptions on the change in vegetative regulation in obese youths, we compared the excretion of adrenaline, noradrenaline (NA), dihydroxyphenylalanine (DOPA), and dopamine during various times of the day (9 a.m.–12 p.m., 12–3 p.m., 3–7 p.m., and 7 p.m.–9 a.m.) and the change in the level of catecholamines after the introduction of alpha-DOPA (Fig. 10). We studied two groups of youths 16–18 years old suffering from various degrees of obesity (the first group with a BWI of 25.1–30.0 and the second with a BWI of 30.1–35.0). The ratio of the waste circumference to the volume of the hip in group 1 was 0.94 ± 0.02 , and in group 2 was 0.93 ± 0.02 , thus exceeding the generally adopted critical value of 0.9 for men. The results were compared with those for healthy youths of the same age. We compared the levels of IRI and cortisol in these groups. We clearly established the presence of hyperinsulinemia in the obese youths. In the healthy ones, the IRI level was $5.1 \mu\text{U/ml}$, in group 1 (with obesity) it was 13.0, and in group 2 it was $15.7 \mu\text{U/ml}$. The cortisol content also differed: in healthy youths it was 659.9, and in obese patients it was 724.4 nmol/ml.

The results of determining the daily rhythm of excretion of catecholamines and their precursors with the urine in the studied groups indicated an authentic drop in the excretion of adrenaline, dopamine, DOPA in the evening (3–7 p.m.) and at night (7 p.m.–9 a.m.) with moderate obesity (BWI=25.1–30.0) and a drop in the excretion of adrenaline, NA, dopamine, and DOPA in the evening and at night with pronounced obesity (BWI=30.1–35.0). In the healthy youths, a similar daily rhythm was observed only for adrenaline and DOPA.

When comparing the parameters of catecholamine excretion with the urine in youths of the control group and in patients with moderate obesity, we established an authentic drop in the excretion of dopamine at night (182.3 ± 4.02 and $128.8 \pm 17.7 \text{ ng/min}$) and an authentic increase in the excretion of NA in the morning (6.1 ± 0.9 and $12.9 \pm 1.7 \text{ ng/min}$). With a pronounced degree of obesity, we also observed an authentic drop in the night excretion of dopamine in comparison with that in healthy persons (128.3 ± 4.02 and $122.2 \pm 9.3 \text{ ng/min}$), while the excretion of NA authentically exceeded the value in the control group both in the morning (6.1 ± 0.9 and $12.8 \pm 1.8 \text{ ng/min}$) and at night (5.1 ± 0.4 and $7.7 \pm 1.1 \text{ ng/min}$).

The established trend of an increase in the excretion of adrenaline and DOPA with the urine in obesity in comparison with excretion in healthy persons is not authentic owing to the high variability of the individual values.

Fig. 10. Daily Excretion of Catecholamines with the Urine in Persons with a Various Degree of Obesity.

To estimate the synthesizing and reserve possibilities of the sympathico-adrenal system, we studied the excretion of catecholamines and their precursors with the urine with the use of the functional test with alpha-DOPA proposed by Vasiliev and Chugunov. The excretion of NA during the first three hours after taking 0.1 g of alpha-DOPA creased authentically by 964.8% in group 1 and by 387.5% in group 2 in comparison with 2294%

Table 4. Excretion of Noradrenalin with Urine after Taking Alpha-DOPA.

Noradrenaline, ng/min	Morning, 9 am–12 pm	Noon, 12 pm–15 pm	Evening, 15 pm–19 pm	Night, 19 pm–9 am
Control group				
Background	6.13±0.94	7.78±1.51	4.99±0.98	5.12±0.42
After taking α-DOPA	146.75±21.36 ^a (+2294%)	27.22±10.34 (+250%)	11.90±3.44 (+138%)	4.97±0.66 ^c (-2.9%)
1st group				
Background	12.96±1.67	12.27±3.17	9.09±2.17	9.82±3.39 ^c
After taking α-DOPA	138.0±30.92 ^a (+964%)	48.8±10.78 ^{a,b} (+298%)	16.43±3.17 ^c (+80.7%)	6.79±1.5 ^c (-30.9%)
2nd group				
Background	12.79±1.82	15.29±1.47	9.75±1.07 ^c	7.71±1.08 ^c
After taking α-DOPA	49.56±9.97 ^a (+387%)	47.73±7.27 ^a (+212%)	16.01±3.58 ^c (+64.2%)	7.86±1.43 ^{d,e} (+1.9%)

The difference of the parameters is authentic:

^a before and after taking α-DOPA;

^b in the daytime and in the morning;

^c in the evening and in the daytime;

^d at night and in the evening;

^e at night and in the morning.

in healthy youths (Tables 4 and 5). Similar dynamics were registered with respect to adrenaline, namely, an authentic increase by 86.7% in group 1 in comparison with 112.8% in the control group. With pronounced obesity, an authentic growth in the excretion of adrenaline after the introduction of alpha-DOPA was not established authentically.

Inspection of Tables 4 and 5 reveals that there is a clear relation between the degree of obesity and the metabolic disorders.

The adaptation of the organism of animals and humans to oxygen fasting (hypoxia) was studied by many authors. Experiments with animals showed that adaptation to hypoxia occurs with a sharp intensification of anaerobic glycolysis with a growth in the concentration of lactic acid in the blood and an increase in the lactate/pyruvate ratio. The lactic acid level is a very important criterion of adaptation of an organism under conditions of hypoxia, and its increased level under these conditions is inversely proportional to the physical workability of a person. Persons with a high level of anaerobic glycolysis have a high ratio of the content of lactic acid to the level of pyruvic acid [37, 64, 109, 125, 591, 554, 601, 608].

The relation between the glucose level in the blood and the absorption of glucose by the myocardium was studied by many authors, mainly experimentally. It was found under clinical conditions that glucose is used in glycolysis for supporting anaerobic metabolism. It was proved experimentally that the rate of absorption of glucose by the cardiac myocytes from the extracellular space is limited by the rate of tissue transportation of glucose through a cell membrane. There is a clear relation between the rate of transportation and that of absorption of glucose under the influence of insulin, and also under conditions of hypoxia. Much attention in the experiments was devoted to studying glycolysis, i.e. the decomposition of glucose and glycogen in the myocardium, when lactate forms under anaerobic conditions. In normal oxidative metabolism, glycolysis results in the formation of pyruvate, which under aerobic conditions decomposes in the Krebs cycle. Under anaerobic conditions, glycolysis is the only source of ATP. In the absence of oxygen, the rate of glycolysis grows several times owing to the Pasteur effect. In deciphering the biochemical essence of the Pasteur effect, we can say that it consists in an increase in the rate of lactate formation under anaerobic conditions. When an animal inhales a hypoxic mixture, the rate of glucose absorption grows, and instead of the absorption of lactate by the myocardium (which occurs under normal conditions), the emergence of lactate from the cardiac myocytes is observed.

In confirming the significance of glycolysis in the energy metabolism of the myocardium, we must note that the main role in regulating the rate of glucose absorption by the myocardium cells is played by the rate of glucose transportation. The latter may change (grow) under the effect of insulin, and also under conditions of hypoxia. Here the flow of substances grows because of the higher activity of phosphofructokinase that limits the total rate of glycolysis. Under aerobic conditions with a normal oxygen concentration, pyruvate entering the Krebs cycle is the final product of glycolysis. Under anaerobic conditions, lactate is the final product of glycolysis. In moderate ischemia of the myocardium, the rate of glycolysis grows. The myocardium utilizes lactate in a conventional quiet situation, absorbing 10% of oxygen from the entire oxygen of the air. If much work is being done, the oxygen consumption grows to 60%. The lactate and FFA compete for the oxygen absorbed by the myocardium in connection with the fact that each of these compounds may be the main nutritive substance depending on its level in the blood. The main metabolic paths of pyruvate transformation are aerobic oxidation with the aid of pyruvate dehydrogenase and in the citric acid cycle, and anaerobic transformation into lactate [83, 114, 206, 277, 346, 486, 619].

What is the increased level of pyruvic acid in the blood associated with?

Table 5. Excretion of Adrenalin with Urine after Taking Alpha-DOPA.

Adrenalin, ng/min	Morning, 9 am–12 pm	Noon, 12 pm–15 pm	Evening, 15 pm–19 pm	Night, 19 pm–9 am
Control group				
Background	5.31±1.01	5.68±1.98	4.53±1.19	2.67±0.43 ^a
After taking α-DOPA	11.30±1.53 (+112.8%)	8.44±2.75 (+48.6%)	3.21±0.62 (-29.2%)	1.82±0.37 ^{a,c} (-31.8%)
1 st group				
Background	9.24±2.24	6.58±1.08	6.79±2.89	6.06±1.78 ^d
After taking α-DOPA	17.25±6.49 ^a (+86.7%)	10.72±1.65 ^a (+62.9%)	5.46±0.85 ^c (+19.6%)	2.63±0.51 ^{a,d,e} (+56.6%)
2 nd group				
Background	6.34±1.24	9.35±1.48	5.04±0.72 ^c	6.52±1.96
After taking α-DOPA	8.33±1.23 (+31.4%)	10.20±1.29 ^b (+9.1%)	4.66±1.01 ^c (-7.5%)	4.98±1.29 (-23.6%)

The difference of the parameters is authentic:

^a before and after taking α-DOPA;

^b in the daytime and in the morning;

^c in the evening and in the daytime;

^d at night and in the evening;

^e at night and in the morning.

The authenticity of the difference of background levels in two groups is not determined.

In the oxidation of pyruvate by oxidative phosphorylation, ATP forms, and the pyruvate level drops accordingly. If a high level of pyruvic acid is preserved, this indicates that the formation of ATP in the Krebs cycle is inhibited.

Under anaerobic conditions, glycolysis proceeds with the participation of a large number of enzymes. The glucose decomposes into pyruvic acid. The following are the basic biochemical stages of glycolysis:

1. Glucose $\xrightarrow{\text{Hexokinase}}$ Glucoso-6-phosphate + ADP-ATP
2. Fructoso-6-phosphate $\xrightarrow{\text{Phosphofructokinase}}$ Fructoso-1,6-biophosphate + ADP-ATP
3. Phosphoenolpyruvate + ADP $\xrightarrow{\text{Pyruvatekinase}}$ Pyruvate + ATP

It was noted in experiments that insulin affects the activity of glycolysis under anaerobic conditions: under the influence of insulin glycolysis grows, while with a lack of it (especially in DM patients) it weakens drastically. The biochemical effect of insulin is

Table 6. Results of an Insulin-Tolerance Test in Practically Healthy Persons.

Glucose, mmol/l		STH, ng/ml	
background	in 30 min	background	in 30 min
4.71	4.44	2.80	62.00
4.40	3.20	1.30	5.10
2.39	1.68	0.40	7.40
3.85	2.77	0.80	2.10
5.55	4.44	0.87	16.20
5.05	3.80	1.40	32.00
4.99	3.60	1.45	25.00
5.55	5.05	0.33	32.00
5.05	4.05	0.75	46.00
4.71	4.44	2.40	52.56

directed at the enzymes hexo(gluco)kinase, phosphofructokinase, and pyruvatekinase [86, 144, 189, 271, 333, 364].

We consider that in this disorder of metabolism an important role is played by insulin resistance, with the simultaneous existence of hyperinsulinemia and hyperglycemia. Consequently, the presence of insulin resistance is confirmed clearly.

How can we prove the presence of insulin resistance in obesity patients?

To solve this problem, we compared the results of an insulin-tolerance test in healthy persons and obesity patients. We selected 10 healthy persons (without dyslipidemia) and 15 patients with obesity caused by adolescent pituitarism. In all the persons, we determined the glucose level before the introduction of insulin and in 30 min after its introduction. We obtained the following results (Tables 6 and 7): in healthy persons, the glucose level dropped quite clearly after the introduction of insulin. Of 10 healthy persons, considerable hypoglycemia was noted in 7. This points to the good reaction of the receptor apparatus to the introduction of insulin. We noted an absolutely different picture in the 15 obesity patients. In three of them, moderate hypoglycemia could be noted. In 10 patients, the glucose level either increased or did not change. The dynamics of the STH level varied.

What is the pathophysiological basis of these disorders in the sensitivity of obesity patients to insulin?

We must stress first of all the fact that we noted hyperinsulinemia in the obesity patients. Numerous clinical and experimental studies showed that very often the disturbance of the tolerance to glucose combined with hyperinsulinemia. It is the insulin resistance of the tissues that leads to the development of compensating hyperinsulinemia. Many

Table 7. Results of an Insulin-Tolerance Test in Obesity Patients.

Glucose, mmol/l		Relative change	STH, ng/ml		Relative change
back-ground	in 30 min		back-ground	in 30 min	
4.39	4.78	+1.09	0.22	6.86	+30.60
5.06	4.28	-1.18	0.20	1.12	+5.57
5.11	5.22	+1.02	0.28	1.60	+5.79
4.44	4.94	+1.11	0.151	0.149	-1.01
4.44	5.11	+1.15	0.25	1.06	+4.24
3.83	3.72	-1.03	0.32	0.22	-1.46
4.78	4.39	-1.09	0.61	1.10	+1.80
4.56	3.56	-1.28	0.52	0.55	+1.05
4.44	4.17	-1.06	1.12	0.42	-2.65
5.44	3.39	-1.61	0.30	2.31	+7.78
3.94	3.61	-1.09	0.67	12.67	+18.94
4.28	4.22	-1.01	0.34	0.32	-1.04
4.28	4.78	+1.12	0.50	1.16	+2.31
4.00	5.39	+1.35	0.18	0.15	-1.18
4.89	5.22	+1.07	1.13	3.06	+2.72

years of observations of patients with a high insulin level in blood showed that IHD developed much more often in them than in persons without a high insulin level in the blood.

The following factors can produce hyperinsulinemia [157, 174, 213, 280, 619]:

- (1) a change in the chemical structure of the insulin itself;
- (2) disturbance of the transformation of proinsulin into insulin;
- (3) the presence in the blood of a large amount of insulin antagonists or the presence of antibodies to insulin;
- (4) improper functioning of the insulin receptors.

It was proved experimentally that the diverse effects of various hormones can be represented as the schematic chain reaction "hormone – receptor – adenylatecyclase – cAMP – proteinkinase – phosphorylation of proteins". A change in the sensitivity (increase or decrease) of the link "receptor – adenylatecyclase" alters the activity of a hormonal pulse. The functional interaction of insulin with a cell occurs at the level of the specific receptors of the cytoplasmatic membranes. The insulin receptors are a complicated group of proteins which made it possible to conclude that the system of receptors in the adipose tissue and transportation system of glucose have different physicochemical characteristics, but both the glucose vectors and the insulin receptors are polypeptides differing in their chemical structure [49, 74, 120, 314, 358, 595, 597].

The transportation and metabolic effects of insulin are a result of binding of the hormone to the membrane receptors. In hyperinsulinemia of any etiology, the number of receptors in the adipose tissue and muscles lowers appreciably, while with normalization of the insulin level the number of receptors is restored. The clinical picture of obesity combines with hyperglycemia, hyperinsulinemia, a reduction of glycogen synthesis in the liver, and enhancement of the glycogenesis process. It is the reciprocal nature of the reaction between the growth in the activity of the enzymes of glycogenesis and the inhibition of the activity of the glycolysis enzymes that disturbs lipid metabolism. Already in the early stages of obesity, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, and a growth in the FFA level are noted in the patients.

When studying the problem of insulin resistance, some authors give attention to hypertriglyceridemia. It was noted that in persons with hypertriglyceridemia, the utilization of glucose diminishes, the secretion of insulin grows, and the level of IRI increases. It was proved experimentally that VLDLP lower the utilization of glucose and, accordingly, stimulate the secretion of insulin, thus causing hyperinsulinemia. As a result, the high level of the IRI stimulates the synthesis of the triglycerides contained in the VLDLP, and the vicious circle closes. Glyconeogenesis is the synthesis of glucose and glycogen from lactic acid. It is not only one of the main adaptive mechanisms of carbohydrate homeostasis, but also an important factor in providing glucose for the energy cycle of an organism.

We can assume that glyconeogenesis is an important regulating facility in the integration of syndrome X. It is the intensification of glyconeogenesis that underlies hyperglycemia and hyperinsulinemia. The excess glucose with the aid of the increased amount of insulin is utilized in the tissues. A result is activation of lipogenesis and obesity. We consider that the enhancement of glyconeogenesis is what triggers off the disturbance of metabolism and the development of syndrome X [65, 70, 203, 279, 405].

It is not so much carbohydrates as fats that are of a major energy significance in an organism. Half of the energy formed in oxidative processes proceeding in the cells (heart, liver, kidneys) is provided by the oxidation of fatty acids. The conversion of carbohydrates into fats occurs in the adipose tissue and is an insulin-dependent process. Fatty acids are oxidized in the cells (mitochondria) which they penetrate into in the form of esters of carnitine and transform there into the active form – acyl-Co-A, which is subjected to beta-oxidation [395, 404, 412, 415, 449, 458].

An important role in the metabolic transformations of lipids is played by LPL, on whose activity the supply of fatty acids to the cells depends.

Fats are also synthesized from glucose with the aid of circulating fatty acids, which reach the fat depots in the form of triacylglycerol in the composition of lipoproteins and

chylomicrons or of lipoproteins synthesized in the liver. Consequently, a fat cell uses either endogeneously generated fatty acids or fatty acids delivered with food and synthesized in the liver for the synthesis of fats. However, in either of these variants, the simultaneous supply of glucose is needed to synthesize alpha-glycerophosphate needed, in turn, for the synthesis of fats. The supply of carbohydrates with food stimulates the synthesis of fats in the adipose tissue considerably [129, 270, 473, 487, 498, 500, 515].

Insulin facilitates the penetration of glucose into the lipocytes, increases its transformation into glycerophosphate and fatty acids. It not only enhances synthesis, but also diminishes the decomposition of fats and the release of fatty acids from the adipose tissue. Fatty acids are synthesized under the influence of insulin as follows: the penetration of glucose into a cell is facilitated, glycolysis increases, this leads to the formation of glycerophosphate, and the latter is used in fatty acid esterification.

Lipolysis is also inhibited under the influence of insulin. This occurs by regulation of the cAMP level. In DM, the activity of lipase is increased, and under the influence of insulin its activity drops with the simultaneous stimulation of phosphodiesterase that destroys cAMP. In DM, lipogenesis attenuates, while lipolysis in the adipose tissues increases with the corresponding growth in the amount of fatty acids. The latter, in turn, have an unfavorable effect on the metabolism of carbohydrates.

The distorted metabolism of carbohydrates in DM consists in suppression of carbohydrate oxidation in the liver and enhancement of fat oxidation. The increased synthesis of carnitine in the liver in DM facilitates the greater oxidation of the fatty acids [87, 101, 271, 302, 333, 345, 365, 460].

In recent years, the important role of glucagon in DM as a contrainsular hormone is being widely discussed. Clinicians noted that in decompensated DM when ketoacidosis is quite pronounced, the glucagon content in the blood is sharply increased. The STH suppresses the secretion of glucagon and insulin. It was shown experimentally that the introduction of somatostatine to animals drastically lowers the glucose content because of the drop in glucagon secretion. In insulin-dependent diabetes, the suppression of glucagon secretion with the aid of somatostatine lowers hyperglycemia.

The relation between the somatotrophic hormone (STH) and insulin is exceedingly interesting. Biochemical studies revealed that the secretion of the STH increases with postinsulin hypoglycemia. It was also proved that the STH increases the secretion of insulin. Clinicians noted that in DM patients, the STH concentration in the blood is increased. In this situation, it yields a diabetogenic effect that, in particular, is conducted in three ways [205, 271, 301, 494, 548, 620]:

- (1) an increased discharge of glucose because of glycogenolysis;

- (2) lowering of the absorption of glucose by hepatocytes;
- (3) an increased inactivation of the insulin.

The STH disturbs the sensitivity to insulin of the system transporting glucose and the phosphorylation of glucose in the muscles. In adipose tissue, the STH inhibits the transformation of glucose into fats and causes lipolysis.

A comparison of the dynamics of the content of glucose and the STH after the introduction of insulin (see Tables 6 and 7) reveals that in healthy persons the background value of glucose fluctuates from 5.5 to 2.39 mmol/l, while the background level of the STH ranges from 0 to 2.80 ng/ml. The introduction of insulin causes a hypoglycemic state to appear with a considerable drop in the glucose level in 30 min. Of the 10 healthy persons, in three we could note a tendency to insulin resistance. In the remaining seven healthy persons, a considerable drop in the glucose level was noted. The dynamics of the STH level varies.

What occurs in obesity patients?

A glance at Table 7 shows that insulin resistance is noted in 11 patients (of the 15). It is interesting to note the following paradoxical phenomenon: in seven patients after the introduction of insulin, the glucose level increased, e.g. from 4.0 (background) to 5.39 mmol/l. When comparing this dynamics of the glucose level (insulin resistance) with the quantitative changes in the STH, we also noted paradoxes. First of all, the background level of the STH in obesity patients was much lower: in most patients, the STH content was within 0.22–0.52 ng/ml, and only in one patient was this quantity higher than unity (1.13 ng/ml). The introduction of insulin did not cause the STH level to rise in all patients. It lowered in five of them, and increased very moderately in the others. Only in one patient did the figure exceed 12.67 ng/ml.

The results give us the grounds to assert that syndrome X forms with complete disintegration of the regulatory hormonal processes and violation of the physiological relation between insulin, STH, and catecholamines. A pronounced insulin resistance promotes to a considerable extent the metabolic disorders in the formation of IHD [71, 110, 165, 503, 521, 558].

1.2.4. Syndrome X and Heart Pathology

Obesity causes changes in virtually all the organs and systems of an organism, but the cardiovascular system is the first to be involved in a pathological process. The excess accumulation of fat is attended by definite hemodynamic disorders that together with the metabolic one lead to the development of functional and organic pathology of the cardiovascular system. The following variants of lesion of the given system in obesity are singled

out clinically: adipose dystrophy of the myocardium, hypertension, IHD, and the Pickwickian syndrome. These diseases frequently combine with one another and, moreover, each of them may be accompanied by the development of cardiac insufficiency to some extent or other [171, 186, 222, 225, 405, 430].

Functional disorders of the cardiovascular system, changes (lowering) of the tolerance to physical loads, and disturbance of the vascular tonus form already in the initial stages of obesity. Special attention is given to the fact of the appearance of arterial hypertension with an excessive body weight. The interest is due to the fact that the growth in the arterial pressure (AP) is closely related to hyperinsulinemia and insulin resistance and thus together with dyslipoproteinemias participates in the development of a set of mutually related metabolic disorders that may subsequently cause the appearance of atherosclerosis in obesity patients. However, the question of the etiological factors and mechanisms of the appearance of arterial hypertension with a surplus body weight remains to be answered. The following are considered to be possible causes of the rise in the arterial pressure [400, 406, 430, 436, 447, 469]:

- (1) disturbance of the central and intracardiac hemodynamics, a change in the total peripheral resistance (TPR);
- (2) an increased tonus of the sympathetic nervous system leading to vasoconstriction, an increase in the cardiac ejection and the excretion of renin by the kidneys that facilitates, in turn, the production of aldosterone;
- (3) lowering of the excretion of sodium by the kidneys because of hyperinsulinemia and insulin resistance;
- (4) a change in the intracellular concentration of cations and the subsequent increase of the sensitivity of the cells to vasoconstricting agents as a result of hyperinsulinemia and insulin resistance disturbing the functioning of the membrane pump;
- (5) the direct stimulation by insulin or insulin-like growth factors of the hyperplasia of the smooth muscle cells and cardiac myocytes leading to narrowing of the arterioles and hypertrophy of the heart.

To determine the pathological changes in the cardiovascular system in obesity, we compared the tolerance to a physical load in 30 healthy youths and 35 youths with obesity.

