A C T A U N I V E R S I T A T I S L O D Z I E N S I S
FOLIA BIOCHIMICA ET BIOPHYSICA 2, 1983

Józef Kędziora, Grzegorz Bartosz

METABOLIC DISTURBANCES CAUSED BY ADDITIONAL ACROCENTRIC CHROMOSOME G-21*

The question of biochemical mechanisms leading from the appearance of extraneous chromosome G-21 to profound changes at an organismal level known as Down's syndrome is intriguing and important in view of the social significance of this congenital illness. In this paper, metabolic alterations found in the case of Down's syndrome are reviewed, emphasis being paid to changes in the blood plasma and blood cells. On the basis of literature data and own studies a tentative scheme of sequence of metabolic disturbances in Down's syndrome is put forward.

Human beings are exceedingly diverse. They differ from one another in their normal physical, physiological and mental attributes. They also differ in whether they suffer from particular diseases or other abnormalities. These variations are caused in part by differences in environmental conditions in which they live. But they also depend on inborn differences. Indeed, it is very probable that no two individuals whit the exception of monozygotic twins are exactly alike in their inherited constitutions. Analysis in molecular terms of the nature and effects of such genetically determined differences forms the subject matter of human biochemical genetics.

It is well known that classical genetics led to the concept of gene as the fundamental biological unit of heredity and postulated that it must possess three basic properties. It has to have a specific function in the cell, and hence in the

* This paper is based on a plenary lecture presented at "International Symposium on Bioenergetics and Proteins Functionally Dependent on ATP" (Uniejów 1977).

organism as a whole. It has to be capable of exact selfreplication so that its functional specificity would be preserved from one cell generation to the next. Finally, although an extremely stable entity, it has to be susceptible to occasional sudden change or mutation which could result in the appearance of a new unit or allele differing functionally from the original one but self-replicating in its new form.

It has been shown how such units are arranged in linear order in chromosomes, each gene having its own characteristic position or locus, how they are transmitted to an individual from his parents via the sperm and ovum so that they are usually present in pairs, one member of a pair being derived from one parent and one from the other, and how because of mutational changes in previous generations multiple allelic forms of a gene can occupy a particular gene locus so that individual members of a natural population may differ from one another in their characteristics according to the specific nature of the alleles that they happened to have received from their parents.

There were four major steps which made it possible to begin to understand the nature of the genetical diversity in molecular terms. The first was the discovery that the particular chemical substance which endows a gene with its characteristic properties is DNA. The second was the elucidation of the molecular structure of this substance. The third was the recognition that the primary role of DNA in cells is to direct the synthesis of enzymes and other proteins. The fourth was the unravelling of the genetic code that is the relationship between the structure of nucleic acid and the structure of protein.

Rapid development of molecular biology and advances in research in cell structure and function revealed an immense complexity of these processes. Phenomena creating phenotype are even more complex and hard to interpret as they must be looked upon as a combination of action of genome and of a variety of environmental agents. In view of a highly complicated pattern of cooperation of cell organelles analysis of cells in which these processes are fairly simple seems at present very purposeful. This research line has been followed, among others, in studies of Down's syndrome - an unfortunately frequent inborn anomaly constituting an important social problem in modern societies

where various demographic reasons promote a tendency for later metherhood.

Investigations of biochemical disturbances in Down's syndrome were initiated by J e r o m e et al. [1] who in 1960 revealed for the first time a reduced excretion of some urine components in patients suffering this disease (xanthurenic acid, indophenolacetic acid and indolic acid). This observation became a starting point in studies of further connections between the chromosomal anomaly (trisomy G-21) and metabolic alternations. Most of subsequent investigations concerned differences in levels of metabolites of main metabolic pathways and of activities of certain enzymes in blood plasma and morphotic elements.

Although there is no consensus on this point [2] we regard it well established that there is a decrease of ATP and 2, 3-DPG levels down to about half of the respective normal values in erythrocytes of patients with Down's syndrome; the same finding concerns the ATP level of blood platelets [3, 4]. The diminished levels of energy-rich compounds points to complex enzymatic disturbances in glycolysis and pentose shunt. One can suspect that as a consequence of this lowered ATP level, generation of glucose-6-phosphate in the first stage of glycolysis may be diminished in spite of unchanged hexokinase activity in blood cells because ATP is a substrate of this reaction. However, accumulation of hexosephosphates and a threefold increase in the glucose-6-phosphate dehydrogenase activity accompanied by an increase in the NADP level contradicts such a possibility [5].

It is generally known that in erythrocytes, ATP is generated mainly in two stages of glycolysis, namely in the process of production of 3-phosphoglyceric acid from 1, 3-diphosphoglyceric acid and in the process of formation of pyruvic acid from 2-phosphoenolpyruvic acid. Therefore the disturbances leading to the observed lowering of ATP level may possibly include a partial inactivation of glyceraldehyde-3-phosphate dehydrogenase or a deficiency of pyruvate kinase, a key glycolytic enzyme catalysing the conversion of phosphoenolpyruvate to pyruvate. The first possibility seems unlikely taking into account increases in the activities of phosphohexokinase and phosphofructo-

kinase, accumulation of inorganic phosphate, increase in hexose diphosphate levels and considerable decrease in the level of 2, 3-DPG [6-8]. The latter compound plays a key role in the generally known cycle of Rapoport-Luebering which has self-regulation abilities by means of a feedback.

