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DEPENDENCE OF IONIZING RADIATION AND OTHERS ENVIRONMENTAL FACTORS IN DOWN'S SYNDROME

Since the very beginning of the existence of humen species its representatives have been trying to meke their life easier. These attempts have induced, among others, struggle egainst harassing diseases, owing to the development of medicine and technology end the civilization progress in general. Nowadays decimating human populations belong to the past and some microorgenisms that depopulated whole continents, practically do not leeve microbiological leboratoriee. More and more efficacious and strong medicines have prolonged the human life-span. However, all these civilization achievemente do not lack some deleterious side-effects. Changes in the economic, sociel etc. systems due to these very achievements heve born new problems.

Dieapperance of some diseases has been accompenied by outbursts of new ones, among them those with respect to which the possibilities of science are still limited., i.e. geneticelly conditioned disorders.

The frequency of these diseases increases which ie not independent of the civilizational progress and its implications. One of euch diseases belonging to most important from e social point of view, due to its abundance and meagre possibilities of treatment is Down'e eyndrome.

Since in 1866 dr Langdon D o w n, medical superintentent of the Earlswood Hoepital deecribed a phenotype typical for the mental defficiency eeeocieted with "mongoloidal" features [38] etiology of this disease, erroneously acknowledged by the Author to be the coneequence of tuberculoeie, was to remain unknown for almost 100 yeare. Only ae late ae in 1959, when L e j e u n e et al. linked the clinical picture to trieomy G [103] and seen a decreased excretion of indolic, indoloacetic and xanthurenic acids in urine of patiente with Down'e syndrome was revealed [76]

both before and after tryptophan loading, the conclusion of a genetically conditioned metabolic defect as a cause of this disease has prompted to intensive comparative biochemicel studies of normal individuals and patients with Down's syndrome.

Clinical picture

The clinical picture of Down's syndrome includes little size, askew eyelids and a characteristic pattern of the epicanthal fold [139]. Head is small, of shortensd anteroposterior diameter. The patients have broad pelms and fingars and characteristic dermatoglyphe irregularities [6, 31, 36, 91, 134]. A permanent feature of Down's syndrome is mental deficiency, developing since first years of life [11]

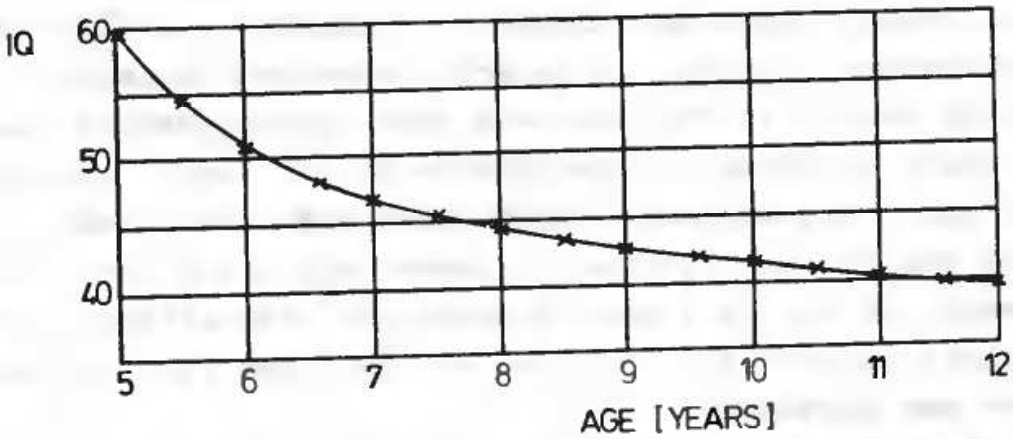

Fig. 1. Dependence between IQ end age in D.S.

Frequent are cardiopathies, persistent arteriel duct, narrowed pulmonary ertery, persistent interauricural orifice and intraventiculer septum losses. Thyroid and suprerrenal glands ere dscreased in size and weight. The patients show increased susceptibility to infections end lymphatic leukemia. Elder patients [over 34] suffer practicelly in 100% to Alzheimer's disease, believed to be conditioned metebolically [61, 125] Increased frequency of visual and auditive effects [7, 51] and lowered blood pressure [136] have been found; EEG shows pathological features in Down's syndrome.

Ceuses of Down's syndrome

Down's syndrome is conditioned geneticelly, and epparently most pertinent to its etiology is the occurence of a pathogenic segment in chromosomes of group *G*. The discovery of additional ecrocentric chromosome 21 in the patients heve given basis to ascribe Down's syndrome to trisomy 21. However the occurrence of similar disturbances in individuals displaying cytogenetic anomelies of other types,

the existence of trisomy *G* without eny phenotype changes end in some cases the presence of Down's eyndrome symptoms in the absence of any perceivable chromosomic elterations [55, 77, 127] require still care in explanation of ethiopathogenesis of this disease. At the moment it is assumed generally that Down's syndrome occurs in cases of trisomy *G*, unbelanced translocetions *D/G* or *G/G* and XXXY or XXYY polysomies [15, 48, 130, 156] Trisomy *G* is believed to be due to non-disjunction or duplication of genetic material. It seems that though the link of the occurence of DS to the chromosomes of group *G* is obvious, e deteiled explenation of the nature of genetic disturbation is still to be elucidated unequivocally. One cannot exclude a possibility of several different causes resulting in clinicelly similar cases of DS. A more precise description of ethiology of this disease can be expected from localization of gene loci of chromosome 21 responsible for individual effects and metebolic disturbences. Up to now, the following gene loci have been located in chromosome 21:

- AVG (antiviral gene), responsible for the selectivity of interferon actions
- genes responsible for: (*i*) indophenolooxidase - (IPO),
  (*ii*) copper-zinc superoxide dismutase - (SOD-1) end
  (*iii*) glycinemide ribonucleotide synthetase (GARS).

However, e general opinion is thet IPO-A and SOD-1 ere synthesized at the some gene locus (21 q 22.1) end represent one enzyme [147]. Determinetion of positions of the gene loci was eccomplished using the cell-hybride technique [169, 170]. Gene dosage effect hes not been studied for GARS but for SOD-1 a 50% surplus in activity was found in trisomic cells (fibroblests in vitro), according to expectations. In the case of AVG the increment was higher than expected but the test applied did not measure the amount of the protein - only effect of its action, eventually dependent on the interferon sensitivity in vitro [75, 76].

Yet in 1980, 2 decades after L e j e u n e, T u r p i n and G a u t i e r demonstreted chromosomal basis of mongolism, some of the seme previously postulated etiological agents are still suspect. Recognition of the cytogenetic basis of DS had indicated the time of ection of whatever the ceusative factors might be but

did not identify them. While the chromosomal basis is more or less known in this disease, the ceusation for the "chromosomal error" is not. Concerning epidemiological espect of DS we must not neglect some social changes having unfortunately a definite enhancing effect on the frequency of DS. An increased risk of so defective progeny was found in elderly femeles [64-67] end males [67--69, 160-162].

