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Bioantioxidants and Synthetic Inhibitors of Radical Processes

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Data are presented for the physicochemical characteristics of bioantioxidants and the influence on their level in the lipids of organs and tissues by radical-process inhibitors introduced into animals. A wide variety of pathological states occurring against the background of changes in the amount of bioantioxidants and the possibility of treating them with the aid of synthetic inhibitors are discussed. The effectiveness of antioxidants is associated with the important role of free-radical oxidation reactions in the lipids of cell membranes.
The bibliography includes 155 references.

CONTENTS

I. Introduction 871
II. Physicochemical characteristics of bioantioxidants 871
III. The influence of synthetic inhibitors on pathological processes involving changes in the level of antioxidants 873
IV. The role of antioxidants in the structure and function of membranes 875

I. INTRODUCTION

On the hypothesis that free-radical mechanism play a major role in the development of pathological processes, Emanuel' and coworkers suggested in 1957 that relatively non-toxic inhibitors of oxidation reactions (antioxidants) be used as protectors against radiation sickness[1]. The inhibitors were regarded as potential protective agents against radiation, capable of decreasing the scale of the damage associated with the intensification of free-radical reactions in cell components under the influence of radiation[2]. In 1957 data were obtained indicating the possibility of using inhibitors as such protective agents[1]; these results were subsequently confirmed[3-7]. However, later it proved impossible to reproduce in a number of investigations the high effectiveness of inhibitors as protective agents against radiation and in some cases it was actually found that preparations of this class intensify the effect of radiation[8]. All these findings required a more profound study of the influence of synthetic inhibitors on cell metabolism. The present author believes that the fundamental questions associated with the use of inhibitors (antioxidants) in medicine are as follows:

1. Can one assume that free-radical process inhibitors manifest in the organism the same properties as in model free-radical reaction systems and is their pharmacological activity associated with their physicochemical constants?
2. Can synthetic inhibitors and the natural antioxidants present in cell components interact and be interchanged?
3. What are the molecular-biological mechanisms of the influence of inhibitors on cell metabolism?

In the present review these questions will be considered in relation to the free-radical processes in the lipid components of the cell.

II. PHYSICOCHEMICAL CHARACTERISTICS OF BIOANTIOXIDANTS

Experiments *in vitro* showed that free-radical oxidation reactions can be suppressed in the lipid fractions extracted from animal organs and tissues[9]. The overall antioxidant activity (AOA) of the lipid fraction depends on the amount, physicochemical properties, and mutual influence of the individual antioxidants present in it, and also on the presence of substances which themselves do not exhibit antioxidant properties but can intensify or weaken the action of antioxidants[10].

It has now been shown that many substances contained in the lipids of animal organs and tissues have the properties of radical-process inhibitors. These include tocopherols, ubiquinones, steroid hormones, thyroid hormones, cholesterol, phospholipids, and certain others. The mechanism of the antioxidant action of these substances has not been established in all cases.

The most thoroughly investigated antioxidants are tocopherols, which exhibit powerful antiradical properties[11-28]. The rate constant for the reaction of α-tocopherol with free radicals k_7, measured by a chemiluminescence method in the model ethylbenzene oxidation initiation reaction at 37°C, proved to be 2.6×10^6 litre mole^{-1} s^{-1}, the corresponding values for γ-tocopherol and δ-tocopherol being 1.3×10^6 and 0.5×10^6 litre mole^{-1} s^{-1} respectively[29,30]. These values exceed by 1–2 orders of magnitude the rate constants for the reactions with radicals of a number of familiar synthetic inhibitors investigated using the same model[31]. One of the interesting characteristics of tocopherols as antioxidants is a high stoichiometric coefficient of inhibition, which is 4.5 for α-tocopherol and 3.5 for γ-tocopherol[10,32]. This large number of chains terminated by one inhibitor molecule can be explained according to the authors by the inhibiting activity of the product formed from tocopherol when it interacts with free radicals. According to Tappel's mechanism, the phenoxy-radical derived from tocopherol is converted into a benzyl radical, reducing at the same time the OH group[33]. As a result of these rearrangements, one α-tocopherol molecule can react with six peroxy-radicals and one γ-tocopherol can react with four peroxy-radicals[32]. Despite their high antiradical activity, tocopherols are weak antioxidants. Thus the inhibition of the oxidation of methyl oleate and arachiden by α-tocopherol is six and three times less effective than the inhibition by the familiar inhibitor 2,6-di-t-butyl-4-methylphenol (ionol)[34,35]. It has been suggested that this is due to the high activity of the radicals formed from tocopherol, which can enter into the chain-propagation reaction and thereby weaken the effect of tocopherol as an inhibitor[36-38].

The contribution of tocopherol to the overall antioxidant activity of mouse liver lipids does not exceed 15–20% and its contribution to the antiradical activity does not exceed 40–60%.[34]

Many investigators attribute a high antiradical activity to ubiquinones, among which coenzyme Q_{10} is the most active[39,40]. The mechanism of their antiradical action is obscure. It is suggested that the ubichromenol form may be active[41]. Like tocopherols, ubiquinones are weak antioxidants[42–46]. Their relative antioxidant effectiveness is smaller by an order of magnitude than that of ionol and by a factor of 2–3 than that of tocopherol[40]. The reduced enolic forms of ubiquinones are comparable to α-tocopherol as regards their antioxidant properties[44,45]. This is because the enolic forms of ubiquinones have higher constants k_7. In our laboratory Khrapova and coworkers are making a comparative study of the antiradical effectiveness of the enolic and quinone forms of natural antioxidants. The greatest difference between the constants k_7 for these forms occurs for tocopherol, which is present in the organism mainly in the phenolic form (see Table).

The rate constants (litre mole^{-1} s^{-1}) for the interaction of the enolic and quinone forms of antioxidants with free radicals.

Antioxidant	Enolic form	Quinone form
Tocopherol	$2.6 \cdot 10^6$	$1.7\ 10^3$
Ubiquinone	$2.1 \cdot 10^5$	$5 \cdot 10^3$
Vitamin K	$3.9 \cdot 10^6$	$5 \cdot 10^3$

The ratio of the rate constants for different forms of vitamin K, which is present in lipids mainly as the quinone, is also fairly large. For ubiquinone, the difference between the rate constants is smaller, which demonstrates the ease of its transition from the oxidised to the reduced form and conversely (see Table). The contribution of ubiquinone to the antioxidant properties of liver lipids does not exceed 5–10%.[40]

Much attention has been devoted to the study of hormones as antioxidants. Thyroid hormones have been shown to exhibit antioxidant activity in the model reaction involving the oxidation of methyl oleate[46]. Amongst steroid hormones, the antiradical effectiveness of which has been studied on the basis of the quenching of chemiluminescence[47], oestrogens proved to be the most active. For example, in the model reaction involving induced oxidation of lipids in mitochondria, diethylstilboestrol has a constant k_7 of the same order of magnitude as tocopherol[47]. Adrenaline exhibits weak antiradical properties[38,48]. The antiradical action of hormones is probably associated with the presence of phenolic groups in their molecules.

There are many obscure aspects of the problem of the antioxidant action of phospholipids and its mechanism. Some studies demonstrated antiradical activity in certain phospholipids, for example in phosphatidylcholine[48], while in others it is asserted that the antioxidant activity of phospholipids can be manifested only in those cases where they are mixed with antioxidants, since phospholipids behave as synergistic agents for antioxidants[49,50]. Olcott and coworkers[51] suggested that the only phospholipids with antioxidant activity are those capable of being oxidised under the experimental conditions with formation of a nitroxy-radical, which exhibits antiradical properties.

