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

Bela Matkovics

THE HUMAN PATHOLOGICAL ROLES OF THE SUPEROXIDE RADICAL (O_2^-) AND SUPEROXIDE DISMUTASE (SOD)*

The present lecture is intended to outline the results demonstrating the roles of O_2^- and SOD in human diseases. We shall attempt to bring the literature data into correlation with our own results or with our experimental conceptions.

The human role of the O_2^- radical will be dealt with, first, followed by the SOD changes and their correlations.

The role of the O_2^- radical here is not exclusive. The various radicals formed from molecular oxygen may interact with one another, resulting in further active radicals such as the hydroxyl radical (OH•), singlet oxygen ($^1O_2$), peroxy and hydroperoxy radicals. The multidirectional reaction pathway that results in active oxygen radicals is summarized in detail in the tables to be found in the publication by S i n g h [18]. This compilation was prepared for the symposium dealing with oxygen radicals, organized in Pinawa, Manitoba in 1977 by Whiteshell Nuclear Research Establishment Atomic Energy of Canada, Ltd. The proceedings of the symposium were published in one copy of 28 the volume of the Photochem. Photobiol. The H a b e r-W e i s s and F e n t o n reaction [7] are well known sources of OH• radicals:

$$O_2^- + H_2O_2 \longrightarrow O_2 + OH^- + OH^\bullet \qquad (a)$$

and

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^\bullet \qquad (b)$$

*Lecture delivered on the Polish-Hungarian Syposium "The effect of physical and chemical agents on macromolecules", Łódź (Poland); 18-20th of June, 1979.

Let us consider first the effect of O_2^- radicals on red blood cells (RBC). The damage caused to the formal elements of the blood may be direct or indirect. In both cases the overall result is the same: hemolysis namely lysis of the RBC membrane. This effect, in which the O_2^- radical plays an important role, has been summarized in a Tab. 1 [4].

T a b l e 1

O_2^- radical as potential causes of oxidative hemolysis (details in the text)

Rodnik O_2^- jako potencjalna przyczyna hemolizy oksydatywnej (szczegóły w tekście)

O_2^- **радикал как потенциальная причина оксидативного гемолиза (подробности в тексте)**

Increased formation of O_2^-	Decreased protection against them
1. Via hb. Unstable hbs. Thalassaemia Oxidative drugs e.g. Acetylphenylhydrazine Antimalarials Favism PQ (paraquat) Heat Metal ions (Cu^{2+}, Fe^{2+} etc.) Redox substances 2. Direct effects Radiation Hyperbaric oxygen Porphyria (free porphyrins)	3. Deficiencies of: Glucose-6-phosphate dehydrogenase 6-Phosphogluconate dehydrogenase Glutathione peroxidase (GPx) Glutathione reductase Glutathione Synthetase Catalase SOD Vit. E

The mechanism is dealt with in two figures. Figure 1 outlines the hem pocket of the oxyhemoglobin (oxyhb) molecule. Small

changes may lead quickly to the formation of methemoglobin (methb). Such a change may be caused by the water molecule or small anions; these donate an extra electron to molecular to molecular oxygen converting this to the O_2^- radical, Fe^{2+} is oxidized to Fe^{3+}, and methb is formed from oxyhb.

Figure 2 summarizes the mechanisms which protect the RBC from hemolysis.

Together with Tab. 1 Fig. 2 sheds more light on the details of each mechanism.

Reduced glutathione (GSH) and oxyhb form the first line of defence of the RBC against oxidative damage. The second protective line includes -SH material and polyunsaturated fatty acids (PUFA). Finally, oxidation of the PUFA by lipid peroxidation (LP), leads to irreversible damage of the RBC membranes and to hemolysis.

One of the most important of the above factors leads to hemolysis directly, and the other one indirectly (see Tab. 1). The same refers to the inherited factors too. A direct hb effect is involved in thalassaemia, for example, while a decrease of the defence against the O_2^- radical results indirectly from the various inherited enzyme defects, mainly the decrease of the SOD synthesis, or acatalasemia, for instance. We shall not deal here with hemolyses caused by different radiation effect.