An increase in the ATPase activity in erythrocytes [9] may also contribute to the lowering of the ATP level in patients with trisomy G-21. However, the extent of this increase is not sufficient to account for the whole of the decrease in ATP concentration.

Research into the structure and function of the red blood cell in various pathological cases has been always of great interest for many authors [10-14]. When comparing erythrocytes of patients with Down's syndrome with those of normal subjects, significant differences were found concerning, among others, the content of hemoglobin and physicochemical properties of the membrane. Osmotic resistance of erythrocytes from patients with Down's syndrome is shifted towards solutions of lower NaCl concentrations as far as the maximal resistance is concerned. Since the minimal osmotic resistance coincides for patients with Down's syndromy and for normal subjects, it means that the amplitude of osmotic resistance is greater for erythrocytes of patients with trisomy G-21. This is reflected especially in the shape of osmotic resistance-fragility curves [15] (Fig. 1).

Noteworthy are changes in the levels of erythrocyte sodium and potassium. We observed an increased level of sodium and a decreased level of potassium in red cells of trisomics G-21. These cells contain approximately 5 mmole Na^+ more and 5 mmole K^+ more less per litre cell water than normal erythrocytes [15].

Studies on ATP level in blood platelets of patients with Down's syndrome revealed a decrease of this parameter paralelling the situation in the red cell. Recent investigations have shown that blood platelets, despite the lack of nucleus and thus their inability do division possess active metabolism and specific complex internal structure connected with their function in the process of hemostasis, viz. aggregation and colt retraction [16]. The exact mechanism of morphological, biochemical and physiological changes occurring during the process of blood

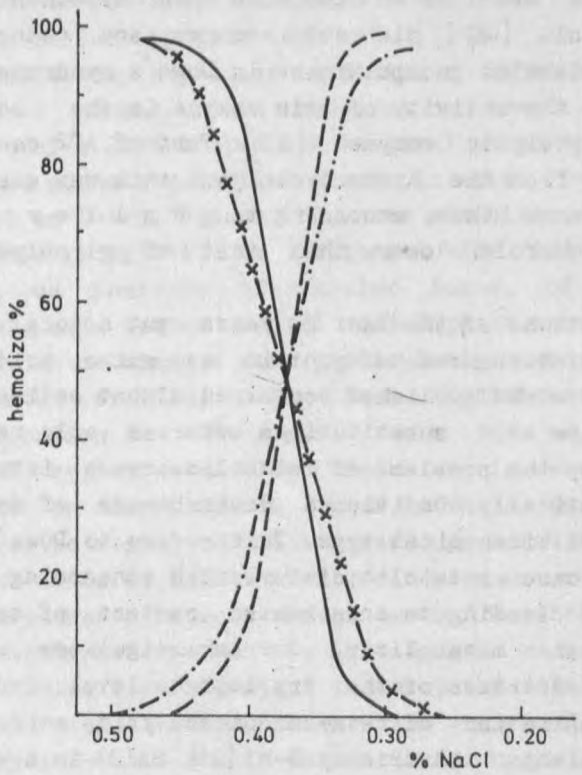

Fig. 1. Osmotic fragility of erythrocytes of normal subjects (----) and patients with Down's syndrome (——)

Oporność osmotyczna erytrocytów osób normalnych (----) i pacjentów z zespołem Downa (——)

Осмотическая резистентность эритроцитов нормальных доноров (---) и больных синдромом Дауна (——)

clotting and their connection with metabolism of blood cells has not been fully elucidated in spite of extensive research. The decreased levels of ATP and ADP in blood platelets of patients with trisomy G-21 may be caused by inhibition of formation of these energy-rich compounds or by alterations of platelets ability to store these compounds in the form of metabolically inactive "storage pool" participating only in the process of clotting. They may be conditioned by inhibition of glycolysis which is a basis process providing energy for blood platelets [4, 17-21]. A decrease of the NAD level by about 51% with respect

to the control level is in line with this hypothesis. However, D o e r y et al. [22] did not observe any changes in the activity of platelet phosphokinase in Down's syndrome though it is known that the activity of this enzyme is the lowest from among all glycolytic enzymes [23]. Part of ATP can be derived in platelets from the Krebs cycle but this way seems to be of lesser importance since, according to W a l l e r et al. [24] its rate is tenfold lower than that of glycolysis in these cells.

Investigations of the last 20 years put special emphasis on hereditary disturbances of protein and amino acid metabolism [25-28]. The works published concerned almost entirely point defects of amino acid substitutions whereas only relatively few papers took up the problem of metabolic errors involving amino acids in genetically conditioned disturbances of morphological-functional and biochemical type. This refers to Down's syndrome too. In this case metabolic disturbances concerning tryptophane were reported leading to a decreased content of serotonin and other tryptophan metabolites. Our investigations indicated a considerable decrease of the tryptophane level and an increase of the concentration of beta-aminoisobutyric acid (BAIBA) in plasma of patients with trisomy G-21 [29] BAIBA is a catabolite of thymine and does not appear in plasma under normal physiological conditions or is present in trace amounts. Despite the increase in the concentration of this compound in blood plasma of trisomics G-21, it was not found in their erythrocytes. The absence of BAIBA in the erythrocytes may be due to its inability to penetrate the erythrocyte membrane which in turn may be conditioned by spacial configuration of this compound [30-31].