The problem of the antioxidant activity of cholesterol is widely discussed in the literature. Cholesterol was found to have a weak influence on chemiluminescence in model systems[48,52]. However, it has not been established whether the quenching of the chemiluminescence by cholesterol is chemical or physical. The cholesterol concentrations at which an effect is observed are fairly large (0.01 M), which makes it necessary to treat with much caution conclusions concerning the antiradical properties of cholesterol. The behaviour of cholesterol in model lipid oxidation systems is fairly complex. The experimental result depends on the cholesterol concentration, the rate of oxidation of the model lipid, and the duration of oxidation. Thus it has been shown[53] that, in the oxidation of methyl oleate, cholesterol exhibits antioxidant properties in the range of moderate concentrations, while lower and higher experimental concentrations actually accelerate oxidation. The antioxidant activity increases with time. These findings can be accounted for if cholesterol is regarded as the substrate of joint oxidation with methyl oleate and when account is taken of the fact that the cholesterol oxidation products may be antioxidants. Indeed it was shown that cholesterol is oxidised via a free-radical mechanism[54] and that its oxidation can be retarded by radical-reaction inhibitors[55].

Thus the main lipid components of membranes—phospholipids and cholesterol—can play a decisive role in the changes of the overall antioxidant activity in lipids, but the mechanism of this influence is complex and at present has not been finally elucidated.

Summarising the foregoing, the following points may be noted:

1. Many substances present in the lipid phase of cells exhibit antioxidant and antiradical properties. The characteristic features of most of them are a relatively low antioxidant effectiveness.
2. The overall antioxidant activity of the lipid fraction is determined by the interaction of its components. The contributions of individual antioxidants to the antioxidant activity of lipids are comparable.
3. Although the antiradical properties of natural antioxidants vary within wide limits, this does not have a significant influence on their antioxidant properties, probably because of the high activity of the radicals derived from the inhibitor, which enter into the chain-propagation reaction and weaken the antioxidant properties of the inhibitor.

It has now been shown that endogenic antioxidants inhibit the lipid oxidation processes *in vivo* and fulfill their antioxidant function together with their other specific functions. In order to establish the role of natural antioxidants in cell metabolism, it is extremely important to elucidate the question of their interaction and capacity for interchange. It is known that many diseases entail a simultaneous decrease of the amounts of various antioxidants. For example a decrease of the concentration of not only tocopherol but also ubiquinones has been observed in vitamin E deficiency[56].

The changes in the amount of natural antioxidants in liver lipids following the introduction of tocopherol into animals have been studied[57,58]. Together with an increase of the steady-state concentration of tocopherol in lipids, there is a significant accumulation also of other natural antioxidants. According to the authors, this is a consequence of the preferential consumption of the added tocopherol in free-radical oxidation reactions, which is confirmed by an

increase of the concentration of tocopherylquinone—one of the final reaction products of tocopherols in these processes[58,59]. Similar results were obtained also in experiments where ubiquinone had been introduced[40]. These results indicate indirectly the importance of the antioxidant properties of tocopherols and ubiquinones, on the one hand, and the absence of specificity in the inhibition of the free-radical oxidation of lipid, on the other.

In certain cases the deficiency of natural antioxidants can be made good by synthetic inhibitors. Thus certain synthetic antioxidants eliminate many symptoms of vitamin E deficiency, while others are inactive[60-63]. In order to establish the principle if the selection of synthetic inhibitors to make good the deficiency of the organism's own antioxidants, it is necessary to compare their effects.

The influence of the introduction of various inhibitors on the system of natural antioxidants has been studied[64,65]. It has been established that only inhibitors with antiradical activity k_7c (c is the inhibitor concentration in lipids) comparable to that of natural antioxidants are capable of replacing them in the free-radical oxidation of lipids and of increasing the steady-state concentration of natural antioxidants. Thus the introduction of propyl gallate increases the concentration of tocopherol in mouse liver lipids by a factor of 1.5, the concentration of tocopherylquinone decreasing. This supports the hypothesis that the rate of utilisation of tocopherol decreases owing to the competitive inhibition of the free-radical oxidation of lipids by the synthetic inhibitor. The overall antioxidant activity of lipids increases following the introduction of synthetic inhibitors both due to the presence of the synthetic inhibitor in lipids and, when preparations with high values of k_7c are introduced, as a result of the increase of the concentration of natural antioxidants.

Thus the influence of synthetic inhibitors on the amount of natural antioxidants in lipids can be accounted for on the basis of the usual competitive relations for two or several inhibitors. However, in experiments with the introduction of synthetic inhibitors into animals, phenomena were also observed, which cannot be simulated experimentally. Thus it has been found that, following the introduction of large amounts of synthetic inhibitors, AOA of lipids in animal organs initially increases to a maximum and then falls significantly below the normal values[66,67]. It has been suggested that synthetic inhibitors, which have many properties in common with natural antioxidants, suppressed their synthesis or enhance the reactions in which they are consumed[66]. The dependence of the degree of reduction of the level of lipid AOA by synthetic inhibitors on their ability to inhibit oxidation reactions has been investigated[65]. It was found that the reduction is greater the higher the relative antioxidant effectiveness of the inhibitor. When 2,6-di-t-butyl-4-methylphenol is introduced into animals in a dose of 100 mg kg^{-1}, the concentration of tocopherol in lipids falls[65] and tocopherylquinone accumulates at the same time[58]. The results of these studies suggested a relation between the ability of the synthetic inhibitors present in lipids to inhibit oxidation reactions and the rate of consumption of the antioxidants.

In order to determine the cause of the change in the consumption of antioxidants, the rate of generation of free radicals in lipids was studied by a chemiluminescence method[58]. When AOA of lipids is altered by the introduction of synthetic inhibitors, a related change in the capacity of lipids for oxidation is observed. Lipids exhibit a greater ability to form radicals the higher their antioxidant activity. In other words, with increase of the amount of antioxidants, the composition of lipids changes in such a way that the rate of generation of free radicals from them increases with a corresponding increase in the rate of consumption of antioxidants[69]. Thus, after the introduction of tocopherol into animals, AOA increases by a factor of two and the capacity of their lipids for oxidation increases by a factor of about ten. Similar data were obtained after the introduction of propyl gallate and 2,6-di-t-butyl-4-methylphenol as well as in other processes associated with a change in the level of AOA of lipids. It is noteworthy that the relation between AOA of lipids and their capacity for oxidation on the one hand and the corresponding rate of consumption of antioxidants on the other is satisfactorily linear[64].

The existence of this relation ensures the maintenance of a constant level of oxidation reactions in lipids regardless of whether their AOA has changed as a result of the change in the amount and quality of the natural antioxidants or as a result of the presence of synthetic inhibitors. The product k_7c determines which antioxidants, endogenous or those introduced into the organism, will be the first to be consumed and hence whether or not AOA of lipids will fall below the normal value.

Thus synthetic inhibitors of radical processes can be used to induce specific changes in AOA of lipids and probably to influence the course of diseases where a change in AOA of lipids is a significant factor.

III. THE INFLUENCE OF SYNTHETIC INHIBITORS ON PATHOLOGICAL PROCESSES INVOLVING CHANGES IN THE LEVEL OF ANTIOXIDANTS

It has now been shown that, in the development of a wide variety of pathological states, there is a change in AOA of the lipids in the organs and tissues[10,70].