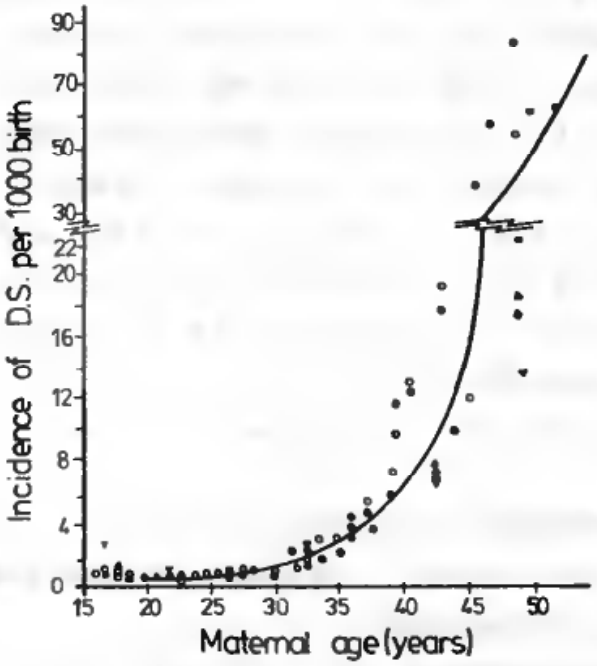

Fig. 2. Maternal age and risk of D.S. conception

It is noteworthy that the effect of parental age is seen even in second generation [131]. Sociological trends favouring lete pregnancy (second marriages, professional career preceding conception) may leed towards the increase in the aberration frequency in future. In 1961 [145] the world frequency of DS among live births wes 0.34%. Lately the incidence of newborns with this disease decreased slightly but when introducing a correction for the interruptions and removel of foetuses with this enomaly (still more frequent due to development of prental diagnostics) a constant increese in the frequency of DS must be concluded. Moreover, the figures represent only one third of all 21 trisomics conceived; it has been estimated that two third are spontaneously aborted [142]. The actuel frequency of 21 trisomy is, therefore, closer to one in 200-250. What is the cause of the high rate of ebnormal chromosome segregation during gametogenesis. The unknown element is the particular factor (or factors) unique to eging thet cause difficulties in older parents. The review of verious factors correleting with DS frequency, es mitotic and hormonal drug use, ionizing radietion etc. indicates that occurrence of mutagenic factors, apparently responsible for the increase in the percent abundence of G/G translocations in developed countries [65] is not indifferent to the epidemiology of DS. It was first demonstrated in Drosophila melanoga-

ster [129] that aged females exposed to radiation show en increase in nondisjunctional progeny wherees eging alone does not. The relevance of these findings to the humen situations confirmed expectations [172]. The seme increase in exceptionel offspring of irradiated females was found end there was no detectable effect of maternel age in the absence of radiation.

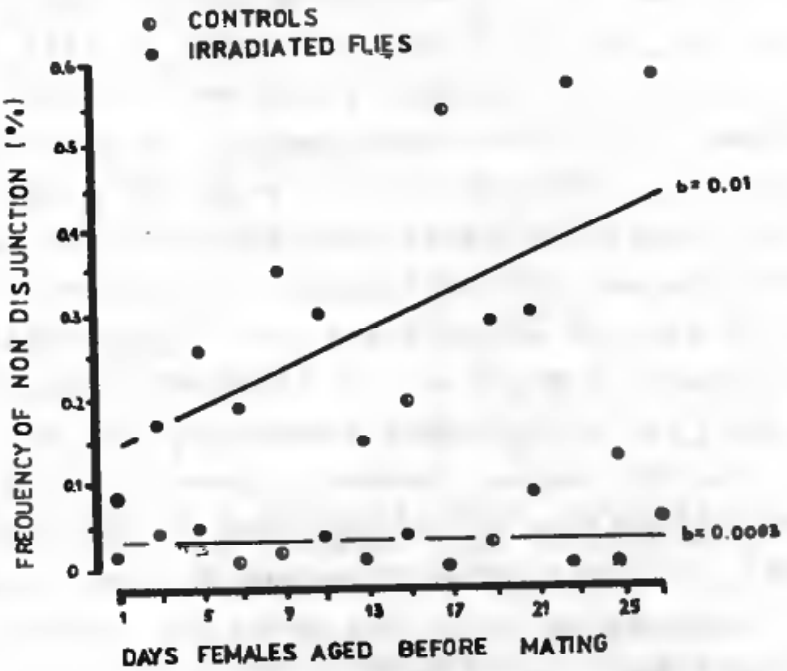

Fig. 3. Increase with age of aneuploid progeny of irradiated female Drosophile (cited after I.A. Uchida)

However the suggestion of an association between meternal rediation and trisomy was met with scepticism. A prospective analyeie by S c h u l l and N e e l [153] of the effects of atomic bombe dropped on Hiroshima and Nagaseki produced negative result. On the other hand no data concerning spontaneous ebortions among conceptione under those conditions were obtainable. Because of the conflicting data and the errors inherent in a retrospective study U c h i d a et al undertook in 1969 a prospective investigetions. A significantly higher number of autoeomal aneuploids were born after the mothere were irradiated: a frequency of 10 : 1 [171]. Also retrospective etudies by Sigler et al in the USA and A l b e r m a n et al. in England confirmed the findings of previous study [3, 155]. The human epidemiological etudies thus agree with the experimental evidence found in Drosophila. Of course a juetifiable criticiem is that human can hardly be compared with Drosophila be-

cause of not identicel mechanism of meiosis. In order to receive results of a more comperable nature, a memmal is more appropriate.

H e n d e r s o n et al. suggested that an increased frequency of univalents essociated with a reduced frequency of chiasmeta in first meiotic metaphase of the oocytes of aged mice may be a reflection of an increesed frequency of non-diploid embryos. An abnormal number of chromosomes should be seen in next metaphase after non-disjunction [108]. In order to test this hypothesis U c h i d a et al. irrediated young and old mice to whole body. 21 chromosomes (i.e. hypermodal counts) were found only in irradiated mice [173]. Compering two irradiated groups the increased frequency of hyperploid cells was significantly higher in the older animals. However the difference in frequency between young and aged mice wes not significant in non-irradiated group. Similar results found Y a m a m o t o et al. [189] and R e i c h e r t et al. [135]. Analogous investigations ere impossible in humans for obvious reason. Recently however the effect of rediation on the segregation of chromosomes in somatic cells was observed [174]. Trisomic cells occurred 4 times es frequently in irradiated lymphocytes as in the controls, moreover significantly higher frequencies of cells with an extra X or No. 21 were found. These results may be relevant to the frequent occurrence of these chromosomes in eneuploidy.