Mention may now be made of diseases affecting one organ or the entire organism, in which an increase in the quantity of the O_2^- radical plays an important role.

Primarily from the work of M c C o r d [11] it is known that in vitro the O_2^- radicals possess the ability to depolymerize hyaluronic acid. Direct consequences of this publication were those investigations that attempted to clarify the roles of O_2^- and SOD in rheumatic diseases. Unfortunately, a uniform picture has not yet developed in this field but in our view it is worth the trouble. By the hypothesis of McCord and coworkers O_2^- formed in greater amount, or possibly a decreased SOD activity, leads to the first attach which develop on the commencement of rheumatic diseases, this is one part of our working hypothesis too. Further quite similarly to autocatalytic processes, in time the other factors destroy themselves; mainly the recurring inflammations, and then later the destruc-

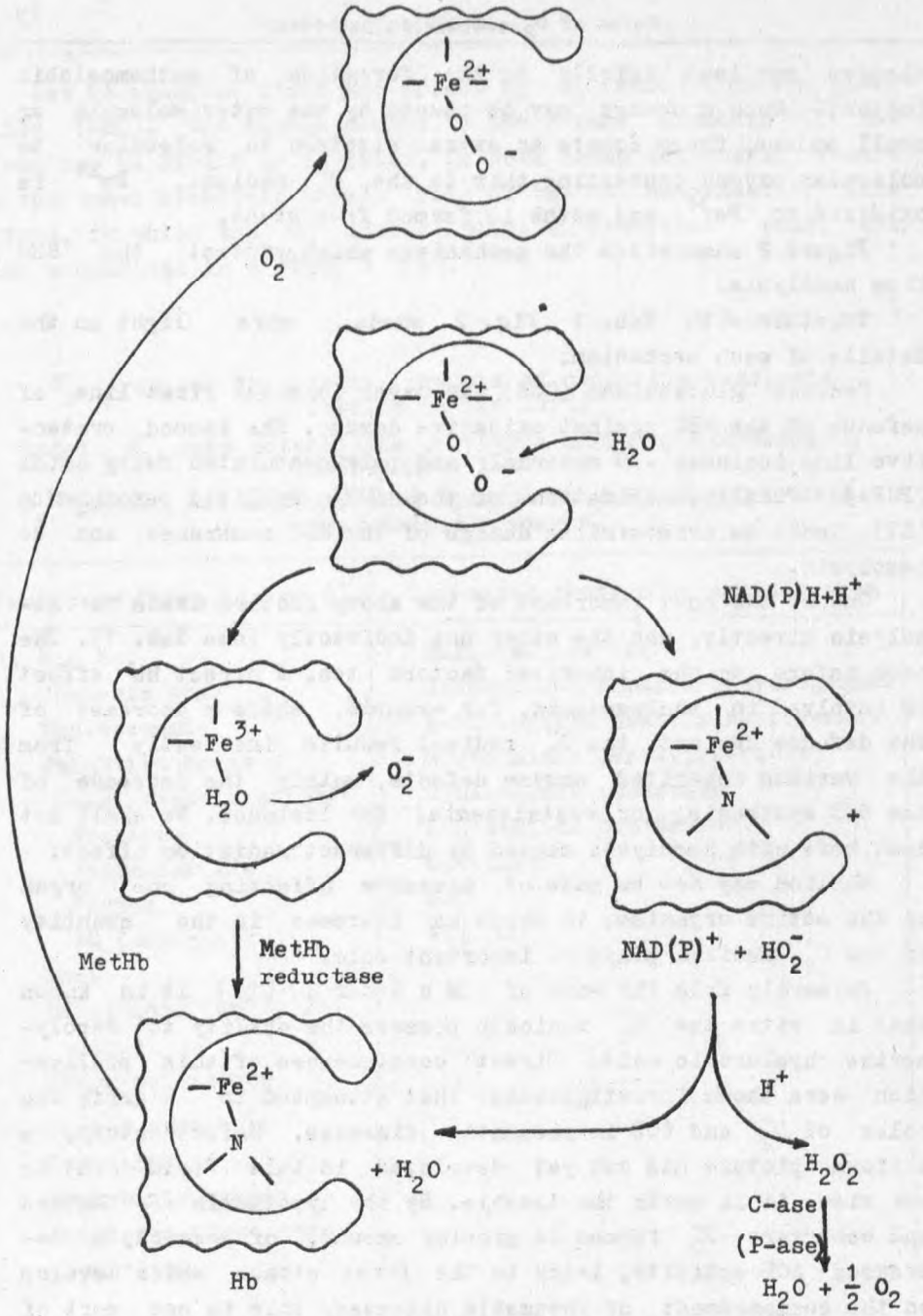

Fig. 1 The sketch of some reactions of hem pocket of oxyhemoglobin (HbO_2)

Schemat niektórych reakcji w kieszeni hemowej hemoglobiny

Схема некоторых реакций в гемовом кармане гемоглобина

