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ANTIOXIDANTS IN PEDIATRICS. (REVIEW)

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ABSTRACT

The development of oxidative stress with a predominance of oxidative activity is characteristic of all diseases. Significant pathological disorders in the redox system are especially characteristic in childhood due to the immaturity of the enzymatic component of antioxidant defenses. The oxidative "flash" is physiological in nature, as it is necessary for adaptation to the exposure at the beginning of the stress effect on the body. This protective reaction can lead to the depletion of the components of the antioxidant system with excessive oxidative stress, which is accompanied by damage to cells and tissues and the development of a pathological process. The phenomenon of antioxidant cooperative chains in mitochondria to protect cells from oxidative stress is considered. The emerging imbalance in the redox system justifies the replacement therapy with the use of antioxidants. The possibility of using herbal medicines in children with diabetes is being considered. The paper presents studies on the use of antioxidants in children with diseases of the respiratory tract and the cardiovascular system, with Computer Vision Syndrome, with nephrological and neurological pathologies, and with hereditary diseases. The clinical efficacy of Dimephosphone, Polyoxidonium, Mexidol and Skulachev ions is discussed. The question of the side effects of antioxidants, the duration of their use and possible combinations is considered.

KEYWORDS: oxidative stress, antioxidants, pro-oxidants, treatment, prevention, children.

A mandatory component of the pathogenesis of various diseases is the rapid reaction of the body to the impact presented to it.[1-3] Low molecular weight signaling molecules with powerful prooxidant activity are synthesized in response to stress (hypoxia) in cells by non-enzymatic means: free radicals, reactive oxygen species (ROS), reactive nitrogen species (RNS) and active carbonyl compounds (ACC).[2-4] These compounds actively oxidize biosubstrates, integrate in protein molecules, change their structure and reduce function.[5] Such an action of signaling molecules characterizes oxidative stress, which is advisable to protect against the effects of adverse factors and allows the body to avoid significant damage.[1, 4] Usually, the physiological level of reactive oxygen radicals is maintained at a low level with the help of enzyme and non-enzyme antioxidant systems involved in redox homeostasis (redox functions). Usually, the physiological level of reactive oxygen radicals is maintained at a low level with the help of enzymatic and non-enzymatic antioxidant systems involved in redox homeostasis (redox functions). Antioxidants maintain this balance by limiting the development of radical processes and damage to cell membranes.[1, 4, 6-8] With more powerful and prolonged exposure, the balance between pro- and antioxidants is disturbed, the accumulation of signaling molecules begins to act as a pathological risk factor for inflammation, apoptosis, and necrosis, especially in children due to a possible delay in the maturation of the components of the antioxidant system.[1, 2, 5, 6] Both systems in the body have specific enzyme and non-enzyme components.[7, 8]

Prooxidant systems. Prooxidant systems include NADPH oxidase, monoamine oxidase, xanthine oxidase, cytochrome oxidase and other enzymes with a powerful oxidative effect. They are quickly activated by stress hormones (cortisol, adrenaline, parathyroid hormone). These enzymes are involved in the bactericidal function of phagocytes, increasing the production of free radicals (O^{2-}, OH^{-}, NO^{-} and others) increase the production of proinflammatory cytokines: IL8, IL1, IL2, IL6, interferon-gamma, tumor necrosis factor – alpha (TNF-alpha), platelet activation factor.[4, 7-9]

Non-enzyme prooxidants (endogenous and exogenous) include elements Fe^{2+} and Cu^{2+} with variable valence and all molecules containing reactive free radicals that are incorporated into cell and tissue molecules.[1, 3] These elements, being in a free state, act as oxidizing agents, aggressively and firmly bind to oxidized "molten protein globules", "tighten" them, changing their function and

antigenic properties, which is a risk of developing autoimmune pathology.[10-12]

The Se^{2+} ion (a cation with variable valence) and the Zn^{2+} ion have antioxidant activity, in contrast to Fe^{2+} and Cu^{2+} ions. The Zn^{2+} cation competes with iron ions for the protein binding site. The aggression of Fe^{2+} and Cu^{2+} is also prevented by metallothioneins, which bind excessive amounts of these metals. The ions Se^{2+} and Zn^{2+} have antioxidant activity in contrast to Fe^{2+} and Cu^{2+} ions.[11]

A number of factors stimulate oxidative stress with increased synthesis of ROS. These are some medications (methotrexate); metals (Fe, Cu), pesticides, physical activity, emotional stress; weather sensitivity.[11, 12] It should be mentioned that an increase in motor activity in children stimulates not only the synthesis of pro-oxidants, but also the synthesis of antioxidant enzymes, normalizes the redox balance in the body.[3, 19] An important factor is pathological conditions, which will be discussed later.