Epidemiological studies investigating the possible role of radietion exposure in the mothers of DS offspring have been conducted recently in various countries.

It is noteworthy that although obtained data were in 2 cases negative, all significant results were positive. Unfortunately the data from the various studies cannot be pooled since the metodology ie not uniform. However, taking into eccount known observatione - it eeems highly logical to avoid unnecessary exposure to radiation that might be partly responsible for the genetic burden of humane. It is very probably, that more frequent (or epidemic) viral hepatitie [176] has pointed to alterations in the immune system. Though more detailed etudiee did not confirm the relation between increased sueceptibility to some diseases and Down's eyndrome, it wae proven that the immune syetem of trisomics shows considerable differencee with respect to that of normal eubjects. The queetion of appropriate selection of control groupe for hos-

pitalized persons arouse many controversies in view of the effect of prolonged hospitelizetion per se on the patients immune system.

Teble 1

Data concerning maternel rediation and Down's syndrome reported from several countries since 1959

Authors	Country	Yeer	Results
Lunn [109]	Scotlend	1959	+ NS
Uchida and Curtis [172]	Ceneda	1961	+ S
Carter et el. [22]	England	1961	- NS
Stevenson et al. [163]	Iceland	1961	+ NS
Schull and Neel [153]	Japen	1962	- NS
Sigler et al. [155]	USA	1965	+ S
Uchida et el. [171]	Canade	1968	+ S
Marmol et al. [111]	USA	1969	+ NS
Stevenson et al. [164]	England	1970	+ NS
Villumsen [178]	Denmark	1970	+ NS
Alberman et al. [3]	England	1972	+ S

+ - Down's syndrome more frequent after irradiation.
- - Down's syndrome less frequent then in control.
S - Significant, NS - Not significant.

E.g. e decreased activity of anti-HAV antibodies was reported for Down's syndrome but the difference with respect to other patients of insitutions for mentally deficient persons (estimated by the SPRIA) Solid Phase Radio Immuno Assey (method) was only 12% while equalling to 87% in comperison to healthy persons [100]. The prolonged insitutionalization was epparently an important factor itself. Preliminary hypotheses on leukemia etiology in mongolism were not confirmed. The "Philedelphia" group *G* chromosome described by Nowell et al. [121] and believed to be a factor predisposing for leukemie in Down s syndrome was then evidenced to belong to the earlier replicating pair G22. This chromosome was demonstrated to occur in other diseases of the erythropoetic system, too [133].

According to the free-radical theory of cancerogenesis by Oberley et el. [122] it seems thet the 30% decrease in the level of Mn-superoxide dismutase (SOD-2) in Down's syndrome cen be responeible for the increased frequency of lymphatic leukemia in mongoliem. The confirmation by Schlesinger et al. in 1973 of the diminution of lymphocyte count in Down's syndrome [148] together with the previoue reports of Bendy and Strass-

m a n on thymic alteration [10] and enlargement of Hassal's corpuscles evidence a possibility of destabilization of the thymus-controlled system. Recent studies by B u r g i o, U g a z i o, L e v i n e and others euthors [18, 19, 105, 106, 175-177] confirmed melfunction of the thymic system [1, 35, 56, 73, 89, 93, 94, 120, 147, 181, 187] dramaticly reinforced with increasing age in trisomics.

The decrease in lymphocyte T count was found to be linked to the presence of HLA-B8 alleles in the patients [49]. The percent of monocytes and EAC (erythrocyte-antibody-complement complex) rosette-forming cells was increased. The effect of such T-cells mitogens es concenevalin A or PHA was weakened. Results of observations and conclusions in this field are presented in Table 2 a where, unfortunately scarcity of place precludes a detailed description of experimental methods used. It is noteworthy that studies on the immunoglobulin level demonstrating a statistically significant increese in IgA, IgG, IgE, IgD [117] while decreese in IgM [94] observed in ceses using healthy children as a control group often do not remain statistically significant in comparison with institutionaled mentally retarded patients without Down's syndrome. This result indicates, that some of the abnormalities found in immunoglobulins in Down's syndrome may be caused by indirect factors due to different conditions of life, usually occuring in trisomics. Because only several reports are in this field identical, while others do not demonstrate full agreement we decided to present them in Table 2, taking into eccount different findings.

T a b l e 2

Some aspects of the immune system in patients with Down's syndrome

Clinicel findings: Increesed incidence of infections, particularly respiratory[126] Increesed incidence of lymphatic leukemia [115] High incidence of Austrelian antigenemia [167, 176] High incidence of thyroid autoantibodies [176]
Immunologic findings: Diminished number of blood lymphocytee [105] Diminished phagocyte activity [143] B cells Normal number [49, 105, 144] Immunoglobulin production [116, 165, 168]

cd. tabeli 2

IgM level, normal or decreased
IgG level, normal or increased
IgA level, normal or increased
IgD level, increased
Defective antibody response to bacteriophage ϕX174 [108]
T cells
Diminished number [105]
Diminished blast transformation with PHA [49, 146]
Diminished delayed skin hypersensitivity to PHA [186]
Deficient interferon production
Respond to thymic humoral factors [56]
Diminished LIF with PHA

Pethology
Spleen: T-zone lymphocytes depleted
Thymus:
Small with severe lymphocyte depletion
Giant and cystic Hassall's corpuscles
Increased cellularity around some HC
Contracted, depleted cortex

Most of investigations of the immune system in DS has been based in observations of whole orgsnism. Only recently started studiss basing on cultured DS fibroblasts [22]. Up to now previous reports do not allow to draw more precisely conclusions. It is noteworthy that our own investigations csrried out using the technique of crossed immunoelectrophoresis indicate a statistically significant decrease of prealbumins and increase of the level of elpha$_2$-macroglobulin and immunoglobulin A [89] Fig. 4, 5.

Biochemical anomalies in Down's syndrome

Perceptible changes in the psttern of peptide maps of cultured fibroblasts do not permit an unequivocal interpretation of underlying changes in view of the complicated repression-induction mechanisms and possible effects of regulatory proteins on structural proteins [182]. In this situation a detailed examination and consideration of changes occurring in simple model systems (red blood cells, blood platelets body fluids) seems to be of great value. Additional advantages of such studies are in possibilities of their application in simpls diagnostic tests and in eventual tests of efficiency of substitutive treatments. Discovery of factors in maternal body fluids which could correlate with the risk of smbryo's abnormality would create a possibility of a preliminary narrowing of recommendations for amniocentesis and, therefore, result in a higher availability of this test in practice. The currently accepted recomendations as, e.g., mother age above 35 [188] lead to