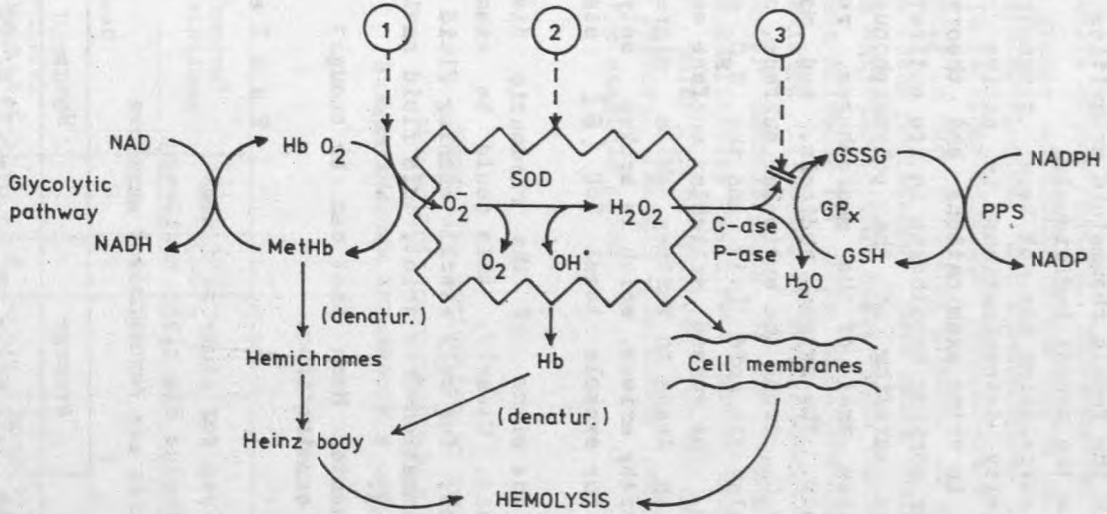

Fig. 2. Production and reduction of activated oxygen radicals and their connections to the glycolytic and pentose phosphate pathways. The action of hemolytic factors listed in Tab. 1 (numbers indicated). GP_x - glutathion peroxidase; PPS - pentose phosphate shunt

Powstawanie i rozkład aktywnych rodników tlenowych i ich związek z glikolizą i cyklem pentozofosforanowym. Wpływ czynników hemolitycznych przedstawiono w tab. 1 (zachowano numerację). GP_x - peroksydaza glutationowa; PPS - cykl pentozofosforanowy

Образование и распад активных кислородных радикалов и их связь с гликолизом и пентозофосфатным циклом. Влияние гемолитических факторов перечислено в таб. 1 (номера указаны). GP_x - глутатион-пероксидаза; PPS - пентозофосфатный цикл

tive factors are connected with autoimmune processes. S c u d d e r et al. [17] compared the SOD activities of RBC from 50 normal and 50 rheumatoid arthritis individuals. No essential difference in SOD values was found between the two groups, however, the RBCCu content in the female rheumatoid arthritics was significantly lower than in the normal individuals.