Antioxidants. Antioxidants (AOs) include various compounds used by the body to reduce the adverse effects of oxidative processes, which are activated when it is necessary to adapt to various stressful influences. The issue of the use of AOs for therapeutic purposes has not been fully resolved. The significance of the disease activity for the use of AOs is discussed, the choice of specific AOs or their complexes, doses, terms of use, the search for markers of efficacy and complications when using AOs in children continues.

The significance of disease activity for the use of AOs is discussed, the choice of specific AOs or their complexes, doses, timing of use, the search for markers of efficacy and complications when using AOs in children continues.[2, 3, 8, 11, 12]

Antioxidant enzymes NADP-reductase, superoxide dismutase (SOD), catalase, glutathione-reductase protect against the outbreak of generation of ROS, RNS, ACC, from proinflammatory agents (for example TNF-alpha), from activation of apoptosis and damage to RNA.[10-13]

SOD has several variants: mitochondrial – Cu, ZnSOD, cytoplasmic – Mn, SiSOD, extracellular – Fe, SSOD. SOD converts the superoxide anion into a less aggressive H_2O_2. Cardiomyopathies, pathology of the central nervous system, respiratory system, cataracts, and a decrease in muscle mass are observed with a decrease in the activity of SOD. The activity of NADH dehydrogenase (1-st complex of the respiratory chain), succinate dehydrogenase (2-nd complex of the respiratory chain) decreases in mitochondria. However, overexpression of Cu,Zn SOD is the cause of neurotoxicity in Down syndrome[14], reduces life expectancy, increases sensitivity to hypoxia.[3, 10, 13]

The mitochondrial and nuclear catalase activity (Fe-dependent enzyme) reduces H_2O_2 production, tissue cell damage, improves myocardial contractile function.[6, 7, 10]

Glutathione peroxidase (GSH PO) is a cytoplasmic enzyme that inhibits the formation of lipoperoxides and H_2O_2, reduces the oxidation of phospholipids.[3, 11] *Glutathione-S-transferase* recycles hydrogen peroxide.[3, 12]

Peroxiredoxins are antioxidant enzymes. They utilize H_2O_2, restore hydroperoxides of lipids, polyenic fatty acids, unsaturated phospholipids, and participate in the detoxification of ROS.[15]

Metallothioneins transport zinc ions to enzymes. Zinc is part of more than 300 enzymes and transcription factors important for adaptation. Zinc deficiency increases the synthesis of proinflammatory cytokines (IL 6, TNF-alpha).[2] *Ceruloplasmin C* is an extracellular alpha–2 globulin that transports copper from the liver to tissues. It contains 3% of body copper and 90% of serum copper, participates in iron metabolism, is activated during stress and autoimmune processes, reduces ROS formation and lipid peroxidation.[11, 12]

In addition to enzyme antioxidants, there are endogenous and exogenous plant and synthetic low molecular weight AOs: glutathione, vitamins E, C, A, group B, uric acid, metal ions Se^{2+}, Zn^{2+} and others that also function as direct traps ("scavengers") of reactive oxygen species.[3, 7, 8] So, *Glutathione* (GSH) acts as a scavenger of ROS. *Succinic acid* participates in the transfer of electrons directly to complex II, bypassing complex I of the mitochondrial respiratory chain. *Niconitamide* is a cofactor of AOs enzymes (dehydrogenases) of the mitochondrial respiratory chain. *Vitamins B1, B2, B6, biotin* are cofactors of AOs enzymes. *Vitamins A, E, C, rutin, quercetin* are exogenous AOs, contribute to the protection of phospholipids of cell membranes under conditions of oxidative stress. *Vitamin A (retinol)* is a coenzyme of flavin-dependent dehydrogenases, stabilizes the structure and functions of cell membranes. L-Carnitine is involved in the transport and oxidation of fatty acids (the main oxidation substrates) in mitochondria.[7, 10] *Uric acid* acts as a trap of ROS in physiological concentrations, but has a prooxidant effect in concentrations greater than 0.25-0.3 mmol.[8]