Coming back to the discussion on the tryptophane deficiency in blood plasma of patients with trisomy G-21, it should be emphasized that tryptophane belongs to exogenic amino acids and the decrease in the content of this compound may be connected either with its insufficient absorption from the digestive tract or with its increased catabolism. Tryprophane is subjected to conversions leading towards 5-OH-tryptamine and indoloacetic acid or kynurenine [32]. In another metabolic pathway it yields nicotinic acid needed for the synthesis of NAD (the level of the latter being diminished in erythrocytes of patients with

trisomy G-21). On the other hand, a lowered level of 5-OH-tryptamine was reported by many authors [33-36] in blood plasma. Serotonin deficiency may cause a decrease in tonus of smooth muscles, blood vessels, and respiratory tracts as well as exert a depressive effect upon the central nervous system [33, 34, 37]. Some authors described cases in which 5-OH-tryptamine [34] as well as L-tryptophane [33] were administered to newborn children with trisomy G-21 in different time intervals. As a consequence, an increase of muscular tonus, of activity and weight as well as a better mental development were observed in the children. These changes were particularly evident during the first six months of life, being less significant in elder children. According to F e r n s t r o m et al. [38], the level of 5-OH-tryptamine in blood plasma and in cerebral tissue is dependent on many hormones whose effects on cells should, among others, be connected with genome derepression and synthesis of new kinds of mRNA, which could be an evidence of a close interdependency between the genome and metabolism.

Within the human organism we distinguish at least two basic scopes of cellular regulation and the scope of total regulation. The above division is caused by the fact that cell constitutes an elementary life unit and in multicellular organism there must be a superior control mechanism assuring a harmonious course of organismal activities [39]. The complex mechanism of metabolic regulation is strictly connected with a periodical activation of genes which enables initiation of processes of protein biosynthesis [26, 40, 41] and genetic suppression mechanisms which might be exemplified by hereditary differences in the synthesis of blood plasma cholinesterase [44-51]. Family studies employing the technique of dibucaine inhibition indicated the existence of three cholinesterase phenotypes which are under control of two allelic genes [52-55]. The decrease of cholinesterase activity observed in blood plasma of patients with trisomy G-21, parallel to changes of the albumin level does not only substantiate the hepatic origin of the enzyme but also indicate a similar regulation mechanism.

D a r l i n g t o n and B e r n h a r d fused mouse liver (hepatoma) cells and human leukocytes into viable hybrids. These hybrids had the ability to produce albumin and release it into

culture medium whereas leukocytes lacked this ability. The authors concluded on this basis that not only liver cells but also leukocytes possess inborn information concerning albumin synthesis but the gene responsible for induction of this process is subjected to repression or inactivation in leukocytes. An agent present in the hybrids of mouse hepatoma cells and human leukocytes is capable of its activation [56].

The discovery of the possibility of obtaining cell hybrids was a forerunner of progress in this field. T a n et al. [57] using mouse-human somatic cell hybrids demonstrated that particular human genes are syntenic and linked some genes to appropriate chromosomes.

In particular they discovered that the gene controlling the synthesis of indophenol oxidase (IPO) A is localised on the human G-21 chromosome. Further investigations showed a characteristic increase in the level of Cu, Zn-superoxide dismutase (SOD-1), an enzyme identified with IPO-A both in erythrocytes [43] and in blood platelets [58] of patients with trisomy G-21 (Fig. 2).

Since a considerable biochemical evidence has been accumulated indicating the existence between phenotypes of simple trisomy G-21 and unbalanced translocations of the 21st chromosome in several aspects, we determined the SOD-1 activity in patients with simple trisomy G-21 and with partial trisomy G-21 due to unbalanced translocations G-21/22 and G-21/14. In patients with simple trisomy an increase of SOD-1 activity was observed with respect to the normal level. However, this activity was slightly lower than the control value in erythrocytes of patients with translocation G-21/22 as well as G-21/14 [59]. This would indicate a clear-cut position effect on gene activities.

By the way, we employed comparative studies of erythrocytes from normal patients and from those with Down's syndrome (simple trisomy) as an auxiliary tool for differentiating between superoxide-mediated phenomena in the red blood cell and those which are not mediated by this free radical species [60].

Glutathione peroxidase activity was also measured in erythrocytes of patients with trisomy G-21 and reported to be increased by 50% [58]. However, studies on nucleated cells, viz. fibroblasts did not substantiate the increased level of gluta-