So far, therefore, a correlation has not been demonstrated between the RBC SOD activity determinations in active rheumatoid arthritics and the in vitro examinations and theory of M c C o r d. Continuing our working hypothesis in its entirety is as follows: the phagocyta bursting of the polymorphonuclear leukocytes (PMNL) and hence that of the macrophages, result high amount oxygen radicals. The oxygen radicals, and mainly the O_2^- anion and the H_2O_2, erode the articular surface, since they depolymerize the hyaluronic acid [11] and the H_2O_2 damaging the SOD protein [3]. The worned articular surface enhances the inflammation, which leads to further PMNLs migrating in. A vicious circle thereby arises, which is broken only by therapeutic intervention, for example local SOD [8] steroid treatment etc.

We wished demonstrate the signs of the rheumatic disease group in the articular fluid. Clearly, this could be examined only in acute inflammations, for only sterile washing fluid may be obtained from the inflammation-free joint, this fluid having a characteristic composition.

A few data are presented here that can be brought into correlation with our own examinations.

T a b l e 2

Normal values for synovial fluid
Wartości normalne dla płynu maziowego
Нормальные значения для синовиальной жидкости

Constituents	Average	Range
Total albumin and globulin	1.72 g/100 cm^3	1.07-2.13 g/100 cm^3
Uric acid	3.6 mg/100 cm^3	3.3-4.7 mg/100 cm^3
Leukocyte count	63/mm^3	13-180/mm^3

B a s e d o n: H o l l a n d e r I. L. (Ed.), Arthritis and allied conditions, Philadelphia, PA (1960).

Our exploratory studies connected with articular fluid were restricted to the peroxide metabolism enzymes (PME) (SOD, P-ase and C-ase), acid phosphatase (APh-ase), uric acid, protein and Cu determinations.

The examination were performed with Dr. I. A. Kordoss. On the basis of our results, the examined cases were differentiated into groups according to the degree of severity as indicated by certain cytological and immunological detections.

It is clear from the Tab. 3/Part B that the PME behave differently in the following groups. In groups I-VI there is always gamma latex positivity. This means that the articular fluid contains antibodies that react with the anti-immune serum. As a reagent suitable for slide agglutination (latex fixation test), Gamma-latex is marked by Human (Budapest). The reagent is applicable for demonstration of the rheumatoid factor (IgM). The other qualitative rapid test that we used was the LE-TEST^R (Hyland, USA), which can be employed for the detection of antinucleoprotein factors. LE-TEST^R-positivity occurred only once or twice in all the examined cases.

Table 3

Enzymatic activities in synovial fluid
Aktywności enzymatyczne w płynie maziowym
Энзиматические активности в синовиальной жидкости

Part A

General notations	None	Very low	Low	Normal	Moderately high	High	Extremly high
Values	0	-	-	N	+	++	+++
SOD U/ml synovial fluid (s.f.)			- 10	N 10-15	+ 15-20	++ 20	
P-ase U/ml s.f.	0		- 1		+ 1-2	++ 2-10	+++ 10
C-ase BU/ml s.f.			- 0.10	N 0.010			

Part B

Group	I	II	III	IV	V	VI	VII	VIII
SOD U/ml	N	N	++	+	N	N	++	N
P-ase U/ml	+++	++	+	0	-	++	0	++
Cu g/ml	-	-	-	-	N	--	--	-
Protein mg/ml	-	N	N	-	-	N	N	-
C-ase BU/ml	N	+	N	-	N	-	N	N
Uric acid mg/100 ml	-	-	N	N	-	++	N	N
APh-ase U/ml	+++	+++	++	++	++	++	+	N
Rhagocyta	+	+	- +	- +	-	-	-	- +
Gamma-latex	+	+	+	+	+	-	-	-

APh-ase = acid phosphatase.

N o t e: The first part of the Tab. 3/Part A shows the notations used in the quantitative evaluation of the measurements, and the ranges of the activity units/ml synovial fluid for the individual enzymes (see Tab. 3/Part A).