The physical load was dosed with the aid of a Siemens Elema veloergometer. In the obesity patients, the BWI was 30.7 with an average body weight of 98.3 kg and a height of 179.4 cm. The load was increased in steps, beginning with 50 W with a further increase by 50 W every three minutes up to the maximum tolerated load. The test was terminated when there was a complaint on physical fatigue.

**Table 8. Veloergometer Parameters in Healthy Persons
and Obesity.**

Parameter	Control group	Obesity patients
Background heart rate, bpm	71.3±2.2	88.8±1.9*
Threshold heart rate, bpm	162.1±2.3	166.2±1.3
Chronotropic heart reserve, bpm	91.1±2.5	77.4±2.0*
Pulse tolerance coefficient, %	102.7±1.3	103.4±0.8
Arterial pressure, mmHg:		
background systolic	115.2±2.7	137.5±1.2*
threshold systolic	186.0±4.6	201.6±4.0*
average initial	91.5±1.6	100.9±1.3*
average threshold	120.7±2.9	124.1±4.2
background diastolic	78.9±1.7	83.3±2.3
threshold diastolic	88.0±3.5	87.2±4.4
Isotropic heart reserve, mmHg	70.1±4.3	64.1±3.6
M _{ab} , W/min	197.3±6.7	168.2±4.6*
Energy tolerance coefficient, %	126.0±2.5	73.4±2.5*
Total power of applied load, kJ	94.7±6.4	67.1±3.8*
Maximum oxygen consumption, l/min	3.7±0.2	3.1±0.08*
Max. oxyg. con./norm. oxyg. cons., %	125.1±2.9	80.7±1.5*
Double product index, units		
initial	82.8±2.7	122.3±3.2*
threshold	302.7±9.2	333.1±7.4*
Energy expenditure index, units	3.5±0.3	5.2±0.2*

*The difference of the parameters is authentic (in comparison with the level in the control group).

The data in Table 8 show that the hemodynamic parameters in the two groups differ both at rest and, especially, under conditions of a physical load. First of all, the heart rate at rest in healthy persons was 71 bpm, and in the obesity patients was 88 bpm. The level of the background systolic arterial pressure in healthy persons was 115.2 mmHg, and in obesity patients was 137.5 mmHg; the diastolic pressure was 78.9 and 83.3 mmHg, respectively. Of special importance is the reaction of the arterial pressure under a physical load: if in healthy persons, the threshold systolic arterial pressure was 186.0 mmHg, in obesity patients it was 201.86 mmHg. The values of the diastolic threshold arterial pressure in the two groups coincided (88.0 and 87.2 mmHg).

What do these parameters indicate?

First of all, they confirm the information on the disorder of metabolism in obesity and, moreover, witness a change in the metabolic processes in the vegetative nervous system, especially in the metabolism of catecholamines.

Adaptation to a physical load is combined with an increased activity of the adenylyatecyclase system and a growth in the number of adrenergic fibers per unit of myocardium

Table 9. Parameters of Hemodynamics in Healthy Persons and Obesity Patients (Data of Echocardiography).

Parameter	Control group	Obesity patients
Heart rate, bpm	57.5±3.1	71.2±1.9
Arterial pressure, mmHg:		
systolic	119.8±2.7	122.6±1.9
diastolic	76.1±2.1	77.6±1.4
average	90.6±3.1	92.6±1.3
Minute volume, l/min	5.7±0.3	7.1±0.2*
Cardiac index, l/min·m ²	3.2±0.2	3.3±0.1
Stroke volume, ml	85.6±4.9	100.2±3.3*
Stroke index, ml/m ²	47.4±2.4	46.2±1.5
Peripheral resistance, dyn·s·cm ⁻⁵	1340.6±78.2	1085.7±39.7*
Unit power, J/min·m ⁻²	39.2±2.0	40.2±1.0
Myocardium weight, g	115.7±7.2	152.4±6.0*
Myocardium weight index	64.5±3.8	70.1±2.4
End systolic volume, ml	35.2±3.4	40.9±2.3
End diastolic volume, ml	121.2±7.2	141.2±4.4*
End diast. vol./end. syst. vol.	1.1±0.07	0.9±0.03*
Ejection fraction, %	70.4±2.1	70.6±1.2
%ΔS	40.1±1.6	41.1±1.1
V _{es} , s ⁻¹	1.4±0.06	1.6±0.06*
Contraction rate, cm/s	5.1±0.06	5.3±0.2
Relaxation rate, cm/s	13.2±1.5	11.8±0.4

* The difference of the parameters is authentic (in comparison with the level in the control group).

weight. This increases the adrenoreactivity of the myocardium. A growth in the number of light H-chains is observed in the "heads" of the myosin molecules. They are carriers of the ATPase activity of the myosin. Simultaneously the power of the "calcium pump" of the sarcoplasmatic network increases, and as a result – the rate and depth of the diastolic relaxation of the myocardium. The growth in the power of the energy supply system lawfully results in a greater resistance of the heart to hypoxia during a physical load [75, 109, 129, 277, 344, 389, 544, 619].

From our viewpoint, of major importance are Meerson's experimental data [386, 387, 388, 389] showing that the energy potential of a cell regulates the activity of its genetic code, i.e. rigorous structural organization of the regulatory mechanisms of a human organism is carried out. An important role in the functioning of the regulatory mechanisms in a cell is played by cAMP. All external factors (a physical load, hypoxia) activate the adrenergic regulation in an organism and promote the formation of cAMP, which is a powerful inductor stimulating the genetic apparatus of a cell. The human myocardium has

an increased adrenoreactivity, i.e. in response to the secretion of noradrenaline, the myocardium reacts by an increase in the inotropic effect (increasing of its contracting ability). Biochemical studies revealed that under the influence of noradrenaline, the activity of adenylatecyclase grows, and it steps up the synthesis of cAMP. In adapted animals, the inotropic effect of catecholamine is increased by the power of the system "adrenoreceptor – adenylatecyclase". The membrane cell systems in an organism (in the myocardium) responsible for the processing of the control signal ensure its increased effectiveness. Adaptation of an organism that is too stressed may terminate either in exhaustion (functional) of the relevant system, or in disintegration of the regulatory adaptive (hormonal) mechanisms of various organs and systems [2, 71, 534, 543].

What is the drop in the parameters of physical activity in obesity associated with?

There is no doubt that the level of the central hemodynamics is an important factor of the ability to perform physical work. To study this matter, we compared the state of the central and intracardiac hemodynamics for 29 youths suffering from obesity of various degrees, and for 30 healthy youths with the aid of the echocardiographic method.

It follows from Table 9 that in youths with obesity the minute volume of the blood is increased to 7.1 l/min (in healthy persons it is 5.7 l/min), while the stroke volume of the blood is increased to 100.2 ml (in healthy persons it is 85.6 ml). A comparison of the parameters indicates that obesity patients have a hyperkinetic type of blood circulation in comparison with the eukinetic type in healthy persons. It should be noted, however, that in obesity patients the cardiac and stroke indexes are not increased and equal the values for healthy persons. Consequently, the hypercirculation of the blood in obesity patients is caused not by the high contracting ability of the left ventricle, but by other factors.

That in connection with the excess body weight the metabolic demands, the required amount of oxygen and nutrient substances grow may be one of the causes of development of the hyperkinetic syndrome. An increase in the volume of the circulating blood and, therefore, in the minute volume of blood regardless of the arterial pressure level is the factor for the compensating supply of oxygen to the tissues under the given conditions.

Simultaneously with the hyperkinetic type of blood circulation, in obesity patients we noted a drop in the total peripheral resistance to $1085.7 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ (in healthy persons it is 1340.6).

What is the pathogenesis of this syndrome?

As a result of an excessive amount of fat deposits, the vascular channel grows and expands, and this lowers the total peripheral resistance.

Inspection of Table 9 shows that in obesity patients the weight of the myocardium of the left ventricle is considerably increased – up to 152.4 g against 115.7 in healthy persons.

The compensating hypertrophy of the myocardium in obesity patients is a heart activity regulating factor for maintaining a normal minute volume. The pathophysiological hypertrophy of the myocardium is based on activation of the synthesis of nucleic acids and proteins and an increase in the heart volume. In obesity patients, myocardium hypertrophy is a result of mobilization of the energy and structural resources of the heart. The hyperfunction of the myocardium, manifest in a growth in the stress, entails a pronounced increase in the consumption of oxygen, the resynthesis of ATP, and a no less pronounced activation of the synthesis of nucleic acids and proteins. The continuous hyperfunction in obesity is attended by the consecutive mobilization of the energy and structural reserves of the cardiac myocytes with subsequent wear (early) of the myocardium and disturbance of its function. The morphofunctional basis of the compensating hypertrophy of the myocardium in obesity is formed by the increased function of the myocardium that activates the genetic apparatus of the cardiac myocytes. This increases the synthesis of nucleic acids and proteins. Hypertrophy of the myocardium is a consequence. In obesity, the myocardium experiences additional damaging factors, in particular a lack of oxygen, and separation of the oxidation and phosphorylation processes [28, 109, 356].

What is the mechanism of action of these damaging factors?

It is assumed that it may be closely related to the influence of catecholamines. It was shown in experiments that moderate ischemia of the myocardium (caused by the dosed narrowing of the coronary arteries or the introduction of large doses of noradrenaline) first lowers the concentration of creatine phosphate and ATP, and then activates the synthesis of nucleic acids and proteins. As a result, the weight of the myocardium grows by up to 30–80%.

What is the pathophysiological mechanism of hypertrophy of the myocardium in obesity?

The following aspects of the effect of lipid metabolism on the metabolism of the myocardium can be noted [45, 109, 190, 333, 338, 366, 486, 543]:

- (1) a large amount of triglycerides concentrate in the myocardium in obesity; they hydrolyze with the liberation of fatty acids;
- (2) the membrane phospholipids may be hydrolyzed by activated phospholipases of the cytosol, which causes the liberation of fatty acids and, possibly, of lysophosphatides;

(3) the intracellular content of fatty acids may grow as a result of their increased absorption by ischemized myofibrills; inhibition of fatty acid oxidation and condensation of dicarbon fragments also occur.

These biochemical processes result in an excessive accumulation of fatty acids and intermediates of their metabolism inside and around the myofibrills. The fatty acids disturb the functioning of the membranes of the myofibrills: they disrupt the transport of Ca^{2+} and the structure of the membrane.

Disruption of the Ca^{2+} transport affects the contraction and relaxation of the myocardium. Lowering of the rate of relaxation of the myocardium may be due not only to disorders in the absorption of Ca^{2+} from the microfibrills, but also to the lowering of its concentration acting in the myoplasma and activating the Ca-dependent ATPase of the sarcoplasmatic network.

The energy deficiency of the myocardium in obesity is also associated with the excessive activation of catecholamines. Their excessive accumulation in the myocardium, in addition to the hyperfunction of the heart, leads to the activation of a set of metabolic mechanisms that may inhibit biological oxidation or lower its efficiency.

The increased decomposition of lipids and phospholipids with improper utilization of their decomposition products is due to the excessive activation of the lipases and phospholipases together with the accumulation of Ca^{2+} in the myoplasma. These enzymes are activated by catecholamines via the adenylatecyclase – cAMP system. The increased decomposition of the neutral lipids under the influence of lipases is attended by the excessive accumulation of fatty acids that are not subjected to beta-oxidation, are not utilized in the Krebs cycle, but are accumulated in the cardiac myocytes. The accumulation in a cell of the fatty acids and lysophosphatides formed in the decomposition of the phospholipids points to the high significance of the lipid mechanism of lesion of the cardiac myocytes. The increased decomposition of the phospholipids and the sharp swelling of the mitochondria inhibit the respiratory train. Lipid damage to the mitochondria separates the processes of oxidation and phosphorylation and disturbs ion transport. The accumulation in the myocardium of the products of decomposition of phospholipids – lysophospholipids (lysophosphatidylcholine, etc.) disturbs the function of the ion channels of membranes and the loss of K^+ by the cells. Electrical instability of the myocardium appears, arrhythmias develop, as well as contractures of the myofibrills with suppression of the contractive function of the myocardium [10, 333, 542, 619].

The pathophysiological basis of the numerous pathological processes consists in disturbance of the structure and function of the cell and intracellular membranes. This is why the restoration of the disturbed membrane relations is an important component of

therapeutic measures. The activity of the membrane structures is of special significance in the development of the pathology of the myocardium. In particular, such basic functions of the myocardium as the excitability of the cells, the conjugation of excitation and contraction, neurohumoral and hormonal regulation of biochemical processes are all associated with the activity of the heart's membrane structures. When studying the pathology of the myocardium, four main problems have to be solved that are closely related to investigating the lesion of cell membranes [131, 256, 306, 332, 389, 537]:

- (1) studying of the structure and function of the mitochondria and (accordingly) the mechanism of the incidence of ischemia of the myocardium cells, in particular, in IHD;
- (2) with syndrome X, studying of the influence on the membranes of cholesterol, peroxide oxidation of lipids, and the relation between the pathology of the membranes and the development of IHD;
- (3) studying of the excitability of the myocardium cells associated with the functioning of the ion channels and the sodium pump;
- (4) studying of electrical phenomena in the myocardium, the appearance of disturbed relations of the calcium metabolism and, accordingly, the process of relaxation of the myocardium and contractility.

All these problems are solved at the junction of several specialities: biochemistry, biophysics, morphology, and internal diseases. A number of scientists showed that in syndrome X there appear tissue hypoxia and ischemia of the myocardium cells pointing to the great significance of the membrane phospholipases in the irreversible lesion of cells. The lipid bilayer of membranes acquire electrical instability and lose their barrier functions. In recent years, major significance in the pathogenesis of atherosclerosis is attached to the peroxide oxidation of lipids. The use of antioxidants inhibiting the peroxide oxidation of lipids was found to affect deeply the lipid composition and physical properties of all membrane structures of the cells, and this may be the theoretical basis for the use of antioxidants as an important therapeutic factor in atherosclerosis.

Experiments showed that the hyperfunction of the myocardium appearing under the influence of sympathetic neurohormones is not attended by a corresponding increase in the coronary blood circulation, and in this connection a discrepancy appears between the requirement of oxygen by the myocardium and its consumption. Suppression of the utilization of oxygen by the myocardium under the influence of catecholamines appears as a result of inhibition of the activity of the cytochromes. The accumulation of catecholamines in the myocardium increases the peroxide oxidation of lipids in the membranes of the cardiac myocytes, which leads to destabilization of the membranes, liberation of proteolytic

Table 10. Content of Glucose, IRI, Pyruvic and Lactic Acids in the Blood Plasma in Type II DM and IHD Patients.

Parameter	Control group	Type II DM patients	IHD patients
Glucose, mmol/l	4.82±0.13	10.33±0.42 ^a	5.13±0.11 ^b
IRI, μU/ml	13.92±1.37	25.12±4.4 ^a	12.92±3.78 ^b
Pyruvic acid, μmol/l	59.03±4.03	105.43±12.2 ^a	70.8±3.64 ^b
Lactic acid, μmol/l	0.8±0.041	0.556±0.12	1.025±0.055 ^b

The difference of the parameters is authentic:

^a in type II DM patients in comparison with the level in the control group;

^b in IHD patients in comparison with the level in type II DM patients.

enzymes, and autolysis of the subcellular structures of the myocardium [227, 406, 409, 416, 609].

In a number of clinical studies, the changes in the ECG and the excess body weight were compared. We noted that an excess weight enhanced disturbance of the bioelectrical activity of the myocardium, the atrial conduction changed, the atrioventricular and intraventricular conduction was disturbed, and the amplitude of the T tooth in the chest leads lowered. Apart from lesion of the myocardium itself, obesity also causes disorder of the activity of the cardiovascular system in connection with the influence of numerous extracardiac factors such as excessive development of adipose tissue that increases the abdominal pressure, a high diaphragm, and its restricted mobility. This diminishes lung elasticity, and increases the intrapleural pressure, which leads to hypoventilation, the retention of carbon dioxide and lowering of the sensitivity of the respiration center, the appearance of hypoxia. All this affects the state of the myocardium.

An important indication of a disorder of metabolism in obesity is a pronounced growth in the weight of the myocardium (its hypertrophy) in youths 16–18 years old. These changes suggest that obesity is attended by a disorder in metabolism (especially of hormonal, carbohydrate, and fat metabolism) that predisposes the development of hypertrophy of the myocardium and the appearance of syndrome X [65, 110, 152, 392, 395, 462].

To study the metabolism disorders in IHD and type II DM, we analyzed the content in the blood plasma of glucose, insulin, pyruvic and lactic acids in 14 patients with IIDM, 52 healthy persons, and 31 IHD patients (Table 10).

In comparison with the healthy persons, the IIDM patients had an increase in the glucose level to 10.33 mmol/l (in healthy persons it was 4.82 mmol/l), in IRI to 25.12 μ U/ml (in healthy persons 13.92), and in pyruvic acid to 105.4 mmol/l (in healthy persons 59.03). The lactic acid content lowered somewhat to 0.55 mmol/l (in healthy persons it was 0.8). In IHD patients, all these parameters differ insignificantly from their level in healthy persons.

What are these changes associated with?

We must recall that hypertrophy of the myocardium in obesity prevents the appearance of a deficiency of energy in the myocardium and the development of acute cardiac insufficiency, i.e. hypertrophy is a compensating state. Physiologists proved that the maximum strength and rate, and also the energy efficiency of a contraction in a hypertrophic myocardium lower, and its functional reserve diminishes with the development of pronounced hypertrophy. A state of an increased wear of the hypertrophic myocardium appears.

Morphofunctional studies showed that in hypertrophy of the myocardium, the density of the sympathetic innervation of the myocardium is disturbed, the consumption of noradrenaline grows and exceeds its resynthesis, and its concentration in a hypertrophic myocardium is from one-third to one-fifth of the initial value. This is just what causes a drop in the positive inotropic influence of the sympathetic section of the nervous system on a hypertrophic myocardium, i.e. the inotropic function of the heart is disturbed. Moreover, in hypertrophy of the myocardium, the unbalanced growth of the myofibrills is attended by a lag in the growth of the arterioles and capillaries (in comparison with the growth in the muscle cells). As a result, the number of coronary capillaries per unit weight of the myocardium diminishes.

In hypertrophy of the myocardium, on the background of lowering of the total number of coronary capillaries, diffusion of oxygen is disturbed and, accordingly, hypoxia of the myocardium appears. As a result, already when resting most of the reserve capillaries are open, and the coronary reserve drops appreciably. In the hypertrophic myocardium, the increased consumption of oxygen is not ensured by its timely greater transportation into the intercapillary spaces, and ischemia zones appear [261, 350, 388, 405, 479].

All this was confirmed under clinical conditions by echocardiography. The volume and weight of the myocardium in IHD patients (not associated with hypertension) grow by 20–30%, i. e. in an ischemic lesion of the myocardium, hypertrophy is manifest early and progresses as ischemia grows.

Fig. 11. Development of Cardiac Insufficiency in Syndrome X.

In obesity, hypertrophy of the adapted myocardium develops when the adaptation reaction transforms into a pathological one. In this disease, improper functioning of the mechanisms responsible for synchronization of excitation and contraction occurs.

The physiological systems of an organism are determined genetically for the timely change of the period of intense functioning during an interval of relative physiological rest [17, 28, 129, 338, 592].

The drop in the rate of relaxation results in the heart not having time to relax completely during the short intervals between contractions, and a phenomenon called the diastolic defect develops. With myocardium hypertrophy in obesity patients, a diastolic defect appears at a lower heart rate and is expressed very sharply in a quantitative respect. This syndrome of an uncompleted diastole is the initial link in the pathological chain of development of insufficiency in blood circulation in obesity patients. It is very important that the efficiency of utilizing oxygen in hypertrophy of the myocardium in obesity patients drops substantially. The reason is a drop in the transportation ability of the coronary arteries with a corresponding drop in the capacity for the aerobic resynthesis of ATP.

The development of insufficiency of a hypertrophied heart is based on the combined loss of capacity of the system of energy supply and of utilization of energy. This lowers the rate of transformation of the chemical energy of ATP into the mechanical energy of contraction, i.e. becomes the cause of depression of the contracting function of the heart (Fig. 11) [102, 152, 388, 392, 434].

After the discovery of insulin receptors, biochemists and clinicians received the possibility of studying the molecular mechanisms of the action of insulin, i.e. of investigating the molecular-biological processes underlying the changes in the activity of intracellular enzymes after insulin is introduced into an organism.

The amount of insulin receptors in persons with obesity and hyperinsulinemia was found to be diminished considerably. It was considered that insulin itself regulates the concentration of the insulin receptors with hyperinsulinemia. The introduction of considerable insulin doses to healthy persons lowered the amount of insulin receptors of blood cells. Correspondingly, fasting during from two to four days was accompanied by a growth in the concentration of the insulin receptors.

The insulin content is of major significance in the development of myocardium hypertrophy. Hyperinsulinemia in obesity patients results in insulin stimulating protein metabolism. It was shown experimentally that the introduction of insulin is attended by a greater inclusion of amino acids into the proteins of the tissues (especially muscles). In alloxan diabetes in animals, the inclusion of methionine into the muscles lowers, while when insulin is introduced it grows.

When comparing the hemodynamic parameters in healthy persons and obesity patients, we found considerable differences. If in the former the minute volume of the blood was 5.7 liters, in youths with obesity it was 7.1 liters. Simultaneously, the stroke volume of the blood in obesity patients increased to 100.2 ml (in healthy persons it was 85.6 ml).

The volume of the circulating blood is an important factor for the compensating supply of tissues with oxygen and various nutritive substances. An increase in the volume

of the circulating blood in obesity is attended by constant hypoxia because the total body weight grows. The coefficient of the effectiveness of circulation is drastically decreased, and this is also associated with the high body weight. Growth of the vascularized adipose tissue considerably expands the vascular canal, and this lowers the total peripheral resistance. We noted a drop in the total peripheral resistance in obesity patients to $1085.7 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ (in healthy persons it was 1340.6).

Most clinicians consider that the development of blood circulation insufficiency in obesity is associated with the increased demand of an organism for oxygen and nutritive substances. This demand is compensated to a certain extent by a growth in the volume of the circulating blood, and also in the stroke and minute volume of the blood. However, the large volume of circulating blood produces a considerable preload on the left ventricle, and its capacity and stroke work grow. A growth in the index of useful power of the left ventricle is noted in patients. This factor constantly stimulates the myocardium and causes hypertrophy. As the disease progresses, the volume of circulating blood, the end-diastolic rigidity of the myocardium, and cardiodilatation grow, while the contractive ability of the heart lowers. All these factors cause cardiac insufficiency to develop.

When comparing the basic parameters of central hemodynamics in healthy persons and in obesity patients (see Table 9), we noted clear distinctions in such an important criterion as the end diastolic volume that in obesity patients is increased to 141.2 ml (against 121.2 in healthy persons).

What do these changes indicate?

First of all, progressing of cardiac insufficiency. The functional characteristic of the myocardium is expressed by the following relation: the contractive ability of the heart is inversely proportional to the ratio between the rate of muscle contraction and the load on the myocardium. The muscular work of the heart is due to components such as a contracting element that readily stretches in rest, can develop a definite force and contract when loaded, and a passive elastic element that retains the same length in a state of rest as the contracting one. The interrelation and functional integration of these structures reflects the state of contractibility of the myocardium. The preload is determined by the length of the myocardium fibers in the diastole period. The quantitative characteristic of the preload depends on the initial length of a muscle fiber at rest, the venous inflow of blood to the heart, and the volume of circulating blood, which grows in obesity patients. Moreover, the venous inflow in them grows, and the preload grows quite logically, which is expressed in an increase in the end diastolic volume [110, 152, 221, 302].

