REGULARITY IN THE PATTERN OF THE METABOLIC REACTION NETWORK

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UDC 577.123

An essentially new approach to the representation of information on metabolism, based on the regularity detected in the pattern of the metabolic reaction network, is discussed. A theoretical substantiation of its presence is given. Metabolic charts are cited for carbohydrates, carboxylic acids, and nitrogen-containing compounds with a regular structure. The possibilities of utilizating the regularity of the metabolic reaction network for the systematization of various information associated with metabolism and the prediction of new information are discussed.

Key words: metabolism, regularity, metabolic reaction network, systematization, metabolic charts.

Why Must New Approaches to the Systematization of Material on Metabolism Be Sought. Traditionally metabolism is considered as a system of metabolic pathways. In this case metabolic pathways connote reaction sequences in the organism for the conversion of some sort of substrate to products, usually excreted into the external environment. Historically the pathways of conversion and formation of compounds that were of interest for physiology and the food industry were primarily studied. For example, the pathway of fermentation of glucose to ethyl alcohol and glycolysis, close to it, the pathway of conversion of acetate to carbon dioxide and water in the tricarboxylic acid cycle, the pathway of urea formation, etc. Gradually individual metabolic pathways merged into a single network of reactions. The originally studied metabolic pathways now began to be called central. The mode of representation of metabolism in the form of a reaction network was most clearly expressed on the metabolic maps of Nicholson [1] and Michal [2]. The maps combine summary data on metabolism in animals, plants, and microorganisms.

As new data are accumulated, it is becoming increasingly evident that the traditional representation of the network of metabolic reactions as a system of metabolic pathways is inconvenient and logically not entirely coherent. Actually, the combination of a large number of metabolic pathways, depicted on the schemes in generalized form, makes the structure of the metabolic reaction network extremely complex and difficult to understand. If we consider that for the organism any metabolic pathway functioning in it is vital, then the distinguishment of central pathways in metabolism becomes extremely arbitrary. The metabolic pathways including reactions in common cannot function simultaneously without interfering with one another. Therefore, while compatible in the structurochemical respect, they proved incompatible as dynamic characteristics of metabolism. However, these contradictions are eliminated if we consider the metabolic pathways not as additive components of the network of metabolic reactions but as the state of this network, manifested in the functioning of its corresponding parts.

As a result of the extension of investigations of metabolism to an ever wider circle of objects, pertaining chiefly to plants and microorganisms, it was revealed that almost all the compounds encountered in living nature can be substrates and products of metabolism. Consequently, in principle the number of metabolic pathways that occur may even exceed the number of compounds participating in metabolism. In this case the use of the concept of the metabolic pathway as an intermediate unit in the systematization of information on metabolism loses its meaning.

Finally, the extensive information on individual compounds and reactions whose association with known metabolic pathways has not been established finds no place within the framework of the existing concepts of metabolic pathways.

The enumerated shortcomings of the traditional representation of metabolism as a system of metabolic pathways make it necessary to seek new approaches to the systematization of the information available on metabolism.

Institute for Protein Research, Academy of Sciences of the USSR, Pushchino, Moscow Province. Translated from Biokhimiya, Vol. 54, No. 6, pp. 883-894, June, 1989. Original article submitted February 17, 1988.

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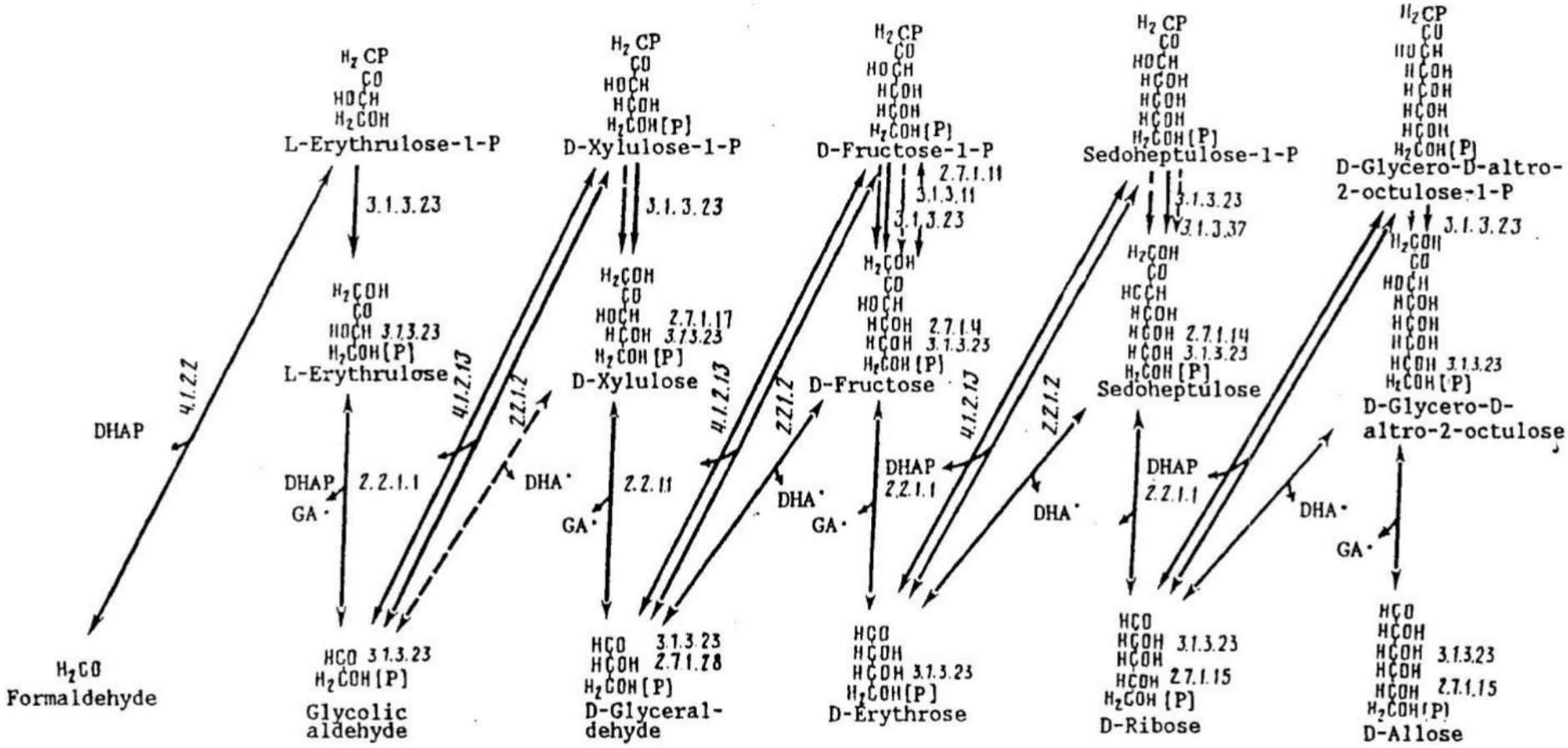