In terms of the change in AOA of lipids, all the pathological states investigated and the changes in cell metabolic processes under the influence of particular environmental factors may be divided into three groups. In the first group radiation damage caused by radiation or by the introduction of radiomimetics[66,69,71-76], the state of stress caused by low temperatures[10,77,78], hyperoxia[79], hyperthermia[80], electrostimulation[81], poisoning with benzene[78], the ageing process[77,82], ischemia[83], etc. may be included among processes occurring at a reduced AOA level. It is important to note that the higher the rate of development of the given pathological state and the greater the involvment of a particular organ, the more marked is the decrease of AOA.

The changes in AOA of the lipids in the organs of tumour-bearing animals[66,68,84-90] and reparative regeneration processes in organs and tissues[91] belong to the second group of processes occurring mainly at an increased level of AOA. As in the first case, there is a relation between the rate of development of the process, the severity of the disease, and the change in AOA[90].

Processes which lead to a change in AOA by stages, for example the induction of malignant tumours (carcinogenesis)[92-94] may be included in the third group †. In the first stage of carcinogenesis, during a period equal to one-third

† Although in the first and second groups there are various stages in the changes of AOA, they continue over a very short time interval compared with the time required for the development of the process, so that one may assume that the processes occur mainly at an increased or reduced level of AOA.

of the time required for the induction of tumours, AOA falls. It increases subsequently, but normal values are reached only after a time interval approximately equal to one-half of the induction period. Finally, the third period is characterised by a sharp increase of AOA. The changes in AOA characteristic of different types of carcinogenesis are of a general type and the curves describing them can be combined into a single general curve[92].

The most interesting and important finding is that a wide variety of pharmacological agents (vitamins, hormones, adaptogens, alkylating preparations, antimetabolites, cytostatic agents, aliphatic acid esters, alkylindolinylamines, supermutagens, etc) influence AOA in doses sufficient for a manifest pharmacological effect. There are preparations which only increase AOA (for example hydroxypyridines), those which only decrease AOA (alkylating agents), and those which can both increase and decrease AOA (adaptogens, radical reaction inhibitors, hormones, antimetabolites, derivatives of nitrosoalkylurea, etc.)[65,71,86,87,90,95-99].

The possibility of using these compounds in the treatment of particular diseases is associated with the nature of the influence of the preparations on AOA. If the pathological process takes place at a reduced AOA level, a wide variety of compounds which increase antioxidant activity have a protective effect, which is more marked the greater the increase of AOA which they induce[69]. On the other hand, preparations which diminish AOA are effective in processes occurring at an enhanced AOA level[71,89,90,95]. For example, all antitumour preparations decrease AOA and the degree of inhibition of tumour growth is greater the more marked and longer lasting is the decrease of AOA by these substances[89,90].

The relation between the influence of the preparation on AOA and on the course of a particular pathological process was demonstrated most strikingly in a study of preparations which can both increase and decrease AOA (depending on the dose) or when the same preparation is introduced at different times during the development of the process occurring with changes in AOA by stages.

As stated above, the introduction inhibitors in small doses increases the antioxidant activity of lipids with subsequent recovery to the normal value, while large doses lead to an increase of AOA and its subsequent fall below normal values. The characteristics of the action of synthetic inhibitors used in the treatment of a wide variety of pathological states of the organism are associated with these properties. Thus it has been established that the ability of the inhibitor to protect against radiation increases with its dose, reaching a maximum for the optimal dose (C_{opt}), and then decreasing. At a certain negative inhibitor dose (C_{neg}) no effect is observed and with subsequent increase of the amount of antioxidant there is a transition from protective to sensitising properties of the inhibitors[74,100-102]. A similar effect is observed when the inhibitors are introduced both before and after irradiation[103]. C_{opt} is the maximum amount of the preparation for which AOA of lipids does not decrease below the normal value[66,74].

A similar dual effect on tumour growth has been observed: small doses of the inhibitor accelerate and large doses retard the development of the tumour. The accelerating effect on tumour growth is observed in the range of doses below C_{opt},[86,89] while antitumour activity is observed for doses greater than C_{opt}.[66,68,88,89] Since the influence on tumour growth is more marked the greater the reduction of AOA by inhibitors, for each preparation there is an inverse relation between its antitumour properties and its ability to protect against radiation[104-106]. The antitumour effect of equimolar doses of preparations is greater the lower the value of C_{opt} for these inhibitors[104]. In the dose range from C_{opt} to C_{neg} inhibitors can be useful in the radiotherapy of tumours[106].

Data for the variation of AOA in tumour growth, on irradiation, and following the introduction of inhibitors led to the prediction and subsequent experimental confirmation[107-109] of the existence of four regions of different effects of the joint application of radical-process inhibitors and irradiation on the tumour and the organism of the tumour-bearing animal. In region I of inhibitor doses and irradiation the preparation protects both the animal and the tumour from the action of radiation. in region II the preparation enhances the action of radiation on both the organism and on the tumour, in region III the preparation protects the tumour but sensitises the organism to the action of radiation, and finally in region IV the preparation enhances the effect of radiation on the tumour and at the same time protects the organism[108].

The available literature data for the anticarcinogenic effect of antioxidants behaving at the same time as radical process inhibitors are extremely contradictory. It has been shown that both natural (vitamin E) and synthetic antioxidants can retard tumour growth[93,94,110-117], have no effect whatever[118-120], and can "promote" carcinogenesis[121-123].

Since in the tumour induction process there are stages involving a decrease and an increase of AOA, different effects can be expected following the introduction of inhibitors in different doses and at different stages of carcinogenesis. Indeed, the introduction of an inhibitor belonging to the class of screened phenols in a dose which only increases AOA led to the arrest of the formation of tumours in the initial period and to a decrease of the percentage of tumours formed. On the other hand, if the same amount of the preparation was introduced at the stage corresponding to the increase of AOA, the tumours appeared sooner. The reverse behaviour was observed when large doses of inhibitors, causing a decrease of AOA were introduced[124]. From these standpoints, the discrepancies in the literature data are not unexpected.

One of the important aspects of the use of inhibitors is their application to protect the organism under stress, in the course of which AOA decreases. Synthetic inhibitors applied in doses increasing AOA exhibit antistress activity and protect animals from hyperoxia[79], poisoning by benzene[78], and stress due to cold[77,78]. The introduction of inhibitors in doses decreasing AOA enhances the effect of the stress-inducing agent[78]. Numerous studies have been made on the protective properties of tocopherol in poisoning by carbon tetrachloride and in intoxication by ozone. These have been reviewed[125].

It has been shown[83] that in the experimental ischemia of kidneys lipid AOA decreases and inhibitors applied in doses increasing AOA exhibit anti-ischemic activity, significantly prolonging the life of the animal.

An important property of the inhibitors, which opens up new fields for their application (for example in tissue and organ transplants), is their ability to influence specifically the rate of cell multiplication. In small doses inhibitors accelerate cell multiplication both in reparative regeneration[91] and when introduced into intact animals, increasing the level of the proliferative activity of the cells of their organs[126]. In doses decreasing AOA inhibitors retard cell multiplication. In the light of these facts, the desirability of employing inhibitors as geroprotectors is evident[127].

Although not all the aspects of the application of radical-process inhibitors have been considered, the principal features of antioxidant therapy are already clear from the data presented:

1. Inhibitor-antioxidants can be used in the treatment of diseases involving a reduced level of AOA. The preparations are more effective the higher the level of AOA following their introduction.

2. Inhibitors can be used also to suppress processes involving an increase of AOA. The inhibiting effect is shown only for inhibitor doses which reduce AOA.