Flavonoids are hydroxy derivatives of flavone, a large class of plant polyphenols with antioxidant properties and the ability to neutralize ROS. They regulate the activity of various enzymes. Of the flavonoids, quercetin, rutin, kaempferol, myricetin, apigenin and luteolin are most often found in food products.[3, 16, 17]

Both enzyme and non-enzyme antioxidant systems (AO systems) are necessary to maintain life by protecting against cell damage under the action of ROS.[3, 8, 18] Antioxidants also potentiate the activity of anti-

inflammatory cytokines IL4, IL10, IL13.[7, 8] Different AOs act at different stages and at different loci of the redox process. Individual antioxidants do not act by themselves, but form antioxidant chains (AO-chains) of successive reactions with an oxidized substrate, complement and enhance the effect of the previous components, and cooperate with other antioxidant compounds. Such a chain of pro-oxidant inhibitors transfers highly reactive radicals from the lipid phase (membranes, lipoproteins) into the aqueous phase, where their detoxification reaction is accelerated: RO^{2-} – tocopherol – COD – ascorbic acid - uric acid.[3, 19]

AO chains take part in electron transfer in mitochondria, and the efficiency of the chains is determined by the work of all antioxidant components. However, a significant increase in the concentration of one component of the AO chain during its exogenous management or a deficiency of another antioxidant (AO) can lead to an inversion of electron transfer in the mitochondrial respiratory chain.[3]

Antioxidants can interact with each other and have complementary effects. The one AO can protect another AO from destruction. Thus, coenzyme Q10 is able to restore vitamin E. Bioflavonoids interact synergistically with other antioxidants, preserve and enhance their activity. Vitamin E protects the beta-carotene molecule from oxidation, and acts as a synergist in combination with selenium.[19]

In this regard, a number of authors believe that the use of antioxidants in plant extracts and in combination drugs containing a complex of vitamins is more effective and safe compared than isolated components.[3, 16, 17, 19]

Oxidative stress and the use of antioxidants in the complex treatment of diseases in children. Stimulation of oxidative stress occurs in pathology associated with signs of local ischemia, which is accompanied by an increase in ROS synthesis. Free-radical pathology in children is characterized by the following clinical symptoms: lethargy, chronic fatigue, decreased response to external stimuli, joint fragility, decreased hemolytic resistance of erythrocytes, predominance of dystrophic processes over reparative ones, growth retardation, decreased immunoresistance, and a tendency to develop infection.[3, 14, 19] This clinical picture resembles the symptoms of mitochondrial dysfunction.[5, 9, 10, 20]

E.B. Menshchikova et al (2012) presented a list of more than 200 diseases for which participation in the pathogenesis of free radical pathology has been proven.[3]

Premature infants are characterized by the immaturity of the antioxidant system. The intensification of lipid peroxidation (LPO) was noted in the syndrome of respiratory disorders, neonatal pneumonia, hypoxic-ischemic lesion of the central nervous system (HIL CNS), retinopathy, bronchopulmonary dysplasia, ulcerative necrotic enterocolitis. The use of AOs (retinol, ascorbic acid, B vitamins) significantly reduced the treatment time of patients.[19, 21, 22] Weakening of antioxidant protection and strengthening processes of LPO processes is an important link in the pathogenesis of diabetes mellitus, pathology of the heart, central nervous system, lungs, kidneys, and gastrointestinal tract in older children.[10, 19, 20]

The pathogenetic role of damage to the membranes of the epithelium of the renal tissue in the formation of dysmetabolic nephropathy, calcium nephrolithiasis, tubulointerstitial nephritis, pyelonephritis has been established. The course of pyelonephritis in children was accompanied by a significant activation of LPO and a decrease in the content of AOs in the blood. The inclusion of AOs in the complex therapy of pyelonephritis shortened the treatment time and increased the duration of remission.[19, 23]