Fig. 1. Main periodic sequence of reactions of monosaccharide metabolism. Here and in other figures: GA — glycoaldehyde bonded to transketolase; DHA — dihydroxyacetone bonded to transaldolase; DHAP — dihydroxyacetone phosphate; Pyr — pyruvate; PEP — phosphoenol pyruvate; UDP, UPP — uridine diphosphate; P — phosphate; PP — diphosphate; AcCoA — acetylcoenzyme A; PrCoA — propionylcoenzyme A; MCoA — malonylcoenzyme A; MmCoA — methylmalonylcocnzyme A; AaTPP — acetaldehyde thiamine pyrophosphate; Ur — urea; G — glycine; AICAR — 5'-amino-4-imidazolecarboxamide ribonucleotide; [P] — phosphates substituted on the closest carbon atom (in formulas); [*n*-P] — phosphate derivatives produced by substitution on the *n*th carbon atom (in the compounds mentioned); [CoA] — coenzyme A derivative of carboxylic acids; [TPP] — thiamine pyrophosphate derivatives of aldehydes; ⇄ — reactions pertaining to phosphate derivatives, coenzyme A, and thiamine pyrophosphate, denoted as [P] or [*n*-P], [CoA], and [TPP], respectively; — — — → presumed reactions; repeated names of compounds are enclosed in parentheses.

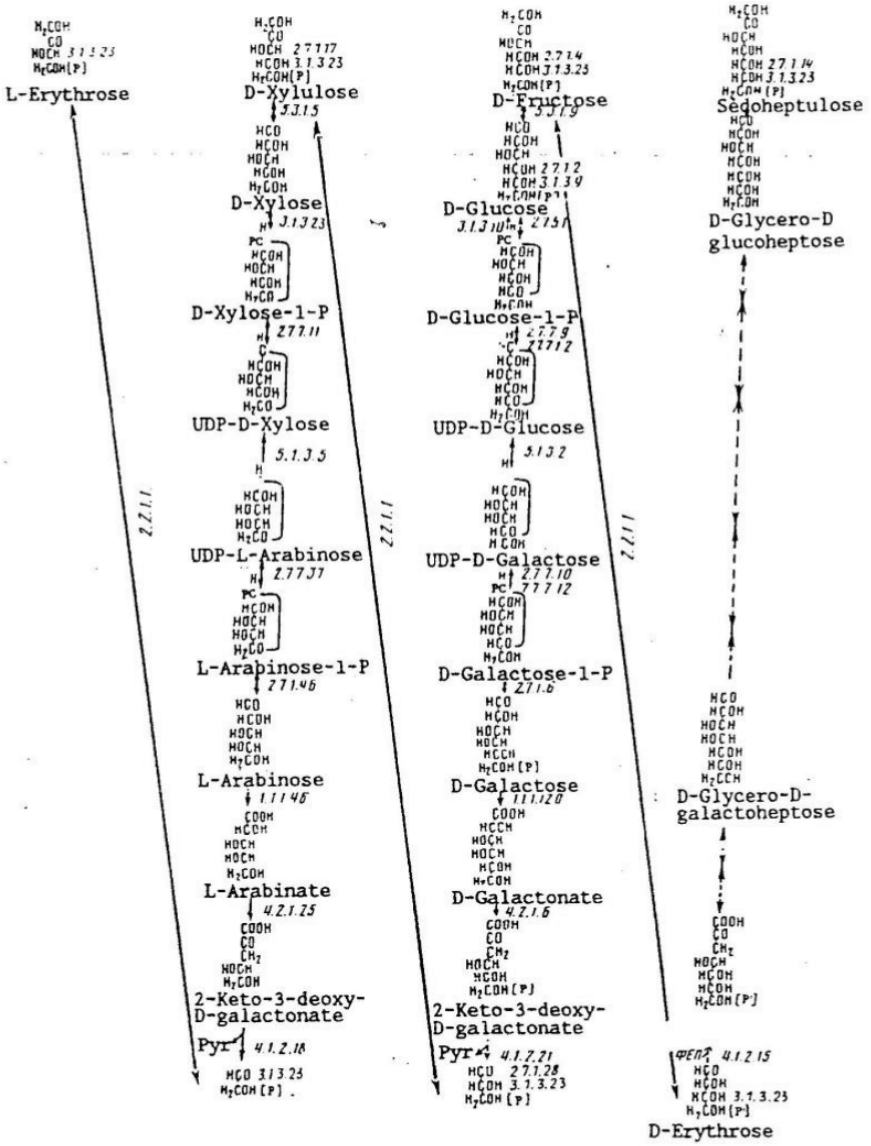

Fig. 2. Supplementary periodic sequence of metabolic reactions of monosaccharides.

METHODS OF INVESTIGATION

Essence of the Proposed Approach to the Systematization of Information on Metabolism. The main shortcoming of the traditional approach to the systematization of information on metabolism — its complexity — is due to the fact that each part of the metabolic reaction network is considered as a unique part, not similar to the rest. At the same time, it is known that in the biosphere many biochemical reactions occur that are similar to one another both in substrates participating in them and products formed and with respect to the coenzymes necessary for the occurrence of these reactions. Moreover, similar conversions are experienced not only by substrates, possessing the same functional groups (functionally analogous), but also frequently by the functionally analogous products formed. This conclusion follows most clearly from an examination of enzyme nomenclature. An attentive analysis shows that in the metabolic reaction network similarity may be observed not only between individual compounds or reactions, but also between complexes of reactions. Moreover, from the participation of functionally analogous compounds in similar biochemical reactions and the continuity of the metabolic reaction network, it follows that thsse complexes include reactions possessing a regular symmetrical structure. Actually, the continuity of the metabolic reaction network suggests that two functionally analogous compounds are necessarily interrelated by at least one reaction sequence, which can be represented in general form as follows:

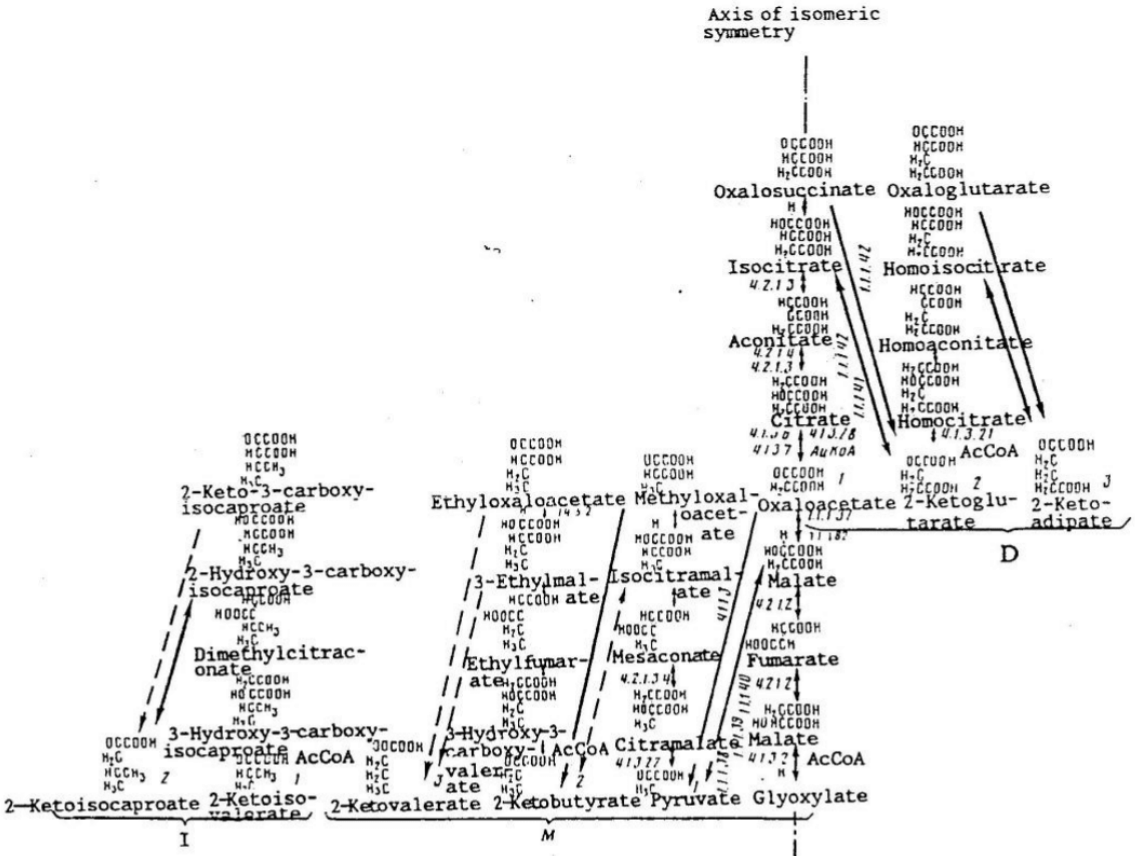

Fig. 3. Periodic sequences characterized by reactions of condensation of acetate with 2-keto acids.

Since functionally analogous metabolites participate in similar conversions, the original reaction chain is continued at both ends, as shown below:

repeating the reactions both with respect to the initial compounds (A_1, A_2) and with respect to their functionally analogous conversion products, denoted by the same letters. It is easy to see that such a sequence consists of repetitive intervals and has a periodic structure. As an example of such sequences we might cite the generally known sequences of reactions of synthesis and cleavage of fatty acids. Thus, the repeating interval of the sequence of fatty acid synthesis includes four reactions: the condensation of acetate (which arises when malonyl-CoA is cleaved) with a growing fatty acid residue, the reduction of the 3-keto acid formed in this case to a 3-hydroxy acid, the dehydration of the 3-hydroxy acid to a 2,3-dehydro acid, and the reduction of the latter to a saturated fatty acid residue, a functional analog of the original residue. In the synthesis of fatty acids these reactions are repeated until the hydrocarbon chain reaches the necessary length. It is easy to note that the corresponding functionally analogous compounds in the repeating intervals are homologs. In the case of digestion of fatty acids, the same reactions proceed in opposite directions.

The detection of periodic reaction sequences of the type examined is the first step on the way to revealing the regularity in the structure of the metabolic reaction network. The second step is to combine them into a general scheme in such a way as to make the regularity latent in the metabolic reaction network obvious.

The factual material used in the work was taken from the book of Dagley and Nicholson [3], Meister [4], the surveys of Bemfeld [5] and Kates [6], and original articles.