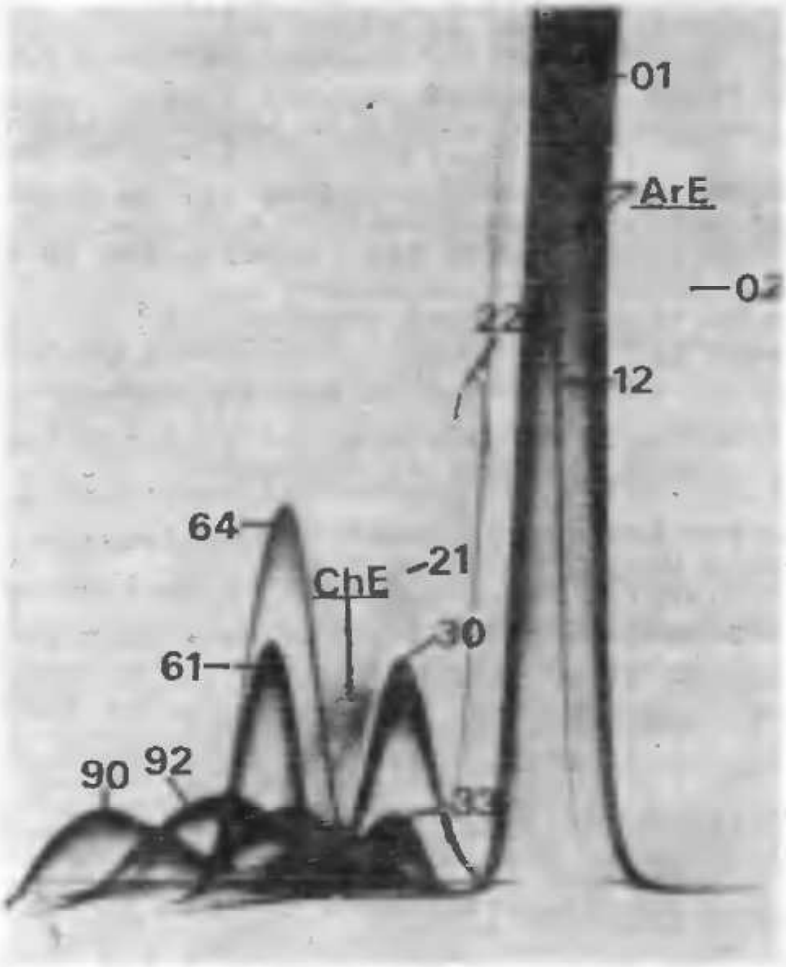

Fig. 4. Crossed immunoelectrophoresis of human blood plasma
O1 - albumin, O2 - prealbumin, 12 - α -1-antitrypsin, 21 - Gc - globulin, 22 - α -1-antichymotrypsin, 30 - haptoglobulin, 33 - α -2- macroglobulin, 61 - transferrin, 64 - hemopexin, 90 - IgG, 92 - IgA, ChE - cholinesterase, ArE - arylesterase

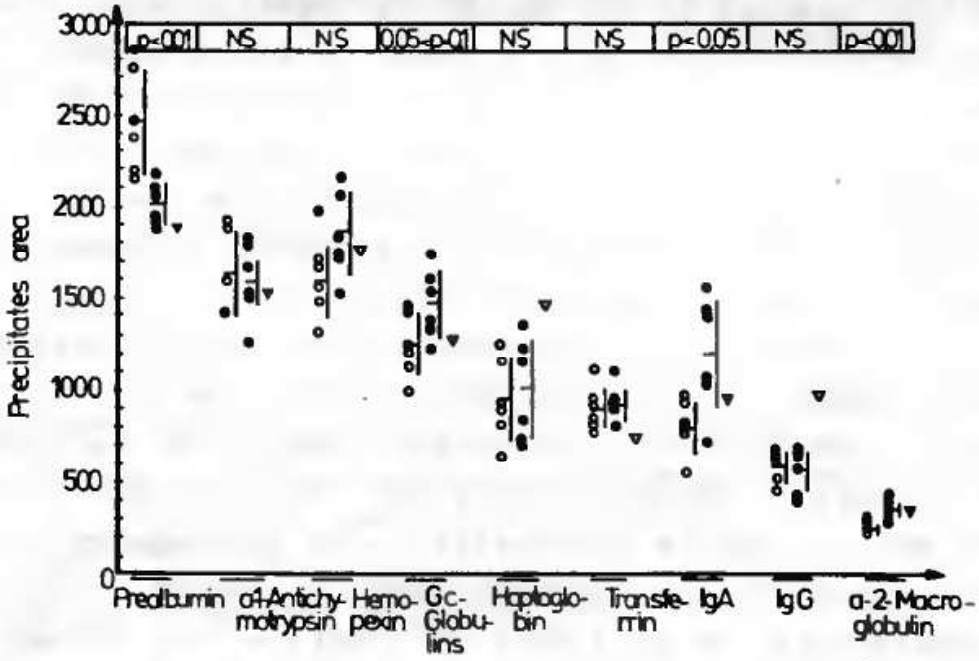

Fig. 5. Surface area below immunoprecipitates of plasma protein fractions for control group, trisomy G-21 and translocations G 21/22

over 90% of erroneously positive results (see Fig. 2). A need for elaboration of a preliminary screening test under conditions of demand for 18000 amnicenteses in Poland yearly [32] is obvious. Success of enother test of this type (AFP level in mother serum) for diagnosis of CNS deficiences [184] allows for some doss of optimism based on this confirmation of the effect of embrionic disturbances on the biochemistry of the mother.

Studiss on the content of energy-rich compounds in morphotic elements of the blood demonstrated a decrease in the level of ATP in blood platelets and red blood cells down to 50% of the value typical for healthy persons [83]. In the red blood cells the ADP level was decreased, too, while concentration AMP increased two-fold [82]. Despite the lack of consensus concerning the decrease in 2,3-DPG [95] our results confirm data on a 50% fall in the concentrstion of this compound in erythrocytes [82, 83]. On the other hand, the levels of HDP, NAD, NADP and inorganic phosphates ere increased [82]. The decrease in ATP and 2,3-DPG may involve inhibition of glycolysis and stimulation of the pentose shunt. A threefold increase in the activity of glucose-6-phosphate dehydrogenase wss reported [140].

Looking for causes of the observed changes in metabolite concentrations one should consider the process of ATP generation in the red blood cell. The only significant process yielding ATP in this cell is glycolysis where ATP synthesis is coupled to conversion of 1,3-diphosphoglycerate into 3-phosphoglycerate (catalyzed by glyceraldehyde-3-phosphate dehydrogenase) and to formation of pyruvate from phosphoenolpyruvate (catalyzed by pyruvate kinase). The established anomalies may involve inhibition of any of these reactions. The decrease in 2,3-DPG level, increase in hexose diphosphate concentrations [80], accumulation of inorganic phosphate as well as enhancements of activities of hexokinase and phosphofructokinase [28, 99, 120] would indicate localization of the primary defect at the level of inhibition of glyceraldehyde-3-phosphate dehydrogenase. The observed increase in ATPass activity [185] may also contribute to the ATP depletion but quantitative data demonstrate that the increased activity of ATPase cannot be responsible for a drop in ATP concentration as high as 50%.