When studying other parameters of the central hemodynamics, we noted that the ejection fraction in healthy persons and obesity patients is the same (70.4 and 70.6%), as is

the degree of lowering of the front and rear size of the left ventricle (% Δ S) during systole (40.1 and 41.1%). However, these coincidences indicate that in obesity patients the myocardium compensates its contracting ability mainly at the expense of a growth in the mass of the myocardium and in the energy expenditures, especially under conditions of a physical load. The sharp drop in the power of the threshold load in veloergometry to 168.2 W/min (197.3 in healthy persons) points to disturbance of the contracting ability of the myocardium and the progressing development of cardiac insufficiency.

In concluding, we can assert that syndrome X is based on definite metabolic disorders that lead to pathological changes in the myocardium. They grow progressively and are manifest clinically in the form of IHD and cardiac insufficiency. In syndrome X, integrative symptoms form that are typical of various metabolic disorders (DM, hypertension, obesity, hyperinsulinemia, and insulin resistance). They all lead to the incidence of atherosclerosis. DM, hypertension, and hypercholesterolemia are undoubted risk factors of cardiovascular diseases, while hyperinsulinemia facilitates their development in combination with obesity and hyperglycemia [184, 227, 457, 484].

Clinical studies of recent years revealed that a growth in the insulin concentration in the blood plasma is an independent risk factor of coronary diseases.

1.3. Pathophysiological Relation between Obesity, Diabetes Mellitus, and Ischemic Heart Disease

An important role in the pathogenesis of atherosclerosis, hypertension, and DM is played by disorders in the metabolism of lipids, in particular by obesity.

Obesity is the excessive growth in body weight because of the surplus accumulation of fat in the depots. Fat is deposited in lipocytes in the form of triglycerides.

The growth in the volume of the lipocytes is attended by a growth in the amount of intra- and extracellular water and protein. The surplus body weight forms at the expense of one-third of water and two-thirds of fat.

The etiopathogenesis of this disease is integrative and consists of disorders in the hormonal balance of an organism, the increased taking of food, energy imbalance, etc. A clinical feature of obesity is the growth in the weight of the adipose tissue as a constituent part of an organism. Obesity generally develops gradually under the influence of a positive calorie balance, a reduced consumption of energy, and in the disintegration of the regulatory and adaptive mechanisms of basic metabolism.

In the economically developed countries, about 20–30% of the population suffer from obesity. It was found that 34 million Americans have a body weight index above

27.8, while up to 20% of the children and adolescents suffer from obesity [128, 270, 295, 539].

Adipose tissue is a metabolically very active substrate and performs vital functions as the main donor of energy-supplying substances. It is the presence of a sufficient amount of adipose tissue that allows an organism under different extremal conditions to adapt itself to an increased energy metabolism. The metabolic processes in lipocytes are regulated with the aid of hormonal and nerve mechanisms. The basic metabolic functions of lipid tissue (lipogenesis, lipolysis, biosynthesis of fatty acids, glycolysis) are closely related to both carbohydrate and protein metabolism. The amount of fat in an organism can be regulated by an increase in the size of the lipocytes (hypertrophy) or by increasing their amount (hyperplasia). We can accordingly distinguish hypertrophic and hyperplastic obesity. Actually, the lipocytes in most persons with pronounced obesity are simultaneously hypertrophied and hyperplastic [247, 272, 316, 373, 474].

Let us consider in greater detail what pathogenetic mechanisms underlie these processes.

The most important physiological regulators of energy metabolism are the hormones of the hypophyseal-adrenal system and the pancreas. A very significant factor in regulating energy metabolism is the synchronous interaction of hormones having both synergism and antagonism. The hormones with a synergic effect include glucocorticoids and catecholamines. Those with an antagonistic effect include glucocorticoids and insulin. Different physiological states of an organism (e.g. fasting) produce an increased activity of the glucocorticoids and catecholamines. Simultaneously, the insulin-like activity of the blood plasma: lowers. Inhibition of carbohydrate metabolism (blocking of the key enzymes of glycolysis and glycogenolysis) with the accompanying activation of the key enzymes of glyconeogenesis and lipid metabolism occurs at this ratio between the hormonal relations. Lowering of the insulin-like activity of the blood ensures the energy stability of an organism under fasting conditions. The physiological significance of hypercatecholemia under conditions of an energy stress in an organism ensures the rapid mobilization of the carbohydrate reserves in the liver and muscles, thus creating conditions for adaptation. The fat-mobilizing effect in the adipose tissue grows under the influence of catecholamines. It is these hormonal relations with an increased energy activity of an organism that make it possible to switch over the carbohydrate type of metabolism to the fat one. This function is achieved by mobilization of the key enzymes of carbohydrate-lipid metabolism. Hypercholesterolemia in fasting develops by an increasing production of glucocorticoids and a simultaneous drop in the insulin-like activity of the blood. At this ratio of the hormones (under conditions of an emotional load), the content of free fatty acids in the blood

Fig. 12. Metabolism of Lipids and Carbohydrates Normally and in Obesity.

grows, and hypercholesterolemia, hyperlipoproteinemia, and hypertriglyceridemia appear. Glucocorticoids are very important for controlling fat and carbohydrate metabolism. They amplify the synthesis of VLDLP in the liver. The growth in the level of the VLDLP in the blood is compensated by the energy production of the adipose tissues [490, 515, 537, 549, 551].

A considerable amount of energy is reserved in an organism in the form of fat deposits. The deposited triglycerides of the adipose tissue decompose under the effect of the hormone-sensitive triglyceridelipase and other lipases to glycerol and free fatty acids, and the latter enter the blood flow. Here the fatty acids combine with albumin and are carried in such complexes to the liver. In the liver cells, in the endoplasmatic network, the fatty acids are used to synthesize triglycerides. The endogeneously synthesized triglycerides, and also those synthesized by the intestine cells from fatty acids and monoglycerols (absorbed from the food), are transported in the form of complexes enriched with triglycerides –

lipoproteins. Of the total energy needed by an organism 90% is provided by the free fatty acids that have a very high rate of metabolism [45, 103, 113, 148, 189, 283, 620].

Under normal conditions, the adipose tissue receives (under the influence of insulin) only 5% of the initial amount of glucose, and nevertheless the formation of triglycerides and their accumulation are closely related to the adequate intracellular supply of glucose. When a person takes surplus calories with food, lipogenesis exceeds lipolysis, which is attended by the increased deposition of triglycerides in the lipocytes. Since in adults the number of fat cells remains constant, this deposition becomes possible only as a result of an increase in the volume of the lipocytes. It is hypertrophy of the fat cells that is the main factor of obesity. The metabolism of lipids and carbohydrates is shown in Fig. 12.

Obesity is attended by many metabolic effects. Whereas in persons with normal metabolism lipogenesis in a fat cell is balanced by lipolysis, with an excessive supply of triglycerides lipogenesis prevails. The volume of the fat cells grows, which underlies the drop in the sensitivity to insulin. These changes (although they do not ensure a growth in lipolysis corresponding to lipogenesis) increase the content of free fatty acids, which inhibit the effect of insulin (especially in the muscles). Here the utilization of glucose is limited, although initially the glucose in a fat cell can still participate in metabolism, and there is a large amount of alpha-glycerophosphate as an acceptor of fatty acids for the synthesis of triglycerides. Hyperlipacidemia, i.e. an increase in the amount of free fatty acids, causes a diminished sensitivity to insulin, which is leveled out by an increased consumption of glucose in the adipose tissue. However, if a fat cell approaches its maximum volume, lipogenesis no longer grows. Lipolysis reaches the same extent as lipogenesis. The space occupied by triglycerides can no longer expand. With pronounced hyperlipacidemia, the peripheral effect of insulin is inhibited, which lowers the sensitivity to this hormone. Strong stimulation of the secretion of insulin occurs, but it is restricted by the genetically caused secreting ability of the islet apparatus of the pancreas.

Since the glucose pool cannot be utilized completely in either the adipose or the muscle tissue, a diabetic situation arises proceeding with glycosuria. With pronounced hyperlipacidemia, insufficient burning up of fats occurs at the periphery, and next their input to the liver grows. The synthesis of triglycerides in the liver increases, which leads to metabolically caused fat dysfunction of the liver. A part of the fats synthesized in an excessive amount is excreted from the liver, so that hyperlipacidemia is followed by hyperlipoproteinemia. The peripheral utilization of glucose lowers, and clearing of the blood serum is slowed down because of the lack of lipoproteinlipase. Hyperlipacidemia results in the appearance of ketonemia and ketonuria. Fig. 13 shows various models of the reactions

Fig.13. Relation of the Fat Cell Size to the Kinetics of Fatty Acids and Glucose.

of glucose and fatty acids, namely, in healthy persons and with compensated and decompensated obesity.

In 1963 P.Randle discovered the glucose-fatty acid cycle and showed that an increase in the glucose level is accompanied by the inhibition of lipolysis in the adipose tissue. If glucose is utilized actively in the muscle tissue, the level of free fatty acids in the blood grows. The dynamic equilibrium of these processes can be represented as follows: normally 50% of the glucose is oxidized to carbon dioxide and water, 40% accumulates in the form of triglycerides, and 5% in the form of glycogen. In DM, these proportions change, which causes disorder of fat metabolism [155, 159, 173, 213, 244].

The membranes of both muscle and adipose tissues have a specific carrier system for D-glucose that is affected by insulin in the transportation of glucose and free fatty acids into cells. An increased inflow of glucose increases the pool of alpha-glycerophosphate. As a result, more fatty acids are bound on these acceptors, and lipogenesis grows.

Further, insulin influences a cell membrane, the activity of adenylatecyclase is inhibited, and the cAMP level lowers. Consequently, insulin is a hormone of fat accumula-

tion and synthesis. In DM, i.e. with a deficiency of insulin, a growth in lipolysis is noted. In connection with the lack of insulin, glucose cannot be supplied to the fat cells in a sufficient amount.

If glucose (the carrier mechanism) is not assimilated in a cell in DM, the major part of the fatty acids through the intercellular space is removed into the blood. The free fatty acids are carried to the liver, where the synthesis of lipoproteins clearly grows. If the ability of an organism to synthesize them does not correspond to the supply of the free fatty acids, pronounced obesity of the liver develops. We can assume that synthesis of apoproteins is disturbed, and this limits the synthesis of the lipoproteins. Diabetic hyperlipacidemia in several hours leads to a growth in the level of triglycerides or lipoproteins. When insulin is introduced, the degree of the hyperlipacidemia lowers, lipolysis diminishes, and lipogenesis increases. Therefore, in DM (with a deficiency of insulin) lipogenesis is inhibited and lipolysis is activated [247, 264, 272, 330, 379].

All clinical and experimental results witness that insulin and free fatty acids play a very important role not only in lipid, but also in carbohydrate metabolism. DM is attended by a growth in the level of the free fatty acids, and a drop in the utilization of glucose in the muscles because the muscle cells switch over to the use of free fatty acids. The glucose accumulates in fat cells and transforms into triglycerides if there is sufficient insulin. If hyperinsulinism develops, lipogenesis becomes excessive. The fraction of the triglycerides in the cells grows, which leads to hypertrophy of the adipose tissue and obesity [384, 418, 422, 450].

Intermediate metabolism of glucose, whose main substrate is lactate, occurs in a human organism in most tissues, where the produced lactate is oxidized in the Krebs cycle and does not enter the blood channel. The main sources of lactate are erythrocytes, the medullary substance of the kidneys, and, possibly, the brain. Under a physical load, the growth in the lactate content in the blood is due to the sharp increase in anaerobic glycolysis in the muscles. In the restoration period after a physical load, after hypoxia 10% of the lactate formed in a person's muscles gets into the blood channel, 15% is oxidized to CO_2 , and 75% of the muscular lactate transforms into glycogen directly in the muscle tissues. The main pool of lactate undergoes metabolism in the Cori cycle. The lactate formed in the tissues is transferred to the kidneys and livers where it transforms into glucose. The latter again enters the tissues and is oxidized to lactate. In the long run, all the circulating lactate is utilized by the organism – 50% in the skeletal muscles and the heart, 30% in the liver, and 20% in the brain and cortical substance of the kidneys.

An important role in regulating the glycolysis enzymes in an organism is played by the synthetic fatty acids. Fatty acids and glucose react in the Randle glucose–fatty acid

cycle whose direction is determined by the concentration and utilization of its substrates. Fatty acids inhibit not only glycolysis, but also the entering of pyruvate into the Krebs cycle by inhibiting the pyruvate dehydrogenase reaction combining cytoplasmatic glycolysis with mitochondrial oxidation processes. Glucose is not only an energy and plastic factor, but also a regulating one. Autoregulation of carbohydrate metabolism is manifest in the increase in the glucose synthesis of glycogen, and also in the inhibition of glycogenolysis and glyconeogenesis by modification of the activity of the relevant enzymes [458, 474, 490]. Lactate blocks the utilization of glucose by tissues and its oxidation in glycolysis and in the Krebs cycle.

Numerous biochemical studies showed that the tissues most sensitive to insulin include the skeletal muscles, myocardium, adipose tissue, liver, cortical substance of the kidneys, connecting tissue, mammary glands, skin, adrenal glands, uterine, and lungs. In the central and peripheral nervous system and in the erythrocytes, insulin does not affect glucose metabolism. The degree of sensitivity of the tissues to insulin is probably determined by the activity of hexokinase or the presence of glucokinase. The tissues absolutely dependent on insulin include the myocardium, skeletal muscles, adipose tissue, liver, and island apparatus of the pancreas. In the myocardium, skeletal muscles, and adipose tissue, up to 96% of the total enzyme activity falls to the share of hexokinase II. The latter is absent or is present in miserable amounts in tissues independent of insulin. At the same time for tissues not sensitive to insulin (the brain, erythrocytes, medullary substance of the kidneys), glucose is the only energy substrate and 95% of it is oxidized by the glycolytic path or lactate with the maximum rate of transportation.

When the content of insulin in the blood is normal, it does not affect directly the transmembrane transfer of glucose in the tissues, but suppresses lipolysis and oxidation of fatty acids, and this, in turn, inhibits glyconeogenesis in the liver and accelerates the utilization of glucose in the muscles.

In accordance with the above mechanism (the Randle cycle), in the regulation of glycemia in a healthy person, the homeostatic and anabolic effect of insulin is 80–90 and 10–20%, respectively. The figures reverse in obesity patients – the homeostatic effect is 10–20%, and the anabolic one is 80–90%. It should be noted that insulin in an organism increases the synthesis of glycogen and protein from glucose 5–6 times, and of lipids – 10 times. This selective sensitivity of lipid metabolism to insulin underlies obesity and other pathologic states associated with hyperinsulinemia. Also, insulin regulates and modifies the activity of many enzymes only in the presence of glucose. Here enzymes such as hexokinase, glucokinase, glycogen-synthetase and glycogen phosphorylase, and pyruvate dehydrogenase are especially significant. The primary reaction of insulin with enzymes

occurs on a plasmatic membrane without direct contact with the intracellular structures [493, 495, 515, 556].

The main cause of relative insulin insufficiency is lowering of the sensitivity of tissues to insulin (insulin resistance), and this is just what leads to compensating hyperinsulinemia. Insulin resistance associated with compensating hyperinsulinemia may be due to [565, 573, 584, 624, 628]:

(1) a changed product of secretion of the beta cells: (a) a change in an insulin molecule, and (b) disturbance of the transformation of proinsulin into insulin;

(2) circulation of the insulin antagonists: (a) an increased content of the hormonal antagonists, (b) the presence of antibodies to insulin, and (c) the presence of antibodies to insulin receptors,

(3) a defect in the target tissues: (a) a defect in the insulin receptors, and (b) a post-receptor defect.

We find this concept to be the most suitable.

The development of insulin resistance of the peripheral tissues in atherosclerosis is very important and the most significant as a result of the action of insulin antagonists: an increase in the level of the hormone antagonists and a defect of the target tissues. Glucocorticoids, hormones of the thyroid gland, and the somatotrophic hormone are physiological antagonists of insulin. Special importance here is attached to glucocorticoids that affect the sensitivity of the cell receptors to insulin, block receptors competitively, and diminish their number.

The clearly pronounced disorders in the hypophysis-adrenal cortex system is possibly related pathogenetically to atherosclerosis of the brain arteries. The development of insulin resistance is associated not only with the influence of glucocorticoids, but also with lowering of the thyroxin level in the blood in atherosclerosis patients.

According to modern concepts, insulin acts physiologically on biochemical processes by means of receptors, which are sections of a cell membrane with a genetically caused molecular structural affinity for insulin. Morphologically, they are integral components of the cell membranes. The insulin receptors in various organs and tissues have a universal structure. The striking similarity of the insulin receptors in cells of adipose tissue, muscles, and the liver is noted. It is very interesting that a physical load affects the number of insulin receptors of erythrocytes and other cells. Similar changes probably occur in the cells of the muscle tissue, and in this connection the oxidation of glucose is enhanced in veloergometry. It was noted in experiments with animals that in genetically caused obesity with the presence of hyperglycemia and hyperinsulinemia, the number of insulin receptors in the myocardium muscle, liver, and adipose tissue diminishes. Similar

Fig. 14. Background Parameters of Lipoprotein Metabolism in Persons with Different Degree of Obesity.

changes are noted in patients with obesity and hyperinsulinemia. It was proved that the concentration of the receptors in the lipocytes and erythrocytes lowers in them [110, 133, 132, 141, 205, 280, 289].

We can thus conclude that the pathophysiological basis of obesity is the increase in the level of free fatty acids in the blood with their following use in the muscles. Energy forms at the expense of the acids, and not of glucose. Obesity is generally attended by hyperinsulinemia and a reduced tolerance to glucose. The appearing hypertriglyceridemia differs from that with a lack of insulin. Clinicians showed that the pathogenesis of hypertriglyceridemia in DM of types I and II differs. In type I (a lack of insulin), although the synthesis of triglycerides is suppressed, their catabolism lowers, and this results in the ap-

Fig. 15. Level of Hormones in Blood in Persons with Different Degree of Obesity.

pearance of hypertriglyceridemia. In type I, often attended by hyperinsulinemia and obesity, hypertriglyceridemia appears because of the growth in triglyceride synthesis in the fat cells and the liver [167, 192, 224, 238].

The metabolism of lipoproteins and the hormonal profile was studied in three groups of patients: a control group including 20 healthy persons from 18 to 20 years old, group 1 including 15 patients from 16 to 18 years old with hypothalamic obesity and a body weight index of 25.1–30.0, and group 2 including 20 persons with hypothalamic obesity and a BWI of 30.1–35.0 (Figs. 14 and 15).

When comparing the background parameters of cholesterol in these groups, we noted clear distinctions, namely, the average cholesterol value in the control group was 150.0 mg/dl, while in group 1 it was 172 and in group 2 – 181.1 mg/dl.

Although the cholesterol content in groups 1 and 2 was not beyond the limits of the normal values for persons of this age, in group 2 it was authentically higher than in the control group.

What are these differences associated with?

In persons with an increased level of total cholesterol in the blood serum (especially of LDLP) and a reduced content of HDLP, disorders in the lipid transportation system and a liability of atherosclerosis are noted. Numerous clinical studies showed that LDLP are the most dangerous. They carry cholesterol into the tissues, including an artery wall. They concentrate two-thirds of the cholesterol content in the blood serum.

When comparing the background values of the triglycerides in these groups, we also noted clear distinctions. In the control group of healthy persons, the triglyceride level in the blood was 72 mg/dl, in persons of group 1 it was 99, and of group 2 it was 136 mg/dl. And although (like the cholesterol content), the average values of triglyceride in the studied groups were not beyond the limits of the normal values for persons of this age group, in obesity patients of groups 1 and 2 the triglyceride level was increased in comparison with the value in the control group.

What is the pathophysiology of these changes in the triglyceride metabolism?

When studying the relation between obesity and disturbance of lipid metabolism, we noted that in obesity patients, the level of triglycerides, NEFA, cholesterol, and the total fraction of pre-beta-LP and beta-LP (VLDLP and LDLP) grows first of all. The growth in the TG level is most typical.

There is a clear correlation between the BWI and the TG level. This is associated with the increased synthesis of the triglycerides in the liver at the expense of the increased formation of FFA, the diminished metabolism of VLDLP, and hypertrophy of the fat cells. In obesity, the cortisol level is increased, and that of the STH is decreased. In the treatment of obesity, atrophy of the adipose tissue occurs (in connection with lipolysis), and 90% of the energy consumed by the organism is supplied by triglycerides [247, 272, 286, 342, 393].

Inspection of Fig. 14 reveals that the background value of the HDLP cholesterol in the control group was 48.2 mg/dl, in group 1 it was 34.9, and in group 2 it was 36.1 mg/dl. These results indicate that in the obesity patients of groups 1 and 2 the HDLP cholesterol level lowered. Numerous investigators showed there to be an inverse correlation between the content of HDLP and triglycerides: a growth in the HDLP level in the blood is attended by a drop in the triglyceride level. The suggestion that this is associated with a change in the activity of LPL because its increase leads to an increase in the content of HDLP cholesterol was confirmed completely in our investigations, namely, in patients of groups 1 and 2 the triglyceride level is increased substantially and the parameters of HDLP cholesterol in the blood are decreased in comparison with these parameters in the control group.

HDLP can transport cholesterol from the peripheral tissues to the liver. An increased concentration of apo-B-LP in combination with lesion of the endothelium facilitates the development of atherosclerotic changes in the vessels. The HDLP contain the main part of apo-A-1. An important role in the catabolism of apo-A-1 is played by the parenchymatous cells of the liver. Some investigators discovered a correlation between the level of LPL in the blood and the concentration of apo-A-1. Forming the main part of the

protein component of HDLP, the apo-A-I ensures the acceptance and transportation of cholesterol into the liver and, accordingly, its catabolism. No differences were found in the content of apo-A-I in the blood plasma in persons of groups 1 and 2 in comparison with its level in the control group.

In going over to an analysis of the apo-B content in the persons being studied, we noted a considerable quantitative difference. In the control group, the apo-B level was 82.4 mg/dl, in group 1 it increased to 104.3, and in group 2 – to 115.3 mg/dl. The apo-B/apo-A-I ratio changed accordingly in these groups. It was 0.62 in the control group, 0.88 in group 1, and sharply increased to 1.02 in group 2.

In view of the major significance of hormonal regulation of lipid metabolism in an organism, we compared both the background level of insulin and the cortisol content in the blood in these groups, and the values under conditions of a lipid load. We gave special attention to insulin. A glance at Fig. 15 reveals that in healthy persons the insulin level (background) was very moderate – 5.1 μ U/ml, in group 1 it was authentically higher – 13.0, and in group 2 it was 15.7 μ U/ml ($p < 0.05$).

What physiological laws ensure the relation between insulin and lipid metabolism?

A growth in the insulin level in the blood is very important. Lipids have a contrain-sular effect [397, 428, 439, 450, 474]. The background concentration of insulin in obesity is sharply increased, and when obesity is more pronounced, the insulin level is higher. This is especially important in the hypothalamic form of obesity, when a higher insulin content is noted in comparison with that in its exogenoconstitutional form. Some authors apart from hyperinsulinemia note a drop in the concentration of the thyroid-stimulating hormone, lower excretion of adrenaline and dopamine in the daily urine, and a growth in the excretion of 17-ketosteroids. The increase in the excretion of glucocorticoids enhances the processes of glyconeogenesis, promotes the development of hyperglycemia, which has a stimulating effect on the insular apparatus. Hyperinsulinemia, in turn, increases lipogenesis, which results in fat deposition. Consequently, obesity is attended by hyperinsulinemia with a drastically diminished biological efficiency of the hormone, i.e. insulin resistance.

It was noted that hyperinsulinemia mainly affects the triglyceride content. The level of total cholesterol correlates less with the insulin level. The content of HDLP cholesterol is inversely proportional to the background insulinemia [547, 555, 562, 573, 599].