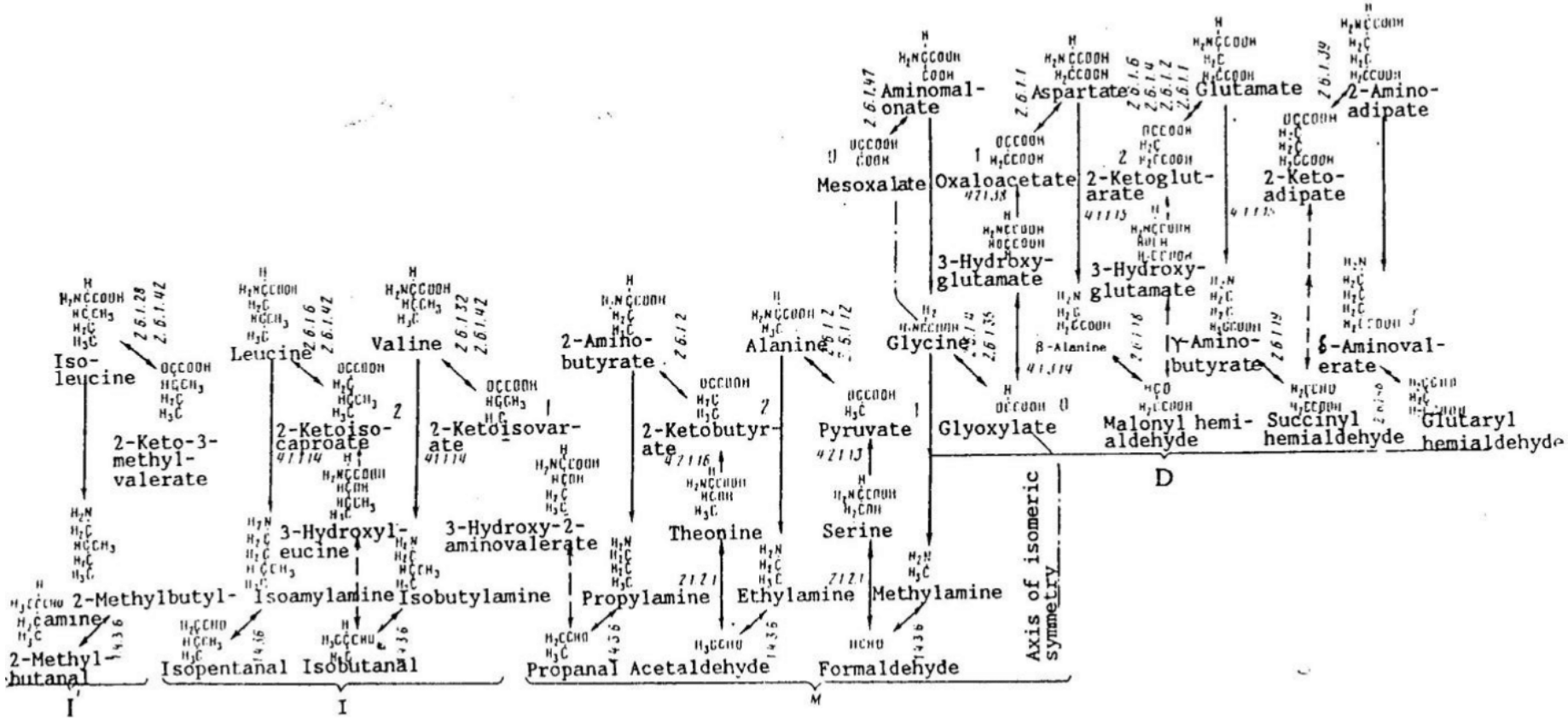

Fig. 4. Periodic reaction sequence of nitrogen-containing compounds.

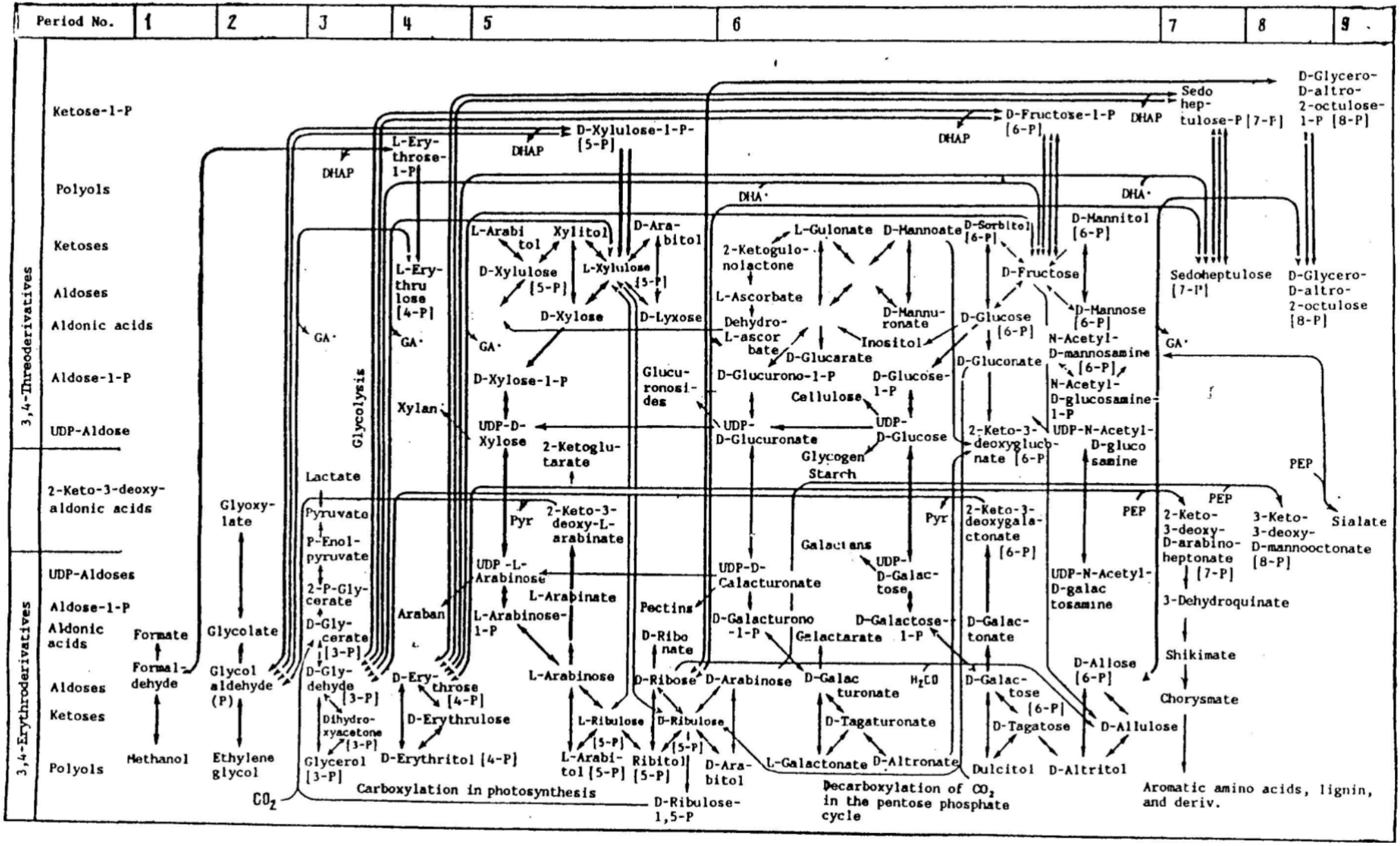

Fig. 5. Scheme of carbohydrate metabolism.