3. Depending on the dose and the method and duration of introduction, the effect of the inhibitor can be reversed. The contradictory data concerning the therapeutic effects of preparations of this class are probably associated with this fact.

4. There is a consistent relation between different aspects of the biological activity of antioxidants, and their effectiveness has been found to depend on their physicochemical constants as inhibitors. This suggests that antioxidant properties are the cause of the wide spectrum of the biological activity of radical-process inhibitors. Furthermore, this justifies an initial selection of antioxidants on the basis of physicochemical models and makes it possible to recommend the synthesis of inhibitors which are most effective in a particular application.

IV. THE ROLE OF ANTIOXIDANTS IN THE STRUCTURE AND FUNCTION OF MEMBRANES

The problem arises of the causes of the significant role of the changes in AOA in the development of the pathological process and of the basis of the therapeutic activity of preparations normalising AOA.

Lipids together with proteins are the most important components of membranes. If it is assumed that antioxidant properties are indeed important for the functioning of membranes, there should be a correlation between the changes in these properties in the membranes of various organelles and the changes in their function, depending on AOA.

Together with the study of the widely known regulatory mechanisms in the cell (such as the repression–derepression of genes, the blocking–deblocking of the genome, the inhibition and activation of enzymes by allosteric effectors, and regulation with the aid of a secondary hormone mediator–c-AMP, etc) much attention is devoted nowadays to the study of the role of membranes in the regulation of cell metabolism. Numerous instances of the experimental confirmation of the Konev–Changeux hypothesis concerning the important role of cooperative transitions in the membrane in the switching of cell metabolism occurred in recent years[128,129].

The receptor function of membranes, compartmentalisation, the contact of properties of cell surfaces, and the transport function of membranes are all aspects of their funtional activity which can be regarded as the most important regulatory mechanisms of the vital activity of the cell. The relation between the structure of membranes and their functions is well known. Structural organisation in its turn is closely related to the physicochemical properties of the main components—lipids and proteins. The presence of antioxidants in the lipid phase of the membranes has been regarded by a number of workers as an obligatory condition for the maintenance of the membrane structure, since the development of peroxide oxidation in lipids leads to its breakdown[130,131]. There exists the hypothesis that lipid antioxidants also play an intrinsic structural role in the membrane[132] The changes in AOA of the lipids in liver homogenate have been compared[133] with the changes in AOA of the lipids in various cell fractions. It was observed that both in the lipids from the nuclei and from the microsomes and mitochondria the nature of the changes in AOA is virtually the same as in the homogenate in all the instances investigated.

The fractions of AOA corresponding to lipids of particular organelles are various and change with time, which suggests a redistribution of AOA among the subcellular fractions. The instant of the attainment of AOA maximum is somewhat different for various fractions. Such data have been obtained in the normal physiological variation of AOA—the daily rhythm: after the introduction of a synthetic antioxidant, after the recovery of the weight of the liver following partial hepatectomy, under the influence of radiation, and in tumour growth. Thus the changes in AOA in the organelle lipids are of the same type, although they differ in scale and duration.

It is important to consider whether the change in the functional activity of membranes leads to a change in the antioxidant activity of their lipids. It has been established[134] that, when cells pass from stage G_1 to the stage of DNA synthesis, there is a sharp phased decrease of lipid AOA both in the nuclei and in the entire homogenate. Comparison of the change in the functional state of mitochondria and lipid AOA[133] also shows that an increase of AOA leads to an increase of respiratory control and a transition of the mitochondria to the most completely regulated state. For microsomal fractions, a change in functional activity was observed in processes involving a change in AOA[135].

Thus an increase or decrease of lipid AOA in the homogenate leads to consistent changes of the same type in lipid AOA in the organelle membranes and to corresponding polyfunctional rearrangements of their metabolism.

In discussing the mechanism of the influence of free-radical oxidation reactions in lipids on the functioning of membranes, the following versions may be considered[10]:

1. The appearance of polar peroxy-groups in lipids can lead to a change in the intensity of hydrophobic interactions and can influence lipid–protein bonds in the membrane.

2. The free valence in the lipid components of the membranes can alter the stability of the complexes of enzymes and other macromolecules, for example DNA, with the membrane. Therefore even a slight change in free-radical concentration can alter the cell metabolism.

3. The change in the rate of oxidation reactions in lipids is associated with the change in lipid composition. At the same time it is known that phospholipids are cofactors and effectors for enzymes and that a change in their relative content can have a significant influence on metabolism.

4. The functioning of the membrane leads to a change in its conformation or is accompanied by such a change. The structural transitions in membranes are in their turn induced by conformational and phase transitions in proteins or lipids. Therefore a change in the physicochemical properties of lipids can alter the physicochemical properties of the membranes and hence their functional activity.

As stated above, the present author observed that both at the cellular and membrane levels the lipid composition changes in response to an increase in AOA in such a way that the lipids are more easily oxidised. Since the oxidised forms of lipids are more popular, one could postulate that their formation is a method whereby lipids can leave the membrane and their composition can be restored[136,137]. Then an increase of AOA should retard the release of the most readily oxidisable lipids. This should result in an enrichment of the membrane lipids in these fractions, which should in turn accelerate the utilisation of antioxidants.

It has been established[53,138] that the increase of AOA induced by the introduction of synthetic antioxidants leads to an increase of the relative amount of phospholipids and to a decrease of the amount of cholesterol. Changes are also observed among the phospholipid fractions. With increase of AOA, the lipids in the liver cell membranes are enriched in phosphatidylserine, phosphatidylinositol, and phosphatidylethanolamine—the more readily oxidised fractions of phospholipids. A decrease of AOA leads also to a decrease of the relative amount of such fractions and to an enrichment of lipids in sphingomyelin and phosphatidylcholine[136,139]. Thus the changes in the rates of oxidation reactions in lipids and in their compositions are interrelated in a single system, which ensures the steady-state oxidation of lipids.

We shall consider further the results of the change in the relative composition of membrane phospholipids. As stated above, a change in the composition of membrane lipids leads to a change in their microviscosity and influences their structural rearrangements in membranes. This results in an intensification or a weakening of the metabolic activity of enzyme proteins incorporated in the membrane.

To elucidate the influence of AOA on membrane structure, a study was made of the change in the state of biomembrane components using spin probes located preferentially in the lipid or protein phases of the membrane[140]. The following iminoxy-radicals were used for the investigation: 4-capryloyloxy-2,2,6,6-tetramethylpiperidin-1-yloxy-radicals (probe I), and 2,2,6,6-tetramethyl-4,5-benzo-1,2,3,4-tetrahydrocarbolin-3-yloxy-radicals (probe II). Probe I was located preferentially in the lipid components of the membrane and probe II in the protein components. The influence of temperature on the mobility of the spin probes in the membranes of the organelles (nuclei and mitrochondria) in the cells of organs in intact animals and following the introduction of synthetic antioxidants was investigated. At 27° and 40°C there was a general conformational transition in the membranes, revealed with the aid of both probes. An increase in lipid AOA by the introduction of the antioxidant displaces the conformational transitions towards lower temperatures. It is interesting to note that the microviscosities in the membrane lipids and proteins vary in the opposite directions: the rotational mobility of the radical increases in lipids and decreases in proteins. An extremum is reached in the lipid phase 24 h sooner than in the protein phase. Thus the introduction of the antioxidant leads to the formation of a more "liquid" lipid component and to a more viscous protein component.