It ie noteworthy that ATP depletion due to pyruvate kinase deficiency (as in non-apherocytic hemolytic anemia) [53, 132] invol-

ves an increase, not decrease in the level of 2,3 DPG [137]. This relation is in sgreement with the hypothesis discussed above.

In the case considered, the observed increase in glucose-6-phosphate dehydrogenase activity [140, 142] may be due to induction of a compensative mechanism that in the presence of excess of hexosephosphate esters links the glycolytic pathway and the pentose shunt at the stage of conversion of glucose-6-phosphate into 6-phosphogluconate with NADP as hydrogen acceptor.

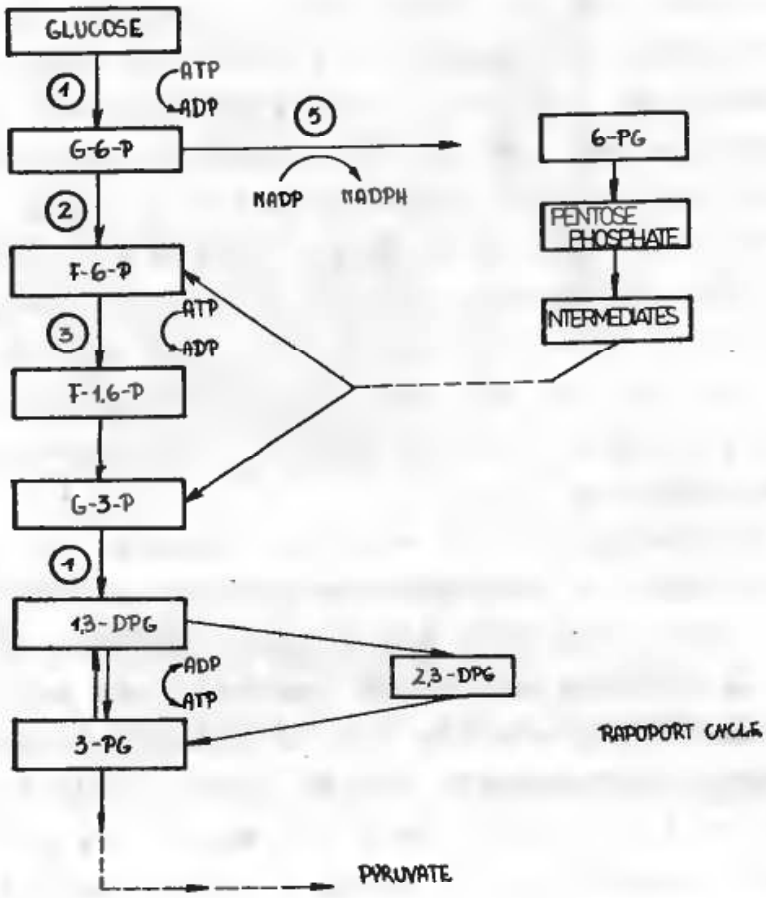

Fig. 6. Possible reactions between glycolytic pathways and pentose shunt in D.S.

In spite of suggestions that decreased ATP level is accompanied by increased susceptibility of erythrocytes to hemolytic agents [74] no enhancement of hemolysis was revealed in individuals with trisomy G. According to B e u t l e r [13, 14] the extent of hemolysis depends on the level of glutathione. A decrease in reduced glutathione leads to accumulation of H_2O_2 which initiates hemolysis.

However, the level of glutathione peroxidase, a H_2O_2 - utilizing enzyme is increased by 50% in erythrocytes of patients with Down's

syndrome [86] which should prevent accumulation of H_2O_2 and subsequent hemolysis.

Studies of hemolytic resistance of the red cell membrsne in trisomics 21 demonstrated a shift of the maximal resistance towards lower NaCl concentrations, with minimal resistance showing no deviations from values typical for controls. This results in e broader amplitude of osmotic resistance and in an altered pattern of the "osmotic fragility-resistance" curves.

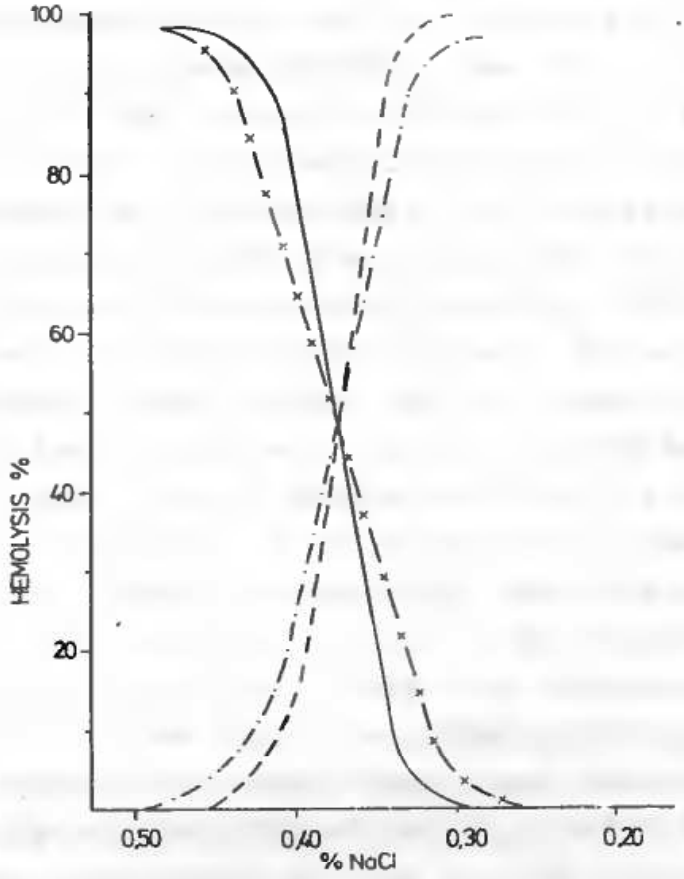

Fig. 7. "Osmotic fragility-resistance" curves in trisomics and healthy control

An increased sodium content and a decreased potassium content of erythrocytes of patients with Down's syndrome is noteworthy. Kinetic analysis of permeation of these ions across the membrane leads to a conclusion that K^+ ions activate the sodium pump and that this permeation corresponds to an enzymatic reaction of Na^+-K^+-ATPase [104]. The enzyme has two active centers, one for sodium and the other for potassium. This mechanism could explain the observed differences in ion concentrations.