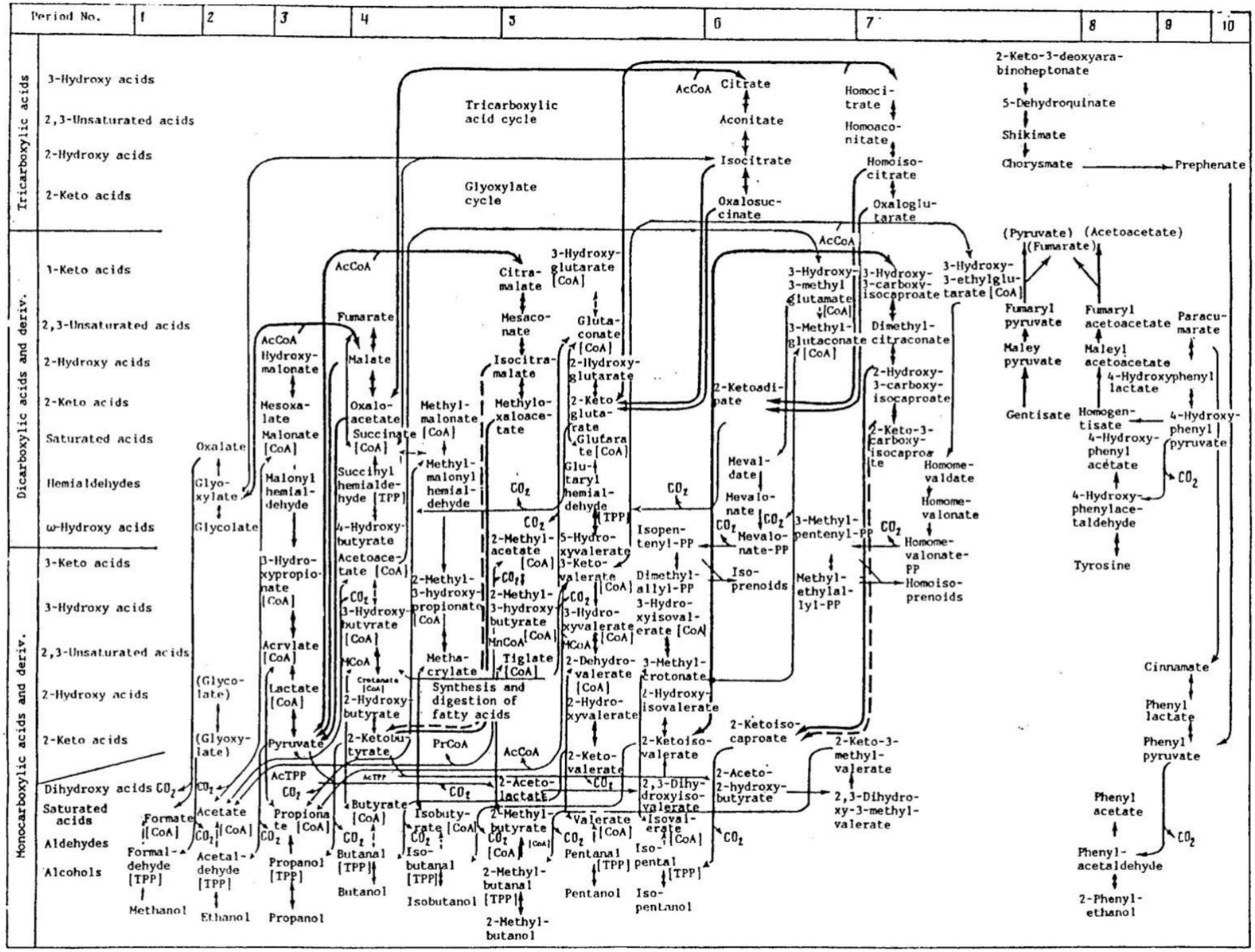

Fig. 6. Metabolic chart of carboxylic acids and their derivatives.

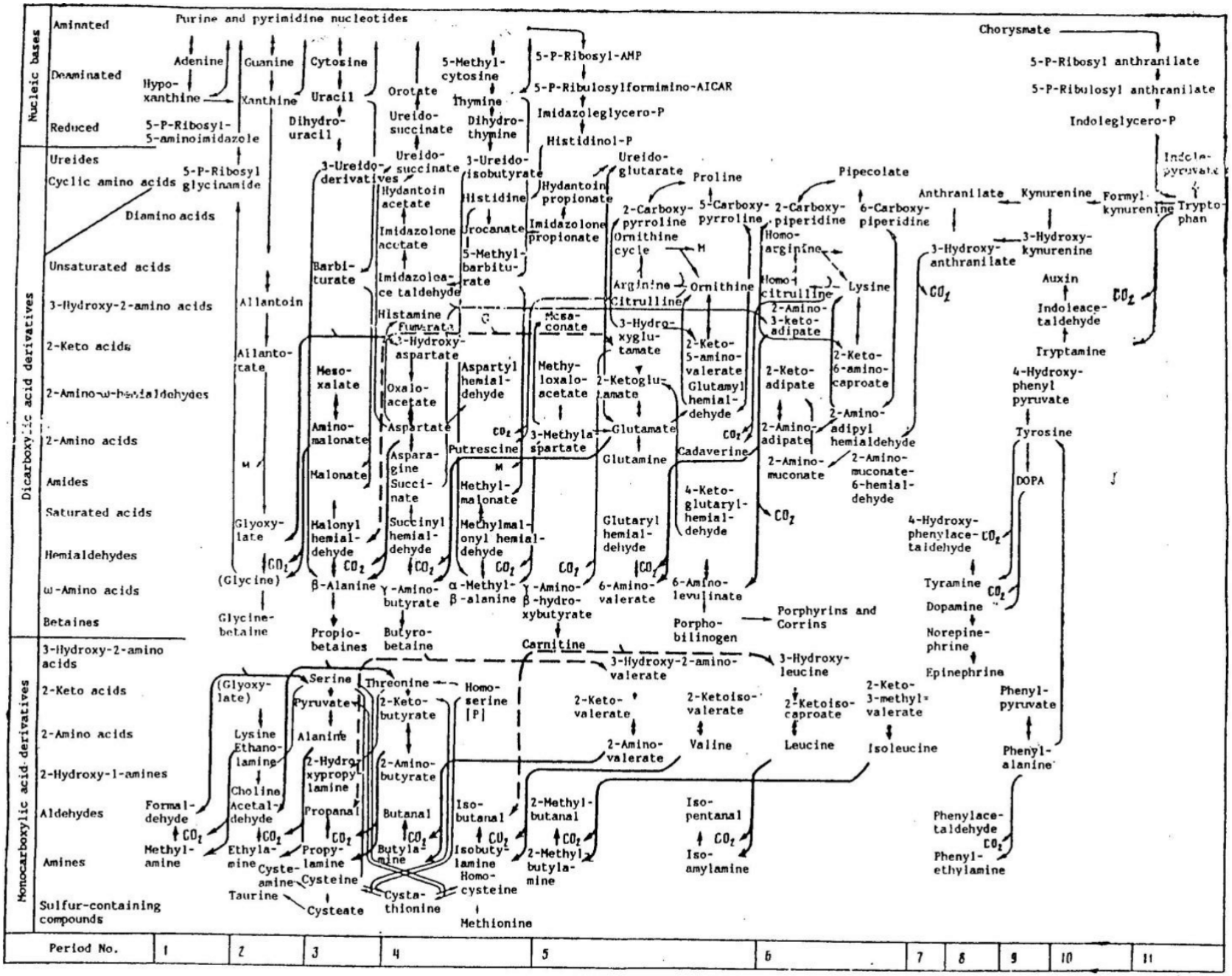

Fig. 7. Metabolic chart of nitrogen-containing compounds.

RESULTS AND DISCUSSION

Variants of Presentation of the Structure of the Metabolic Reaction Network in Regular Form. Periodic reaction sequences are detected not only in the fatty acid metabolism but also in one form or another in the metabolism of the carbohydrates, carboxylic acids with a short carbon skeleton, and nitrogen-containing compounds. It should be emphasized here that in contrast to the sequence of the reactions of synthesis and digestion of fatty acids, most of these sequences do not function as metabolic pathways but represent only the symmetrical components of the metabolic reaction network.