AOs are used in pediatric gastroenterology in patients with gastroduodenitis, gastric ulcer, duodenal ulcer, chronic pancreatitis. A decrease in the level of activity of SOD and glutathione peroxidase was found in children with exacerbation of chronic gastroduodenitis, which reflected the depletion of antioxidant protection. The use of an antioxidant complex (multivitamins) increased the activity of intracellular enzymes.[24]

Pronounced oxidative stress was detected in cardiovascular pathology. The use of antioxidants (coenzyme Q, a complex of water-soluble vitamins, vitamins A, E) in children with vegetative-vascular dystonia and heart rhythm disorders made it possible to achieve positive dynamics.[25]

In childhood, there are a number of chronic genetic diseases in which there is a need for the use of antioxidants. These conditions include connective tissue diseases, renal osteopathies, osteogenesis imperfecta, hereditary diseases of the nervous system[10, 20, 26], Paget's disease[27], and Down's syndrome.[14] The use of energy metabolism enzyme cofactors (nicotinamide, riboflavin, thiamine, lipoic acid, biotin) reduced the development of mental retardation, muscle weakness, lactic acidosis, ophthalmoplegia, and cardiomyopathy in these children.[10, 20, 26]

Currently, in various pathological conditions, medications and dietary biologically active additives (dietary supplements) containing natural antioxidants are used to relieve the imbalance in the pro-oxidants - antioxidants system. These are vitamins A, E, C, D, L-carnitine, flavanoids (rutin, quercetin), cofactors of AO enzymes (dehydrogenase) vitamins B1, B2, B6, niconitamide (vitamin PP or B3), biotin (coenzyme R, vitamin H, vitamin B7), lipoic acid (lipoate, α-lipoic acid, thioctic acid).[3, 16, 17, 19, 26] These natural antioxidants can be used both as a separate medicine and in a multivitamin complex.

Medicinal plants and phytopreparations containing antioxidants. The use of phytopreparations containing natural antioxidants is widely used in the treatment of diseases of the cardiovascular system, gastrointestinal tract, nervous system, and respiratory organs in both adults and children.[17, 23, 28, 29, 30]

Currently, one of the serious problems of pediatrics is the deterioration of vision in children due to the development of Computer Vision Syndrome (CVS) as a result of prolonged use of computers. The main reason for the development of CVS is the overstrain of the accommodative apparatus of the eye due to the fundamental difference between the image on paper in the form of continuous lines and the image on the monitor in the form of less contrasting discrete points, luminous and flickering (pixels). Pixels do not have clear boundaries, which leads to fatigue and the development of accommodative dysfunctions.[31]

Asthenopia is the main manifestation of CVS. Its symptoms are irritation of the eyeballs, flaccid hyperemia of the conjunctiva, sensations of "sand" in the eyes, dryness and burning, lacrimation, which leads to the evaporation of the tear film and the development of "dry eye" syndrome in users of electronic devices. Currently, in addition to the treatment of CVS, the use of antioxidants is recommended, which strengthen the vascular wall, improve microcirculation in the vessels of the eyes and visual functions.[32]

To relieve visual fatigue in children from 7 years of age, Strix® medicine and dietary supplements Strix® Forte and Strix® Omega based on Vaccínium myrtíllus fruit extract are used. They are different combinations of antioxidants (vitamins A, E, Vaccínium myrtíllus standardized extract, lutein, minerals selenium and zinc). Strix® Omega additionally contains a combination of omega-3 polyunsaturated fatty acids.[31, 32]

Phytotherapy is especially popular in the treatment of chronic diseases that require long-term and sometimes constant medication. There is an opinion that medicines from plants are safer, side effects are less common than in the treatment with synthetic drugs.[17, 19, 28, 29, 30, 33]