The second part of the Tab. 3 (see Part B) contains the summary, about which a few words will be said. It may be seen at a glance that the most left-hand column of the Part B shows the most positive signs; on proceeding from left to right the number of positive signs decreases (as the serial number increases). On the basis of the gamma-latex reaction, columns I-V mean fresh inflammation, which may be a first inflammation, but most often is an acute recurrence. Group VI is the group of patients with gout, or a strong tendency to this.

With the collaboration of Dr. J. J. Árvay, they repeated the examinations of S c u d d e r et al. [17] on active rheumatic patients at the National Rheumatology and Balneotherapy Institute (Budapest). The results are presented in the following Tab. 4.

Table 4

Some chosen physico-chemical properties of blood from patients with arthritis (gout) and control group

Wybrane właściwości fizykochemiczne krwi u pacjentów z artretyzmem i u osób kontrolnych

Некоторые физикохимические свойства крови у больных артритом и у контрольной группы

Part A

Parameters	Control		Rheumatoid arthritic patient					
	n = 10		A n = 4		B n = 20		C n = 16	
	average	range	average	range	average	range	average	range
SOD U/g hb	623	474-929	683	562-904	338	45-474	642	494-850
Sedimentation mm/h	14	6-20	17	15-20	45	20-68	45	23-104
RBC iron µq/100 ml	70	60-105	70	42-143	74	22-122	53	14-121
RBC copper µq/100 ml	119	67-161	144	95-175	150	99-188	152	58-219

Part B

Parameters	Control		Rheumatoid arthritic patient							
	n = 10		A n = 5		B n = 8		C n = 23		D n = 4	
	average	range	average	range	average	range	average	range	average	range
C-ase U/g hb	4.3	2.6-5.8	4.3	3.9-4.6	2.1	1.7-2.5	4.0	2.8-5.7	7.3	6-9.2
Sedimentation mm/h	14	6-20	18	15-20	43	31-104	43	21-70	56	24-68
RBC iron uq/100 ml	70	60-105	61	22-143	40	20-77	75	14-124	65	20-104
RBC copper µq/100 ml	119	67-161	142	95-175	166	115-200	143	58-218	172	139-219

N o t e: It can readily be seen that, with appropriate classification, differences can be detected as regards the RBC SOD, C-ase and also Cu content in the active, but treated rheumatics.

Of course, the depressed SOD level does not always mean a rheumatic disease, but in general it may be a symptom or a consequence of some acute or chronic systemic disease. These disease types also leave their mark in the metabolism of the RBC (more simply, they are accompanied by a change in SOD activity, which usually means an SOD decrease).

We have therefore given a working hypothesis in this case, and supported this with data groups in the field of articular systemic diseases. Naturally, this does not yet mean the proof of the working hypothesis. In our view, many fundamental examinations will be necessary in this field, in the interest of confirmation from various aspects.

Only mention will be made of another topic, the human aspects of which we have investigated. These examinations were performed on animals with diabetes induced experimentally with chemical agents (naturally, here too we cannot give an assumption proved in every respect from an experimental point of view; at the moment I can only report data which fit in with our hypothesis).

In diabetes, which is well-known similarly to become a disease affecting the entire organism, the oxidative damages will be greater than in other diseases. Because of these enhanced oxidative damages, all those symptoms subsequently develop which are manifested in vascular sclerosis, neuritis and cataract. In the medical terminology, these are the secondary symptoms of diabetes. For the patient, however, these changes too are primary and are very frequently the causes of death.

I should like to state here one of our fundamental conceptions in connection with diabetes development, and with vertebrate metabolism types in general. According to this, humans and given species of vertebrates in general can be divided into two or more groups as regards the type of the oxidative metabolism. Significant differences can be demonstrated in the different groups in the activities of the oxidative metabolism enzymes. Hence, in a further conception, diabetes develops primarily in individuals inheriting a higher oxidative metabolims. Somatostatin and insulin, for example, are well known to be oxidizable substances.

Let us consider first our own human data relating to SOD and in general the other PME. These measurements refer to treated

diabetics of various origins. The data apply only to human RBC (Tab. 5).