Here we shall discuss some periodic sequences (Figs. 1-4), as well as the method of construction of the metabolic charts (Figs. 5-7) demonstrating the regularity of the structure of the metabolic reaction network.

The sequences in Fig. 1-4 are arranged so that their repetitive intervals are formed by vertical columns, while functionally analogous compounds are placed in horizontal rows. For more compact organization of the material, certain phosphate derivatives, derivatives of coenzyme A, and derivatives of thiamine pyrophosphate are presented arbitrarily in the figures in the form of abbreviated notations of phosphate and coenzyme substituents in brackets next to the substituted functional groups of the original compounds. In this case the reactions pertaining to the original compounds are denoted by continuous arrows, while the reactions pertaining to the arbitarily represented derivatives are denoted by arrows broken at the corresponding end. The dotted arrows denote presumed reactions, but not yet delected in nature.

In carbohydrate metabolism at least two periodic reaction sequences are detected. The basis of one of them, arbitrarily called the main sequence (Fig. 1), consists of reversible reactions of condensation of aldoses with dihydroxyacetone and glycol aldehyde. In these reactions the carbon skeletons of the monosaccharides are synthesized. If we neglect reactions of phosphorylation and dephosphoryiation that are not directly associated with changes in the carbon skeleton of the monosaccharides, then the transition from a lower homolog to a higher one in one interval of the sequence can be considered as a two-step process. In the first step dihydroxyacetone condenses with a D-aldose, leading to the formation of a D-ketose with a D-threo-configuration of the hydroxyl group at the third and fourth carbon atoms. In the second step glycol aldehyde is split off from this ketose. As a result, a higher homolog of the original aldose is formed, differing from it by one —$HCOH^-$ group.

A substantial portion of this sequence is contained in the pentose phosphate pathway of digestion of glucose and is readily detected if we represent the transfer of fragments of monosaccharide molecules (for example, glycol aldehyde or dihydroxyacetone in the transketolase or transaidolase reactions, respectively) not in the traditional way — in the form of an interaction of ketoses and aldoses, leading to the formation of new ketoses and aldoses — but in the form of individual reactions of digestion of ketoses to aldoses and the corresponding fragment or condensation of aldoses with the corresponding fragment. The sequence in Fig. 1 also includes a reaction of cleavage of fructose-l,6-diphosphate into phosphoglyceraldehyde and dihydroxyacetone phosphate, characteristic of the pathway of glycolysis and fermentation. The remaining reactions were detected in various organisms, regardless of their metabolic pathways [5].

Repetitive intervals of another sequence (Fig. 2), arbitrarily called supplementary, were compiled from nine reactions. Transition from the higher homolog to the lower one in the repeating intervals of the supplementary sequence occurs through the following conversions: transfer of glycolic aldehyde to aldose in the transketolase reaction, isomerization of the 3,4-D-threo-ketose formed to the corresponding aldose, two reactions leading to the formation of a UDP-derivative of the aldose, epimerization of 3,4-L-threo-UDP-aldose to 3,4-L-erythro-UDP-aldose, two reactions leading to the fromation of the free aldose, oxidation to aldonic acid and dehydration to 2-keto-3-deoxyaldonic acid, and digestion of the latter to pyruvate and a lower homolog of the original aldose, differing by one —HCOH-unit. Figure 2 presents four incomplete intervals of this sequence. The existence of a large fraction of intermediate reactions and compounds of the fourth interval is still only speculative.

In the metabolism of the carboxylic acids, in addition to the long sequences of reactions of synthesis and digestion of fatty acids discussed in the preceding section, an additional series of comparatively short sequences with a periodic structure is detected. Three monotypic sequences from this series, arbitrarily denoted by the letters M, D, and I, are shown in Fig. 3. The repetitive intervals of the sequences consist of five reactions: condensation of acetyl-CoA with a 2-keto acid, reactions of dehydration and hydration, which isomerize the 3-hydroxy acid to a 2-hydroxy acid, and reactions in which the 2-hydroxy acid is converted to a higher homolog of the original 2-keto acid as a result of oxidation and decarboxylation. The sequences M and D differ in that the number of carboxyl groups in the compounds in the intervals of the sequence D is one greater than for the corresponding compounds in the interval of the sequence M. A peculiarity of the first interval of sequence D is the fact that it consists of reactions of the tricarboxylic acid cycle. These are the reactions of condensation of oxaloacetate with acetyl-CoA, two reactions leading to isomerization of the citrate thereby arising to isocitraie, and the reactions of oxidation and decarboxylation in which a higher homolog of oxaloacetate — 2-ketoglutarate — is formed from

isocitrate. The sequence I is characterized by the fact that its compounds are isomeric homologs of the compounds constituting the intervals of the sequence M. In the series of dicarboxylic 2-keto acids, common to all three sequences, unique symmetry is observed, called isomeric. Its essence is that the keto adds equidistant from oxaloacetate are isomers.

In the metabolism of the nitrogen-containing compounds, four monotypic reaction sequences are detected (see Fig. 4). Three of them differ among themselves by the same characteristics as the reaction sequences of carboxylic acid metabolism M, D, and I, discussed above, and therefore they are denoted analogously. The fourth consists of compounds isomeric to the third and is denoted as Г. The repetitive intervals of these sequences consist of five reactions: amination of 2-keto acids to 2-amino acids, decarboxylation of 2-amino adds to amines, deamination of amines to aldehydes, condensation of aldehydes with glydne, leading to 2-amino-3-hydroxy adds, and, finally, deamination of 2-amino-3-hydroxy acids to higher homologs of the original 2-keto acids. A distinguishing feature of the enumerated reactions is the fact that they all proceed with the partidpation of pyridoxal coenzyme. The isomeric symmetry discussed above is present in these sequences in two series of functionally analogous compounds. Moreover, the axis of symmetry passes through glycine and glyoxylate.

Tne periodic sequences dted in Figs. 1-4 constitute only part of those that can be detected in the metabolic reaction network. However, this is suffident to construct metabolic schemes with a pronounced regular structure. The basis of the structure of the charts is formed by a combination of these sequences. The sequences are shifted in this case in such a way that, on the one hand, their periodic form and the placement of functionally analogous compounds in horizontal rows are preserved, but on the other, compounds with the same number of carbon atoms in the skeleton are arranged along the vertical in compact portions of the charts. Such isocarbon portions consist of the corresponding compounds of the repetitive intervals of the periodic sequences and therefore can be called periods of the schemes. The names of the rows are dted on the left side of the charts, and the periods are numbered according to the number of carbon atoms in the skeleton of the compounds constituting them. To facilitate identification of the sequences of Figs. 1-4, the reactions of these sequences are pointed out with heavy arrows on the charts.