The change in the antioxidant properties of membrane lipids in tumour growth and under the influence of radiation[140] also altered the microviscosities of lipids and proteins and the conditions governing the structural rearrangements in the membrane. These findings can be accounted for by a change in the composition of the lipids in these processes, since it is known that a change in the cholesterol : phospholipids ratio and in the relative content of phospholipids alters the viscosity of the membrane components and the phase transition temperatures[141,142].

The second and no less important aspect is the influence of the change in the composition of lipids on the relative rates of the enzymatic reactions for which these lipids are effectors or cofactors.

It is known that the removal of phospholipids deactivates many enzymes and leads to the loss of their sensitivity to particular regulating agents[143,144]. The addition of phospholipids and cholesterol restores the activity of these enzymes and their sensitivity, the reactivating effect being frequently related specifically to the addition of a particular phospholipid. Thus β-hydroxybutyrate dehydrogenase is reactivated by phosphatidylcholine[145,146], adenylate cyclase by phosphatidylinositol[147], and FAD-dependent malate deydrogenase by cardiolipin[148]. The addition of phosphatidylserine to adenylate cyclase restores its sensitivity to glucagon[149] and the addition of phosphatidylinositol restores its sensitivity to noradrenaline[150]. It is extremely interesting that phospholipids behave as allosteric effectors for many regulating proteins[143]. This is not suprising, since the majority of the regulatory proteins have a quaternary structure enriched in non-polar aminoacids, for which hydrophobic interactions are extremely characteristic.

In view of the foregoing, it becomes understandable why a change in AOA leading to a change in lipid composition alters the structural viscosity of lipids, the lipid–protein linkages in the membrane, and the rate of the enzymatic reactions for which phospholipids are effectors. Owing to this, a change in the rates of oxidation reactions in lipids causes a transition of the cell to a new metabolic state characterised by new relations between the rate of particular enzymatic reactions.

The influence of lipids on regulating proteins permits an explanation of the possibility of switching the cell metabolism from one pathway to another when the composition of phospholipids is altered We may quote as an example the experiment in which a synthetic antioxidant was introduced into animals with a consequent increase of the concentration of phosphatidylethanolamine in liver microsomes together with an increase of AOA. According to model experiments[151], the addition of total phospholipids or of individual components reactivates or increases the activity of glucose-6-phosphates. It was of fundamental importance to establish the possiblity of regulating the activity of enzymes by lipids *in vivo*. In our laboratory Molochkina and Dzhalyabova observed that, simultaneously with the increase of the concentration of phosphatidylethanolamine, the activity of glucose-6-phosphatase increases in liver microsomes. A similar relation obtains not only following the introduction of antioxidants, but also in other processes accompanied by a change in AOA of lipids and hence in the concentration of phosphatidylethanolamine.

From the same standpoint, it is possible to explain also the role of lipids in the regulation of the rate of cell proliferation. As stated above, an increase of AOA leads to an increase of the concentration of phosphatidylserine and phosphatidylinositol, which function as effectors for adenylate cyclase. The influence of lipids on the activity and sensitivity of adenylate cyclase—the enzyme responsible for the formation of cAMP—makes it possible to explain the role of antioxidants in the regulation of cell proliferation at the molecular-biological level. Studies have been published recently in which much attention was devoted to the change in the composition of lipids during the synthesis of DNA. It is suggested that phospholipids form complexes with a DNA molecule, altering its stability, and are essential for the initiation of the synthesis of DNA[153,154]. Furthermore, *in vivo* experiments established the influence of phospholipids on the matrix activity of the gene and a difference between the amounts of phospholipids in repressed and derepressed genes[154]. It has been shown[155] that a change in AOA and composition of nuclear lipids is associated with a change in DNA synthesis. An increase in the amount of sphingomyelin in nuclear lipids against the background of a sharp decrease of AOA at the beginning of DNA synthesis is particularly significant.

The above experimental data show that the change in the antioxidant properties of lipids, caused both by a change in the amount of intrinsic natural antioxidants and by the

introduction of non-toxic synthetic inhibitor-antioxidants, alters significantly the cell metabolism. The importance of the change in the antioxidant properties is associated with the role of membranes in the regulation of cell metabolism, the functional activity of the membranes being altered when the physicochemical characteristics and the composition of the membrane components are changed.

In view of the foregoing factors, synthetic inhibitor-antioxidants can be usefully employed to act specifically on a wide variety of processes occurring with change in AOA of lipids.