The relation between insulin and the lipid metabolism processes was shown in experiments and under clinical conditions. It was noted that insulin, on the one hand, stimulates lipogenesis and thus facilitates the accumulation of cholesterol in the tissues of the vessels, and on the other, by inhibiting the processes of lipolysis, it lowers the mobilization of lipids from the wall of the vessels. It was noted that the degree of insulinemia regulates

the content of total cholesterol, HDLP cholesterol, and triglycerides, i.e. the insulin level is not only a damaging factor for the development of atherosclerosis, but also affects the plastic processes in the cells of vessels. It was noted, in particular, that in hyperinsulinemia, the rate of proliferation of endothelium cells, muscle cells, and fibroblasts alters. Therefore, a relation appears between the degree of glycemia, the insulin content in the blood, and the lipoprotein level in the blood and in the endothelium of the vessels. There is a direct correlation between the level of insulin and triglycerides and an inverse one between the content of insulin and HDLP cholesterol [56, 75, 112, 153, 602, 614].

An important role in regulating the insulin level is played by the hypothalamus-hypophysis system. The possibility of the pathological influence of the hypothalamo-hypophyseal-adrenal gland system on glucose-insulin homeostasis via the growth hormone, which is an antagonist of insulin, was shown. The influence of cAMP and cGMP on the effect of insulin was studied insufficiently.

In the opinion of a number of authors, it is the receptor apparatus of the cells, the system of cAMP and cGMP (including in the liver cells) that determine the influence of glucocorticoids on lipid metabolism in an organism.

When studying the hormonal profile in obesity patients (see Fig. 15), we found that the level of cortisol in the control group was 659 nmol/ml. Its growth in groups 1 and 2 because of the large scatter of the results was not authentic.

Comparisons of the parameters of the metabolism of lipoproteins in healthy persons and obesity patients of groups 1 and 2 suggested that a prediction of the development of IHD can be confirmed by a summary analysis of the lipid and hormonal parameters. The atherogenesis index is such an integrating parameter. By comparing the index in different groups, we found it to be 2.2 in the control group, 4.1 in group 1, and 4.2 in group 2. Consequently, the development of IHD in patients of groups 1 and 2 is more likely.

After analysis of the background comparisons of the lipid and hormonal parameters in the control group and obesity patient groups, we studied lipid and hormonal metabolism under conditions of a lipid load in the persons of these groups to establish the influence of the taking of fat food on the dynamics of lipid disorders and the reserve possibilities of an organism for processing the lipids supplied with food, and also for determining the groups of risk of IHD development associated with DLP.

It is expedient first of all to consider the investigations devoted to studying not only the reactions of the lipid spectrum, but also the change in the hormonal parameters in response to a fat load. These studies mainly consider matters connected with the secretion of insulin, and the state of carbohydrate metabolism in response to the introduction of exogenous fat.

Fig. 16. Influence of Lipid Load on the Content of Lipids and Apoproteins in the Blood in Persons with Different Degree of Obesity.

A lipid load enables one to uncover the different disorders in the system of lipid transportation and study the processes of accumulation of cholesterol in an arterial wall directly after the taking of food.

Physiological studies showed the secretion of insulin to be closely related to the taking of food. Under the influence of the introduction of exogenic proteins, fats, and carbohydrates (that decompose to glucose, amino acids, and fatty acids), insulin is secreted depending on the amount of food taken. In the 1970s, the concept appeared that insulin acts on cell metabolism by means of the receptors of the cell membranes. Special significance was attached to the receptors of cells of the adipose tissue, liver, muscles, and blood cells.

In recent years, special attention is being given to cAMP as a mediator of biochemical processes. Under the influence of insulin, the suppression of adenylatecyclase occurs. The formation of cAMP lowers, but the content of cGMP grows. It was noted in numerous experiments that the introduction into animals of STH leads to a diabetogenic effect. In DM patients, decompensation (the appearance of ketoacidose) is attended by an increase in the STH level in the blood. It should be noted that the metabolism of some substances drastically alters the nature of the course of DM. For example, free fatty acids and ketone bodies are insulin antagonists, and their increased formation (occurring in DM) sharply changes the level of insulin in the blood [154, 164, 212, 238, 253, 269].

In going over to an analysis of the results of a lipid load (Fig. 16) in healthy persons of the control group, we note that the cholesterol level in three and nine hours did not practically change with respect to the background (150, 142, 152 mg/dl).

What is such a stability of the results associated with?

Apparently, with the good compensating possibilities of a young healthy organism.

Numerous studies revealed that the changes in the cholesterol content in the blood serum at the expense of food fats are chiefly due to changes in the concentration of LDLP cholesterol and to a smaller degree of VLDLP cholesterol. When saturated fats in the food are replaced with polyunsaturated ones, the rate of LDLP synthesis falls, while that of catabolism grows. A result is lowering of the intravascular level of LDLP. In healthy persons, the drop in the cholesterol content in the blood serum caused by polyunsaturated fats is explained by the increased excretion of it.

Moreover, a high content of HDLP is an important factor for stabilizing the cholesterol level in the blood with a lipid load.

With a lipid load, the triglyceride level changes considerably. The background value of triglycerides was 72 mg/dl, in three hours after the load it increased to 150, and in nine hours it dropped to 54 mg/dl.

What factors ensured these dynamics of the triglyceride level?

After the taking of fat food, the "food" triglycerides resynthesized in the cells of the small intestine pass out into the intestinal lymphatic vessels in the form of chylomicrons, and then through the pectoral lymphatic duct enter the blood flow. Normally over 90% of the triglycerides is absorbed.

The triglycerides taken with food in the lumen of the intestine decompose into free fatty acids and monoacylglycerols, and in this form are absorbed by the epithelial cells of the intestine, where they are included in the composition of the chylomicrons. The main function of the latter is the transportation of the food triglycerides via the intestinal lymphatic vessels and the pectoral lymphatic duct into the blood flow. Proteins are contained

Fig. 17. Influence of Lipid Load on the Level of Hormones in the Blood in Persons with Different Degree of Obesity.

in the chylomicrons in a very small amount, but play the main functional role. The main protein component in the lymph chylomicrons is apo-B (up to 20%), the remaining part is apo-A and apo-C. The apoprotein B-48 is synthesized only in the cells of the intestine. If this protein is absent, the chylomicrons lose apo-A, but acquire apo-C and apo-E that are supplied to them by the HDLP. Triglycerides may be synthesized from endogenic fatty acids in the small intestine, but their main source is the liver, and also adipose tissue [316, 342, 412, 444, 452].

When analyzing the dynamics of the HDLP and apo-A-I content, we noted the sufficient stability of these parameters and the absence of a reaction to the lipid load. The level of apo-B changed more actively under a fat load. Its background value was 82 mg/dl, in three hours the apo-B level increased to 93, and after nine hours it dropped to the initial value (83 mg/dl). It was shown in numerous clinical and experimental studies that the level of apo-B reflects very clearly the content of LDLP in the blood plasma. Under the conditions or a lipid load, the formation of lipoproteins occurs with the aid of chylomicrons that form in the small intestine.

Lipid metabolism both at rest and especially under conditions of a lipid load is due to hormonal regulation, mainly at the expense of insulin and glucocorticoids. Fig. 17 shows that in healthy persons of the control group, the IRI in the blood plasma increased in three hours after a lipid load from 5.1 to 9.04 $\mu\text{U/ml}$. In nine hours, the insulin level dropped to the initial values (4.4 $\mu\text{U/ml}$).

What is the relation between the activity of insulin and lipid metabolism?

This problem was discussed widely by both physiologists and clinicians because the prophylaxis and treatment of atherosclerosis, especially in DM patients, must be conducted with a view to these relations. Numerous investigations revealed that a high level of insulin in the blood plasma stimulates the synthesis of fatty acids in the liver. This effect is manifest in the following [490, 508, 523, 547, 555, 604]:

(1) the flow of substrates formed in glycolysis in the Krebs cycle increases; of special importance here is the growth in the activity of acetyl-CoA-carboxylase;

(2) insulin has a direct stimulating effect on acetyl-CoA-carboxylase;

(3) utilization of glucose by the pentose path in connection with the increasing insulin level leads to the appearance of an increased amount of reduced NADP, which is an important component of fatty acid synthesis. It was shown that fatty acids are chiefly synthesized in the liver, and not in the adipose tissue, and these acids are then transported in the composition of VLDLP into the adipose tissue, where they accumulate in the form of triglycerides. The adipose tissue absorbs the circulating triglycerides at an increased rate under the influence of insulin. Stimulation of LPL occurs;

(4) the inhibiting effect of insulin with respect to the hormonesensitive lipase in the fat cells was studied by many authors. The lipase catalyzes the hydrolysis of triglycerides and frees fatty acids. Such an antilipolytic effect of insulin increases the total amount of fat in an organism.

Considerable importance in matters of regulation of lipid metabolism is attached to the activity of the hypothalamo-hypophyseal complex, which can be estimated indirectly by the cortisol content in the blood. We can see from Fig. 17 that the level of cortisol in the blood of healthy persons of the control group dropped from 659.9 nmol/ml (background) in three hours after a lipid load to 559.2, and in nine hours to 534.6 nmol/ml. However, this drop was not authentic. Apparently, the physiology of this process is associated with the activity of the hormonesensitive lipase of the adipose tissue. Catecholamines increase the activity of the hormonesensitive lipase of the adipose tissue and enhance the fat-mobilizing effect. Under conditions of an emotional stress, synergism of catecholamines and glucocorticoids appears in the metabolism of proteins and fats. The major part of the FFA is absorbed by the liver and participates in the resynthesis of the triglycerides. It is interesting to note that in the regulation of fat metabolism, the glucocorticoids and catecholamines react like synergists, while in the regulation of carbohydrate metabolism, these hormones are antagonists. Under the influence of glucocorticoids, the most important enzymes of glycolysis – hexokinase and phosphorylase – are inhibited. Carbohydrate metabolism is switched over to fat metabolism by means of glucocorticoids. Under various

conditions (emotional stress), an advanced growth in the content of glucocorticoids and catecholamines is observed [120, 193, 280, 600, 620, 622].

It is interesting to note that in healthy persons, the integrative reactions of the lipid and hormonal units of metabolism retain a stable atherogenic index under conditions of a lipid load (2.2, 2.2, 2.5) and a stable apo-B/apo-A-1 ratio (0.62, 0.67, 0.60). This points to a clear physiological relation between all the regulatory systems of an organism.

Thus, in analyzing the reaction of a healthy organism (control group) to a lipid load, we noted that an increase in the content of triglycerides and apo-B (atherogenic components of lipid metabolism) is compensated by a moderate increase in the level of apo-A-1 and stable values of the HDLP (antiatherogenic components of lipid metabolism). The regulating influence of insulin (a moderate increase in its concentration) and cortisol (a drop in its level) makes it possible to retain a stable atherogenic index within 2.2–2.9. Accordingly, it is very important to compare the reaction of healthy persons of the control group and obesity patients. Of special significance is the hormonal regulation of lipid metabolism under conditions of taking fat food.

When comparing the parameters for patients of group 1 (moderate obesity) and the control group, we noted a difference, primarily in the background figures – if the cholesterol level in the control group was 150 mg/dl, in group 1 it was 171.7. Accordingly the triglyceride content increased from 72 to 99 mg/dl. The drop in the level of HDLP was considerable: if in healthy persons it was 48 mg/dl, in group 1 it dropped to 35 mg/dl. Accordingly, the apo-A-1 level dropped to 117 (in the control group it was 132 mg/dl). These facts indicate that the antiatherogenic protection of the organism in obesity patients was reduced considerably. As should be expected, the content of the atherogenic components of the blood increased: if in healthy persons the apo-B level was 82 mg/dl, in group 1 patients it increased to 104.

In analyzing the reaction to a lipid load in patients of the control group, we made an assumption on the important role of insulin in regulating lipid metabolism, especially when taking fat food. A comparison of the background values of insulin in the control group and in group 1 confirmed this. If the background level of insulin in the control group was 5.1 $\mu\text{U/ml}$, in group 1 it was 12.97.

The growth in the insulin content in the blood in group 1 patients was attended by an increase in the cortisol level to 724.4 nmol/ml (instead of 659.9). All the disorders of lipid and hormonal metabolism were produced by a growth in the atherogenic index to 4.1 (in the control group it was 2.2).

In analyzing the reaction of group 1 patients to a lipid load, we noted that the cholesterol level did not experience any special changes (172, 169, and 184 mg/dl).

A clear dynamics of the triglyceride level was revealed: from the background value of 93 mg/dl it grew to 180.6 in three hours and failed to return to the normal value (128.5 mg/dl) in nine hours.

What is the pathophysiological mechanism of such a prolonged retaining of hypertriglyceridemia?

As already noted, the triglycerides of the chylomicrons are exogenic fats and contain food fats. The duration and level of the increased chylomicronemia depend, on the one hand, on the LPL concentration, and on the other, on the amount and composition of the introduced fats, and also on the amount of carbohydrates in the food. If carbohydrates are taken together with fats, the chylomicron level after a lipid load diminishes,

Many investigators note the relation between the insulin content in the blood and the triglyceride level. In some patients, this is explained by obesity that is attended by hypertriglyceridemia. In other patients obesity is absent, but there is resistance to insulin.

When analyzing in group 1 patients the reaction of the antiatherogenic fractions (HDLP and apo-A-1), we noted the absence of positive dynamics: the level of HDLP cholesterol was 35, 32, and 35 mg/dl, and that of apo-A-1 was 117, 122, and 121 mg/dl. This indicates that under conditions of taking fat food, the antiatherogenic function of the organism is lowered.

It was quite logical to assume that the atherogenic components of lipid metabolism are activated under conditions of a lipid load. When analyzing the dynamics of the apo-B content in group 1 patients, we noted that the background level of 104.3 mg/dl grows in three hours to 118.3 and in nine hours remains at the level of 114.7 mg/dl, unlike the dynamics in the control group, where the apo-B content after nine hours dropped to the background value.

Apo-B is the main protein component of LDLP, VLDLP, and chylomicrons. Catabolism of apo-B-LP occurs in the peripheral tissues. By combining with the receptors on the plasmatic membrane of the cells, apo-LP is transported into the cells, where the hydrolysis reactions occur. A growth in the content of apo-B in the blood is one of the risk factors of IHD development. The pathogenetic significance of the growth in the level of apo-B is associated with disturbance of the reaction of lipoproteins with receptors because of the appearance of dyslipoproteinemia, and also because of the modification of apo-B or under the influence of insulin in the blood serum and esterified fatty acids. There are also numerous biophysical transformations in a vessel wall. First of all, electrostatic reaction of the apo-B particles with glycosaminoglycans appears or hydrophobic reaction with elastin – the main component of the connecting tissue. These biophysical phenomena retain the LDLP in a vessel wall [347, 351, 365, 446, 484, 502].

When going over to an analysis of the dynamics of the insulin level in response to a lipid load in group 1 patients, we noted considerable changes: if the background level of insulin as 12.97 $\mu\text{U/ml}$, in three hours it grew to 20.4 and in nine hours dropped to 8.6 $\mu\text{U/ml}$.

The degree of lipacidemia and hyperlipidemia under the influence of insulin may lower rapidly, at the same time lipolysis lowers and lipogenesis grows. The deficiency of insulin in an organism retards lipogenesis and increases lipolysis. We can conclude from this that FFA, like insulin, are a decisive factor in regulating not only lipid, but also carbohydrate metabolism.

The deficiency of insulin increases the free fatty acid level and lowers the utilization of glucose in the muscles. This is why the muscle cells switch over to an energy donor – the free fatty acids. Accordingly, under conditions of a short supply of insulin, glucose accumulates in the adipose tissues and transforms into triglycerides.

We consider that in obesity, the number of receptors to insulin changes in all the organs and tissues, and this is what ensures the development of hyperinsulinemia under conditions of a lipid load.

Changes in the hypothalamic-hypophyseal system were noted in group 1 patients. The increased background cortisol value of 724.4 nmol/ml (659.9 in the control group) under the influence of a lipid load also dropped in three hours to 541.1 and in nine hours to 457.5 nmol/ml.

Pathophysiological studies revealed a direct relation between the glucocorticoid content and the level of hyperlipoproteinemia. A very important relation was established between hypertriglyceridemia and the excretion of free cortisol with the urine. We consider that the growth in the level of VLDLP cholesterol and LDLP triglycerides in IHD patients is associated with the high cortisol level, and pathogenetically, most likely, glucocorticoids disturb the metabolism of lipids by lowering the activity of heparin-dependent LPL. A growth in the cortisol level inhibits the effect of the LPL. It was shown experimentally that the high level of glucocorticoids in the blood is the primary factor of lesion of the endothelium and intima of the vessels, and also of the growth in the adhesiveness of the thrombocytes, retards reparative processes in a vessel wall, and inhibits the growth of endothelial cells [50, 87, 139, 175, 542, 558].

In group 1 patients, the atherogenic index grows to 4.1. After a lipid load, it grows to 4.3 in three hours, and to 4.5 in nine. These changes appear in connection with a growth in the level of total cholesterol and a drop in the content of HDLP cholesterol. Consequently, we can conclude that the prognostic characteristic with respect to the development of IHD for group 1 patients is unfavorable.

When analyzing the parameters for group 2 of obesity patients (a BWI of 30.1–35.0), we noted further progress in disorders of lipid metabolism. First of all, the cholesterol level increased to 181.1 mg/dl (the background value for healthy persons was 149.7). The triglyceride level also changed considerably: it increased to 136 mg/dl against 72.2 in the control group. In group 2, as in group 1 patients, the background level of HDLP lowered to 36 mg/dl. Accordingly, the apo-A-1 level was only 114 mg/dl against 132 in the control group. The background increase in the apo-B level in group 2 patients to 115 mg/dl (against 82 in the control group) was exceedingly unfavorable, from our viewpoint. The hormonal regulation of lipid metabolism with the aid of insulin and cortisol was disturbed considerably: if in group 1 patients the background insulin level was 12.97 μ U/ml, in group 2 it increased to 15.7. The high background level of cortisol (719.6 μ U/ml) supplements the picture of the disturbance of the hormonal regulation of lipid metabolism in group 2 patients.

The relation between the activity of insulin and the disturbance of lipid metabolism was studied by many authors under both clinical and experimental conditions. Attempts to find a relation between the content of cholesterol and that of insulin were not successful. It was noted that in hyperinsulinemia, the level of the endogenic triglycerides grows, which facilitates the development of atherosclerosis. To confirm this assumption, we observed type 1 DM patients whom insulin was introduced to. The level of not only glucose, but also of triglycerides lowered [89, 103, 122, 136, 166].

In going over to an analysis of the response of group 2 patients to a lipid load, we noted further enhancement of the pathological changes. The cholesterol level did not virtually change (the background was 181 mg/dl, in three hours the level was 175, and in nine it was 183.9 mg/dl. Special attention was attracted by the changes in the triglyceride level. The background TG level was 136 mg/dl, in three hours it was 238, and in nine hours it remained at 196 mg/dl.

What is the pathogenesis of this phenomenon?

In the metabolism of lipoproteins, a very important role is played by the lipolytic enzymes LPL and liver triglyceridlipase. They affect not only the plasma concentration of the lipoproteins, but also the content of the products of their decomposition in the blood, i.e. of LDLP and remnants. The status of the receptor apparatus on the surface of the membranes is the biochemical basis of these physicochemical reactions [203, 222, 247, 264, 286].

The level of the antiatherogenic components of lipid metabolism (HDLP and apo-A-1) is lowered in the same proportion as in group 1, and does not change under the influence of a lipid load. The content of apo-B changes more significantly. If in group 1, the

background value of 104 mg/dl under the influence of a lipid load increased to 118, in group 2 patients the background level of 115 increased to 138 and remained at the level of 131 mg/dl in nine hours after a lipid load. Clinical studies showed that the functional reaction of apoproteins with tissue elements ensures a system of lipid transportation in an organism, and accordingly the formation of atherosclerotic changes in the vessels. The directed transitions of apoproteins between lipoproteins of various classes in fasting or when taking food ensure in every person an individual nature of the physiological relations of lipid metabolism. The apo-B/apo-A-1 ratio determines the relation between the intensity of transportation of cholesterol into the tissues and the rate of its removal from the cells. An increase in the content of apo-B-LP is generally attended by the increased transportation of cholesterol into the tissues and the cell membranes [272, 288, 297, 342, 384, 422].

When analyzing the ratio in healthy persons (0.62) and in patients of group 1 (0.88) and group 2 (1.02), we noted that in disturbances of lipid metabolism in group 1 and 2 patients the transportation of cholesterol into the tissues and membranes of the cells grows.

When going over to an analysis of the hormonal regulation of lipid metabolism in group 2 patients, we noted the progress of hyperinsulinemia in them: the background IRI level was 15.7 μ U/ml, in three hours it was 26.5, and in nine hours was 19.31 μ U/ml.

These laws of the progress of hyperinsulinemia and dyslipidemia suggest a clear integrative relation between the content of insulin, triglycerides, and apo-B.

Insulin acts on cells in several stages [439, 450, 463, 482, 490]:

(1) binding of the hormones to the membrane receptors (it is very important that this relation depends on the insulin concentration in the blood, the number of receptors, and the affinity of the receptors for insulin;

(2) transformation of this hormone-receptor reaction into a transmembrane signal;

(3) the formation of an intracellular pulse;

(4) the subsequent chemical modification of various enzymes and transportation systems leading to the final biological effects of insulin.

Disorders leading to the development of insulin resistance may appear in each stage of this physicochemical train.

Insulin resistance is an integral concept characterizing all cases of a reduced biological effect of insulin with its normal concentration and activity. The mechanism of action of insulin may be disturbed even in hyperinsulinemia.

Insulin resistance develops very often in obesity patients, and the level of NEFA and the content of lactic acid rise. The normal tolerance to glucose in obesity requires an increased insulin level in the blood. The sensitivity of the receptors to insulin in obesity is reduced.

In summarizing, we can conclude that in the control group of healthy persons (and moreover in groups 1 and 2), the background parameters of the lipid and hormonal spectrum have a high variability. The lipid load enhances still more the mosaic nature of the picture and generally discloses in persons with a high degree of obesity more pronounced changes in the parameters being studied. Whether or not the changes in a number of parameters found in three hours after a load remain can be solved only in repeated observations. Nevertheless, even background disturbances of a lipid and hormonal nature are present in persons with a high degree of obesity, which suggests the probable further deepening and enhancing of the defects already existing in the metabolic units of the lipoproteins and hormonal status.

1.4. Disorders of Lipid Metabolism in Ischemic Heart Disease Patients

Most authors consider that the clinical picture of IHD is a result of manifestation of atherosclerosis of the coronary arteries of the heart. However, pathologo-anatomic studies did not confirm a direct correlation between the degree of stenosis of the coronary arteries and the extent of the clinical symptoms. The explanation is that many factors participate in the pathogenesis of IHD, and the integrative nature of the effect of hormonal, lipid, and coagulating factors suggests a mosaic interaction.

The participation of lipoproteins in the development of atherosclerotic changes in an arterial wall can be represented pathogenetically as consisting of several units [32, 36, 201, 234, 291, 310, 344]:

- (1) the deposition of lipids in a vessel wall, and also processes of proliferation and necrosis, whose most important component are smooth muscle cells;
- (2) synthesis of the main proteins of the connecting tissue of a vessel wall (collagen and elastin) occurring in smooth muscle cells; when atherosclerosis develops, structural changes occur in the smooth muscle cells that transform them into fibrocytes and disturb the production of collagen and elastin. As a result, the arteries become sensitive to mechanical effects;
- (3) penetration of LDLP and VLDLP from a vessel lumen into an intima with the subsequent penetration into an arterial wall;
- (4) penetration of the lipoproteins into an arterial wall (and their accumulation) that occurs more actively in disturbance of the intactness of the endothelium; damage to the endothelium may be associated with both hemodynamic factors and with increased agglutination and adhesion of thrombocytes to an arterial intima;
- (5) lesion of the endothelium leading to progressing proliferation of the smooth muscle cells and development of atherosclerosis.