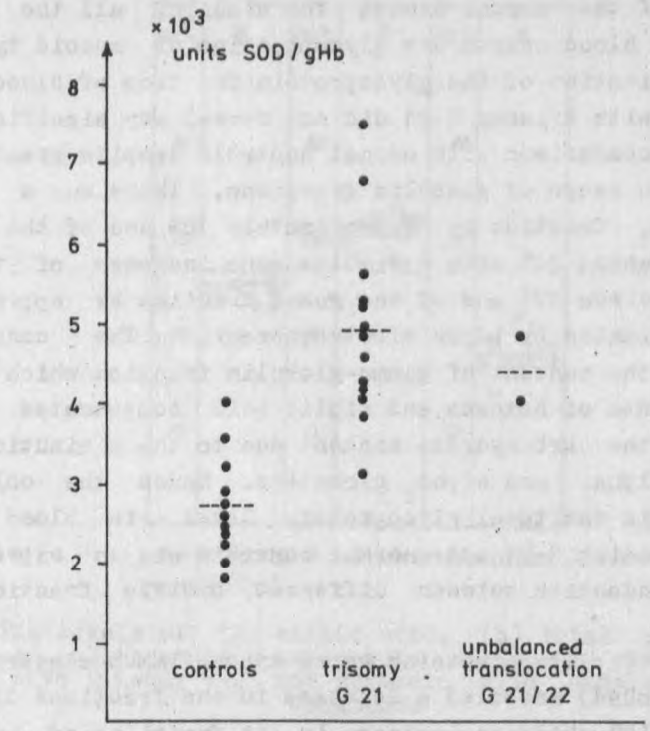

Fig. 2. SOD level in erythrocytes from normal donors, patients with trisomy G-21 and patients with unbalanced translocations

Poziom SOD w erytrocytach osób normalnych, pacjentów z trisomią G-21 i pacjentów z niezrównoważonymi translokacjami

Содержание СОД в эритроцитах нормальных доноров, больных с трисомией G-21 и больных с неуравновлиенными транслокациями

thione peroxidase while confirming the increased activity of SOD-1 [61].

An interesting point concerning the regulation of protein synthesis in the Down's syndrome is the reported decrease in the mangano-SOD (SOD-2) localised in mitochondria by one-third [62]. According to a recent free-radical theory of cancerogenesis proposed by O b e r l e y and B u e t t n e r [63] this would explain the increased probability of developing acute leukemia in trisomics G-21.

Investigations of many authors concerned albumin and globulin

fractions of the serum. Except for albumin, all the globulin fractions or blood serum are glycoproteins of mucoid type [64--69]. Determination of the glycoprotein fraction of blood plasma in patients with trisomy G-21 did not reveal any significant differences in comparison with normal controls despite great alterations in the range of globulin fractions. There was a decrease of the $alpha_1$ fraction by approximately 18% and of the $alpha_2$ fraction by about 24% with a simultaneous increase of the beta fraction by circa 17% and of the gamma fraction by approximately 52% when estimated by paper electrophoresis. The considerable increase of the content of gamma-globulin fraction which contains certain amounts of hexoses and sialic acid compensates for the decrease in the carbohydrate content due to the diminution of the content of $alpha_1$ and $alpha_2$ globulins. Hence the only slight differences in the total glycoprotein level in blood plasma between trisomics G-21 and normal controls are an expression of balancing tendencies between different protein fractions [70] (Fig. 3).

Studies of plasma proteins using cross immunoelectrophoresis (to be published) revealed a decrease in the fractions of prealbumins, and IgH while an increase in the fractions of hemopexin, GC-globulin, $alpha_2$-macroglobulin and IgA. The changes in the levels of immunoglobulins are of special importance since they may be responsible for the immunodeficiency observed in Down's syndrome [71].

The serum $beta_1$ globulin fraction contains, among others, the iron transport protein, transferrin (Tf) [72, 73]. The synthesis of transferrin is regulated by a number of allelic genes. Most of humans have genotype Tfc/Tfc [74]. The lack of transferrin in blood plasma is a rare genetic disturbance described only in individual cases [75-77]. In patients with Down's syndrome a considerable decrease of iron was observed both in whole blood and in blood plasma (in cases with trisomy G-21 as well as in cases of translocations G-21/22 and G-21/14) [78].

In all these cases the level of transferrin was studied and was found to be decreased, too, in patients with trisomy G-21; in patients with translocations G-21/22 and G-21/14

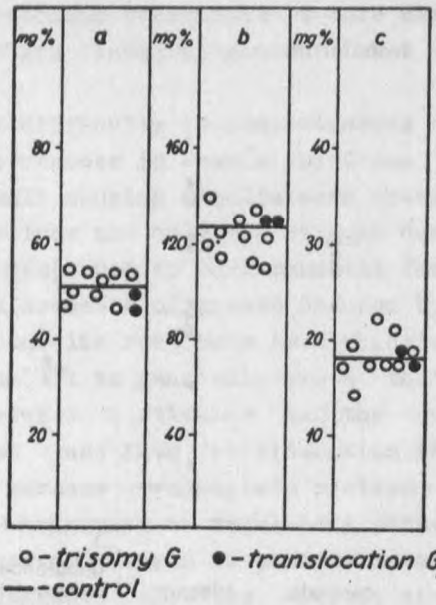

Fig. 3. The levels of: (a) sialic acid, (b) total protein-bound hexoses and (c) seromucoid hexoses in serum of normal donors, patients with trisomy G-21 and patients with unbalanced translocations

Poziomy: (a) kwasu sialowego, (b) całkowitych heksoz związanych z białkiem i (c) heksoz seromukoidu w surowicy dawców normalnych, pacjentów z trisomią G-21 i pacjentów z niezrównoważonymi translokacjami

Содержание: (a) сиаловая кислота, (b) полные белок-связанные гексозы, (c) гексозы серомукоида в сыровотке нормальных доноров, больных с трисомей G-21 и больных с неуравновешенными транслокациями

particularly low levels of transferrin were observed [79] (Fig. 4).