REFERENCES

1. E. B. Burlakova, B. G. Dzantiev, G. B. Sergeev, and N. M Emanuel', Symposium, "Biokhimicheskie i Fiziko-Khimicheskie Osnovy Biologicheskogo Deistviya Radiatsii" (Biochemical and Physicochemical Principles of the Biological Action of Radiation), Izd Moskov Gos. Univ., Moscow, 1957, p.10.
2. N. M. Emanuel', Symposium, "Pervichnye Mekhanizmy Biologicheskogo Deistviya Ioniziruyushchikh Izluchenii, Trudy MOIP" (The Primary Mechanisms of the Biological Action of Ionising Radiation, Transactions of MOIP), Izd. Nauka, Moscow, 1963, Vol.VII, p.73.
3. F. Pozza and G. Verza, Boll. Soc. Ital. Biol. Sper., 36, 1120 (1960).
4. H. Ershoff and C. W. Steers, Proc. Soc. Expil. Biol. and Med., 104, 274 (1960).
5. A. A Gorodetskii, V. A Baraboi, and V. P. Chernetskii, Dokl Akad. Nauk Ukrain. SSR, 12, 1635 (1960).
6. A. A. Gorodetskii, V. A. Baraboi, and V. P. Chernetskii, Radiobiologiya, 1, 781 (1965).
7. R. Huber and E. Schrober, Strahlentherapie, 119, 308 (1962).
8. R. B. Strelkov and L. F Semenov, Radiobiologiya, 6, 578 (1966)
9. E B. Burlakova, N. M. Dzybuba, and N. P. Pal'mina, Biofizika, 10, 766 (1965).
10. "Bioantioksidanty v Luchevom Porazhenii i Zlokachestvennom Roste" (Bioantioxidants in Radiation Sickness and Malignant Growth), Izd. Nauka, Moscow, 1975.
11. "International Conference on Vitamin E and Its Role in Cellular Metabolism", Annalen New York Acad Sci., 203, (1972).
12. A. L. Tappel, Vitamins, Hormones, 20, 493 (1962).
13. H. S. Olcott and O. H. Emerson, J. Amer. Chem. Soc., 99, 1008 (1937).
14. H. S. Olcott and J. Van der Veen, Lipids, 3, 331 (1968).
15. C. H Lea and J. Ward, J. Sci. Food Agric., 10, 537 (1959).
16. C. H. Lea, J. Sci. Food Agric., 11, 212 (1960).
17. E. L. Hove and L. Hove, J. Biol. Chem., 156, 623 (1944).
18. H. P Kaufmann and H. Gartoff, Fetteu. Seifen., 63, 339 (1961).
19. H. P Kaufmann, H. Gartoff, and K. G Vekunde, Fetteu. Seifen., 64, 309 (1962).
20. L. A. Witting, Lipids, 2, 109 (1967).
21. L. A. Witting, Arch. Biochem. Biophys., 129, 142 (1969).
22. H. H. Lips, J. Amer. Oil Chem. Soc., 34, 513 (1957).
23. J. Green, A. T. Diplock, J. Bunyan, D. McHale, and I. R. Muthy, Brit. J. Nutr., 21, 69 (1969).
24. A. T. Diplock, M. A. Cowthorne, E. A. Murrell, J. Green, and J. Bunyan, Brit. J. Nutr., 22, 465 (1968).
25. W. A. Skinner, Lipids, 5, 134 (1970).
26. W. A. Skinner and R. M. Parkhurst, Lipids, 6, 240 (1971).
27. C. Kanno, M. Hayashi, K. Yamauchi, and F. Tsugo, Arch. Biol. Chem., 39, 873 (1970).
28. C. Kanno, K. Yamauchi, and T. Tsugo, Arch. Biol. Chem., 34, 1632 (1970).
29. S. A Aristarkhova, E. B Burlakova, and N. G. Khrapova, Izv Akad Nauk SSSR, Otd. Khim. Nauk, 1483 (1965)
30. S. A Aristarkhova and N. G. Khrapova, Symposium, "Bioantiokisliteli" (Bioantioxidants), Izd. Nauka, Moscow, 1975, p.196.
31. E. T. Denisov, "Konstanty Skorosti Gomoliticheskikh Zhidkofaznykh Reaktsii" (The Rate Constants of Homolytic Liquid-Phase Reactions), Izd. Nauka, Moscow, 1971.
32. N. G. Khrapova, Symposium, "Vitaminy" (Vitamins), Izd. Naukova Dumka, Kiev, 1975, No.8, p.22.
33. F. W. Knapp and A. L. Tappel, J. Amer. Oil Chem. Soc., 38, 151 (1961).
34. S. A. Aristarkhova, E. B. Burlakova, and N. G. Khrapova, Biofizika, 18, 857 (1973)
35. S. A. Aristarkhova, E. B. Burlakova, E. N. Kukhtina, N. G. Khrapova, I. K. Sarycheva, and R. P. Evstigneeva, Voprosy Pitaniya, 34 (1974).
36. E. B. Burlakova and N. G. Khrapova, Symposium, "Teoriya i Praktika Zhidkofaznogo Okisleniya" (Theory and Practice of Liquid-Phase Oxidation), Izd. Nauka, Moscow, 1974, p.244.
37. E. T. Denisov, Uspekhi Khim., 42, 362 (1973) [Russ Chem. Rev., No. 3 (1973)].
38. E. T. Denisov and N. M. Emanuel' Kinetika i Kataliz, 14, 824 (1973).
39. Yu. M Petrusevich, Symposium, "Bioantioksidanty" (Bioantioxidants), Izd. Nauka, Moscow, 1975, p.247.
40. E B. Burlakova, Yu. A. Zaslavskii, S. F. Terekhova, and N. G. Khrapova, Dokl. Akad. Nauk SSSR (In the Press).
41. G. I. Samokhvalov and E. A. Obol'nikova, Uspekhi Khim., 36, 1012 (1967) [Russ. Chem. Rev., No. 6 (1967)].
42. A. Mellors and A. L. Tappel, J. Biol. Chem., 241, 4353 (1966).
43. A. Mellors and A. L. Tappel, Lipids, 1, 282 (1966).
44. E. H. Gruger and A. L. Tappel, Lipids, 5, 332 (1970).
45. E. H. Gruger and A. L. Tappel, Lipids, 6, 147 (1971).
46. E. Ware and P. Wisher, Expt. Cell. Res., 10, 556 (1956).
47. Yu. A. Vladimirov, P. V. Sergeev, R. D. Seifulla, and Yu. M. Rudnev, Mol. Biol., 7, 247 (1973).
48. Yu. M. Petrusevich, G. V. Kossova, and O. R. Kol's, in "Sverkhslabye Svecheniya v Biologii" (Ultraweak Luminescence in Biology), Izd. Nauka, Moscow, 1972, p.133.
49. N. M. Emanuel' and Yu. N. Lyaskovskaya, "Tormozhenie Protsessov Okisleniya Zhirov" (Inhibition of Fat Oxidation Processes), Pishchepromizdat, Moscow, 1961
50. M. S Olcott and E. J Kuta, Nature, 183, 1812 (1959).
51. J. T. Weil, J. Van der Veen, and H. S. Olcott, Nature, 219, 168 (1968).
52. S. F Terekhova, A. V. Alesenko, and E. B. Burlakova, "Tezisy Dokladov IV Mezhdunarodnogo Biofizicheskogo Kongressa" (Abstracts of Reports at