The content of free fatty acids in the serum is very insignificant. After a fat food load, a considerable part of the FFA forms from the food fats along the path of their transformation into chylomicrons. Under the influence of the adipose tissue lipase, the triglycerides of the fat depots decompose into glycerol and fatty acids that either go to synthesize triglycerides or enter the blood.

The FFA are given up by the adipose tissue under the influence of hormonal and nerve regulation. Of especially great significance in this process is the level of glucose in the blood.

Cholesterol esters play the main role in the transportation of unsaturated fatty acids, especially if patients have a genetically determined deficiency of the enzyme LCAT (that forms in the liver). Here the level of unesterified cholesterol grows in the blood plasma and membranes of the erythrocytes of patients as a witness of the disturbed evacuation of cholesterol [58, 77, 90, 115, 128].

Lipolysis proceeds in an adipose tissue with the aid of a hormone-sensitive lipase whose activity is inhibited by insulin. When the blood contains insufficient insulin, the lipolysis of the adipose tissue grows, and the level of the circulating fatty acids increases. With an excess of insulin, the activity of the hormone-sensitive lipase lowers, and the level of the FFA in the blood drops accordingly. The supply of the FFA as a substrate is also regulated by insulin.

An important role in lipid metabolism is also played by LPL, which hydrolyzes lipoproteins rich in triglycerides in the capillaries of the adipose tissue and the skeletal muscles, where it is bound to the glycosaminoglycans localized on the surface of a capillary endothelium facing the lumen of a vessel. The enzyme is activated by apo-C-11, and is inhibited by sodium chloride and protamine sulfate. If LPL hydrolyzes lipoproteins rich in triglycerides chiefly within the capillaries of a vessel wall, the liver lipase hydrolyzes them in the liver.

LPL is synthesized under the influence of insulin, and when there is a lack of the latter, there is also a deficiency of LPL. In the extreme forms of insulin insufficiency, the LPL level is very low, which leads to the accumulation of lipoproteins rich in triglycerides in the blood (diabetic lipemia). The process is compensated by the introduction of exogenous insulin [136, 148, 155, 159, 167, 173].

A number of authors consider that the atherogenic nature of lipoproteins enriched with triglycerides is due to the fact that their lipoproteinlipolysis occurs not only on the endothelium of the capillaries, but also on the surface of the larger arteries where a high local concentration of LDLP is created. Owing to the very small size of these intermediates of proteinlipolysis, they can penetrate into an arterial wall through interendothelium

gaps. Morphological studies of the vessels of atherosclerosis patients revealed that an increased LDLP concentration in the blood plasma is attended by an increased amount of LDLP and apo-B in the intima of arteries and by increased hyperplasia of smooth muscle cells. It was established in biochemical studies that with definite types of hyperlipidemias, the rate of synthesis of the apo-B contained in VLDLP and LDLP is increased.

Clinico-biochemical investigations showed that the level of apo-B-100 in LDLP particles reflects the tendency of atherogenesis more exactly than the level of LDLP cholesterol. The inverse correlation between the lowering of the HDLP content and the frequency of developing IHD is also authentic. Accordingly, the parameter apo-A-1 shows the level of the atherogenic nature better than the HDLP cholesterol. As a result of the electrostatic reaction of apo-B with glycosaminoglycans or hydrophobic reaction with elastin (components of the connecting tissue), particles of LDLP are retained in a vessel wall [224, 247, 260, 272, 282, 288,].

It was proved that the key role in atherogenesis is played by the reaction of lipoproteins with smooth muscle cells of the middle membrane of an arterial wall. An important role here is played by the cell membranes. The latter react with lipoproteins because a number of parameters of the cell membranes coincide with those of the surface layer of lipoprotein particles. Molecules of unesterified cholesterol are an essential part of cell membranes. It is cholesterol that affects the macromolecular structure, permeability, and electrical potential of a membrane. With an increased cholesterol content in a membrane, the latter becomes dense, its permeability both for ions and for nonelectrolytes diminishes, and the activity of the membrane enzymes drops, and which is especially important, including that of adenylatecyclase. The accumulation of cholesterol in a membrane disturbs its vitally essential transportation and metabolic functions. When animals are fed cholesterol, the proliferation of the smooth muscle cells of the medium membrane of the aorta was registered. Apo-B is an essential component of the atherosclerotically damaged arteries.

That the functioning of carbohydrate and lipid metabolism is related was assumed long ago, although the number of publications on this topic is insignificant. Biochemical studies showed that in atherosclerotic lesion of the vessels, patients showed an increased activity of the alpha-glycerophosphate shunt, an increase in the amount of metabolites and co-enzymes (malate, lactate, pyruvate, NADP, oxaloacetate).

All these changes are based on suppression of the activity of glyceraldehydophosphatedehydrogenase, malatedehydrogenase, and lactatedehydrogenase.

It is in connection with this relation between carbohydrate and lipid units that all clinicians consider DM as an important factor facilitating the development of IHD [68, 189, 210, 316, 326, 363].

The risk factors of IHD (hypercholesterolemia, increased arterial pressure, smoking, DM, excess body weight, IHD in close relatives, hypoalpha-cholesterolemia) play an active role in the formation of pathological changes in the coronary blood flow by disturbing the sufficiency of blood supply to the myocardium, creating a deficiency in the demand of the myocardium for oxygen, etc.

Lipid metabolism in IHD patients is closely related to the functional state of the coronary vessels. In the period of a coronary spasm, metabolism is sharply disturbed in the zone of ischemia, the catecholamine level grows, and the peroxide oxidation of lipids increases [116, 386, 387, 388, 389, 625].

To study the relation between the morphological lesion of the coronary vessels and disorder in lipid metabolism, we conducted clinical investigation of 39 patients with various forms of IHD from 27 to 60 years old, all men. The latter circumstance was due to two reasons: (i) in males the influence of the hormonal background on the level of lipid metabolism is less pronounced, and (ii) the effect of alcohol on the functioning of organs and systems in males is manifest more clearly than in females.

The influence of alcohol on the development of hypertriglyceridemia was described by many clinicians. The mechanism is probably as follows: ethanol is oxidized mainly in the liver, which leads to the additional formation of FFA participating in the synthesis of triglycerides. In alcoholism patients, the HDLP level grows (at the expense of HDLP₂ and HDLP₃), probably as a result of the increase in the activity of LPL with the regular taking of alcohol.

All the patients we observed had no accompanying diseases leading to secondary dyslipidemias (diseases of the liver, kidneys, arterial hypertension, DM, hyper- and hypothyreosis, obesity). The diagnosis of IHD was made on the basis of physical examination, electrocardiography, veloergometry, and selective coronarography. The coronarograms were appraised by the classification of Yu.Petrosian and L.Zingerman. Of the 39 patients, 33 had myocardial infarction in their case history; nine persons had it twice.

For control purposes, we studied 20 healthy persons from 20 to 25 years old without diseases, with normal parameters of lipid metabolism.

By the results of the coronarographic investigations, all the patients with IHD were divided into two groups, the first (17 patients) with moderate lesion of the coronary arteries, and the second (22 patients) with a pronounced lesion of them.

When comparing the results of studying lipid metabolism in healthy persons and IHD patients, we noted clear distinctions of the background parameters – the background level of cholesterol in healthy persons was 167 mg/dl, and in IHD patients it was 281 mg/dl.

Hypercholesterolemia in animals is one of the widespread models of development of atherosclerosis and determining the role of cholesterol in atherogenesis. However, why "atherogenic" factors appear in hypercholesterolemia still remains a puzzle.

It was proved that atherosclerosis appears when the coordinated regulation of the metabolism of lipoproteins in the blood plasma and cholesterol in the cells vanishes. In this case, the function of the key regulators in this coordination is played by LDLP receptors. This is why most clinicians consider that "genetic (family)" atherosclerosis appears on the basis of molecular defects of the lipoprotein receptors. Various biochemical processes appear when the content of cholesterol in the blood grows and when the speed of its forward and reverse transportation into the cells of the cardiovascular system organs alters. A major significance here is attached to activation of the peroxide oxidation of lipids in the cells and tissues. To prevent the damaging effect of hypercholesterolemia on various enzymatic systems (including the membrane ATPases), diverse antioxidants are very popular.

The peroxide oxidation of lipids is an important physiological process in an organism and constantly proceeds in the cell membranes. The process, together with renewal of the membranes, plays the role of a very important link in the biosynthesis of prostaglandins, leukotrienes, and also in the processes of phagocytosis and a change in the structure of the intracellular membranes [15, 185, 320, 373, 429].

The lipid triad consisting of three biochemical processes is an important biochemical link in the peroxide oxidation of lipids. The first of them includes the stage of a primary deficiency of ATP, inhibition of the cycle of tricarboxylic acids, glycolysis, ATP-dependent cation pumps, and the accumulation of fatty acids. This triggers off the second process with inhibition of the cycle of tricarboxylic acids and the appearance of a deficiency of energy-rich phosphorus compounds. The third process consists in activation and the subsequent inhibition of glycolysis, the accumulation of fatty acids that is attended by inhibition of the slow channel of the electrogenic entry of Ca^{2+} into the cardiac myocytes and depression of the contracting function of the myocardium. This lipid triad produces very important changes in the lipid bilayer of the membranes of the cardiac myocytes. Damage to the membranes, potentiation of the excess of catecholamines, activation of lipases and phospholipases appear. The surplus of fatty acids and lysophospholipids on the

Fig. 18. Content of Lipids and Apoproteins in Blood in IHD Patients.

membranes is attended by activation of the peroxide oxidation of the lipids and damage to the membranes [458, 494, 498, 509, 555].

When comparing the triglyceride parameters in healthy persons and in patients with IHD in groups 1 and 2 (Fig. 18), we noted authentic differences. If in healthy persons the triglyceride level was 70 mg/dl (on an average), in group 1 IHD patients it was 124, and in group 2 it was 157 mg/dl.

The growth in the triglyceride level in the blood is an integrative parameter associated both with the nature of a patient's diet, the level of hormonal activity, and with physical activities. With a carbohydrates diet during a long time, the level of insulin in the blood increases, and this boosts the synthesis of endogenous triglycerides. The pathogenesis

Fig. 19. Influence of Lipid Load on the Content of Lipids and Apoproteins in Blood in IHD Patients.

of hypertriglyceridemia is due, on the one hand, to disturbance of the excretion of triglycerides from an organism because of the drop in the activity of extrahepatic LPL, while on the other, resistance to insulin appears, and as a consequence lipolysis of VLDLP is disturbed.

With an increased physical load, the triglyceride level in the blood plasma lowers in connection with the fact that the activity of LPL in the muscles and adipose tissue grows, and accordingly the rate of removal of triglycerides from an organism increases. Moreover, physical activities increase the level of HDLP (especially HDLP₂), which is very important for DM patients [42, 193, 571, 572, 614, 628].

It was noted in many investigations [189] that there is a correlation between the triglyceride level and the frequency of development of IHD, although these correlations are weaker than in hypercholesterolemia. It was noted previously that in 82% of persons who had had myocardium infarction, the background level of triglycerides increased.

A major importance in the pathogenesis of IHD is attached to the level of the HDLP cholesterol. The antiatherogenic function of the HDLP inhibits the formation of atherosclerotic plaques. A glance at Fig. 19 shows that in healthy persons the HDLP cholesterol level was 52 mg/dl, in group 1 IHD patients it was 39, and in group 2 patients it was 37.

A significant feature of the metabolic changes in atherosclerosis is the maintaining of a balance between the inflow of cholesterol into the cells in the composition of the LDLP (especially of cholesterol esters) and its removal from the peripheral cells into the liver with the aid of the HDLP. An important role here is played by the rate of the intracellular synthesis of cholesterol and the sensitivity of the vessel wall cells to hormonal regulation. It was proved clinically and experimentally that the HDLP in atherosclerosis patients have a diminished ability or accepting cholesterol from the smooth muscle cells of the aorta. In these persons on a background of hypercholesterolemia, the amount of glucocorticoid receptors of the blood lymphocytes grows. An obvious law was noted, namely, in atherosclerosis patients with an increased content of LDLP and VLDLP, the number of glucocorticoid receptors and the glucocorticoid sensitivity of the peripheral tissue cells lower. The combination of all these factors increases the synthesis of cholesterol, and it accumulates in the cells. The rate of cholesterol synthesis correlates with the number of cellular glucocorticoid receptors [15, 50, 210, 270, 301].

It was noted that the degree of acceptance by the HDLP of the cellular cholesterol correlates with the activity of the intracellular prostacyclin that catalyzes the process. The drop in the ability of the HDLP to accept cholesterol from the cells of the arteries and other tissues is connected with a decrease in the synthesis of prostacyclin.

Since the disorders in the process of formation of triglycerides and HDLP cholesterol may be associated with the quantitative aspect of lipoproteinlipolysis, we obtained the separate fractions of the HDLP. In healthy persons, the fraction of HDLP_{2B} was 33% and of HDLP_{3B} was 21%. In IHD patients, accordingly, these parameters were 10.2% and 7.8% in group 2, and we noted that persons with a low level of HDLP_{2B} (IHD patients) had an increased triglyceride level in the blood plasma.

The main part of the apo-A-1 is in the HDLP. A major role in the catabolism of apo-A-1 is played by the parenchymatous cells of the liver. Some authors discovered a correlation between the LPL level in the blood and the apo-A-1 concentration. Forming

the main part of the protein component of the HDLP, apo-A-1 ensures the acceptance and transportation of the cholesterol into the liver and, accordingly, its catabolism.

Inspection of Fig. 18 shows that in healthy persons the apo-A-1 level was 141 mg/dl, in group 1 IHD patients it was 118, and in group 2 it was 119 mg/dl.

As already indicated, the apo-B/apo-A-1 ratio is an important criterion of atherogenesis in healthy persons and IHD patients. It determines the relation between the intensity of transportation of cholesterol into the tissues and the rate of its removal from the cells. A growth in the level of apo-B-LP is generally attended by the greater transportation of cholesterol into the tissues and cell membranes.

After comparing the apo-B/apo-A-1 values in healthy persons equal to 0.72 and in IHD patients (1.24 in group 1 and 1.50 in group 2), we concluded that the higher figures may indicate a greater intensity of cholesterol transportation into the tissues in patients with a pronounced lesion of the coronary arteries.

The average background level of insulin in healthy persons was 6.1 $\mu\text{U/ml}$, in group 1 IHD patients it was 7.0, and in group 2 it was 14.6. The transportation and metabolic effects of insulin are a result of binding of the hormone to the membrane receptors. In hyperinsulinemia of any etiology, the number of receptors in the adipose tissue, liver, and muscles diminished appreciably [286, 316, 326, 342, 487].

To establish the latent forms of disturbance of the metabolism of lipoproteins and their hormonal regulation, we used a single food fat load. The results obtained when using a functional load test will reflect more accurately the dynamic state of the mechanisms regulating the metabolism of the lipoproteins. As indicated, the group with atherogenic dyslipidemias included persons for whom on a hungry stomach the content of cholesterol was above 200 mg/dl, that of triglycerides was above 200, and that of HDLP cholesterol was under 35 mg/dl.

It follows from Fig. 19 that the cholesterol level under the influence of a lipid load remained almost unchanged both in healthy persons (background value 167 mg/dl, in three hours it was 161, in six hours it was 164, and in nine hours it was 171 mg/dl) and in IHD patients. In group 1, the dynamics of the cholesterol content was 231, 218, 225, and 228 mg/dl, and in group 2 it was 281, 281, 267, and 301 mg/dl.

Triglycerides showed a more outstanding dynamics of the metabolic disorders under a lipid load. The physiological reaction in healthy persons was clearly expressed. The background was 102 mg/dl, in three hours the figure was 244, in six hours – 308, and in nine hours it was 133 mg/dl. An absolutely different picture was noted in IHD patients. The reactions in group 1 were 124, 234, 342, and 285 mg/dl, while in group 2 the changes were sharper: 157, 280, 483, and 368 mg/dl.

We see that the main defect of the metabolic disorders in IHD is that the physiological norm of the triglyceride level in nine hours after a lipid load is not restored.

What are these disorders associated with?

After the taking of food, chylomicrons are detected in the intestine. They form in the cells of the mucous membrane of the small intestine and pass into the lymphatic tracts. After getting into the blood channel, the chylomicrons experience numerous changes, in particular phospholipids are detached or are exchanged for other lipid fractions. The triglycerides of the chylomicrons are exogenic fats and contain the fats from food. The duration and level of increased chylomicronemia depend on the amount and composition of the introduced fats, and also on the amount of carbohydrates in the food. If the latter are taken together with fats, the chylomicron level after a lipid load diminishes.

The level of endogenic triglycerides in the blood depends on the caloricity (energy value) of the food, the fraction of carbohydrates, the kind and amount of mono- and disaccharides in the carbohydrate part of the food, and on the consumption of alcohol [385, 399, 419, 474].

The increase in the triglyceride level is especially noticeable in patients with hyperlipoproteinemia induced by carbohydrates. The qualitative composition of them is very important here – the TG level increases especially clearly when fructose or alcohol are consumed.

Biochemical investigations showed that between the level of the lipids (triglycerides) in the blood and that of heparin a relation exists. A clarification factor was discovered that acts on VLDLP and hydrolyzes triglycerides with the formation of FFA and heparin. It is LPL. A role in its activation is played by insulin, catecholamines, and STH. The above data show that in IHD patients, the activity of lipoproteinlipolysis is lowered.

We attach great significance to the dynamics of HDLP cholesterol under conditions of a lipid load. In healthy persons, the content of this cholesterol remains at the background level of 52 mg/dl (in three hours it was 51, in six it was 53, and in nine hours it was 53 mg/dl). The picture was absolutely different in IHD patients – for group 1 the figures were 39, 37, 36, and 37 mg/dl, and for group 2 – 37, 36, 34, and 28 mg/dl.

Numerous clinical and epidemiological investigations showed that the risk of IHD development is closely related to the low level of HDLP and does not usually depend on the total cholesterol content in the blood plasma. Experiments with animals revealed that only HDLP has the unique ability of accepting cholesterol from the cell membranes. This is connected with the fact that the biochemical composition of HDLP differs from that of

HDLP and VLDLP. The high-density lipoproteins have a large fraction of phospholipids and apo-A-1, which is absent in LDLP (where apo-B is present) [508, 515, 547, 561, 572].

The antiatherogenic function of HDLP is due to the fact that it accepts unesterified cholesterol from the membranes of the smooth muscle and endothelial cells of vessels, and also from VLDLP and chylomicrons when their triglycerides are hydrolyzed in the blood plasma. Biochemical studies showed that the transformation of free cholesterol into the esterified compound occurs with the participation of the enzyme LCAT. Its substrates are free cholesterol and lecithin contained in HDLP. The esterified cholesterol forms on the surface of the HDLP particles containing apo-A-1 combined with apo-D and LCAT. Numerous studies showed that the esterified cholesterol is transported into the liver with the aid of HDLP₂, where it is transformed into bile acids and excreted from the organism.

The antiatherogenic function of HDLP consists of an integral system including several units:

- (1) a protein-lipid structure of the surface monolayer that ensures incorporation of the nonesterified cholesterol into it;
- (2) an enzyme system that with the aid of LCAT reacts with its activator – apo-A-1 (inhibitor apo-A-2);
- (3) a system of nonenzymatic directed transportation of the cholesterol esters including lipid-transporting proteins.

Most scientists consider that this integral system under physiological conditions ensures the antiatherogenic function of the HDLP. It was noted that the activity of the LCAT and the intensity of removal of the esterified cholesterol from the surface of the HDLP particles depend on the inflow to the small spherical HDLP particles of nonesterified cholesterol both from lipoproteins enriched in triglycerides (chylomicrons and VLDLP) and from cell membranes [48, 64, 210, 594, 611, 614].

The activity of development of the atherosclerotic process depends on the relation of the intensities of the following nonenzymatic processes:

- (1) transportation of cholesterol esters in the composition of HDLP into the liver for excreting cholesterol from the organism;
- (2) transportation of cholesterol ethers in the composition of VLDLP and LDLP into the smooth muscle and endothelial cells of a vessel wall.

Disturbance of the normal ratio of the activities of these processes leads to the progressive development of IHD. On the surface of VLDLP, the amount of low-molecular hydrophilic proteins and high-molecular hydrophobic apo-B affects the physicochemical properties of the surface layer of these lipoproteins. Of special importance is the state (physicochemical) of the VLDLP for the intensity of penetration of the cholesterol esters

through the surface layer into the nucleus of particles. The degree of activity of LCAT is closely related to this process. When the activity diminishes, the cholesterol esters are transported to a greater extent to the VLDLP. The rate of the reaction catalyzed by LCAT depends not only on the amount and activity of the enzyme, but also on the concentration and composition of the substrates, activators and inhibitors of lecithin, free cholesterol, apo-A-1, and cholesterol esters.

In IHD patients, clinicians noted a drop in the activity of LCAT whose combination with the low level of HDLP cholesterol is especially unfavorable. A drop in the fraction of polyunsaturated fatty acids together with a growth in the fraction of saturated ones was noted. It was assumed that the drop in the complexing of lecithin with cholesterol is probably due to the lower activity of the LCAT and results in diminishing of the amount of cholesterol transported by the HDLP, i.e. a drop in the level of HDLP cholesterol is noted.

When analyzing the dynamics of the apo-A-1 content under the influence of a lipid load (see Fig. 19), we noted a clear distinction between the groups of healthy persons and IHD patients. In the former, the background level of apo-A-1 was 141 mg/dl, in three hours it was 138, in six hours it was 148, and in nine hours it was 156 mg/dl, i.e. a moderate increase was noted. The situation was different for the IHD patients. The background in group 1 and 2 patients was 118 and 119 mg/dl, respectively. In group 1 the apo-A-1 level in three hours was 119, in six hours it was 121, and in nine hours it was 117 mg/dl. The relevant values for group 2 were 116, 118, and 118 mg/dl.

The level of atherogenesis of lipoproteins in the blood flow is closely related to the following biochemical processes: (i) the rate of synthesis of cholesterol and lipoproteins, (ii) the rate of separation of cholesterol from the blood flow, (iii) the rate of excretion of cholesterol from the organism. An important role in maintaining the cholesterol level in an organism is played by the liver and small intestine. Especially importance in these processes is attached to the liver, because it synthesizes and excretes over 50% of the atherogenic lipids in an organism. In the peripheral tissues, atherogenic lipoproteins are mainly utilized, while cholesterol is excreted chiefly with the aid of the HDLP. In other words, the peripheral tissues are "programmed" for the utilization of cholesterol from the HDLP circulating in the blood flow. The metabolism of cholesterol in an organism is carried out with the aid of numerous enzymes, especially LCAT [33, 116, 270, 278, 291].

The biochemical process of cholesterol evacuation with the aid of HDLP is carried out in two ways: (i) via an aqueous phase according to the gradient of concentration, and (ii) by direct contact with the plasmatic membrane of a cell, including with the participation of HDLP receptors.

The main mass of the cholesterol is transferred from the cells into the blood through the aqueous phase, the HDLP functioning like a pump in the cycle of cholesterol pumping. The reaction of the HDLP particles with the cells is accomplished with the aid of a receptor protein and is attended by the appearance of a whole cascade of reactions in a given cell, namely, (i) pumping of cholesterol not only from the plasmatic, but also from the internal membrane, (ii) secondary pulse-mediators appear in a cell and activate the synthesis of cholesterol and block its esterification, and (iii) the capture of lipoproteins and fragments of cells modified by lipoproteins by macrophages playing the role of janitor cells.