The metabolism of iron, its transport and its incorporation into the porphyrin structure of hemoglobin and other hemoproteins is also influenced by copper. In serum the latter is almost totally bound to ceruloplasmin [80, 81]. The copper content of serum shows also a significant decrease in the group of patients with trisomy G-21. The iron/copper ratio in patients with Down's syndrome lies considerably below the borderline of normal values as far as the blood plasma levels are concerned [78].

It is noteworthy that despite the low copper level in plasma

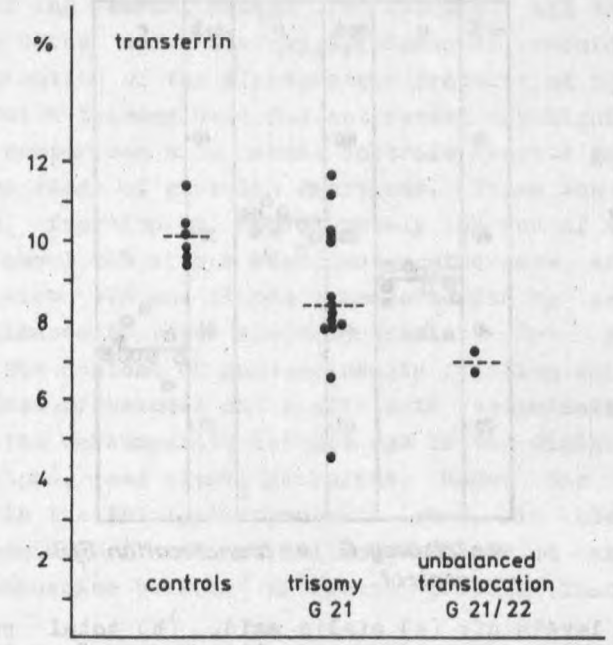

Fig. 4. Transferrin level in blood serum of normal subjects, patients with trisomy G-21 and patients with unbalanced translocations

Poziom transferyny w surowicy krwi osób normalnych, pacjentów z trisomią G-21 i pacjentów z niezrównoważonymi translokacjami

Уровень трансферина в сыворотке крови нормальных доноров, больных с синдромом Дауна и больных с неуравновешенными транслокациями

of patients with Down's syndrome, the level of Cu, Zn-SOD in their erythrocytes was about 50% higher in comparison with control group [82]. This indicates that the copper level in plasma has no influence upon the SOD-1 content [82, 83].

From the investigations of various authors and those performed by us we can conclude that the presence of additional acrocentric chromosome in trisomy G-21 results not only in an increased activity of genes located in this chromosome but also disturbs the cooperation of genes located elsewhere. The overdosing effect of SOD-1 coded by a gene ascribed to chromosome G-21 is quite understandable but the cause of a threefold increase of the activity of glucose-6-phosphate dehydrogenase or an increase in

the level of glutathione peroxidase is more difficult to explain as these enzymes are coded by genes linked to other chromosomes.

An additional difficulty in understanding of the mechanism of metabolic disturbances in Down's syndrome comes from the diversity of stimuli causing simultaneous changes in cellular metabolism. They include not only the stimuli due to altered genome but also changed responses to environmental factors.

Currently the sequence of events induced by external stimuli and leading to metabolic responses is elucidated for a broad range of phenomena. It is generally known that when dealing with the connection between a stimulus and the cellular regulatory mechanism one must take into consideration the following pattern: stimulus --→ hormone --→ adenylate cyclase --→ cAMP --→ specific protein kinase --→ transport or regulatory protein [84, 85].

The broad scope of changes in protein metabolism observed in Down's syndrome suggests that the genetic disturbance must influence the processes of transcription and translation of genetic information. The effect of aneuploidy on the m-RNA synthesis would partially explain the dysproteinemia typical for this syndrome [86-88] and would be in line with the report of I n g e n i t o who found an additional protein fraction designated as X_1 in the blood plasma of patients with Down's syndrome [89]. The observed form of dysproteinemia may depend not only on alterations at the level of transcription but also on those at the level of translation. The activation of the mRNA-ribosome complex depends on many factors, among them on the pool of energy-rich compounds, e.g. ATP. The revealed decrease in the level of ATP in blood cells of patients with Down's syndrome could influence this process.

It is well known that GTP is one of the regulators of translation [90]. This compound is present in increased amounts in erythrocytes of patients with Down's syndrome. This might influence the protein biosynthesis prior to erythrocyte maturation and may contribute to shifts observed in the ratios of different haemoglobin fractions [91].

Disturbances in protein synthesis in trisomy G-21 are of multidirectional nature with simultaneous increases in the levels of some proteins (e.g. glucose-6-phosphate dehydrogenase) and de-

creases in the levels of other ones (e.g. acetylcholinesterase in erythrocytes and cholinesterase in blood plasma).

On the basis of the above considerations a greatly simplified scheme of metabolic disturbances in Down's syndrome is being proposed (Fig. 5).

The additional information introduced into genome in the case of Down's syndrome leads to a highly complicated pathological phenomenon. Of course, it is not easy to distinguish between those events which are due directly to an increased amount of genes localised in additional chromosome and various compensatory indirect effects. The metabolic homeostasis which is attained in this syndrome is shifted with respect to the normal point in the biochemical phase space and is much less advantageous to the organism. This is evidenced already at the cellular level as an increased rate of aging was observed in cultured fibroblasts derived from trisomics G-21 [92]. At the organismal level, a known syndrome of pathological changes develops.