the Fourth International Biophysical Congress), Moscow, 1972, Vol.2, p.74.
53. N. T. Aleshina, E. B. Burlakova, and S. F. Terekhova, Vop. Med. Khim (in the Press).
54. O. Hellinger, H. Hensinger, and O. Hug, Biophysik, 6, 193 (1970).
55. G. Tirzitis and B. Krustinya, "Referaty Nauchnykh Soobshchenii III Vsesoyuznogo Biokhimicheskogo S'ezda, Riga, 1974" (Abstracts of Communications at the Third All-Union Biochemical Congress, Riga, 1974), Vol.2, p.153.
56. E. E. Edwin, A. T. Diplock, J. Bunyan, and J. Green, Biochem. J., 79, 91 (1961).
57. S. A. Aristarkhova, E. B. Burlakova, and N. G. Khrapova, Biofizika, 19, 688 (1974).
58. S. A. Aristarkhova, E. B. Burlakova, and N. G. Khrapova, Symposium, "Lipidy v Organizme Zhivotnykh i Cheloveka," (Lipids in Animal and Human Organisms), Izd. Nauka, Moscow, 1974, p.20.
59. S. A. Aristarkhova and E. B. Burlakova, Symposium, "Materialy po Biokhimii Vitamina E i Selena i ikh Primenenie v Meditsine i Zhivodnovodstve" (The Biochemistry of Vitamin E and Selenium and Their Applications in Medicine and Animal Husbandry), Izd. Naukova Dumka, Kiev, 1973, p.9.
60. A. S. Csallany and H. H. Draper, Arch. Bioch. Biophys., **92**, 462 (1961).
61. H. Dam and H. Granados, Acta Physiol. Scand., 10, 162 (1945).
62. H. Dam, J. Kruse, J. Prange, and E. Sondergaard, Acta Physiol. Scand., **22**, 299 (1951).
63. B. Roslyn and S. Afin, in "Advances in Lipid Research", Acad. Press, New York–London, 1963.
64. S. A. Aristarkhova, E. B. Burlakova, and N. G. Khrapova, Symposium, "Materialy po Biokhimii Vitamina E i Selena i ikh Primenenie v Meditsine i Zhivodnovodstve" (The Biochemistry of Vitamin E and Selenium and Their Applications in Medicine and Animal Husbandry), Izd. Naukova Dumka, Kiev, 1973, p.22.
65. E. B. Burlakova, S. A. Burobina, and N. G. Khrapova, Dokl. Akad. Nauk SSSR, 200, 461 (1971).
66. E. B. Burlakova, N. M. Dzyuba, N. P. Pal'mina, and N. M. Emanuel', Dokl. Akad. Nauk SSSR, 163, 278 (1965).
67. E. B. Burlakova, N. M. Dzyuba, and N. P. Pal'mina, "Svobodnoradikal'nye Protsessy v Biologicheskikh Sistemakh, Trudy MOIP" (Free-Radical Processes in Biological Systems, Transactions of MOIP), Izd. Nauka, Moscow, 1966, p.202.
68. E. B. Burlakova and N. P. Pal'mina, Biofizika, 11, 54 (1966).
69. E. B. Burlakova, "Trudy IV Mezhdunarodnogo Biofizicheskogo Kongress, Doklady Simpoziumov, Pushchino, 1975" (Proceedings of the Fourth International Biophysical Congress, Reports at Symposia, Pushchino, 1975), Vol.3, p.41.
70. I. I. Ivanov (Editor), "Bioantiokisliteli" (Bioantioxidants), Izd. Nauka, Moscow, 1975.
71. A. V. Alesenko, E. B. Burlakova, N. M. Dzyuba, L. V. Slepukhina, and N. M. Emanuel', Radiobiologiya, 4, 718 (1966).
72. A. I. Zhuravlev, Symposium, "Rol' Perekisei i Kisloroda v Nachal'nykh Stadiyakh Radiobiologicheskogo Effekta" (The Role of Peroxides and Oxygen in the Initial Stages of the Radiobiological Effect), Izd. Akad. Nauk SSSR, Moscow, 1960, p.56.
73. A. S. Arkhipov, Yu. P. Kozlov, and E. B. Burlakova, Radiobiologiya, 7, 623 (1967).
74. E B. Burlakova and N. M. Dzyuba, Biofizika, 11, 54 (1966).
75. N. P. Pal'mina, Radiobiologiya, 12, 737 (1972).
76. "Svobodnoradikal'nye Sostoyaniya i Ikh Rol' pri Luchevom Porazhenii i Zlokachestvennom Roste" (Free-Radical States and Their Role in Radiation Sickness and Malignant Growth), Moscow, 1971.
77. E. B. Burlakova, Symposium, "Fiziko-Khimicheskie Mekhanizmy Zlokachestvennogo Rosta" (Physicochemical Mechanisms of Malignant Growth), Izd. Nauka, Moscow, 1970, p.9.
78. A. V. Slepukhina, Candidate's Thesis, Institute of Chemical Physics, USSR Academy of Sciences, Moscow.
79. E. Ya. Kaplan, E. B. Burlakova, and L. V. Slepukhina, "Tezisy Konferentsii Ispol'zovanie Vliyaniya Povyshennogo Deistviya Kisloroda na Organizm, Rostov, 1970" (Abstracts of Reports at the Conference on "The Use of the Enhanced Influence of Oxygen on the Organism, Rostov, 1970"), p.42.
80. A. L. Shepelev, O. I. Pustovoitova, and L. V. Belikova, "Referaty Nauchnykh Soobshchenii III Vsesoyuznogo Biokhimicheskogo S'ezda, Riga, 1974" (Abstracts of Communications at the Third All-Union Biochemical Congress, Riga, 1974), Vol.1, p.165.
81. B. V. Leonov, N. A. Lomova, and I. A. Rudakov, Radiobiologiya, 3, 518 (1963).
82. E. B. Burlakova, E. M. Molochkina, and N. P. Pal'mina, "Trudy IX Mezhdunarodnogo Kongressa Gerontologov, Kiev, 1972" (Proceedings of the Ninth International Congress on Gerontologists, Kiev, 1972), Vol.3, p.842.
83. A. V. Alesenko, M. V. Bilenko, E. B. Burlakova, A. A. Mol'nar, V. N. Perekrest, and L. N. Shelenkova, Byul. Eksper. Biol. i Med. (in the Press).
84. I. I. Ivanov and B. N. Tarusov, Symposium, "Fiziko-Khimicheskie Mekhanizmy Zlokachestvenno Rosta" (Physicochemical Mechanisms of Malignant Growth), Izd. Nauka, Moscow, 1970, p.112.
85. N. P. Pal'mina, Candidate's Thesis, Institute of Chemical Physics, USSR Academy of Sciences, Moscow, 1968.
86. E. B. Burlakova, N. I. Dubinskaya, E. V. Koperina, and N. P. Pal'mina, Biofizika, 11, 1008 (1966).
87. E. B. Burlakova and N. P. Pal'mina, Biofizika, 12, 1032 (1967).
88. N. P. Pal'mina, and E. B. Burlakova, Biofizika, 18, 166 (1973).
89. N. P. Pal'mina and E. B. Burlakova, Symposium, "Fiziko-Khimicheskie Mekhanizmy Zlokachestvenno Rosta" (Physicochemical Mechanisms of Malignant Growth), Izd. Nauka, Moscow, 1970, p.185.
90. N. P. Pal'mina and E. B. Burlakova, Symposium, "Aktual'nye Voprosy Sovremennoi Onkologii" (Urgent Problems in Modern Oncology), Izd. Moskov. Gos. Univ., Moscow, 1973, No.3, p.86.
91. E. B. Burlakova, N. P. Pal'mina, and N. I. Ruzhinskaya, Izv. Akad. Nauk SSSR, Ser. Biol., 134 (1971).
92. E. B. Burlakova and E. M. Molochkina, Biofizika, 18, 293 (1973).
93. E. M. Molochkina and N. B. Kal'nova, Symposium, "Fiziko-Khimicheskie Mekhanizmy Zlokachestvenno Rosta" (Physicochemical Mechanisms of Malignant Growth), Izd. Nauka, Moscow, 1970, p.173.
94. E. B. Burlakova and E. M. Molochkina, Biofizika, 13, 443 (1968).