It is necessary to dwell on the use of medicinal plants in diabetic patients. There are medicinal plants that have hypoglycemic properties. More than 100 medicinal plants are known to reduce blood glucose levels in diabetic patients.[3, 17, 28, 29] The hypoglycemic effect of plants is diverse, but its mechanisms are not fully understood. E.B. Menshchikova et al (2012) studied the mechanisms of the antioxidant action of a number of hypoglycemic medicinal plants (*Achillea santolina* herb, *Allium cepa* bulbi, *Allium sativum* bulbi, *Aloe vera* folia, *Ananas comosus* L. folia, *Annona squamosa* folia, *Brassica oleracea* flores, *Citrus unshiu* Marc. fructus, *Laminaria japonica*, *Musa sapientum var. Paradisiaca*, *Panax ginseng* radices, *Petroselinum crispum* folia, *Plantago depressa var. Montana* folia, *Rhodiola rosea* rhizomes cum radices, *Rosa rugosa* radices, fructus, *Trifolium alexandrinum* (inflorescentia), *Viburnum dilatatum* fructus, *Zingiber officinale* Rosc rhizome. All of them not only reduced blood glucose levels, but also had an antioxidant effect. Plant extracts stabilized biological membranes, reduced the level of peroxidation products in the blood and tissues (malonic dialdehyde, diene conjugates, glycated Hb, lipid hydroperoxides, NO).[3] Plant extracts increased the content of the SH group, glutathione, and the activity of antioxidant enzymes in the blood and tissues (liver, kidneys, heart). *Laminaria japonica* reduced the activity of xanthine oxidase in the liver. *Panax ginseng* radices reduced apoptosis, the activity of cyclooxygenase-2 and 3-nitrotyrosine in the kidneys. *Plantago depressa* repaired damage to the pancreatic islets of Langerhans. *Zingiber officinale Rosc*. and *Viburnum dilatatum* reduced the level of glucose in the blood and tissues (liver, kidneys, pancreas).[3]

Many antidiabetic herbal remedies have been developed that contain antioxidants. Effective medicinal plants for diabetes are also *Centáurium spp., Gnaphálium uliginósum*, *Galéga officinális*, *Menyanthes trifoliáta*, *Cichórium íntybus*, *Althaéa officinális*, *Arália eláta*; *Sophóra*, *Phaséolus vulgáris*, *Fragária vésca*, *Rubus caesius, Rubus fruticosus*, *Morus nigra and Morus alba*, *Sórbus aucupária*, *Júglans régi*, *Zingiber officinale* Roscoe.[28, 29, 33 34]

Plant-based drug Arphasetin-E (Russia) is effectively used to treat mild to moderate type 2 diabetes in adults and children over 12 years of age.[35] Arphasetin-E and antidiabetic herbal preparations reduce blood glucose and cholesterol levels, increase carbohydrate tolerance, enhance the glycogen-forming function of the liver, improve the functions of the pancreas, liver and kidneys, relieve swelling.[3, 17, 28, 35, 36] Dietary supplement Nutri-Cleanse (Vitamax, USA) showed a good antidiabetic effect in patients from 14 years of age. The complex normalized the level of cholesterol and glucose in the blood, the work of the gastrointestinal tract, bile ducts and pancreatic ducts, kidneys, respiratory tract, and actively removed toxins.[36]

Antidiabetic herbal medicines can be used as monotherapy in combination with a diet only for mild type 2 diabetes. The use of medicines from plants by other patients is possible only as an addition to special antidiabetic drugs (insulin, sulfonamides, metformin). Doses of these drugs should be reduced carefully against the background of herbal medicine.[17, 28]

However, mention should be made of Evert A. B., et al (2014), in which the authors believe that there is no conclusive evidence of the efficacy of medicinal plants to normalize blood glucose levels in diabetes mellitus. The authors indicate that many plant preparations are not standardized, differ in the content of active components

and can interact with other drugs.[37] It is important to note that the chemical composition of plants depends on their geographical origin, collection process and storage conditions.[29, 34]

V.A. Kurkin (2016) also draws attention to the fact that at present there remains the problem of standardization of medicinal plant materials and herbal remedies, especially those containing phenolic compounds.[17] Given the high popularity of phytotherapy in the complex treatment of diseases, work should be carried out to improve the quality of herbal medicines, to control the content of active ingredients and to objectively assess clinical efficacy.

Synthetic atioxidants. In addition to natural antioxidants, synthetic antioxidants are also used to correct disorders of the redox system in diseases. Synthetic antioxidants (Russia) used in medicine include Dimephosphone, Polyoxidonium, Mexidol and Skulachev ions.