However, we hope that a deeper understanding of the ordering of metabolic changes observed in this disease will enable to introduce new, more effective means of correction of these disturbances and will be a significant step in the development of molecular medicine. We have this goal in mind when performing further biochemical and biophysical studies of molecular mechanisms underlying this syndrome.

REFERENCES

[1] Jerome H., Lejeune J., Turpin R., Compt. Rend. Acad. Sci. (Paris) 251, 474 (1960).

[2] Knull H. R., Bronstein W. W., Porter P. J., Experientia 34, 1133 (1978).

[3] Kędziora J., Hübner H., Kański M., Jeske J., Leyko W., Pediat. Res. 6, 10 (1972).

[4] Kędziora J., Korelacja między zaburzeniami biochemicznymi a anomaliami chromosomalnymi w zespole Downa, Łódź (1974).

[5] Rosner F., Ong B. H., Paine R. S., Mahanand D., New. Engl. J. Med. 273, 1356 (1965).

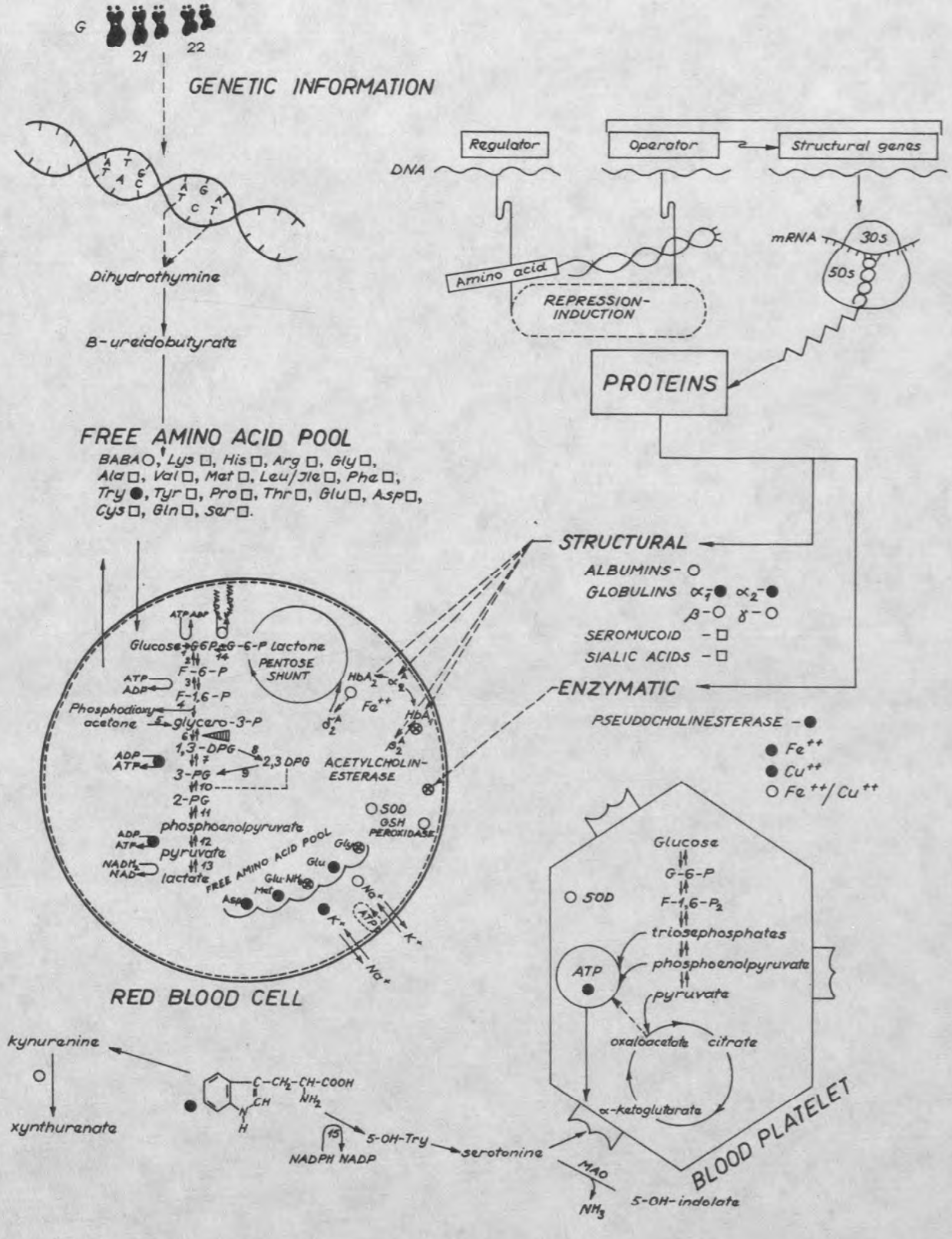

Fig. 5. A tentative scheme of sequence of metabolic disturbances in Down's syndrome