95. N. M. Emanuel', Symposium, "Khimicheskaya Kinetika i Tsepnye Reaktsii" (Chemical Kinetics and Chain Reactions), Izd. Nauka, Moscow, 1966, p.531.
96. E. B. Burlakova, Symposium, "Fiziko-Khimicheskie Mekhanizmy Avtoregulyatsii" (Physicochemical Mechanisms of Autoregulation), Izd. Nauka, Moscow, 1968, p.15.
97. E. A. Baglei, Candidate's Thesis, Kiev, 1968.
98. A. V. Alesenko and E. B. Burlakova, Symposium, "Fiziko-Khimicheskie Mekhanizmy Zlokachestvennogo Rosta" (Physicochemical Mechanisms of Malignant Growth), Izd. Nauka, Moscow, 1970, p.5.
99. E. B. Burlakova and N. P. Pal'mina, Biofizika, 18, 166 (1973).
100. E. B. Burlakova, V. T. Gaintseva, L. V. Slepukhina, N. G. Khrapova, and N. M. Emanuel', Dokl. Akad. Nauk SSSR, 155, 1398 (1964).
101. N. M. Emanuel', E. B. Burlakova, K. E. Kruglyakova, and I. I. Sapezhinskii, Izv. Akad. Nauk SSSR, 182 (1966).
102. N. M. Emanuel', I. I. Pelevina, G. A. Afanas'ev, L. P. Lipchina, and E. B. Burlakova, Symposium, "Voprosy Tkanevoi Radiochuvstvitel'nosti" (Problems of the Sensitivity of Tissues to Radiation), Izd. Nauka, Kazakh SSR, Alma-Ata, 1971, p.16.
103. E. B. Burlakova, N. M. Dzyuba, L. B. Slebukhina, and N. M. Emanuel', Symposium, "Voprosy Tkanevoi Radiochuvstvitel'nosti" (Problems of the Sensitivity of Tissues to Radiation), Izd. Nauka, Kazakh SSR, Alma-Ata, 1971, p.129.
104. E. B. Burlakova, V. D. Gaintseva, L. V. Slepukhina, N. G. Khrapova, and N. M. Emanuel', Dokl. Akad. Nauk SSSR, 164, 934 (1965).
105. E. B. Burlakova, V. D. Gaintseva, and N. M. Emanuel', Izv. Akad. Nauk SSSR, Biol., 511 (1966).
106. E. B. Burlakova, N. G. Khrapova, V. N. Shtol'ko, and N. M. Emanuel', Dokl. Akad. Nauk SSSR, 169, 688 (1966).
107. E. B. Burlakova and V. D. Gaintseva, Izv. Akad. Nauk SSSR, Ser. Biol., 764 (1971).
108. E. B Burlakova, V. D. Gaintseva, and N. P. Pal'mina, Dokl. Akad. Nauk SSSR, 213, 1451 (1973).
109. N. P. Pal'mina, V. D. Gaintseva, and E. B. Burlakova, Symposium, "Radiochuvstvitel'nost' Normal'noi i Opukholevoi Tkani" (The Sensitivity of Normal and Tumour Tissues to Radiation), Alma-Ata, 1974, p.82.
110. O. S. Frankfurt, L. P. Lipchina, T. V. Bunto, and N. M. Emanuel', Byul Eksper. Biol. i Med., 8, 86 (1967).
111. E. Bonmassar, R. Dallavalle, and G. Guilliani, Arch. Ital. Pathol clin. Tumori, 11, 245 (1968).
112. S. L Haber and R. W. Wissler, Proc. Soc. Exp. Biol., Med., 111, 774 (1962).
113. W. G. Jaffe, Exp. Med. Surg., 4, 278 (1946).
114. R. J. Shamberger and G. Rudolph, Experientia, 22, 116 (1966).
115. L. W. Wattenberg, J. Nat. Cancer Inst., 48, 1425 (1972).
116. L. W. Wattenberg, Fed Proc., 31, 633 (1972).
117. L. W. Wattenberg, J. Nat. Cancer Inst., 50, 6, 1541 (1973).
118. A. T. Cameron and S. Meltzer, Amer. J. Cancer, 30, 55 (1937).
119. S. S. Epstein, S. Joshi, J. Andre, J. Forsyth, and P. N. Mantel, Life Sciences, 6, 225 (1967).
120. A. Haddow and H. Russell, Amer. J Cancer, 29, 363 (1937).
121. M. Gubergrits and U. Kirso, Vop. Onkol., 16, 8, 96 (1970).
122. R. K Boutwell and D. K. Bosch, Cancer Res., 19, 413 (1953).
123. L. G. Lowntree, A. Stenberg, G. M. Dorrance, and E. F. Ciceone, Amer. J. Cancer, 31, 359 (1937).
124. E. B. Burlakova and E. M. Molochkina, Vop. Onkol., 20, 62 (1974).
125. I. I. Ivanov, M. N. Merzlyak, and B. N. Tarusov, Symposium, "Bioantiokisliteli, Trudy MOIP" (Bioantioxidants, Transactions of MOIP), Izd. Nauka, Moscow, 1975, Vol. 52, p.30.
126. A. V. Alesenko, E. B. Burlakova, and N. I. Dubinskaya, "Svobodnoradikal'nye Sostoyaniya i Ikh Rol' pri Luchevom Porazhenii i Zlokachestvennom Roste" (Free-Radical States and Their Role in Radiation Sickness and Malignant Growth), Moscow, 1971, p.5.
127. L. K Obukhova, Uspekhi Khim., 44, 1911 (1975) [Russ. Chem. Rev., No. 10 (1975)].
128. S. V. Konev, S. L Aksentsev, and E. A. Chernitskii, "Kooperativnye Perakhody Belkov v Kletke" (Cooperative Transitions in Cell Proteins), Izd. Nauka i Tekhnika, Minsk, 1970.
129. J P. Changeux, J. Tiery, Y. Tung, and C. Kittel, Proc. Nat. Acad. Sci., USA, 57, 35 (1967).
130. Yu. P. Kozlov, V. S. Danilov, V. E. Kagan, and M. V. Sitkovskii, "Svobodnoradikal'noe Okislenie Lipidov v Biologicheskikh Membranakh" (Free-Radical Oxidation of Lipids in Biological Membranes), Izd. Moskov. Gos. Univ., Moscow, 1972.
131. A. L. Tappel, Fed Proc., 32, 1870 (1973).
132. W B. Seufert, G. Beacheshe, and M. Belanger, Biochim. Biophys. Acta., 211, 356 (1970).
133. A. V. Alesenko, G. V. Archypova, E. B. Burlakova, V. N. Gobety, and S. F. Terechova, "Ninth International Congress of Biochemistry, Stockholm, Abstracts Book", Stockholm, 1973, p.407.
134. A. V. Alesenko and E. B. Burlakova, Dokl Akad. Nauk SSSR, 207, 1471 (1972).
135. E. M. Molochkina, E. B. Burlakova, M. I. Drhalyabova, N. P Palmina, and B. F. Sinkov, "Abstracts of Papers at the 12th World Congress of the International Society for Fat Research, Milan, 1974", p.154.
136. E. B Burlakova, "Tezisy Simp. Dokladov III Vsesoyuznogo Biokhimicheskogo S'ezda, Riga, 1974" (Abstracts of Reports at the Symposia of the Third All-Union Biochemical Congress, Riga, 1974), p.184.
137. E. B. Burlakova, "Abstracts of Papers at the 12th World Congress of the International Society for Fat Research, Milan, 1974", p.155.
138. G. V. Arkhipova and E. B. Burlakova, Radiobiologiya, 14, 828 (1974).
139. G. V Arkhipova and L. N. Shishkina, Inform. Byul., Radiobiologiya, (1975) (in the Press).
140. A. N. Goloshchapov, E. B. Burlakova, Yu. A. Zaslavskii, and N. S. Kirillov, Symposium, "Strukturnaya Labil'nost Membran i Ee Rol' v Regulyatsii Funktsional'noi Aktivnosti Kletok" (The Structural Lability of Membranes and Its Role in the Regulation of the Functional Activity of Cells), Minsk, 1974, p.25.
141. E. Oldfield and D. Chapman, Biochem. Biophys. Res. Comm., 43, 610 (1971).
142. P. Overaht and H. Träuble, Biochemistry, 12, 2625 (1973).

143. R. Coleman, Biochim Biophys. Acta., 300, 1 (1973),
144. D. Zakim, J. Biol., Chem., 245, 4953 (1970).
145. B. Fleischer, A. Casu, and B. Fleisher, Biochem. Biophys. Res. Comm., 24, 189 (1966).
146. A. N. Goloshchapov, E. B. Burlakova, Yu A. Zaslavskii, and N. S. Kirillov, Symposium, [no title given (Ed. of Translation)].
147. A. Rethy, V. Tomimosi, and A. Trevisiani, Arch. Biochem. Biophys., 147, 36 (1971).
148. J. Tobari, Biochem. Biophys Res. Comm., 15, 50 (1969).
149. G. S. Levey, Biochem. Biophys. Res. Comm., 43, 108 (1971).
150. G. S. Levey, J. Biol. Chem., 246, 7405 (1971).
151. S. M. Duttera, W. L Byrné, and M. C. Ganoza, J. Biol. Chem., 243, 2216 (1968).
152. F. A. Manzolli, J. H. Muchmore, B. Bonora, S. Capitant, and S. Bartoli, Biochim. Biophys. Acta, 340, 1 (1974).
153. F. A. Manzolli, J. H. Muchmore, B. Bonora, A. Sabioni, and S. Stefoni, Biochim. Biophys. Acta, 277, 251 (1972).
154. H. G. Rose and J. H. Frenster, Biochim. Biophys. Acta, 106, 577 (1965).
155. A. V. Alesenko, "Abstracts of Papers at the 12th World Congress of the International Society for Fat Research, Milan, 1974", p.154 [Sic! of Ref. 135 (Ed. of Translation)].

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