Consequently, the significance of the HDLP as the most important unit of the anti-atherosclerotic process was proved with the aid of numerous clinical and experimental data.

The level of HDLP in the blood is closely related to the nature of the diet and with the inclusion in it of polyunsaturated fatty acids [50, 70, 234, 310, 338, 351].

A growth in the apo-B level in the blood is one of the risk factors of IHD development. The pathogenetic significance of the increase in the level of apo-B is associated with disturbance of the reaction of lipoproteins with receptors because of the appearance of dyslipoproteinemias and also because of modification of the apo-B or under the influence of the insulin of the serum and esterified fatty acids. Of interest are the results obtained by M.Ruda who studied unstable and stable stenocardia, compared the change in the level of apo-B in these groups of patients, and showed that in patients with unstable stenocardia the apo-B level is higher, while the apo-B/apo-A-I ratio exceeds unity. Analysis of the results of coronarography is very important. It was noted that in the patients of both groups the changes revealed in coronarography are approximately the same, there are no differences in atherosclerotic lesion, but there is a relation between the clinical course and the apolipoprotein level. With a severe course of the disease, the atherogenic shifts of apolipoproteins progressed, while with a favorable course they did not change.

When comparing in our studies the parameters of apo-B for healthy persons and IHD patients under lipid load conditions, we see clear distinctions: if in healthy persons, the apo-B level did not practically change (background – 100 mg/dl, in three hours – 100, in six – 86, and in nine – 96 mg/dl), in IHD patients the considerably increased background value was retained in the course of the lipid load. In group 2 the figures were 174, 168, 177, and 171 mg/dl. In group 1 the apo-B level was also high – 145, 133, 152, and 153 mg/dl.

Accordingly, the apo-B/apo-A-I ratio in healthy persons remains at a low level. In group I IHD patients, the background value was 1.24, in three hours it was 1.1, in six it

Fig. 20. Influence of Lipid Load on IRI Level in Blood in IHD and DM Patients.

was 1.28, and in nine it was 1.21. In group 2, the results were still more vivid: 1.50, 1.49, 1.45, and 1.51.

When analyzing the spectrum of lipids and apolipoproteins in the blood plasma in group 2 patients, we can note the following: the background parameters of the level of lipids and apoproteins in IHD group 2 patients were higher than in group 1. A fat load makes it possible to reveal the more pronounced atherogenic shifts of the lipid parameters and the level of apoproteins in the blood plasma in group 2 patients. This indicates the deeper disorders in the lipid transportation system of the blood plasma in these patients [89, 101, 115, 128, 148].

What are these disorders in lipid metabolism in IHD patients associated with? What hormones regulate these changes in metabolism?

We consider that insulin is the most significant regulating hormone in IHD patients. Our investigations (especially under conditions of a lipid load) conform this. We can see

from Fig. 20 that in healthy persons (with the absence of disintegration of the regulating adaptive mechanisms) a lipid load produces a very moderate reaction of the insulin level in the blood: the background is 5.2 $\mu\text{U/ml}$, in three hours it is 10.8, in six it is 11.6, and in nine it is 5.0 $\mu\text{U/ml}$. In IHD patients, these changes are sharper: the figures for group 1 are 7.0, 17.5, 10.3, and 13.0 $\mu\text{U/ml}$, and for group 2 are 14.6, 34.9, 23.9, and 18.3 $\mu\text{U/ml}$. It follows from the above data that the evolution of the insulin level in group 2 of IHD patients points to the high significance of hyperinsulinemia in the pathogenesis of IHD development.

What pathophysiological mechanisms are triggered off in IHD patients with hyperinsulinemia and disturbance of lipid metabolism?

We agree with the opinion of many authors that in IHD patients hyperinsulinemia is noted (often in combination with hyperglycemia) caused by a diminished tolerance to glucose. The pathophysiological essence of this process consists in an increase in the amount of FFA in the blood that is associated with a disorder in the function of the liver. In IHD patients, the increased formation of lipids is due to the activation of lipogenesis of the adipose tissue, when lipids form from glucose and acetate.

Physiological studies showed that in pronounced hyperglycemia, an organism begins to actively perform a glycogen-forming function under the influence of insulin. In hypoglycemia, the glycogenolytic effect is activated. Insulin is a very important hormonal regulator of the formation of glycogen. It increases the permeability of the membranes to glucose, stimulates the activity of glucoso-6-phosphate facilitating the formation of lipids, carbohydrates, and acting on proteosynthesis and the inhibition of proteolysis [164, 166, 170, 222, 223].

Clinicians proved that the degree of utilization by the myocardium of a substrate strictly correlates with the level of metabolism of a number of hormones. The number and quality of the nutrient substances utilized by the myocardium are closely related to the processes of lipolysis and glycogenolysis in the liver and adipose tissue. The functioning of these organs and tissues determines the concentration in the blood and consumption by the myocardium of glucose and free fatty acids. The insulin concentration is a very important unit in the regulation of the level of glucose and FFA in the blood. Glucose-insulin mixtures have been finding an application in practical cardiology during many years, but the pathophysiological aspects of the action of these mixtures were not established. The role of carbohydrates in hypoxia of the myocardium (stenocardia, myocardium infarction, etc.) is especially important for supplying energy to the heart. Experimental studies proved the biological efficiency of insulin in the absence of glucose too (its influence on the transportation of amino acids, fatty acids, potassium, etc.). Insulin can stimulate anabolic

processes in a cell, enhance reparative reactions, maintain equilibrium of protein metabolism, and raise the level of creatine phosphate in the myocardium.

Insulin is considered as the only universal anabolic hormone lowering the level of glycemia. Numerous clinical observations reveal that hypoinsulinemia produces deep disorganization of the metabolic processes in the myocardium, liver, and muscles. In experiments, hypoglycemia leads to the more rapid appearance of disturbances of the conductance in the myocardium. Hyperinsulinemia in the process of development of atherosclerosis may facilitate the change in the vessel permeability and infiltration of atherogenic lipids into the arteries. The inadequacy of the insulin present in an organism is expressed primarily in the lowering of the tolerance to carbohydrates. Disorders of the secretion of insulin and glucose are the main factors facilitating the development of coronary diseases [247, 251, 279, 294].

A very important matter in the insulin supply to an organism is the discrepancy between the absolute concentration of the hormone in the blood and its biological efficiency. Hyperinsulinemia in IHD patients can be considered as a compensating reaction of the beta cells aimed at normalization of carbohydrate metabolism.

The problem of the relative insulin insufficiency is quite involved. One of the hypotheses consists in that in IHD patients, the reactive sensitivity of the peripheral tissues to insulin lowers. Most clinicians consider that the pathophysiological basis of this phenomenon is the hyperactivity of hormonal and metabolic antagonists such as cortisol, the growth hormone, triglycerides, FFA, and uric acid. Lowering of the vessel permeability is another cause of the peripheral inefficiency of insulin [260, 309, 330, 397, 398, 421].

These comparisons show that the adipose tissue can use "bound insulin" for the normal functioning of metabolic processes in an organism. Lowering of the sensitivity of the adipose tissue to insulin in IHD patients was noted by many authors. The presence in IHD patients of a high level of FFA on an empty stomach and after a glucose load is one of the facts confirming these assumptions.

The membrane of a fat cell has two types of hormonal receptors: (i) receptors that react to stimulation by catecholamines, and owing to this the formation of cAMP increases with the participation of adenylatecyclase (which activates lipolysis), and (ii) insulin receptors that inhibit the activation of adenylatecyclase by these stimulating hormones.

Stimulation of insulin receptors is attended by lowering of the cAMP concentration and the suppression of lipolysis. These aspects are extremely important. Consequently, a fat cell membrane can react both to stimulation of lipolysis under the effect of catecholamines and to inhibition of lipolysis under the influence of insulin. The stimulation of the insulin receptors occurs very illustratively in DM, when the absence of insulin leads to

uncontrolled stimulation of the intracellular lipase by lipolytic hormones. As a result, a clearly expressed mobilization of FFA from the fat cells is noted. A similar reaction is observed in emotional stress and a physical load, when FFA is mobilized from a depot or as a result of the increased secretion of adrenaline from the medullary substance of the adrenal glands into the general blood flow. In all cases of stress, the mobilization of fats, being a reply to an emotional tension, physical load, or to an increased demand for energy, increases the content of fatty acids needed to produce energy in various tissues of an organism [463, 469, 475, 522, 573, 621, 624].

During recent years, clinicians give great attention to the exchange of lipids between the blood plasma and erythrocytes. The interest is due to the fact that the metabolism of substances in cells (including in erythrocytes) depends on the structural and functional features of a cell membrane. The structural lipids, in addition to the mechanical function of separating the liquid spaces in cells, are also important for the metabolism of substances in a cell. Lipids play the main role in regulating cell permeability and transporting various substances through a membrane. In a number of cases, phospholipids are the main partners in enzymatic processes in cells. Cholesterol and phospholipids are the main components of the structure of membranes. In normal erythrocytes, the cholesterol/phospholipid ratio is 0.8. In atherosclerosis, this coefficient grows sharply to 1.2–1.4 as a result of an increase in the cholesterol content in a membrane that has the following duties: (i) it is a structural component of a plasmatic membrane ensuring its functioning, and (ii) it is a transportation form of free cholesterol that is rapidly exchanged with the lipoproteins of the plasma. The overloading of an erythrocyte membrane with cholesterol produces an increased rigidity of the erythrocyte, lowers its deformability, and changes its hemodynamic properties [495, 469, 621, 628].

In view of the major importance of the exchange of lipids between the blood plasma and erythrocytes, we studied the lipid and phospholipid spectra of the blood plasma and erythrocyte membranes in 12 IHD patients and 15 healthy persons.

In the patients, the cholesterol level in the blood plasma was increased considerably, on an average up to 233 mg/dl (in the healthy persons it was 184 mg/dl). We noted a growth in the content of triglycerides, LDLP cholesterol, VLDLP cholesterol, and a drop in the level of HDLP cholesterol. We considered the pathophysiological fundamentals of these disturbances and noted only a growth in the index of atherogenesis in the IHD patients to 4.25 (in the healthy persons it was 2.2).

Many clinicians and experimenters attach major importance to the state of the phospholipid spectrum of the blood plasma. It follows from Fig. 21 that especially sharp

Fig. 21. Phospholipid Spectrum of Blood Plasma in IHD Patients.

disturbances are noted in the content of lysophosphatidylcholine (LPC) and sphingomyelin (SM).

It is considered that the phospholipids of the plasma mainly perform the function of biological detergents and together with the apoproteins increase the solubility of nonpolar lipids. The main part of the plasma phospholipids is formed by lecithins and SM. The high surface activity of the phospholipids is of major significance for building up a lipoprotein and its exchange with the plasma. It was proved in recent years by using tracer fatty acids that there is a close relation between the metabolism of polyunsaturated fatty acids and the phospholipids of the blood.

The content of LPC in the phospholipid spectrum in IHD patients (see Fig. 21) grows to 6.55% (in healthy persons it is 3.75%), and of SM drops to 10.59% (in healthy persons it is 19.23%).

In recent years, great attention is being given to the lipid composition of the erythrocytes in connection with their participation in the metabolism of lipids and to their influence on the hemodynamic functions of an organism. Special importance in these studies is attached to the composition of the lipid layer of an erythrocyte membrane [22, 36, 46, 123, 228].

The lipid layer of an erythrocyte membrane simultaneously has fluidity and order of its structure. The latter, on the one hand, is needed for the processes occurring between the membrane and environment (the reception of information, metabolism of energy and matter). On the other hand, the vital activities require that the components of a membrane

Fig. 22. Phospholipid Spectrum of Erythrocyte Membranes in IHD Patients.

could contact one another and form short-living complexes. The phospholipid composition of an erythrocyte membrane affects many of its functional properties. Among them are regulation of the active and passive transportation of organic substances and electrolytes through a cell membrane, sensitivity to the action of hormones, and participation in blood coagulation processes. The change in the phospholipid asymmetry affects the adhesion of an erythrocyte to a vessel endothelium, which results in disturbance of microcirculation.

In the membrane of erythrocytes in IHD patients, the fraction of cholesterol increases moderately to 52.8% (the norm is 44.6%), the content of phospholipids drops substantially to 28.5% (against 46.2% in healthy persons), the fraction of triglycerides does not virtually change, but the FFA content grows to 3.07%. Of special significance, from our standpoint, is the change in the cholesterol/phospholipid ratio. If in healthy persons it is 1.08, in the IHD patients it is 1.82. The SM fraction also drops sharply to 14.95% (against 19.6% in healthy persons).

Consequently, in IHD patients, considerable changes are observed in the phospholipid spectrum of the erythrocyte membranes (Fig. 22).

What do these changes indicate?

Phosphatidylcholine (PC) and phosphatidylethanolamine (PEA) together with cholesterol are the main structural components of a cell membrane. We attach great significance to the ratio PEA/PC for appraising the structural and functional state inside a membrane.

The cholesterol/phospholipid ratio reflects the rheological properties of erythrocytes. An isolated growth in the cholesterol level in a membrane without increasing the cholesterol/phospholipid ratio changes the viscosity of the blood and disturbs its rheological properties. A growth in the level of total cholesterol in the blood plasma and a change in the cholesterol/phospholipid ratio in a membrane are attended by lowering of the fluidity of the lipid phase of a membrane, increasing of the volume of an erythrocyte and of its rigidity, and by lowering of the deformability of a cell. This results in thickening of the basal membrane of the endothelium of vessels, slowing of the blood flow, and increasing of aggregation of the elements [121, 226, 353].

Moreover, a change in the phospholipid spectrum of the membranes of erythrocytes in IHD patients disturbs the function of the cytoplasmatic receptors. This relates first of all to the insulin receptors on the membranes of the erythrocytes. Experiments showed that the transportation and metabolic effects of insulin are a result of the binding of the hormone with membrane receptors. Changes in the phospholipid composition of the erythrocyte membranes affect both the number of these receptors and their functional activity.

It was noted that in IHD patients with an excess body weight the sensitivity of the fat cells to insulin is reduced. In connection with the fact that in obesity the activity of the LPL is disturbed, and the latter is controlled by the insulin-glucose system, changes in the sensitivity of the receptor apparatus and correspondingly of cAMP appear. Biochemical studies showed that the cAMP level regulates the activity of the LPL. The cAMP activity in a cell, in turn, depends on the action of the enzymes adenylatecyclase and phosphodiesterase that synthesize and decompose cAMP. The synthesis of cAMP is stimulated by hormones such as adrenaline, glucagon, and ACTH. The influence of insulin on the cAMP level in a cell can be characterized as an inhibiting one: it increases the activity of phosphodiesterase and enhances the decomposition of cAMP.

The enzyme systems ensuring the activity of a cell can be divided into several groups: (i) supporting the active transportation of nutritive substances in a cell from the environment, (ii) ensuring the energy reaction of a cell, (iii) regulating the synthesis of a protein and nucleic acids, (iv) ensuring cell mitosis, and (v) participating in the biosynthesis of proteins and polysaccharides.

Analysis of the state of the enzyme systems in the myocardium cells in cardiac insufficiency in IHD patients revealed various pathological changes: (i) the amount of FFA circulating in the blood may grow as a result of hydrolysis of the deposited triglycerides, (ii) the membrane phospholipids can be hydrolyzed by the activated phospholipases of the cytosol, which leads to the liberation of fatty acids, (iii) the intracellular content of fatty acids may grow as a result of their absorption by ischemic cells, inhibition of fatty acid

oxidation, and condensing of the bicarbon fragments. All the above processes terminate in the accumulation of fatty acids and their metabolism products within and around the cells of an ischemic myocardium. The fatty acids have a complicated influence on the functioning of a membrane – they can either stabilize or disturb the membrane structure.

In summarizing, we can conclude that a major role in disorders of lipid metabolism in IHD patients is played by an increased level of cholesterol in the blood. The latter is a factor that considerably modifies the structural and functional properties of biological membranes in various organs and tissues, and it is this property that determines its leading role in the pathogenesis of atherosclerosis [83, 176, 292, 516].

The mismatch of the two cholesterol flows in an organism – the transported cholesterol in the lipoproteins circulating in the blood and the cholesterol in the cells, is the molecular prerequisite of atherosclerosis.

Experiments on animals showed that a cholesterol load on them alters the sensitivity of the thrombocytes to some aggregation inductors, in particular to adrenaline. Vessel walls enriched in cholesterol were distinguished by an increased sensitivity to the vasoconstrictive effect of potassium depolarization. We can thus conclude that cholesterol is an important factor in regulating the functional state of both the vessels and thrombocytes. An increased cholesterol content in the blood causes the development of vasomotor and thromboembolic disorders dangerous for an organism. Even transient hypercholesterolemia is the cause of development of regional dycirculation. The regions of the blood channel where there are defects of the vascular endothelium are the weak spot.

In a postischemic syndrome, disturbance of the structural and functional properties of the membranes of erythrocytes reaches a critical level. When changes in the cell membranes lower their sorption properties, the erythrocytes become a source of thromboplastic substances and energy products that create favorable conditions for thrombus formation and blood coagulation.

We can conclude that in IHD patients, disturbance of lipid metabolism is based on the hormonal disintegration of the regulatory adaptive mechanisms, and the role of insulin is especially important.

In IHD, the structural and functional properties of the erythrocytes are altered drastically, the cholesterol/phospholipid ratio equals 1.2–1.4 instead of 0.8. This overloading of an erythrocyte membrane with cholesterol increases its rigidity, lowers its ability of deforming, and changes the hemodynamic properties.

1.5. Lipid Metabolism Disorders in Diabetes Mellitus Patients

Diabetes mellitus and atherosclerosis are diseases with similar disorders of lipid metabolism attended by hypercholesterolemia, hypertriglyceridemia, and hypoalphacholesterolemia.

A disorder in metabolism in DM occurs chiefly because of tissue insulin insufficiency. The metabolism of carbohydrates, and also of fats and proteins is disturbed. Not only insulin, but also the contrainsular hormones glucagon, somatostatine, glucocorticoids, and catecholamines are included in the chain reaction of the damaging hormonal units. In biochemical investigation of metabolism processes (under conditions of insulin insufficiency), there were noted a lower penetration of glucose into the muscle and fat cells, disturbance of oxidative phosphorylation, and lowering of glycogen synthesis. Hyperglycemia in DM ensures a better penetration of glucose into a cell. The disturbed participation of glucose in the supply of energy to an organism includes fats and proteins into energy metabolism as a compensation. As a result, an increased amount of FFA, ketone bodies, and amino acids appears in the blood. The increased supply of FFA into the liver causes the greater synthesis of triglycerides [155, 168, 171, 203, 231, 247].

The metabolic disorders in DM are thus attended by numerous functional disorders such as tissue hypoxia, dyslipoproteinemia, hormonal homeostasis, metabolic acidosis, angiopathies, and electrolytic disturbances. A special significance is acquired by the relation between disorders of the oxygen-transportation function of the blood, its coagulating system, and as a consequence, the development of microangiopathies. Tissue hypoxia in DM patients is realized according to the following scheme: erythrocyte membrane – plasma – capillary wall – tissue. An increased content of lipids in the blood plasma of DM patients impairs the transcapillary diffusion of oxygen.

In hypoxia of any genesis, acidosis appears in the myocardium as a result of anaerobic glycolysis. The utilization of pyruvic acid in the Krebs cycle is inhibited, and the increased transformation of pyruvate into lactic acid begins. Moreover, intracellular acidosis destabilizes the membranes of the lysosomes and causes hydrolytic enzymes to emerge from them, thus increasing their activity. All this lowers the energy potential of the cardiac myocytes. Great attention is attached to the peroxide oxidation of lipids in the myocardium. Activation of the free-radical peroxide oxidation of lipids (FPOL) may be associated with the accumulation of fatty acids under conditions of hypoxia, and also in DM and obesity. The growth in the FPOL is generally combined with activation of the sympathico-adrenal system [320, 399, 418, 429, 458].

It was shown under clinical conditions that in DM a growth in the production of the ACTH, STH, and also of glucocorticoids and catecholamines occurs.

Fig. 23. Synthesis and Decomposition of Triglyceride in Adipose Tissue Cells Normally and in DM.

With an excessive physical load, destruction of the mitochondrias, expansion of the canaliculi of the endoplasmatic network, and fragmentation of the myofibrills may appear. An oxygen deficiency, disturbance of enzymatic processes, and an excess accumulation of catecholamines in the myocardium may be the pathophysiological bases of a physical overload. This leads to the appearance of disseminated necrosis.

Experimental studies showed a cell membrane to be the most important point of application of insulin action in an organism. The active mechanisms of a cell membrane

Fig. 24. Main Directions of Disturbed Relation between Insulin and Glucose.

pass over the influence of insulin to various aspects of the vital activities of a cell including its genetic function. Of special importance in the regulation by insulin of the permeability of a cell membrane. The Na-K-dependent ATPase is the point of application of insulin in a membrane.

A glance at the scheme in Fig. 23 shows that in healthy persons insulin regulates lipogenesis. With the aid of a specific carrier system (in membranes of both muscle and fat cells), insulin ensures an increased inflow of glucose to cells, which creates a greater pool of alpha-glycerophosphate. This causes a greater amount of fatty acids to be fixed on the cell acceptors, and lipogenesis increases [421, 438, 439, 463, 467].

In DM (and accordingly with a deficiency of insulin), glucose in accordance with the carrier mechanism is not assimilated in a sufficient amount, and the major part of the fatty acids enters the blood, and then the liver, thus creating a favorable medium for lipoprotein formation. This biochemical process often causes liver adiposis in DM patients.

Consequently, a deficiency of insulin underlies the inhibition of lipogenesis and activation of lipolysis.

We thus see that free fatty acids, like insulin, play a decisive role in the regulation of not only lipid, but also of carbohydrate metabolism. A deficiency of insulin (both absolute and relative) increases the level of the FFA and at the same time lowers the utilization of glucose, so that the muscle cells, as already noted, are switched over to FFA as an

energy donor. Glucose accumulates in the fat cells and transforms into triglycerides if the amount of insulin is sufficient. Should hyperinsulinism appear for some reason or other, the lipogenesis becomes excessive, the fraction of triglycerides in the cell space grows, this leads to hypertrophy of the adipose tissue and, finally, to obesity (Fig. 24).

To date, the role of hyperinsulinemia in the development of atherosclerosis was proved. The atherosclerotic changes in the vessel walls in DM patients introduce complications into the course of angiopathies and, in particular, of cardiopathy, which leads to early invalidism and death [475, 488, 495, 522, 547].

An increased level of lipids in the blood and a high arterial pressure are the two main factors causing the development of IHD and atherosclerosis. But DM patients have features that are due to the greater frequency and combination of risk factors such as hyperlipoproteinemia, arterial hypertension, increased blood coagulation, and also the presence of hyperglycemia, microangiopathies, and changes in insulin secretion. In DM patients, three biochemical aspects of regulation of the transportation of lipoproteins in the plasma can be singled out [551, 570, 579, 585, 611]:

- (1) an increased production of lipoproteins rich in triglycerides;
- (2) lowering of the hydrolysis of triglycerides by the action of LPL;
- (3) disturbance of the catabolism of lipoproteins rich in cholesterol.

Insulin affects both the synthesis of triglycerides and their withdrawal from circulation. Many investigators note the correlation between the content of insulin in the blood and the triglyceride level. This is sometimes attended by obesity which, in turn, is associated with hypertriglyceridemia. However, such a relation is also retained in people not suffering from obesity, but having resistance to insulin. Endogenous triglycerides are synthesized in the liver from fatty acids and glucose. Insulin, by acting on the liver, stimulates the synthesis of triglycerides. With a deficiency of insulin, the synthetic activities of the liver are suppressed. The synthesis and decomposition of lipoproteins rich in triglycerides are regulated in an organism by two enzymes: a hormonosensitive lipase and lipoproteinlipase.