Dimephosphone reduces lactate acidosis, stimulates AO enzymes, stabilizes the phospholipid layer of cell membranes, reduces ROS synthesis, increases ATP synthesis in mitochondria, improves tissue respiration.[10, 26, 38]

Polyoxidonium (Azoximeri bromidum) is an antioxidant, detoxifier, immunomodulator. It binds excess iron, reduces the synthesis of free radicals, of pro-inflammatory cytokines and the inflammatory response, stabilizes cell membranes, increases the activity of phagocytes. It is used in children from 3 years of age for the treatment of influenza, acute respiratory viral infection, inflammatory processes of the oropharynx, allergic diseases, including hay fever and bronchial asthma.[3, 39]

Mexidol is a powerful antioxidant. The active substance is Ethylmethylhydroxypyridine succinate. The drug is effective in the complex treatment of neurological diseases (acute cerebrovascular accidents, traumatic brain injury and its consequences, dyscirculatory encephalopathy in the decompensation phase, prevention of dyscirculatory encephalopathy).[40] The drug is also used in the treatment of patients with acute ischemic stroke[41], treatment of cognitive impairment, anxiety[42], hypothyroidism[43], multiple sclerosis[44], cardiovascular diseases.[45] Mexidol is used mainly in adults.

There are isolated reports of the successful use of mexidol in newborns with intrauterine growth retardation in hypoxia - an ischemic lesion of the central nervous system (HIL CNS).[46] J.M. Akserova (2011) found that infants had an antioxidant effect on body cells, including endotheliocytes.[46] Research by Levitina (2001) showed that the use of mexidol in newborns with HIL CNS reduced motor disorders, manifestations of increased neuro-reflex excitability and autonomic dysfunction, quickly stopped morphological changes according to neurosonography by the end of the acute period of the disease. There was an increase in the activity of antioxidant enzymes, a decrease in the level of diene conjugates, normalization of the spectrum of phospholipids, and restoration of the structural and functional modification of cell membranes.[47] One of the recent studies has shown the efficacy and safety of mexidol in the complex treatment of attention deficit disorder in children from 6 to 12 years old.[42] Allergic reactions are possible in children when using Mexidol.

Skulachev ions (SkQ-1; plastochinonyldecyltriphenylphosphonium bromide). SkQ-1 these lipophilic organic cations act in mitochondria as direct inhibitors of ROS, a "molecular electric locomotive" of electrons in the respiratory chain [48]. SkQ-1 is part of Vizomitin eye drops, which is a keratoprotector that reduces the risk of developing age-related cataracts. It is used from the age of 18 with corneal-conjunctival xerosis and the initial stage of age-related cataract.[48] Clinical trials of eye drops with SkQ1 Vizomitin Forte for age-related macular degeneration and the first phase of a clinical trial of Vizomitin Ultra are underway now in Russia.

E.Yu. Plotnikov et al found that SkQ-1 has a pronounced nephro- and neuroprotective effect.[49]

SkQ-1 has also been shown to stimulate wound healing. This opens up the possibility of using the drug in surgery in the future.[50] There are no data from clinical studies in patients under 18 years of age.

When carrying out antioxidant therapy, it must be remembered that antioxidants can have side effects as a result of increased sensitivity of the body to the drug and in case of its overdose (in particular, the therapeutic concentration of tocopherol is slightly lower than its toxic concentration). An overdose of the antioxidant reduces the activity of NADPH oxidase of phagocytes and leads to an increased risk of bacterial infections.[8, 19, 21] The effect of cumulation is rarely observed.[3, 11, 19] It is known that ascorbic acid, tocopherol, polyphenols in the presence of certain concentrations of heavy metals can act as prooxidants.[11]

CONCLUSION

Any diseases, especially in childhood, are characterized by a violation of redox processes in mitochondria with a predominance of oxidative activity. This phenomenon is necessary for the body to adapt to the development of stress, the inclusion of inflammatory and proliferative processes, and the elimination of damaged cells. Oxidative stress sharply depletes the enzymatic and non-enzymatic factors of antioxidant protection, disrupts the balance between pro- and antioxidants. It becomes obvious that it is necessary to maintain a normal level of redox balance with the help of exogenous natural and synthetic antioxidants that maintain this balance, limit

the development of radical processes and damage to cell membranes. Now it is recommended to use in children with various pathologies associated with severe oxidative stress, natural antioxidants, which are the most studied and safe. It is optimal to use in sick children complexes that are balanced in antioxidant components for the prevention and remove of oxidative stress. This problem has not yet been fully resolved due to the lack of knowledge on this problem and the constant revision and refinement of previously obtained information.

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