Schemat roboczy sekwencji zaburzeń metabolicznych w zespole Downa

Рабочая схема последовательности метаболических нарушений в синдроме Дауна

[6] Conway M. M., Layzer R. B., Humangenetik 9, 185 (1970).
[7] Layzer R. B., Epstein C. J., Am. J. Hum. Genet. 24, 533 (1972).
[8] Naiman J. L., Oski F. A., Mellman W. J., Lancet I, 821 (1965).
[9] Whittam R., Ager O. L., Biochem. J. 93, 337 (1964).
[10] Bishop C., Rankine D. M., Tallbott I. H., J. Biol. Chem. 234, 1233 (1959).
[11] Horst A., Patologia molekularna, Warszawa (1966).
[12] Kaplan I. C., Beitler E., Biochem. Biophys. Res. Comm. 29, 605 (1967).
[13] Nakao M., Nakao T., Yamozoe S., Yoshikawa H., J. Biochem. 49, 484 (1961).
[14] Nakao K., Wada T., Kaminyama T., Nakao M., Nagano K., Nature 194, 877 (1962).
[15] Kędziora J., Hłyńczak A. J., Jeske J., Kański M., Pol. Endocrinol. 23, 63 (1972).
[16] Waller H. D., Löhr G. W., Grignani F., Gross R., Thromb. Diathes. Haemorrh. (Stuttgart) 3, 520 (1959).
[17] Airaksinen E. M., J. Ment. Defic. Res. 15, 244 (1971).
[18] Linneweh F., Löhr G. W., Waller H. D., Gross R., Enzymol. Biol. Clin. 2, 188 (1963).
[19] Murer E. H., Biochim. Biophys. Acta 172, 266 (1969).
[20] Wachowicz B., Zesz. Nauk. UŁ 42, 37 (1971).
[21] Wachowicz B., Diagn. Lab. 9, 165 (1973).
[22] Doery J. G. G., Hirsh J., Garson O. M., de Gruchy G. C., Lancet 2, 895 (1968).
[23] Boullin D. J., O'Brien R. A., J. Physiol. 212, 287 (1971).
[24] Smith E. K. M., Farrington D., Sydiuk L., Canad. J. Physiol. Pharm. 50, 791 (1972).
[25] Eldjarn L., Jellum E., Stokke O., Clin. Chim. Acta 40, 461 (1972).
[26] Harris H., Triangle 10, 41 (1971).
[27] Hsia D. Y. Y., Inborn errors of metabolism, New York (1966).

[28] Lingan T. A., Science 162, 579 (1968).
[29] Kędziora J., Endokrynol. Pol. 24, 149 (1973).
[30] Hoare D. G., J. Physiol. 221, 311 (1972).
[31] Christensen H. N., Riggs T. R., Ray N. E., J. Biol. Chem. 194, 41 (1952).
[32] Cooper J. R., Melcer J., J. Pharmacol. Exptl. Ther. 132, 265 (1961).
[33] Airaksinen E. M., Ann. Clin. Res. 5, 1 (1973).
[34] Bazelon M., Paine R. S., Cowie V. A., Hunt P., Houck I. D., Mahanand D., Lancet I, 1130 (1967).
[35] O'Brien D., Groshek A., Arch. Dis. Childh. 37, 17 (1962).
[36] O'Brien D., Blood 24, 309 (1964).
[37] Jun-Bi-Tu, Lancet 2, 715 (1965).
[38] Fernstrom J. D., Wurtman R. J., Science 178, 414 (1972).
[39] Horst A., Problemy genetyki medycznej, ed. Efroimson W. P., Horst A., Warszawa (1972).
[40] Fritz P. J., White E. L., Vesell E. S., Pruitt K. M., Nature New Biol. 230, 119 (1971).
[41] Harris H., The principles of human biochemical genetics, Amsterdam-London (1971).
[42] Hartman P. E., Roth J. R., Adv. Genet. 17, 1 (1973).
[43] Sichitiu S., Sinet P. M., Lejeune J., Frézal J., Humangenetik 23, 65 (1974).
[44] Clark S. W., Glaubiger G. A., Ladu B. N., Ann. N. Y. Acad. Sci. 151, 710 (1968).
[45] Gaffney P. J., Lehman H., Hum. Hered. 19, 234 (1969).
[46] Goedde H. W., Gehring D., Hofmann R. A., Biochim. Biophys. Acta 107, 391 (1965).
[47] Heyworth E., Firth F. M. J., Lancet 2, 1422 (1967).
[48] Kalow W., Staron N., Canad. J. Biochem. Physiol. 35, 1305 (1957).
[49] Scott E. M., Biochem. Biophys. Res. Comm. 38, 902 (1970).

[50] Scott E. M., Weaver D. D., Wright R. C., Am. J. Hum. Genet. 22, 369 (1970).
[51] Scott E. M., Ann. Hum. Genet. (London) 37, 139 (1973).
[52] Atland K., Goeddе H. W., Biochem. Genet. 4, 321 (1970).
[53] Gutsche B. B., Scott E. M., Wright R. C., Nature 215, 322 (1967).
[54] Hodkin W. E., Giblett E. R., Levine H., Gauer W., Motulsky A. G., J. Clin. Inv. 44, 486 (1965).
[55] Liddel J., Lehmann H., Silke E., Nature 193, 561 (1962).
[56] Ruddle F. H., Kuherlapati R. S., Sci. Amer. 7, 36 (1974).
[57] Tan Y. H., Tischfield J., Ruddle F. M., J. Exptl. Med. 137, 317 (1973).
[58] Sinet P. M., Michelson A. M., Bazin A., Lejeune J., Jerome H., Biochem. Biophys. Res. Comm. 67, 910 (1975).
[59] Kędziora J., Bartosz G., Leyko W., Rożynkowa D., Lancet I, 105 (1979).
[60] Bartosz G., Kędziora J., Jeske J., Leyko W., Int. J. Radiat. Biol. 31, 197 (1977).
[61] Feaster W. W., Kwok L. W., Epstein C. J., Am. J. Hum. Genet. 29, 563 (1977).
[62] McKusick V. A., Ruddle F. H., Science 196, 390 (1977).
[63] Oberley L. W., Buettner G. R., Cancer Res. 39, 1141 (1979).
[64] Atkin I., Rundle A. T., Humangenetik 21, 81 (1974).
[65] Bötiger L. E., Carlson L. A., Clin. Chim. Acta 104, 152 (1959).
[66] Falholt W., Menini E., Lous R., Acta Med. Scand. 160, 323 (1958).
[67] Himmel A., Schmidt M., Pol. Tyg. Lek. 17, 1 (1962).
[68] Kellen I., Biochemie, Klinik und Laboratoriumsdiagnostik, VEB Thieme G., Leipzig 1960.