In erythrocytes of patients with trisomy *G* the glycolytic rate is controlled mainly by regulation of such allosteric enzymes as

hexokinase, phosphofructokinase, pyruvate kinase and glyceraldehyde-3-phosphate dehydrogenese. Parker and Hoffman (cited after) linked ion transport through membranes to activities of some glycolytic enzymes: phosphoglycerate kinase and glyceraldehyde-3-phosphate dehydrogenase. This would be in agreement with the inactivation of the latter enzyme hypothesized previously. The magnitude of the alterations in ion concentrations (decrease in K^+ end increase in Na^+, both by about 5 mEq per 1 intracellular fluid) suggests a simple disturbance of the exchange in the ratio 1 : 1.

Determination of the level of ATP in blood platelets of individuals with Down's syndrome showed alterations similar to those found in erythrocytes. In spite of the lack of nucleus, blood platelets have active metabolism connected with the function performed by these cells in hemostasis [180] The observed decrease in the levels of ATP and ADP may be due either to a depressed ability to accumulate these compounds in the metabolically inert and participating only in the clotting process "storage pool" or to decreased synthesis of energy-rich compounds, e.g. by inhibition of glycolysis. A decrease in NAD (by about 51% with respect to the control) would favor the latter possibility. No changes were found in the phosphohexokinase activity [37] but, on the other hand, activity of this enzyme is the lowest from among all glycolytic enzymes [58]. The Krebs cycle can be neglected in these considerstions due to its 10-fold lower efficiency as compared with glycolysis in the blood platelets [34].

From among other results, an almost 4-fold increase in AMP conten should be mentioned. The ATP/ADP ratio equalled 1.32 for patients with trisomy 21 while 1.62 for healthy persons and individuals with translocation *G/G* [82].

The level of serotonine, accumulated in blood platelets from plasma by means of active transport is lowered in Down's syndrome by about 40% [16, 112]. The hampered accumulation of 5-hydroxytryptamine by platelets of trisomics *G* [8, 75] was ascribed to decrsased incorporation of this compound into the "storage pool" due to the decreased ATP content [17]. Another hypothesis postulated a main role of the increased Na^+ content in blood platelets of patients with Down's syndrome [113]. This hypothesis is in agreement with reports on the inhibition of serotonine uptaks by mammalian blood platelets due to increased Na^+ content [159]. However, studies by Mc C o y [114] of serotonine uptake by platelets of healthy persons and of

patients with trisomy, previously depleted of sodium, demonstrated that though the uptake by platelets from trisomics increased with decreasing Na^+ content, this increase was not sufficient to secure proper uptake rate at a sodium level typical for platelets of healthy persons.

Down's syndrome is associated with hereditary disturbances in protein and amino acid metabolism. They include among others decreased urinary excretion of xanthurenic and indoloacetic acids, mentioned previously, and decrease in serum tryptophan and serotonine [79, 123]. An interesting result from among our own studies [81] is the presence of beta-aminoisobutyric acid (BAI-BA), a thymine catabolite, in blood serum of trisomics G; this compound occurs only in trace amounts, if any, in serum of healthy persons. In spite of a considerable concentration in serum, BAIBA was absent from erythrocytes. It indicates membrane impermeability for this compound, probably due to its configuration [24, 63].

Coming back to the established tryptophan deficiency in Down's syndrome, one should remind that it is an exogenous amino acid, so its deficiency can be due not only to an accelerated catabolism but also to a hampered uptake. Metabolism of tryptophane leads to nicotinic acid, a constituent of NAD (which is decreased in erythrocytes of trisomics) and, on the other hand, to 5-hydroxytryptamine; a low level of the latter in blood platelets and serum of patients with Down's syndrome was stated by many Authors [9, 123, 124]. Serotonine deficiency results in decreased muscular tonus, including blood vessels, and has a depressive effect on the CNS [2, 9, 79]. Administration of both L-tryptophane and serotonine [2, 9] during the first months of life brought about a disappearance of these effects in the patients. According to Fernstrom, the level of serotonine is affected by a lot of hormones which act, among others, by de-repression of genome and induction of mRNA synthesis [123] which could evidence a close interplay between the genome and the metabolites. Analysis of amino acid levels in erythrocytes of patients with Down's syndrome [82] showed increases in those of valine, leucine and isoleucine, and decreases in those of methionine, aspartic acid, glutamic acid, glutamine and glycine [81]. Augmented concentrations of amino acids with branched chains are in agreement with the high level of BAIBA in the serum of trisomics as beta-aminoisobutyric acid is formed as a catabolite of

these amino acids [138]. The decreased levels of other amino acids in erythrocytes of children with Down's syndrome are in line with our previous reports on the decreased contents of purine and pyrimidine nucleotides. The amino scids in question participate in the synthesis of the purine ring. Glutemate deficiency may lead to decreaeed concentrations of vitamin B_6. As vitamin B_6 is s coenzyme of kynureinase, enzyme catalyzing the finsl step of the tryptophan--kynurenine-hydroxykynerenine-3-hydroxyanthranilate pathway, vitamin B_6 deficiency disturbs kynurenine metabolism. This leads to formation of xenthurenic acid, present in patients with trisomy *G* [123]. Pyridoxal phosphate (vitamin B_6) takes part in amino acid transport into cells [25] which may explain further sbnormalities in ths distribution of these compounds with respect to the control [87]. The observed decrease in the content of methionine, a methyl donor, may implicate a defficient methylation in Down's syndrome, described by C a r e d d u et al. [20].

Studies of amino acid transport across the erythrocyte membrans [82] demonstrated a lower permeation rate for glutamic acid (by 42%), glycine (by 28%) and alanine (by 20%). The permeation rate of leucine did not differ with respect to the control. Choline transport [183] did not differ in a statistically significant manner, too, in spite of the postulated [101] disturbances in choline metabolism in Down's syndrome due to the common susceptibility to Alzheimer disease in this syndrome [12, 41]. Alzheimer disease is believed to be conditioned by a cholinergic mechanism since a decreased activity of acetylocholinesterase, an enzyme involved in choline permeation into neurons [60], was found in this illness [34]. In these studies, transport was monitored using substrates labeled with radioactivs carbon.

A set of anomalies was described concerning hemoglobin in Down's syndrome. Structural studies ravealed increased HbA_2 and slight decreases in HbA_1, and HbA_3 that may be conditioned by disturbed balance between synthesis of beta and delta chains. Functional studies demonstrated increased oxygen affinity of hemoglobin from trisomics reeulting in a leftward shift of oxygen dissociation curves [82].

The shape of oxygen dissociation curves is sigmoidal but the Hill coefficient describing the heme-heme interaction is decreased down to 2.73 which is in agreement with the low levels of 2,3-DPG

and ATP in red blood cells of individuals with trisomy 21 [190] and to a general enhanced oxygen affinity.