Table 5

Some chosen parameters of blood from diabetics patients and control group

Wybrane parametry krwi osób kontrolnych i diabetyków

Некоторые параметры крови контрольных доноров и диабетиков

Parameters	Controls	Diabetics
Glucose mg/100 ml blood	81.5 ±10.4	210.3 ±54.7
Protein mg/ml plasma	89.4 ±4.6	78.3 ±15.1
Protein mg/ml hemolysates	589.8 ±131.5	501.2 ±172.9
GSH-POD U/ml hemolysates	6.43 ±0.62	16.45 ±0.54
C-ase BU/ml plasma	0.400 ±0.141	0.027 ±0.001
C-ase BU/ml hemolysates	0.458 ±0.055	2.15 ±0.08
SOD U/ml hemolysates	203.5 ±40.3	3.0 ±0.3

N o t e: The Tab. 5 shows the most important parameters and enzymatic activities measured by human blood samples. The C-ase values are expressed in Bergmeyer Units (BU) ($n = 100$, $\bar{X} \pm S$).

The following table presents similar enzyme activities measured in rats with experimentally-induced diabetes (Tab. 6).

In the animal experiments, of course, there was also a possibility for comparison of the (normal and diabetic) values of the enzyme activities of the different organs.

When these data are examined together, the differences are striking: 1) in human blood the protein values lower, 2) the glutathione peroxidase activity is about 3 times higher than in the normal cases, 3) the catalase activity of the RBC is about 5 times that of the normal, 4) RBC SOD activity is very low.

These facts point to an enhanced H_2O_2 production and decomposition, and a decreased O_2^- resistance.

The data from the animal experiments support these same observations [10].

There is other literature evidence in support of our hypothesis:

1. It is known that the cause of the rapid occlusion of the ductus arteriosus and umbilical artery after birth is the elevated O_2 tension (O_2 toxicity) and decreased SOD activity of these arteries [6].

Table 6

The influence of chemically-induced diabetes on the activity of SOD, P-ase, C-ase values for rats

Wpływ cukrzycy indukowanej chemicznie na aktywności SOD, peroksydazy i katalazy u szczurów

Влияние химически индуцированного диабета на активности СОД, пероксидазы и каталазы у крыс

Organs	SOD U/g w.t.w.; $\bar{X} \pm S$		P-ase U/g w.t.w.; $\bar{X} \pm S$		C-ase BU/g w.t.w; $\bar{X} \pm S$	
	controls	diabetics	controls	diabetics	controls	diabetics
1	2	3	4	5	6	7
Liver	4 000 ±600	2 500 ±300	0.0	200 ±19	4.80 ±0.43	15.90 ±1.21
Kidney	1 200 ±151	327 ±41	0.0	0.0	0.36 ±0.04	0.926 ±0.100
Spleen	560 ±50	272 ±36	963 ±91	2 810 ±205	2.40 ±0.21	0.235 ±0.040
Testes	960 ±63	308 ±31	407 ±41	100 ±9.4	0.41 ±0.03	0.88 ±0.02
Whole brain	240 ±24	185 ±22	120 ±10	160 ±12	0.040 ±0.004	0.038 ±0.010
Lung	210 ±20	241 ±26	872 ±86	1 070 ±100	0.26 ±0.02	0.210 ±0.020
Pancreas	310 ±31	128 ±10	136 ±13	280 ±30	0.195 ±0.010	0.117 ±0.007

Table 6 (contd.)

1	2	3	4	5	6	7
Heart muscle	480 ±47	263 ±29	2 690 ±300	1 583 ±96	0.245 ±0.023	0.440 ±0.050
Skeletal muscle	300 ±27	223 ±30	105 ±10	220 ±24	0.110 ±0.009	0.160 ±0.010
Hemolysate*	696 ±68	525 ±50	11 666 ±1 000	1 172 ±131	2.670 ±0.310	4.140 ±0.390

*U/ml.

N o t e: SOD, P-ase and C-ase values in normal rats; effect on them of chemically-induced diabetes (w.t.w. = wet tissue weight; n = 10) (C-ase activity values are given as before).

This is illustrated in the following Tab. 6, in which these two arteries, with their low SOD values, differ from the other two arteries examined, the pulmonary artery and the thoracic aorta.