[69] Schmidt M., Dmochowski A., Laskowski S., Czarnecki M., Wierzbowska B., Pol. Tyg. Lek. 23, 881 (1968).
[70] Kędziora J., Wachowicz B., Endokrynol. Pol. 25, 14 (1974).
[71] Reiser K., Whitcomb C., Robinson K., MacKenzie M. R., Am. J. Ment. Def. 80, 613 (1976).
[72] Huff R. L., Hennessy T. G., Austin R. L., Gargia I. F., Roberts E. M., Lawrence J. H., J. Clin. Invest. 29, 1041 (1950).
[73] Sen A. K., Post R. L., J. Biol. Chem. 239, 345 (1964).
[74] Bearn A. G., Cleve H., The metabolic basis of inherited diseases, New York (1966).
[75] Heilmeyer L., Keller W., Vivelo O., Keiderling W., Betke K., Wöhler F., Schultze H. E., Deut. Med. Wschr. 86, 1745 (1962).
[76] Mazur A., Greem S., Farleton A., J. Biol. Chem. 235, 595 (1960).
[77] Whebey M. S., Jones L. G., J. Clin. Invest. 42, 1007 (1963).
[78] Wachowicz B., Kędziora J., Endokrynol. Pol. 25, 9 (1974).
[79] Kędziora J., Witas H., Bartosz G., Leyko W., Jeske J., Rożynkowa D., Experientia 34, 712 (1978).
[80] Surgeon B., Braubraker C., J. Dis. Child. 92, 254 (1956).
[81] Zgirski A., Łoza E., Zesz. Nauk. UŁ 37, 15 (1970).
[82] Kędziora J., Jeske J., Witas H., Bartosz G., Leyko W., Acta Biol. Med. Germ. 36, 779 (1977).
[83] Alexander N. M., Benson G. D., Life Sci. 16, 1025 (1975).
[84] Jerome H., Lejeune J., Turpin R., C. R. Acad. Sci. (Paris) 251, 474 (1960).
[85] Langan T. A., Science 162, 579 (1968).
[86] Benson P. F., Nature 215, 1290 (1967).
[87] Rundle A. T., Clin. Genet. 4, 520 (1973).

[88] Stein Z., Susser M., Guterman A. V., Lancet I, 305 (1973).
[89] Ingenito E. F., Lancet I, 979 (1968).
[90] Kerr J. M., Cohen N., Work T. S., Biochem. J. 98, 826 (1966).
[91] Kędziora J., Gondko R., Jeske J., Kański M., Leyko W., Genet. Pol. 15, 139 (1974).
[92] Schneider E. L., Epstein C. J., Proc. Soc. Exptl. Biol. Med. 141, 1092 (1972).

Department of Physiology
Physiological-Biochemical Institute
WAM, Łódź

Department of Biophysics
Institute of Biochemistry and Biophysics
University of Łódź

Józef Kędziora, Grzegorz Bartosz

ZABURZENIA METABOLICZNE
SPOWODOWANE PRZEZ NADMIAROWY AKROCENTRYCZNY CHROMOSOM G-21

Zagadnienie biochemicznych mechanizmów pośredniczących pomiędzy obecnością nadmiarowego chromosomu G-21 a istotnymi zmianami na poziomie organizmalnym, określanymi mianem zespołu Downa, jest interesujące i ważne ze względu na znaczenie społeczne tego wrodzonego schorzenia. Artykuł daje przegląd zmian metabolicznych, stwierdzonych w przypadku zespołu Downa, zwracając szczególną uwagę na zmiany zachodzące w plazmie krwi i w krwinkach. Na podstawie danych literaturowych i wyników własnych badań zaproponowano schemat sekwencji zmian metabolicznych w zespole Downa.

Юзеф Кендзёра, Гжегож Бартош

НАРУШЕНИЯ МЕТАБОЛИЗМА,
ВЫЗВАННЫЕ ДОБАВОЧНОЙ ХРОМОСОМОЙ С-21

Вопрос биохимических механизмов, ведущих от присутствия добавочной хромосомы С-21 до глубоких изменений на организмальном уровне, известных под званием синдрома Дауна, является интересным и важным из-за общественного значения этой врожденной болезни. В статье осмотрели метаболические нарушения, обнаруженные в синдроме Дауна, обращая особенное внимание на изменения в плазме крови и в клетках крови. На основе литературных данных предлагается схема последовательности метаболических изменений в синдроме Дауна.