Lipolysis in an adipose tissue occurs with the aid of a hormonosensitive lipase (HSL) whose activity is inhibited by insulin. With an insufficiency of insulin in the blood, the lipolysis of the adipose tissue grows and the level of circulating fatty acids increases. With an excess of insulin, the activity of the HSL lowers, and the level of FFA in the blood lowers accordingly. The supply of the FFA as a substrate is also regulated by insulin [45, 118, 133, 180, 201, 310, 584].

An important role in lipid metabolism is also played by LPL. It hydrolyzes the lipoproteins rich in triglycerides in the capillaries of adipose tissue and skeletal muscles,

where it is bound to the glycosaminoglycans localized on the surface of a capillary endothelium facing the lumen of a vessel. The enzyme is activated by apo-C-2 and is inhibited by sodium chloride and protamine sulfate. The LPL hydrolyzes lipoproteins rich in triglycerides mainly in the capillaries of vessel walls, while the liver lipase hydrolyzes them in the liver.

LPL is synthesized under the influence of insulin, when there is a deficiency of the latter there is also one of LPL. In extreme forms of insulin deficiency, the LPL level is very low, which leads to the accumulation in the blood of lipoproteins rich in triglycerides (diabetic lipemia). This process is compensated by the introduction of endogenous insulin. Consequently, depending on the form of DM, there are various mechanisms of development of hypertriglyceridemia: in DM of type I, direct suppression of triglyceride synthesis in the liver occurs. This is compensated by the excess supply of FFA from the adipose tissue, but here the removal of triglycerides from circulation is disrupted. In DM of type II that is attended by hyperinsulinemia or in obesity, the synthesis of endogenous triglycerides by the liver and the formation of triglycerides are enhanced [87, 96, 234, 381, 392, 537].

In DM of both types I and II, a correlation was revealed between the level of hypertriglyceridemia (HTG) and glycosylated hemoglobin. P.Janka and his co-workers in 1987 singled out hyperinsulinemia combined with HTG as a syndrome – a risk factor of the development of atherosclerosis in DM.

Apart from HTG, in DM patients a growth in the cholesterol level in the blood plasma was noted more frequently than in persons without disorders in carbohydrate metabolism. The influence of insulin on cholesterol metabolism has been studied insufficiently. Experiments showed the overwhelming influence of alloxan diabetes on the synthesis of cholesterol. On the other hand, the introduction of insulin via the portal vein leads to the enhanced inclusion of acetate into the cholesterol. Insulin stimulates the synthesis of cholesterol in the liver tissue, where it influences HMG-CoA-reductase (3-hydroxy-3-methylglutaryl-CoA-reductase) – an enzyme limiting the reaction rate in the metabolism of cholesterol.

The activity of this enzyme in the liver of rats with alloxan diabetes is very low, but insulin restores it to the normal value. According to P.Polumbo (1978), in DM patients there is both a growth in the synthesis of endogenous cholesterol and retardation of its excretion. On the basis of numerous observations, R.Stout in 1985 postulated the influence of uncontrolled hyperglycemia in DM on the increase in the production of cholesterol and also on the relation between the level of triglycerides and the excretion of bile acids – a product of cholesterol metabolism. The production of triglycerides rich in VLDLP and bile acids may be associated with the synthesis of cholesterol, which is presumably in-

creased in the early, uncontrolled stages of DM. DM patients both with a deficiency of insulin and with hyperinsulinemia suffer from hyperphagia. The latter, in turn, leads to hypertrophy of the mucous membrane of the intestine and a growth in the activity of HMG-CoA-reductase. Consequently, hypercholesterolemia may be due to an increase in the synthesis of sterol in the small intestine, its excess supply with the food, and in increase in its absorption [76, 145, 159, 167, 214].

The path of penetration of cholesterol into a cell in LDLP by means of a receptor is the main factor for maintaining normocholesterolemia. Improper utilization of cholesterol may be a result of a deficiency or activity of the cell receptors, and also of changes in the structure of the LDLP themselves, e.g. the glycosylation of LDLP in DM patients, and the formation of autoimmunity complexes. R.Stout [555] considers that the mechanism of action of insulin is most likely associated with a growth in the number of LDLP receptors than with a growth in the affinity for them.

Investigations of the HDLP in DM patients have a contradictory nature. The protective role of the HDLP in DM remains unclear. It was shown that the level of HDLP cholesterol in type II DM patients is lowered. Some authors determine in these patients the presence of a negative correlation between the content of HDLP and the level of glycosylized hemoglobin, which was not observed in type I DM patients. The treatment of DM with the aid of a diet or sulfonyl-urea drugs normalizes the level of the HDLP. The restored activity of the LPL after the introduction of insulin increased the level of HDLP cholesterol, possibly in the catabolism of VLDLP. R.Eckel and his co-workers in 1981 found that in type I DM patients the level of HDLP cholesterol was slightly higher than in the control group, while the ratio of the high-density and low-density lipoprotein cholesterol is considerably higher in the patients. These changes correlated with the level of the HDLP₂ cholesterol.

In type II DM with hyperinsulinemia, there is a low level of the HDLP cholesterol. This is apparently associated with the fact that the point of application of insulin in type II DM is the liver, and not the peripheral tissues (as in type I DM). Here the activity of the liver lipase participating in the catabolism of the HDLP increases. This is what explains the low values of the HDLP cholesterol in type II DM patients and their high disposition to atherosclerosis. By one hypothesis, the protective influence of HDLP cholesterol on the risk of incidence of IHD consists in the participation of HDLP in the reverse transportation of cholesterol from the tissues that lowers its accumulation in an arterial wall. This is what we call a cholesterol-acceptor function. By another hypothesis, HDLP or one of their components prevent the formation of thrombi on the surface of the atherosclerotic plaques,

e.g. by stabilizing the prostacyclin in a vessel wall as a result of prolonging the duration of its functioning. This process occurs via apo-A-I [203, 214, 239, 275, 288, 342].

Experiments with a culture of fibroblasts and endothelial cells revealed that HDLP can block the receptors of LDLP cells, after which the accumulation of cholesterol in the cells lowers.

Consequently, the content of HDLP cholesterol in DM depends on the type of the disease, the presence or absence of obesity, the degree of control of the course of the disease, and the kind of treatment.

The disorders of lipid metabolism in DM depend directly on the form and severity of the diabetes. A change in the lipid content in the blood may be a result of the increase in the delivery of substrates for the synthesis of lipids, their increased synthesis, and the incomplete excretion of their metabolism products.

The question of the role of HTG in the development of IHD and atherosclerosis to date is under discussion. Some authors give HTG the leading place among the risk factors of IHD development. The Framingham investigation showed that HTG is an independent IHD risk factor (men with a normal level of HDLP cholesterol are an exception). Individual epidemiological studies failed to confirm the leading role of HTG among the risk factors [393, 415, 422, 450, 487].

An increased triglyceride level in the blood plasma of DM patients may underlie the accelerated development of atherosclerosis indirectly via other lipid fractions, but the triglycerides may also give a direct atherogenic effect. It was found that HTG has a toxic effect on the endothelium of vessels, increases the aggregation of thrombocytes, and lowers the fibrinolytic activity of the blood. A direct correlation between the level of glycemia and the triglyceride content in the blood was noted.

Currently, morphologists studying atherosclerosis do not single out separately atherosclerosis typical of DM. They consider that in IHD and in DM the transformation of the smooth muscle cells or macrophages is the key link in the formation of an atherosclerotic plaque. A major significance in this transformation is attached to disorders in the metabolism of lipids and lipoproteins. The most important for the development of atherosclerosis is a combination of an increased level of cholesterol, LDLP, VLDLP, and apo-B with a reduced content of HDLP, and all this is clearly connected with the development of IHD.

The Framingham studies showed the presence of a clear inverse correlation between the level of HDLP cholesterol and the frequency of development of IHD independent of the sex. A protective effect of high concentrations of HDLP cholesterol was manifest in patients up to 80 years old, whereas low values of HDLP cholesterol were associ-

Fig. 25. Level of Lipids in Blood in DM Patients.

ated with an increased risk of atherosclerosis with any level of total cholesterol in the blood.

We studied the lipid and phospholipid spectra of the blood plasma and membranes of the erythrocytes in all persons under observation. Blood was taken from on ulnar vein after 12 hours of fasting and before the taking of sugar-containing preparations. A 0.6% solution of ethylenediamine tetraacetic acid was used as an anticoagulant. The erythrocyte material was obtained by threefold washing with a 0.89% solution of sodium chloride, and next 0.5 ml were taken from the deep layers of the precipitate. The suspension of erythrocytes and plasma was frozen and stored at -18°C not over one month. The lipids of the plasma and erythrocytes were extracted with a mixture of chloroform and methane in a ratio of 2:1. Separation into fractions was performed by thin-layer chromatography on Silufol plates. A system consisting of hexane, diethyl ether, and glacial acetic acid in a

proportion of 80:20:2 was used to separate the lipids, and one consisting of methanol, chloroform, and bidistilled water in a proportion of 60:20:4 to separate the phospholipids. The lipid spots were determined with a 10% alcohol solution of phosphoromolybdenic acid. The following fractions of the lipids were determined: total phospholipids (TP), free cholesterol (FC), FFA, TG, cholesterol esters (CSE) and the spectrum of phospholipids: LPC, PC, SM, and PEA. The fractions were registered in a Karl Zeiss Jena densitometer EP1-65. The lipid fractions were estimated by calculating the areas of the relevant peaks of the substances, using the formula $S=h/\alpha$, where h is the height and α is the width taken at half the height of a peak.

Each lipid fraction was expressed in percent. When analyzing the results of the investigations, we used the relation:

$$\frac{FC + CSE}{PL}$$

The triglyceride content was determined by the enzymatic method in an autoanalyzer Olly 300 (Finland), the total cholesterol by the enzymatic method in a biochemical analyzer FP-901 of the firm Labsystem (Finland), and HDLP cholesterol in the supernatant after precipitating the LDLP and VLDLP with heparin and manganese dichloride by the procedure of Klimov *et al.* [292].

In performing all the work, we constantly used intralaboratory control of the quality with the aid of control serums.

Inspection of Fig. 25 shows that in type I DM patients the level of triglycerides, LDLP cholesterol, VLDLP cholesterol, and AI is increased and the level of HDLP cholesterol is lowered in comparison with the control group, while in type II DM patients the level of triglycerides, VLDLP cholesterol, and AI is increased and that of HDLP cholesterol is lowered. The content of total cholesterol in the plasma for the type I DM (148 mg/dl) and type II DM (123 mg/dl) patients did not differ from that in the control group and was within the normal values of this parameter established for the given age group.

The high level of triglycerides in the blood plasma in type I DM patients did not correlate with the body weight index and the glucose level in the blood, although an increased glucose level is known to stimulate triglyceride synthesis. In the labile course of DM with phenomena of dysinsulinemia, processes can be observed that inhibit and activate the system of lipases. The inhibiting effect on the HSL of the adipose tissue and the activating one on the LPL and liver triglyceridelipase result in lowering of the mobilization of free fatty acids from the adipose tissue, but accelerate the catabolism of the VLDLP formed in the liver with the production of free fatty acids. Lowering of the insulin level in the blood causes the intense supply of FFA from the adipose tissue into the liver and the

development of HTG. The type I DM patients we studied showed a considerable lowering of the level of HDLP cholesterol (29.0 mg/dl).

When analyzing the correlations between the level of total cholesterol and the content of glucose in the blood, triglycerides, LDLP cholesterol, VLDLP cholesterol, and HDLP cholesterol in type I and II DM patients, no correlation was found between the content of cholesterol and glucose in the blood, triglycerides, VLDLP cholesterol and LDLP cholesterol, although in type I and II DM the content of VLDLP cholesterol is authentically increased (in type I DE patients it is 29 ± 5.4 mg/dl, and in type II ones it is 29 ± 6.2 mg/dl). In type I DM, the content of LDLP cholesterol is authentically increased (89 ± 5.4 mg/dl against 72 ± 12.9 mg/dl in the control group).

What is the pathophysiology of the process of the increase in the content of LDLP and VLDLP in DM?

We consider that there are three pathophysiological factors, namely, (i) lowering of the HDLP level, (ii) nonenzymatic glycosylation, and (iii) the number of LDLP receptors.

Most clinicians attach special importance to the first factor – lowering of the HDLP level in DM. This is due to the fact that the HDLP stimulates the catabolism of LDLP and VLDLP. If the level of the HDLP drops (in DM), the catabolism of the LDLP and VLDLP is disturbed accordingly. Our results indicate that the HDLP level in type I DM patients is lowered to 29 ± 3.8 mg/dl, and in type II – to 27 ± 3.1 mg/dl.

It was shown in experiments that the HDLP also regulate the level of apo-B. With a high level of the HDLP, the activity of the apo-B receptors on the cells of the peripheral tissues grows, and the catabolism of the apo-B is accelerated accordingly, i.e. the atherosclerotic process is inhibited [508, 547, 551, 561].

Moreover, the high level of the VLDLP (especially in combination with HTG) is due to biochemical disturbances in DM: the increased supply of FFA from the fat depots to the liver, activation of triglyceride synthetase and HMG-CoA-reductase – specific enzymes of the liver and endothelial cells.

It was established in biochemical investigations that in diabetes mellitus, the VLDLP contain more cholesterol than is normal, while the LDLP contain an increased amount of triglycerides. All these factors facilitate the development of atherogenesis in DM patients.

These enzymes play a key role in lipid metabolism, and their activity is regulated by the endocrine system. It is very important that the LPL is controlled by the "insulin-glucose" system. Experiments showed the activity of LPL to drop when the insulin level lowers. The coordinating role in the regulation of the LPL is played by cAMP. It is just via cAMP that hormones affect the activity of these enzymes.

How is the level of cAMP regulated in a cell?

As indicated earlier, the cAMP content is determined by the reaction of two enzymes – adenylatecyclase and phosphodiesterase. These enzymes participate in the synthesis and decomposition of cAMP. The synthesis of cAMP is stimulated by adrenaline, glucagon, and ACTH. Insulin increases the activity of phosphodiesterase and increases the decomposition of cAMP. The thyroid-stimulating hormone (TSH) inhibits the activity of LPL, while thyroxin increases the sensitivity of lipases to the effect of adrenaline and thus stimulates lipolysis [54, 280, 301, 310, 597].

The influence of the thyroid hormones increases the release of FFA from the adipose tissue and their utilization.

The second pathophysiological factor of disturbing lipid metabolism in DM is nonenzymatic glycosylation. Clinicians noted that the atherogenic type of dyslipoproteinemia in DM patients is encountered very often. An important role in disturbance of the biochemical properties of the lipoproteins in DM patients is played by their nonenzymatic glycosylation. The attachment of glucose to HDLP with the formation of the glycosylized form of the HDLP alters the functional properties of these lipoproteins, prevents the transportation of cholesterol from the tissues into the liver and the participation of the apoproteins of HDLP in the synthesis of LPL, and lowers the antiatherogenic properties of the HDLP.

Matters are similar with LDLP and VLDLP. DM is accompanied by the hyperproduction of glycosylized LDLP and VLDLP with a change in their functional properties and with inhibition of the reaction with specific receptors. This transformation of the LDLP and VLDLP increases their capture by fibroblasts and endotheliocytes. This is attended by the development of hypercholesterolemia and lipid infiltration of a vessel wall with the appearance of sources of atherosclerosis [351, 365, 381, 516].

Many authors consider that the crossing binding of plasma proteins to the matrix proteins of vessel walls (to the collagen part) by means of the products of pronounced glycosylation and binding of the insoluble matrix components of the basal membrane with one another by means of the same products is the main pathogenetic unit of diabetic micro- and macroangiopathies. This relation results in the formation of complexes that are the site of attachment of other proteins of the plasma, and this results in the cascade growth of the process.

An important place in the normal homeostasis of a vessel wall is relegated to macrophages that "purify" the vessel wall from denaturated protein complexes. In DM patients, an excess accumulation of the products of pronounced glycosylation occurs, equilibrium of homeostasis shifts in the direction of a drop in the processes of removal of

the denaturated protein complexes, and proliferation thus grows. Two main pathogenetic units of vascular complications in DM are considered: glycosylation, and the polyol path of glucose metabolism [58, 163, 176, 567].

The third cause of the growth in the level of LDLP and VLDLP is the number of LDLP receptors. Clinical observations of children with family hereditary hypercholesterolemia proved that a genetic defect in the LDLP receptors causes the formation of "atherogenic dyslipoproteinemia" with a clinically severe manifestation of atherosclerosis. With a genetic defect in the LDLP receptors, the cholesterol content in the blood cells, fibroblasts, and liver cells is not increased, but its level varies. This is why more importance is attached to the number of LDLP receptors rather than to the total cholesterol content. In the works of D.Goldstein and M.Brown, who were awarded the Nobel Prize (1985), it was noted that in healthy cells the synthesis of cholesterol stops as soon as LDLP is added to the medium because 25-oxycholesterol – a very strong inhibitor of cholesterol synthesis from acetate – forms from a part of the LDLP cholesterol captured via the receptors [73, 76, 83, 88, 106].

In the opinion of these authors, the mismatch of two cholesterol flows, namely, the transportation cholesterol in the lipoproteins circulating in the blood and the cholesterol in cells, is the main molecular prerequisite for the development of atherosclerosis in an organism. The authors evaluated the pathogenesis of atherosclerosis from the physicochemical, biochemical, and physiological viewpoints. They noted that under conditions of hypercholesterolemia, the LDLP stop synthesizing cholesterol: receptor endosytosis of the LDLP sets in and the formation of cholesterol ethers is activated, i.e. a balance in cholesterol metabolism is achieved as a result of coordination between its "inflow" and "deposition" in the cells. In the hepatocytes that synthesize and absorb the major part of the lipoproteins, the intense inflow of the cholesterol into the cells is associated with activation of the synthesis and secretion of the lipoproteins.

Since the development of IHD in DM patients is closely related to the development of disorders in lipid metabolism, the progressing of atherosclerotic changes is generally combined with a growth in the level of triglycerides and cholesterol, especially of the latter contained in the low-density lipoproteins [126, 136, 168, 192, 214].

On the other hand, the HDLP cholesterol has an antisclerotic effect. A number of investigations revealed a negative correlation between the content of HDLP cholesterol and the level of triglycerides. It was shown that the content of HDLP cholesterol depends on the body weight (its level is diminished in persons with obesity). In DM patients, a negative correlation was found between the content of alpha-cholesterol and the triglyc-

eride level in the blood. The latter correlation was found only in type II DM patients, and was not discovered in type I patients.

The growth in type I DM patients of the LDLP level to 89.0 mg/dl (against a normal value of 72.0) and of the VLDLP level to 29.0 mg/dl (against 14.0 in healthy persons) that we revealed is exceedingly important for the progressing of IHD. The growth in the LDLP level is closely related to the lowering of the HDLP cholesterol one. Biochemical studies showed that the supply of free and esterified cholesterol to cells is regulated by receptors of LDLP, whereas its emergence from the cells is controlled by the HDLP receptors (mainly by apo-A-1). In DM, the level of HDLP cholesterol is reduced drastically, it being 29.0 mg/dl in type I DM patients and 27.0 in type II ones (against 41.0 in healthy persons).

In connection with the sharp drop in the content of HDLP cholesterol (with the relevant drop in the level of apo-A-1), the emergence of the cholesterol from the cells is retarded, and it accumulates in the cells.

Of special significance in the metabolic disorders in DM, in our opinion, is the disintegration of the cyclic nucleotides in the cells under the influence of a deficiency of insulin.

An important role in the metabolic processes in the blood plasma is played by the phospholipids, which play (chiefly) the role of biological detergents. Together with the apoproteins, they facilitate an increase in the solubility of nonpolar lipids. In combination with proteins, they can retain cholesterol, its esters, and neutral fats in the micellar form in an aqueous solution. The increased surface activity of the phospholipids is very important for the construction of lipoproteins and their exchange with the plasma. Between individual lipoproteins, the exchange of phospholipids occurs, and simultaneously exchange between the lipoproteins and cell membranes takes place. Studies with the use of tracer fatty acids showed that there is a close relation between the metabolism of polyunsaturated fatty acids and phospholipids of the blood [177, 221, 237, 247, 257].

Of the phospholipids, PC (lecithin) and sphingomyelin are constantly present in the blood plasma. The phospholipids are synthesized in virtually all the tissues, but chiefly in the liver. One of the phospholipids – lecithin – enters the plasma from the chylomicrons.

Phospholipids are an essential and very important component of all cell membranes. In rest and under a physical load, a constant exchange of PC and SM occurs between the plasma and erythrocytes. These phospholipids are constantly present in the blood plasma and maintain the nonpolar lipids (triglycerides and cholesterol esters) in a soluble state.

Fig. 26. Phospholipid Spectrum of Blood Plasma in DM Patients.

A comparison of the phospholipid content in the blood plasma of type I and II DM patients and of the control group revealed considerable distinctions. The fraction of LPC in type I DM patients was 4.46%, in type II patients was 5.77%, and in the control group was 3.75%. The SM content in DM patients of both type I (8.91%) and type II (6.59%) is lowered considerably (in the control group it is 19.23%). The PC content differs insignificantly: it is 73.9% in type I DM patients, 75.4% in type II, and 68.6 % in the control group (Fig. 26).

In the involved process of incidence and progressing of atherosclerosis in patients with IHD and DM, the exchange of lipoproteins between the blood and cell elements, in particular erythrocytes, is of a major significance. Studying of the lipid composition of the membrane of erythrocytes is interesting not only from the viewpoints of the quantitative

migration of lipids from the blood plasma into the membranes, but also from the viewpoints of disorder of the rheological properties of the blood in IHD and DM patients. The lipids contained in the membrane of an erythrocyte can be divided into polar ones (phospholipids, glycolipids, sphingolipids) – 60% and neutral ones (sterols) – 30%. The membranes also contain triglycerides and FFA (about 10%).

The cholesterol/phospholipid ratio in all biological membranes is 1. The phospholipids in a membrane are present in approximately the following proportion: PC – 30%, PEA – 28%, and SM – 25%. As already indicated, the lipid bilayer of a membrane is its basic structural unit and maintains its liquid-crystalline state. Physiological studies showed that a lipid bilayer of an erythrocyte membrane simultaneously has fluidity and order of the structure. Owing to the order of its structure, an erythrocyte carries out a number of processes occurring between the membrane and its surroundings (the reception of information, an exchange of energy and substances). Changes in the surroundings affect the composition of an erythrocyte membrane, the degree of its "adhesion" to the endothelium of the vessels changes, and the aggregative ability is disturbed.

Cholesterol and phospholipids are the main components of biomembranes. The former, responsible for 23% of the total mass of a membrane's lipids, is a very important regulator of the membrane in an erythrocyte. It acts like a shuttle transferring glucose, amino acids, and salts. Cholesterol is what ensures the difference in the physicochemical state of a membrane, and it is in two forms – free and esterified. If an erythrocyte membrane is too dense, the cholesterol "liquefies" it, as it were; conversely, if a membrane is too "liquid", the cholesterol compacts it. Consequently, the state of aggregation of the membrane of erythrocytes is ensured to a considerable extent with the aid of cholesterol. There is a constant exchange of cholesterol between the erythrocytes and blood plasma [282, 362, 378, 417].

The cholesterol of erythrocytes, like that of the plasma, relates to the readily exchanged pool of this substance in an organism.

Cholesterol is transferred between the erythrocytes and lipoproteins of the plasma in both direction. The process is not enzymatic, requires no energy, and terminates in 6–20 h. It was noted in experiments that a cholesterol molecule when incorporated into a membrane may have a liquefying effect and increase the mobility of the fatty acid chains, or a condensing one and compact them. A surplus of cholesterol in a membrane increases the microviscosity of the bilayer and lowers the rate of many reactions. The amount of membrane cholesterol depends on the activity and amount of the specific membrane receptors and the ratio in the blood plasma of the LDLP (as cholesterol donors) and HDLP (as acceptors of it).