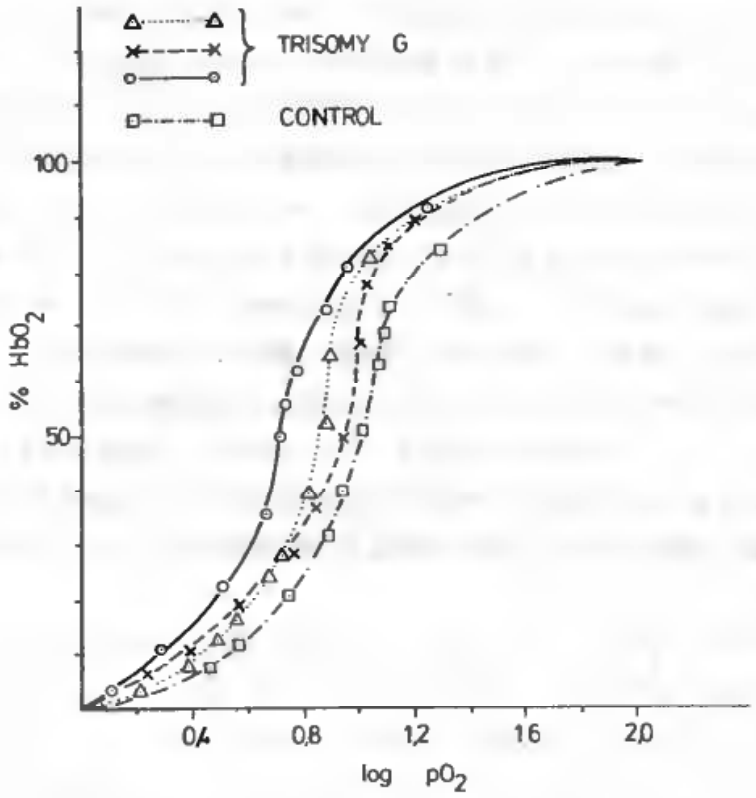

Fig. 8. Oxygen dissociation curves in D.S.

It is noteworthy that in spite of different etiopathogenesis, many common features, are observed in Down's syndrome and in Duart typs hemoglobinopathy ($\alpha_2\beta_2$ 62/E6 Ala-Pro).

Observations on the models of red blood cell and blood platelet suggest that the scope of biochemical anomalies in Down's syndrome is very broad and that they affect other tissues, too. This is reflected by changes in the protein pattern of blood serum [81, 96].

The decreass in albumin and α_1 - as well as α_2 -globulin (by 18 and 24%, respectively) with concomitant increese in beta (by 17%) and gamma-globulins (by 52%), decreases in activities of some enzymes (like acetylcholinesterase and pseudocholinesterase), and simultaneoue increases in activities of other enzymes (like glucose-6-phosphate dehydrogenase [140] or phosphofructokinase [43] evidence simultaneously proceeding processes of induction and repression in the field of protein metabolism.

In the organism, at least two chief levels of functional control can be distinguished: cellular control and whole-body control.

The complex mechanism of metabolic regulation is coupled to the periodic activation of gene function which conditions initiation of protein biosynthesis [45, 57, 58] or (due to genetic supression) inhibition of protein production [154]. This can be exemplified by the occurrence of genetic differences in production of serum cholinesterase [26, 47, 52, 62, 149, 150]. Family studies employing dibucaine inhibition tests point to the existence of three cholinesterase phenotypes controlled by two allelic genes [5, 54, 107]. The decrease in cholinesterase activity parallel to albumin changes in blood observed in Down's syndrome indicates the hepatic origin of the enzyme and a similar control mechanism.

Ths β_1-globulin fraction contains, among others, transferrin [70, 152], a protein responsible for iron transport. In Down's syndrome the transferrin level was found to be significantly decreased, both in trisomy and in *G/G* or *D/G* translocations [82, 90].

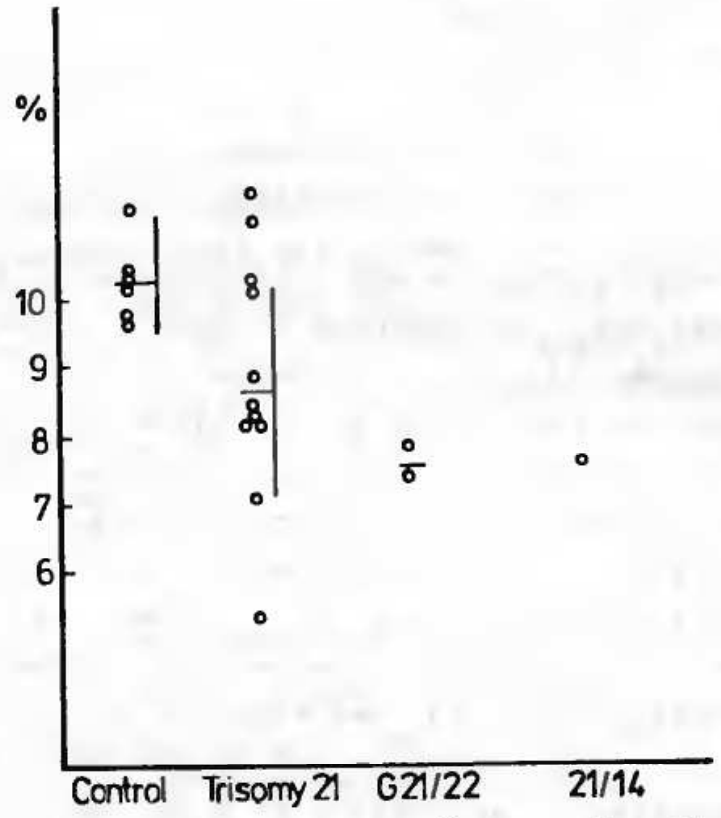

Fig. 9. Transferrin level in trisomy *G*, translocations *G/G* and *D/G* and healthy control

In all these cases a decreased iron level was found both in serum and in whole blood [179].

Iron metabolism is connected with copper, bound in serum mainly in ceruloplasmin [166, 192]. Both the iron level and the Fe/Cu ra-

tio in serum of patients with Down's syndrome are much lower than the respective control values. The increased (by 50%) level of Cu, Zn-SOD in erythrocytes of these patients demonstretes the lack of relationship between the erythrocyte SOD and the copper level in the serum [3, 85]. While the increase in Cu, Zn-SOD (identified with IPO-A although some our studies on patients with translocation [85, 88] do not confirm this identity) can be explained by the gene dosage effect, the 3-fold increase in the activity of glucose-6-phosphate dehydrogenase or glutathione peroxidase (coded by chromosomes other than 21) is more difficult to understend. Udoubtedly the main role can be ascribed to some external factors participating in the control of genome activity, according to the pattern:

stimulus - hormone - adenyl cyclase - cAMP - specific protein kinase - protein (contractile, transporting or regulatory protein).