T a b l e 7

Bovine fetal arterial SOD

SOD w tętnicach płodowych cieląt

СОД в плодовых артериях телят

Tissue	SOD U/mg protein
Umbilical artery	1.97 ±0.16
Ductus arteriosus	2.32 ±0.33
Thoracic aorta	3.45 ±0.31
Pulmonary artery	3.67 ±0.32

At the same time, an ionizing radiation effect forming the oxygen radical, for instance, causes arteriosclerosis in experimental animals [1].

The enhanced tendency of diabetics to arteriosclerosis can therefore be explained on the above basis.

2. Early formation of cataract in diabetics can similarly be well explained in the light of the more recent examinations. The lens of the eye is protected by SOD against O_2^-, and by C-ase against H_2O_2 [2]. A decrease in the activity of either of the two enzymes would well account for the early cataract in diabetics. From this aspect comparative investigations have been performed only on the rat retina [5]. It would be interesting to compare these measurements for the various parts of the rat eye.

Table 8

Comparison of blood and retinal SOD activity of normal and diabetic rats

Porównanie aktywności SOD w siatkówce i w krwi szczurów normalnych i diabetycznych

Сравнение активности СОД в сетчатке и в крови нормальных и диабетных крыс

Tissue	SOD µq/g protein		
	n	control	diabetic
Retina	42	0.87 ±0.05	0.61 ±0.03
Blood	12	81.2 ±5.1	51.3 ±7.1

Clearly, these examinations should be, and will be repeated on human enucleated eye and on extirpated cataract in diabetics (Fig. 3).

Much work is still required in the interest of providing further evidence in favour of the above suggestions.

If our hypothesis mentioned in the introduction is true in diabetes, then the aging process of the cell and other differences observed in this field can also be well explained on the basis that the activities of the oxidative enzymes may differ from group to group. Thus, in those possessing a higher oxidative enzyme activity, the "fast burners", the more intensive cell oxidative damage leads earlier to the aging of the cells and of

the entire organism. However, let us not deal with gerontology, but mention a few facts:

1. S y l v i a et al. [19] could demonstrate a difference to electric stimulus in the change of rate of microcirculation and terminal oxidation (the respiration chain) in the cerebral tissue of young and aged rats (a slower regenerative ability was detected in the aged rats). This is naturally only an isolated example; we could also refer to certain of our own investigations and observations in this case too [12]. Of course, these did not form systematic examinations relating to old age.

2. Many authors refer to the publication by P a c k e r et al. [15] in connection with this problem of aging. The title of their work was "Antioxidants versus aging".. Their final conclusion was that the antioxidants are substances of similar importance to the vitamins: they protect the organism not only from aging, but also from tumorous damage, by inhibiting the formation of the more strongly carcinogenic intermediates; among others, they protect the DNA from the damage caused by peroxide (Fig. 4).

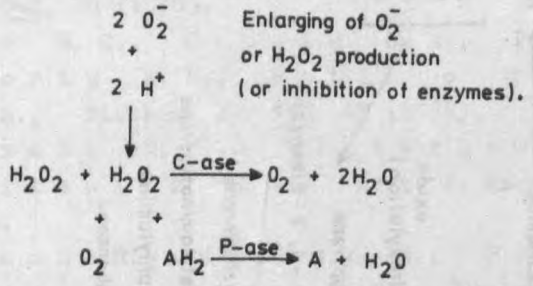

Fig. 3. Cataractogenesis
Powstawanie katarakty
Катарактогенез

Let us return briefly to the fact that inflammation occurs in the two systemic diseases (rheumatic diseases and diabetes) I mentioned previously. A considerable proportion of the inflammatory processes develop on the action of histamine. It emerged from the observations of O h m o r i et al. [13] that the xanthine oxidase - xanthine system causes histamine release from