The basis of the structure of the metabolic chart of carbohydrates in Fig. 5 consists of the main and supplementary sequences, depicted in Figs. 1 and 2, respectively. The sequences on the chart are combined according to common transketolase reactions. The regular network obtained as a result of the combination of the sequences, supplemented by other compounds and reactions legitimately related to it, forms the scheme of carbohydrate metabolism. The chart includes 14 rows of functionally analogous compounds and nine periods. The rows are subdivided into two types. The first part of the scheme presents the rows of ketose-l-phosphates, polyols, ketoses, aldoses, aldonic acids, aldose-l-phosphates, and uridine diphosphates of aldoses (UDP-aldoses) with a threo-configuration of the hydroxyl groups at the third and fourth carbon atoms. In the lower part the rows of compounds of the same classes but with an erythro-configuration of the hydroxyl groups at the third and fourth carbon atoms are placed in reverse order. The upper and lower parts of the scheme and its periods legitimately link reversible reactions of condensation of D-aldoses with two- and three-carbon fragments leading to the formation of ketoses with a 2,4-D-threo-configuration of the hydroxyl groups and 2-keto-3-deoxyaldonic acids. In particular, the n and n + 2 periods of the scheme (beginning with n = 2) are linked by transketolase reactions in which glycolic aldehyde is transferred from ketoses of the upper row to aldoses of the lower row with the formation of new ketoses of the upper row. The periods n and n + 3 are linked by aldolases and transaldolase reactions. In the aldolase reactions there is a reversible digestion of the ketose-l-phosphates of the upper row to dihydroxyacetone phosphate and aldoses of the lower row, as well as that of 2-keto-3-deoxyaldonic acids to pyruvate and aldoses of the lower row. In the transaldolase reactions there is a transfer of dihydroxyacetone from ketoses of the upper row to aldoses of the lower row. The sixth and fifth periods of the scheme are linked by reactions of decarboxylation of UDP-uronic acids to the corresponding pentoses at the level of the upper and lower rows of aldoses. The transition from monosaccharides with a 3,4-D-threo-configuration of the hydroxyl groups to monosaccharides with a 3,4-L-erythro-configuration of the hydroxyl groups within the fifth and sixth periods occurs with the aid of epimerization reactions. These are reactions of conversion of UDP-D-xylose to UDP-D-arabinose, UDP-D-glucuronate to UDP-D-galacturonate, and UDP-D-glucose to UDP-D-galactose. Another type includes reactions of epimerization of ketoses: D-ribulose to D-xylulose and D-allulose to D-fructose. The variety of the monosaccharides within the periods is formed on account of the conversion of the carboxyl group of ketoses to a D- or L-hydroxyl group both when they isomerize to aldoses and when they are reduced to polyols. Also characteristic are reactions of oxidation of aldoses to aldonic acids. As a result of dehydration, the aldonic acids can be convened to 2-keto-3-deoxyaldonic acids. The widespread reactions of phosphorylation and dephosphorylation of monosaccharides are carried out by the enzymes kinases and phosphatases (Figs. 5,6,7).

Different parts of the scheme of carbohydrate metabolism are carried out in various organisms [5]. Most of the reactions of the scheme are detected in microorganisms. The digestion of glucose by bacteria along the 2-keto-3-deoxyphosphogluconate pathway, including reactions of oxidation of glucose-6-phosphate to 6-phosphogluconate, dehydration of 6-phosphogluconate to 2-kcto-3-deoxy-6-phosphogluconate (sixth period of the scheme), and digestion of the latter to D-glyceraldehyde phosphate and pyruvate (third to sixth periods), has been studied in detail. Higher organisms are characterized by digestion of glucose along the pathway of glycolysis and in the pentose phosphate cycle. The pathway of glycolysis consists of conversion of glucose to fructose-l,6-bis-phosphate in reactions of isomerization and phosphorylation (sixth period of the scheme), digestion of fructose-l,6-bis-phosphate by aldolase to D-glyceraldehyde phosphate and dihydroxyacetone phosphate (third to sixth periods), and-conversion of the latter to lactic acid (third period). The essence of the digestion of glucose in the pentose phosphate cycle consists of oxidation of glucose-6-phosphate to 6-phosphogluconate (sixth period) and decarboxylation of the latter with the formation of carbon dioxide and ribulose-5-phosphate (fifth to sixth periods). The dynamic equilibrium of the reaction network of monosaccharide metabolism, disrupted in this case, is restored by a redistribution of the substance of ribulose-5-phosphate between ketoses and aldoses (including glucose) in epimerase, isomerase, transaldolase, and transketolase reactions. The scheme also presents reactions of formation of polysaccharides from UDP-derivatives of the corresponding monosaccharides. Three of them: xylan, cellulose, and chitin, constructed from aldoses of the upper row, not only have a similar chemical structure but are also similar in physicochemical properties and are widespread in nature.

The basis of the structure of the scheme of carboxylic acid metabolism in Fig. 6 was obtained by combining the sequences depicted in Fig. 3. As can be seen on the scheme, the combination is reduced to rotation of the M and I sequences around the axis of isomeric symmetry and their superposition upon the sequence D. The regular network formed as a result, supplemented by the reactions of synthesis and digestion of fatty acids and a number of other reactions, constitutes the scheme of carboxylic acid metabolism.

The scheme of carboxylic acid metabolism includes 19 rows of functionally analogous compounds and 10 periods. The rows are subdivided here into three types: rows of monocarboxylic acids and their derivatives, rows of dicarboxylic acids and their derivatives, and rows of tricarboxylic acids. Seven of the periods of the scheme are legitimately interlinked by similar reactions. The link between the n and n + 2 periods of the scheme is effected in reactions of condensation of saturated acids and keto acids with two-carbon fragments (acetate, arising in the digestion of acetyl-CoA or malonyl-CoA, glyoxylate, etc.). The link between the n and n + 3 periods is effected in reactions of condensation of saturated acids with propionate, which arises in the digestion of methylmalonyl-CoA. The link between adjacent periods is effected in reactions of decarboxylation of acids of the higher periods. The reactions of condensation of acetyl-CoA with keto acids, reactions of condensation of glyoxylate with saturated acids, and reactions of decarboxylation at the carboxyl group on the third carbon atom link the compounds of rows of adjacent types. The transition between compounds of rows of the same type within periods occurs in reactions of reduction or oxidation of carbonyl groups and in reversible reactions of dehydration of hydroxy acids to 2,3-unsaturated acids.