As it was mentioned previously, the same gene locus was found for Cu, Zn-SOD (SOD-1) and IPO-A thus identifying both these enzymes, estimated hitherto by different methods, as superoxide: superoxide oxidoreductase (EC 1.15.1.1). The activity of this enzyme should be higher in cells of individuals with Down's syndrome, both in simple trisomy and in translocations yielding analogous clinical effects, due to the presence of an additionel locus. Our measurements of IPO-A and SOD-1 in cases of translocations 21/22 and 21/14 do not fully confirm this assumption. When studying IPO level in erythrocytes [88] we found in trisomy 21 values higher (by about 50%) than in translocations. Comparison of SOD-1 and IPO-A activities in erythrocytes of patients with classic phenotype of Down's syndrome and karyotype indicating trisomy 21 or translocation 14/21 or 21/22 we did not reveal the expected increese in activity in cases of translocation [84]. However, a small size of the groups studied and reports being in disagreement with our findings [102]preclude drawing more definite conclusions from these data at present.

The broad range of alterations found in Down's syndrome seems to indicate an effect of information coded in the additional chromosome on trenscription and transletion processes. The hypothesis of genetic induction of m-RNA being the matrix for translation would explain the dysproteinemia observed in Down's syndrome, and could elucidate the report of I n g e n i t o [71] who revealed an additional protein fraction in serum of the patients.

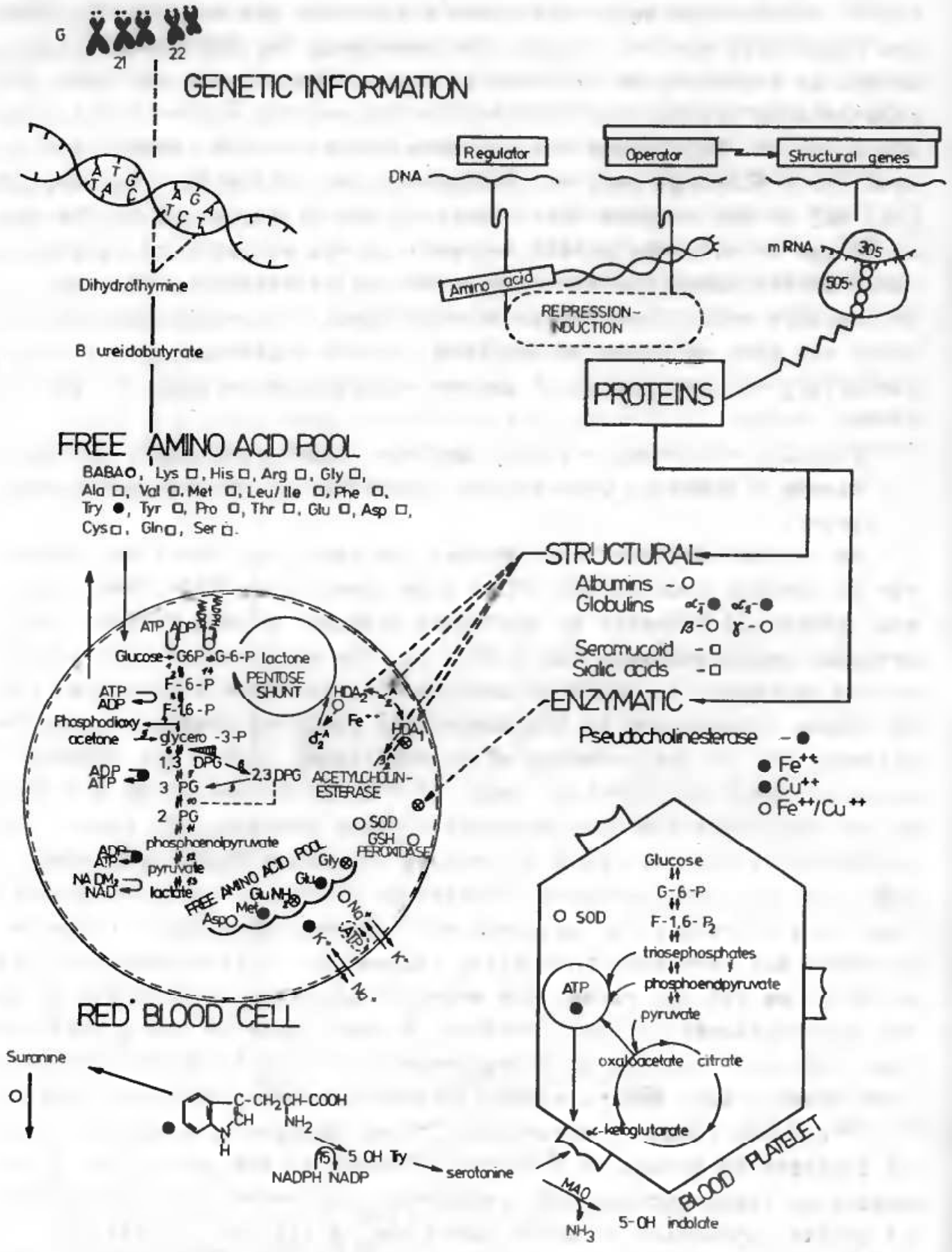

Fig. 10. Changes in biochemical reactions in D.S. in the light of induction-repression mechanism

Considering all the parameters analysed in trisomy 21 one could propose a simplified scheme of biochemicel disturbsnces typical for this disease as due to interaction of seversl gene loci leading, via different levels of metebolic regulation, to e deficiency of energy-rich compounds and changes in the induction and/or repression of protein biosynthesis.

Some of the existing elterations mey be secondary effects of other disturbances.

It seems that a further, more precise localization of gene loci responsible for individuel biochemical processes, confronted with e more complete list of disturbances typical for Down's syndrome should permit elaboration of more detailed mechanisms of metabolic alterations occurring in this diseese.

Moreover, preliminary informetions on biochemical differences between different forms of Down's syndrome, caused by trisomy, unbalanced translocations [81, 83, 140, 141] or persistent mosaicism [12, 158] which do not show distinct phenotype distinctions, point to the importance of comparative studies on different karyological types of the disease. Our knowledge of mechenisms of metabolic changes responsible for the development of mongolism could also profit significantly from analysis of other diseases, either those accompanying frequently Down's syndrome (e.g. Alzheimer diseese) or those explained by causes operating in this syndrome, including metabolic disturbances (e.g. hypothyroidism, iminopeptiduria, Lesch-Nyhans syndrome).

Maszynopis wpłynął do Redakcji 23 III 1981

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Józef Kędziora, Roman Łukeszewicz

ZALEŻNOŚĆ PROMIENIOWANIA JONIZUJĄCEGO I INNYCH CZYNNIKÓW ŚRODOWISKOWYCH W SYNDROMIE DOWNA

Streszczenie

W pracy przedstawiono wyniki badań własnych i piśmiennictwa światowego nt. zespołu Downa, przyczyn jego powstawania i związku aberracji chromosomalnych z czynnikami środowiskowymi.

Omówiono wpływ efektów cywilizacji na częstotliwość powstawania tej skomplikowanej anomalii ze szczególnym uwzględnieniem ewentualnej roli promieniowania jonizującego.

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