The level of phospholipids in the plasma allows us to judge on the cholesterol-acceptor ability of the HDLP, because the esterification of cholesterol is the duty of the phospholipids (lecithin) of the HDLP. An erythrocyte membrane is protected from a surplus of cholesterol by the oxidation and esterification of the cholesterol. The lipoprotein complexes removing the cholesterol from the membranes first esterify it with the aid of LCAT. It was noted that if phospholipids containing large amounts of polyunsaturated fatty acids are added to food, the activity of the cell enzymes and the microviscosity of the membrane of an erythrocyte are restored [419, 473, 487].

An important function in the structure of a membrane is performed by its phospholipid composition: the latter regulate the active and passive transportation of organic substances and electrolytes through a cell membrane, ensure sensitivity to the action of hormones, and regulate the activity of the enzyme systems of succinate oxidase, adenosinetriphosphatase by changing the viscosity of the enzymes, i.e. phospholipids are of a major importance for the formation of multienzyme complexes.

In an erythrocyte membrane, the phospholipid molecules are distinguished according to the degree of saturation of their fatty acid "tails". The PC and SM are in the outer layer of the membrane, while the PEA and phosphatidylserine are in the inner one.

Analysis of the phospholipid composition of various membranes performing various functions revealed that they contain the same set of lipids, but in different combinations.

An unfavorable factor in IHD and DM is the increase in the content of cholesterol in an erythrocyte membrane and the change in the cholesterol/phospholipid ratio.

A drop in the amount of polyunsaturated fatty acids and a growth in that of saturated ones is also important. Under the conditions of insulin and energy insufficiency in DM, conditions are created for the accumulation of products of FPOL, and their biological effect on the cell membranes and receptors deteriorates. This is accompanied by disturbance of the mobility of the fatty acid chains, the passive transportation of ions and nonelectrolytes is inhibited, as is active transportation. The growth in the area of an erythrocyte membrane, and an increase in its rigidity (under conditions of an increased amount of cholesterol in a membrane) detract from the deformability of the erythrocytes, disturb microcirculation, and alter the activity of the membrane enzymes. These biochemical shifts facilitate the proliferation of the smooth muscle cells of a vessel wall. The retarding of the blood flow and increase in the aggregation properties of the forming elements facilitate the development of microangiopathies [395, 501, 524, 605].

In many recent studies, changes in the structural and functional properties of the erythrocytes in DM and disorders in the enzyme composition of a membrane were noted.

Fig. 27. Lipid Spectrum of Erythrocyte Membranes in DM Patients.

Insulin was found to participate in the metabolism of the lipid peroxides and facilitate their utilization. With insulin insufficiency (in DM), conditions are created for the accumulation of products of FPOL and their pathological effect on the cell membranes and receptors. In DM, a growth in the processes of FPOL is noted in the erythrocytes, and lowering of the activity of the antioxidant protection. Consequently, in DM, a change in the fractional composition of the lipids and their fatty acids occurs in an erythrocyte membrane. These shifts facilitate disturbance of the rheological properties of the erythrocytes and, in the long run, the development and progressing of diabetic microangiopathies.

Examination of Figs. 27 and 28 shows that the lipid and phospholipid spectra of erythrocyte membranes in type I DM patients are characterized by a growth in the content of triglycerides to 3.8% (1.23% in the control group), of fatty acids to 4.34%, (2.85%), of esterified cholesterol to 15.30% (4.87%), of the cholesterol/phospholipid ratio of 2.04

Fig. 28. Phospholipid Spectrum of Erythrocyte Membranes in DM Patients.

(1.08), and of the content of phospholipids to 30.5% (46.2%). This indicates a growth in the density of the lipid packing of an erythrocyte membrane, lowering of its deformability, and a growth in the aggregation properties of an erythrocyte. The proportion of the phospholipid fractions changes substantially: the fraction of the SM is lowered to 13.01% (the normal value is 19.6%), which possibly reflects disorder of the receptor sensitivity of a membrane, while the PC level is increased to 4.24% (1.79% in the control group).

The changes in the lipid spectrum of an erythrocyte membrane in type II DM patients was characterized by an authentic increase in the cholesterol fraction to 55.8% (44.6% in the control group) and in the esterified cholesterol to 9.84% (4.87%), lowering of the phospholipid fraction to 29.1% (46.2%), and a growth in the chole-

terol/phospholipid ratio. Moreover, a drop in the fraction of SM to 14.3% (19.7%), PEA to 26.8% (34.9%), and a drop in the PEA/PC ratio were noted.

Consequently, the shifts we discovered in the lipid and phospholipid spectra of the blood and erythrocyte membranes in type I and II DM patients differed authentically from those in the control group of persons in their identical direction and standing out of the changes in the parameters being studied in the direction of their atherogenic nature, but they did not depend on the type of DM. The only exception was the content of LPC in a membrane, which was increased only in type I DM patients.

The PEA/PC ratio, with the same authentically low value in type I and II DM patients, characterizes the change in the fluidity of the lipid phase of an erythrocyte membrane. This results in an increase in the coagulating properties of the blood, disturbance of the trophism of a vessel wall, and in progressing of microangiopathy. The growth in the cholesterol/phospholipid ratio found in type I and II DM patients is associated with impairment of both the macrorheological (an increase in the aggregation of the erythrocytes, a higher viscosity of the blood) and the microrheological properties (diminishing of the deformability) of the erythrocytes. The compacting of the surface layers of a membrane (an increase in the cholesterol/phospholipid ratio) and disturbance of the physicochemical processes in a membrane (diminishing of the PEA/PC ratio) with a drop in the SM fraction in a membrane may possibly hinder the penetration of insulin into the cells of DM patients [60, 130, 180, 424].

The disorder in microcirculation and oxygenation of the tissues in DM affects the physicochemical properties of an erythrocyte membrane. The growth in the cholesterol level in the plasma increases the amount of cholesterol in a membrane. As a result of hyperglycemia and disturbance of microcirculation, the amount of cholesterol in a membrane grows. In hyperlipidemia, the permeability of an erythrocyte membrane drops, and the diffusion of oxygen is disturbed. In DM, molecules of glucose react with the residues of lysine of the membrane proteins, and the amount of glycolisines doubles the normal values. This lowers the mechanical and osmotic stability and reduces the duration of circulation of an erythrocyte.

Opinions diverge with respect to the amount of phospholipids in the erythrocyte membranes in DM patients. Some scientists note a drop in the content of all the phospholipid fractions. A growth in the amount of fatty acids in the membranes points to the activation of phospholipases, which selectively destroy the lipids of a membrane. A special activity of the phospholipases was noted in the period of decompensation of DM [40, 121, 180, 569, 594].

It is the common opinion of all clinicians and experimentators that in DM patients, the level of total cholesterol and the cholesterol/phospholipid ratio increase. These changes lower the fluidity of the lipid phase of a membrane, increase the volume of an erythrocyte, increase the rigidity, and lower the deformability of a cell. This results in thickening of the basal membrane of the endothelium of vessels, slowing down of the blood flow, and a greater aggregation of erythrocytes.

The introduction of insulin to DM patients facilitates the emergence of FPOL products from a cell membrane. These products accumulate as a result of insulin insufficiency and weakening of the antioxidant protection.

Some authors do not exclude the possibility of the participation of FPOL products in the modification of the fatty acid composition of the erythrocyte membranes in DM, especially under conditions of its decompensation.

The accumulation in an erythrocyte membrane of the metabolism products (FFA, FPOL) combined with the accumulation of cholesterol in a membrane disturb the rheological properties of the blood and lead to the development of diabetic angiopathies.

The functioning of the lipid transportation system in DM patients is disordered quite considerably; the principles of the biochemical disturbances of carbohydrate metabolism are similar to those of patients with atherosclerosis [22, 178, 576].

The results of examining two patients in whom the course of DM was made more complicated by hypertension or obesity can serve as examples.

Clinical Examples

Example 1.

Patient B. When 62 years old, she was admitted to the endocrinological department with complaints of general weakness, headaches, poor sleep, and thirst.

DM was established 15 years ago, when the patient began to lose weight, and thirst and general weakness appeared. Examination on an empty stomach revealed hyperglycemia. Her state improved after being given sugar-lowering drugs, and the glucose content in the blood became normal. During 20 years, she has been suffering from hypertension, and is constantly receiving hypotensive therapy.

Objectively: the general state is satisfactory. Height 160 cm, body weight 68 kg. Integuments of normal moistness. Vesicular respiration in the lungs. The heart tones are muffled. The pulse is rhythmic, 72 bpm. The arterial pressure is 160/80 mmHg. The stomach is soft, painless, the liver is not palpated. The general blood and urine tests are without special features. The glucose level in the blood when admitted varied from 12.0 to 14.0 mmol/l. After the increase of the maninil (glibenclamide) dose to three pills a day and selecting an adequate diet, the glucose content in the blood was normalized, and DM was compensated completely.

To determine the state of the patient's lipid transportation system, a fat load was conducted on the basis of 130 g of fat per 2 m².

Parameter	CS, mg/dl	TG, mg/dl	α -CS, mg/dl	apo-A-1, mg/dl	apo-B, mg/dl	IRI, μ U/ml
Value						
after 0 h	224	142	37	121	106	9.1
after 3 h	207	311	35	121	142	15.8
after 9 h	201	359	32	121	157	16.8

Example 2.**Patient K.**

When 56 years old, she was admitted to the endocrinological department with complaints of general weakness, fatigue, thirst, sweating, irritation.

She has been suffering from DM 10 years. The disease was incurred after influenza: thirst appeared, as well as general weakness. During several years, DM was compensated by a strict diet, and then by taking peroral sugar-lowering drugs.

Objectively: the general state is satisfactory, increased nutrition. Height 168 cm, body weight 93 kg. The obesity is proportional. Integuments of normal moistness. Vesicular respiration in the lungs, the heart tones are clear and muffled. The arterial pressure is 140/85 mmHg. The stomach is soft, painless, the liver is not palpated.

The general blood and urine tests are without special features. When taking two pills of maninil (glibenclamide) a day and lowering the caloricity of the food to 1200 kcal a day, the glucose content in the blood became 6.0 mmol/l on an empty stomach and up to 9.0 mmol/l during the day, which indicates compensation of the DM. The patient was also subjected to a fat load.

Parameter	CS, mg/dl	TG, mg/dl	α -CS, mg/dl	apo-A-1, mg/dl	apo-B, mg/dl	IRI, μ U/ml
Value						
after 0 h	302	319	38	130	220	12.0
after 3 h	292	426	36	122	261	15.3
after 9 h	331	716	33	145	308	14.8

The results indicate that both patients have been suffering from type II DM over 10 years. Their age is almost identical. The background parameters of the lipids and the hormonal profile of these patients is different. The cholesterol level in patient B. is 224 mg/dl, and in K. it was 302 mg/dl. A considerable difference was noted in the background values of TG: in B. it was 142 and in K. – 319 mg/dl. The level of HDLP cholesterol in both patients is the same – 37 and 38 mg/dl. The apo-A-1 content in B. was 121 and in K. – 130 mg/dl. A very significant difference was noted in the parameter apo-B. It is 106 mg/dl in B., while it is increased to 220 mg/dl in K. The insulin level in these patients also varies; it is 9.1 μ U/ml in B. and 12.0 in K.

Why are there substantial distinctions in the background parameters of these type II DM patients who took the same drug (maninil) with duration of the disease of 10 and 15 years?

We consider that the pronounced disorders in lipid metabolism in patient K. are due to three factors: disorder in the function of the liver, hyperinsulinemia, and hypercortisolemia. Moreover, she suffers from obesity, which facilitates the development of dyslipoproteinemia.

After administering a lipid load, our assumptions were confirmed. It follows from the above data that the reaction to a lipid load differed. The cholesterol level in both cases did not change substantially. The dynamics of the triglyceride content was more pronounced in K. If in B. after three hours the triglyceride level increased to 311, and after nine hours to 359 mg/dl, in K. the background value was 319, in three hours it was 426, and in nine hours it was 716 mg/dl.

Such a dynamics of the triglyceride level confirms the assumption that the triglycerides in the chylomicrons are subjected insufficiently to lipoproteinlipolysis. As a result, the triglyceride level after nine hours increased to 716 mg/dl; here the dynamics of the apo-B content is very interesting. In B., the background level of apo-B is 106 in three hours it was 142, and in nine hours it was 157 mg/dl. In K., the dynamics was more pronounced: 220, 261, and 308 mg/dl.

The apo-A-I level is also important. Its background level in B. was lowered somewhat – 121, and in K. it was 130 mg/dl. In B. the apo-A-I content did not change under the influence of a lipid load, whereas in K. after three hours it dropped somewhat to 122 mg/dl, and then grew to 145. In other words, the protective function of apo-A-I was stronger in K., and the atherogenesis process tends to normalization, as it were.

The insulin level after three hours increased identically in both patients to 15.3, while after nine hours it was 16.8 in B. and 14.8 $\mu\text{U/ml}$ in K.

Considering the growth in the content of triglycerides, apo-B, the background hyperinsulinemia, and the presence of obesity in K., we can state that hyperinsulinemia combined with obesity lowers lipoproteinlipolysis (with an increase in the triglyceride level after a lipid load) and accordingly leads to progressing of the atherosclerotic changes.

Great significance with HTG in obesity patients is attached by clinicians to damage of a vessel wall (stimulation of thrombus formation).

Apolipoproteins play an important role in lipid metabolism and ensure three very important biochemical reactions: (i) they help, by reacting with phospholipids, to solubilize the esters of cholesterol and triglycerides, (ii) they regulate the biochemical reactions of lipoproteins with enzymes such as LCAT, LPL, and liver lipase, and (iii) they determine

the sites of capture and the rate of degradation of lipoproteins by binding with cholesterol receptors on the surface of cells.

We attach special significance to the growth in the apo-B level in K. as an indication of the disintegration of the regulatory metabolic processes in lipid metabolism.

The pathogenesis of this phenomenon can be explained by disturbance of the process of VLDLP decomposition. As noted, VLDLP in DM contains more cholesterol than is normal. This ensures their increased atherogenic properties. LDLP contain an increased amount of triglycerides. The atherogenic effect of LDLP in DM is due to the circumstance that they are bound by glycosylized collagenic fibers at the places of damage to the endothelium. This leads to disturbance of an aggregation of thrombocytes, the formation of an atheromatous plaque, and disturbance of the prostacyclin/thromboxan ratio in the direction of an increase in the thromboxan level.

A clearly noted difference with a fat load is noted in the content of apo-B: if in healthy persons its background value of 153 mg/dl does not virtually change under the influence of a lipid load, in patient K. with type II DM the background value of 220 mg/dl grows after nine hours to 308. Such a growth in the apo-B level may also affect the formation of an atherosclerotic process and lesion of the endothelial membrane,

Disorder of the lipid metabolism in patient K. is also due to the presence of obesity and insulin resistance. It is exactly the latter that most often appears in DM patients of type II.

When studying the pathophysiological mechanisms of the disorders appearing in DM, most authors consider that insufficiency in the supply of energy to the erythrocytes is the most important link. Under conditions of a deficiency of insulin, it weakens the antioxidant systems and steps up the FPOL processes. This lowers the content in erythrocytes of the most readily oxidized phospholipid fractions and increases the content of the PC and SM fractions difficult to oxidize. These biochemical processes increase the renewal and exchange of lipids between the erythrocytes and plasma. A result is a higher content of phospholipids in the plasma and a lower one in the erythrocytes.

Studying of the lipid composition of an erythrocyte membrane points to the important role of the lipids in its functioning in vascular lesions. In view of the above, correction of the disorders in the lipid spectrum of the blood plasma and erythrocyte membranes is currently an urgent matter.

1.6 Conclusion

Consequently, dyslipidemia and the progressing of atherosclerotic changes are links of one chain. The development of an atherosclerotic process in a person's organism de-

depends on the relation between the intensity of two nonenzymatic processes, namely, the transportation of cholesterol esters in the composition of HDLP into the liver (for the excretion of cholesterol from the organism) and the getting of the esters into an endothelium of a vessel wall. The prevailing of one of the processes determines the degree of activity of atherosclerosis development.

To determine the physiological significance of lipid metabolism, it is necessary to conduct a lipid load. It allows us to appraise the physiological mechanisms and predict the biochemical relations between the various links of lipid metabolism.

We noted that in a lipid load, the content of triglycerides, LDLP and VLDLP change the most clearly. Of special significance in the progress of atherosclerosis is the increase in the apo-B level under the influence of a lipid load. If this dynamics is combined with lowering of the level of apo-A-1, from the prognosis viewpoint we consider this to be an unfavorable symptom of atherosclerotic lesion.

We attach special significance under the conditions of a lipid load to the hormonal regulating factors, especially to a growth in the insulin level. The presence of hyperinsulinemia combined with dyslipidemia is a negative factor witnessing the progress of IHD.

The deep studying of the risk factors of IHD by clinicians, morphologists, and biochemists during recent years brought to light one of the important disorders of metabolism in the pathogenesis of atherosclerosis, namely, syndrome X – a combination of hyperinsulinemia and insulin resistance. Syndrome X is a pathogenetically integrated disorder of metabolism including hyperinsulinemia, DM, and obesity, on the one hand, and disturbance of the tolerance to glucose and hypertension on the other. Degradation of the hormonal-mediator units of metabolism in syndrome X leads to disorder of the physiological regulator mechanisms and to the progressing of IHD.

An important role in the development of syndrome X is played by insulin resistance, which is accompanied not only by hyperinsulinemia, but also by disturbance of the tolerance to glucose, and basal hyperglycemia. The syndrome of insulin resistance forms in an integrative way, including both genetically determined defects of metabolism (disorder of both carbohydrate and lipid metabolism) and acquired pathological states – obesity and hyperinsulinemia.

When studying the biochemical fundamentals of formation of syndrome X, most authors give major attention to glyconeogenesis, which is one of the chief adaptive mechanisms of carbohydrate homeostasis and a very important factor in supplying the energy cycle in an organism with glucose. We agree with the assumption that glyconeogenesis is one of the main regulatory contrivances in the integration of the syndrome X. It facilitates the formation of hyperglycemia and hyperinsulinemia.

When analyzing the hormonal regulation of syndrome X, we arrived at the conclusion that this disease is attended by complete degradation of the regulatory hormonal processes with disturbance of the physiological relation between the content of insulin, STH, and catecholamines. Hypertrophy of the myocardium appearing as a result of activation of the synthesis of nucleic acids and proteins is an important clinical symptom of syndrome X. The clinical manifestation of hypertrophy of the myocardium in syndrome X is its hyperfunction. The increased function of the myocardium in syndrome X is the cause of the increased mobilization of the energy and structural reserves in the myofibrills. This is attended by a growth in their lesion. Ischemia of the myocardium leads to disturbance of the functioning of the membrane phospholipases. Electrical instability of the lipid bilayer of the membranes appears, and they lose their barrier functions. All these morphobiochemical changes in the heart in syndrome X lead to the development of pathological processes in the myocardium that grow progressively and manifest themselves clinically in the form of IHD and cardiac insufficiency.

Disturbance of fat metabolism is one of the important pathogenetic factors of IHD development. The key factor in the metabolic disturbances is an increase in the glucose level that is accompanied by inhibition of lipolysis of adipose tissue. These relations stand out especially clearly in DM. If in DM glucose is not assimilated in a cell, the major part of the fatty acids is removed into the blood via the extracellular space. DM is attended by distortion of carbohydrate-lipid metabolism: lowering of the utilization of glucose by the muscles is attended by switching over of energy metabolism to the use of free fatty acids. The freed glucose accumulates in the fat cells, transforming into triglycerides and disturbing lipid metabolism. An important part in these metabolism disturbances is played by insulin. On the one hand, it stimulates lipogenesis and, accordingly, facilitates the accumulation of cholesterol in such vessels, while on the other, it inhibits the lipolysis processes and lowers the mobilization of lipids from the walls of vessels.

Clinicians and morphologists proved in numerous investigations that the main role in atherogenesis is played by the reaction of lipoproteins with the smooth muscle cells of an arterial wall. It is cholesterol (unesterified) that affects the macromolecular structure, permeability, and electrical potential of a membrane. Great importance in the development of atherosclerosis of the coronary vessels is attached to activation of the peroxide oxidation of lipids in the cells and tissues of an organism that occurs in the development of DM. The key link in disturbance of the peroxide oxidation of lipids in IHD and DM patients is the "lipid triad" that integrates a combination of functioning of carbohydrate and lipid metabolism. The disturbance of various relations (biochemical) in the lipid triad causes

lesion of the cardiac myocyte membranes because of potentiation of the catecholamines and activation of lipases and phospholipases.

Maintaining of the balance between the inflow into the cells of vessels of cholesterol in the composition of the LDLP (especially of cholesterol esters) and its outflow from the peripheral cells into the liver with the acid of HDLP is a significant principle underlying the metabolic changes in atherosclerosis. We noted in our studies that in IHD and DM patients the ability of the HDLP to accept cholesterol from the smooth muscle cells of the aorta is drastically lowered. The value of the ratio apo-B/apo-A-1 is the laboratory biochemical criterion of the atherogenic state in IHD and DM patients. We noted a considerable growth in this ratio for patients with coronarographic registration of IHD.

In studying the regulatory mechanisms of lipid metabolism in IHD patients, we concluded that all the disorders in lipid metabolism in these patients are due to the hormonal disintegration of the regulatory adaptive mechanisms, and the role of insulin is especially important. It is exactly insulin, being absorbed by adipose tissue, and also regulating the pentose and glycolytic cycles of glucose exchange, that stimulates in IHD patients the increased synthesis of fatty acids and triglycerides from the products of carbohydrate metabolism.

In DM, the incidence of insulin insufficiency entails disturbance of the assimilation of glucose, an increase in the FFA level in the blood, and the development of dyslipidemia.

In DM, the development of angiopathies and IHD occurs on the background of an integrative combination of risk factors such as hyperlipoproteinemia, arterial hypertension, increased blood coagulation, and hyperglycemia. An important role in the regulation of lipid metabolism is played by LPL, whose level in DM (on the background of a deficiency of insulin) is lowered considerably. A deficiency of LPL in the blood is attended by a growth in the level of lipoproteins rich in triglycerides (diabetic lipemia).

Morphological studies of the vessels in DM patients allowed authors to conclude that in these patients, the transformation of the smooth muscle cells or macrophages is the key factor in the formation of an atheromatous plaque. Biochemical studies here showed the reaction of lipid metabolism units such as an increased level of cholesterol, LDLP, VLDLP, diminishing of the level of HDLP, and a greater content of apo-B in the blood.

Lesion of the vessels in DM of both type I and II is manifest in the form of diabetic micro- and macroangiopathies. Most authors find that the crossed binding of the plasma proteins to the matrix proteins of vessel walls by means of the products of pronounced glycosylation plays a role in the pathogenesis of these lesions.

The deficiency of insulin in DM is attended by degradation of the level of cyclic nucleotides (cAMP and cGMP) that play an important regulatory function in the metabolism of lipoproteins. We proved that in DM patients, the function of the erythrocytes is disturbed because of the appearance in their membranes of a surplus of cholesterol. It is this state that increases the microviscosity of a membrane bilayer and lowers the rate of many enzymatic reactions. Insulin insufficiency in DM favors the accumulation of the products of peroxide oxidation of the lipids in the membranes of erythrocytes. This causes disturbance of the mobility of the fatty acid chains, inhibition of the passive transportation of ions and nonelectrolytes, and also disturbance of the receptor sensitivity of the erythrocytes to HDLP. Lowering of the protection processes in the blood cells of DM patients is an important pathogenetic factor in the development and progressing of diabetic microangiopathies.

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