A large fraction of the aliphatic 2-keto acids — precursors of the corresponding amino acids — are formed and digested in the enumerated reactions. The carbon skeletons of 2-ketoisovalerate and 2-ketoisocaproate — precursors of valine and leucine — are formed in the reactions of condensation of pyruvate and 2-ketobutyrate, respectively, with active acetaldehyde — a thiamine pyrophosphate derivative of acetaldehyde, which arises in the decarboxylation of pyruvate. Through formate, glyoxylate, pyruvate, and 2-ketoglutarate the initial periods of the scheme of carboxylic acid metabolism are linked with the corresponding periods of the scheme of carbohydrate metabolism. The 8th, 9th, and 10th periods combine the reactions of metabolism of aromatic compounds and are linked to the remainder of the scheme by reactions of digestion of gentisate and homogentisate. These periods are linked to the scheme of carbohydrate metabolism through the reactions of synthesis of phenylpyruvate and 4-hydroxyphenylpyruvate.

The reactions of conversion of dicarboxylic and tricarboxylic acids in the upper part of the fourth to sixth periods constitute the tricarboxylic acid cycle — the main pathway of digestion of acetic acid in many organisms — and the glyoxylate cycle — the pathway of conversion of acetic acid to four-carbon carboxylic acids, leading in plants and certain microorganisms from fatty acids through pyruvate to monosaccharides.

The lower part of the scheme presents the initial states of the pathways of biosynthesis and digestion of linear and branched fatty acids. The former build up the hydrocarbon chain as a result of reactions of condensation with acetate (from malonyl-CoA), linking the n and n + 2 periods of the scheme. The latter build up the hydrocarbon chain in analogous reactions with an acetate homolog, propionate (from methylmalonyl-CoA) [6], linking the n and n + 3 periods of the scheme.

The sixth and seventh periods present similar pathways of biosynthesis of mevalonic and homomcvalonic acids — precursors of the isoprenoids (terpenes, steroids, carotenoids, etc.), widespread in living nature, and the less widespread homoisoprenoids, respectively [7, 8].

The scheme of the metabolism of nitrogen-containing compounds from Fig. 7 is based on the sequences of Fig. 4. It is not difficult to see that, like the preceding case, the sequences M, I, and I' on the scheme are rotated around the axis of isomeric symmetry relative to the sequence D. However, in this case the M and D sequences do not coincide for their common compounds: glycine and glyoxylate, but are placed one below the other. This was done to accommodate the common 2-keto acids — precursors of the corresponding amino acids — on the scheme under discussion, as well as on the carboxylic acid scheme. As a result, a uniformity of structures is achieved for seven carboxylic acids and nitrogen-containing compounds. This facilitates the transition from one scheme to another when they are used together.

The scheme of metabolism of nitrogen-containing compounds includes 23 rows of functionally analogous compounds and 11 periods. In this case, just as on the preceding scheme, the rows are subdivided into three types. These are the rows of monocarboxylic acids and their derivatives, rows of dicarboxylic acids and their derivatives, and the rows of nucleic bases.

Adjacent periods of the scheme are linked by reactions of decarboxylation of amino acids. Periods n and $n + 2$ of the scheme are linked by reactions of condensation of glycine with aldehydes or with saturated carboxylic acids. The amino acids are placed in rows below the corresponding keto acids. In the upper part of the fifth period the ornithine cycle — the pathway of urea synthesis in certain organisms — is presented. Homologs of compounds of the ornithine cycle: lysine, homoarginine, and homocitrulline [9, 10], are placed alongside in the sixth period. Similar reactions of biosynthesis and digestion of purine and pyrimidine bases are placed in the upper part of the first to fourth periods of the scheme.

In the middle part of the fifth and sixth periods the pathways of biosynthesis of precursors of porphyrin and chorrine compounds: δ-aminolevulenic acid and porphobilinogen, are shown.

The presentation of the metabolic reaction network on three schemes corresponds to the traditional division of metabolism into three parts: carbohydrate metabolism, fat metabolism, and the metabolism of nitrogen compounds. All three schemes have a similar structure and can easily be combined into one by means of common compounds and reactions. In this case the rows of functionally analogous compounds of the original schemes retain a parallel arrangement on the combined scheme, but the corresponding periods form generalized periods of a higher level of complexity. The possibility of such a combination is an indication of the uniform nature and integrity of the regularity detected in the metabolic reaction network.

The schemes cited provide a far from complete coverage of metabolism. Nonetheless, the volume of material used, in the author's opinion, is quite sufficient to demonstrate the advantages and possibilities of the proposed approach to the systematization of information on metabolism. In particular, supplementation by structural formulas of the compounds and similar schemes done in color might be more convenient and understandable forms of representing the metabolic reaction network than the metabolic charts compiled in the traditional style.

The regularity of the metabolic reaction network permits an ordering of the arrangement not only of metabolites and reactions on the schemes. It opens up the possibility of rational organization of any other information systematically related to metabolism. In particular, correlations are detected between the nomenclature of enzymes and the nature of the arrangement of the reactions on the schemes. On the basis of these correlations, the existing nomenclature can be supplemented and improved. For example, the fourth letter of the code, which currently does not carry information on the properties of the enzymes, can be used to code the position of the substrate in the series of homologs. A similar method can be used in the systematization of proteins that do not possess enzymatic functions but interact specifically with metabolites, for example, antibodies or permeases.

Metabolic disorders caused by the absence of certain essential compounds in the food or by mutations constitute a rather varied picture and are in need of rational systematization. Such a systematization can be performed on the basis of the regulation of the metabolic reaction network. The systematization of natural inhibitors of metabolism and synthetic antimetabolites can be approached analogously.

As can be seen on the schemes, the regularity of the metabolic reaction network is sometimes violated. Evidently searches for causes of these violations in certain cases might lead to the detection of new compounds, reactions, and the enzymes corresponding to them, and in other to the appearance of new theoretical concepts, which impose definite limitations on the regularity of the metabolic reaction network. As an example of a sufficiently reliable prediction of new reactions we might cite the as yet undetected reactions of biosynthesis of known metabolites, denoted on the scheme by dotted lines. It can also be calculated that the heuristic power of the approach being developed is not limited to the prediction of only single compounds and reactions but extends to all the information more or less systematically related to metabolism. For example,

the success of such prediction is extremely probable with regard to synthetic antimetabolites, which in many cases are close structural analogs of the corresponding metabolites.

The size of a journal article does not permit a detailed discussion of all the questions associated with the regularity of the structure of the metabolic reaction network. A more complete exposition of this material is given in the author's book [11].

In conclusion, the author would like to express deep gratitude to Academician A. S. Spirin for his support and direct aid at ail stages of this work.

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