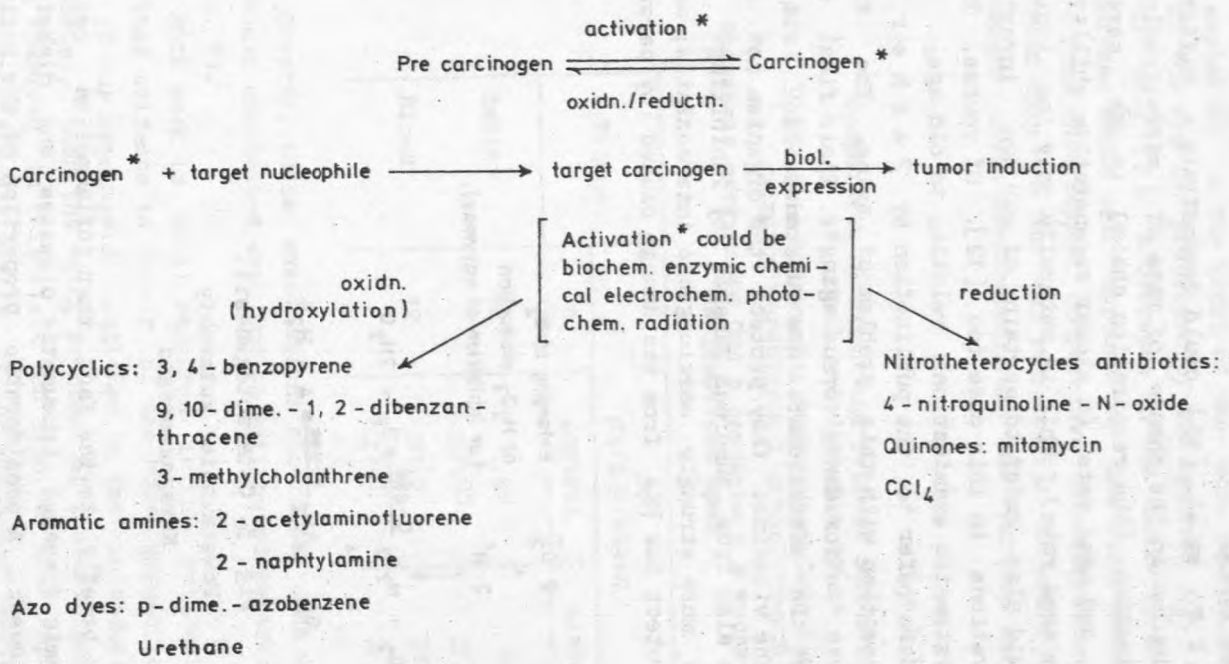

Fig. 4. Redox model for chemical carcinogenesis
Model redoks karcinogenezy chemicznej
Редокс-модель химического карциногенеза

the peritoneal mast cells. The inductor of the histamine release is H_2O_2.

Injection of H_2O_2 + histamine gives rise to inflammatory rat paw oedema, which is reduced by C-ase. The PME therefore play important roles in the development and also the decrease of inflammation. This is proved not only by the related literature, but by numerous other data too. For instance, depending on their quantities, the antiphlogistics are capable of decreasing the O_2^- anion production [14].

Although have mentioned some animal experimental data, please accept my lecture as primarily thought-provoking with regard to humans, as I intended it.

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Biological Isotope Laboratory
Department of Biochemistry
József Attila University
Szeged, Hungary

Bela Matkovics

PATOLOGICZNA ROLA RODNIKA PONADTLENKOWEGO (O_2^-)
I DYSMUTAZA PONADTLENKOWA (SOD) W ORGANIZMIE LUDZKIM

Artykuł przedstawia zasadnicze wyniki wykazujące role O_2^- i SOD w stanach chorobowych człowieka, opierając się na danych literaturowych i badaniach własnych.

Беля Маткович

ПАТОЛОГИЧЕСКАЯ РОЛЬ СУПЕРОКСИДНОГО РАДИКАЛА (O_2^-)
И СУПЕРОКСИДДИСМУТАЗА (СОД) В ОРГАНИЗМЕ ЧЕЛОВЕКА

Статья представляет главные результаты демонстрирующие роль O_2^- и СОД в болезнях у человека, на основе литературных данных и собственных исследований.