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«TRAINING ACTIVITIES ON FOOD CONTAMINATION CONTROL AND MONITORING WITH SPECIAL REFERENCE TO MYCOTOXINS»

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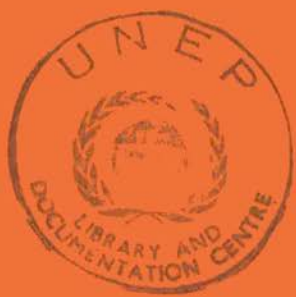
# ALIMENTARY TOXIC ALEUKIA

## (EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, THERAPY)

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# ALIMENTARY TOXIC ALEUKIA

(Epidemiology, etiology, pathogenesis, clinical manifestations, therapy)

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ATA epidemiology

First cases of alimentary-toxic aleukia (ATA) were reported in the USSR in 1932; in 1933 it was revealed in Kazakhstan, in 1934 in Sverdlovsk and Chelyabinsk oblasts, in Bashkiria, West Siberia; Kazakhstan and Kirghizia. In 1935 the disease spread to the Saratov oblast, in 1941 - in the Altai kraj, in 1942 - in Molotov, Kirov and Chkalov oblasts, in 1943 - in the Saratov oblast and in Kazakhstan, in 1944 - in Kazakhstan and Chkalov oblast. Then the incidence dropped abruptly, and sporadic cases alone were registered in certain regions of the USSR from 1951 to 1954. This apparently was the result a thorough large scale preventive and agrotechnical efforts.

The majority of ATA outbreaks occurred between the 50th and 60th geographical parallels; the outbreaks began in April or the beginning of May, reaching the peak in May - mid June and terminating in July, and, as an exception, in October and December. This was due to the consumption by the population of cereals and produce of their procession which wintered in the field. Even in sporadic ATA cases among urban population it was possible to trace the cause: the purchase and consumption of grain, groats or flour of unknown origin in the market. More than that, the toxic grain and flour were accidentally brought to warehouses, mills and bakeries.

It was not always that the cereals, left in the field, became toxic after wintering. This occurred only when intact

rooted plants wintered standing erect, or in swaths, heaps, sheafts, unbundled or in cut spikes and scattered grain because of an inadequate harvesting. The toxic cereals were mainly planted in lowlands whereas on elevated plots they were absent.The accumulation of toxicity in cereals and ATA outbreaks were mainly promoted by autumn rains and warm heavy snows. And quite the opposite a dry autumn and a cold snow-scarce winter prevented ATA outbreaks. All this points to the significance of the weather conditions and the topography which promote the accumulation of the toxic matter in wintering cereals. The wintering cereals differ as to the level of their toxicity. We assume millet to be the most toxic; next intoxicity is buckwheat, whereas wheat, rye, barley, oats, rice and other cereals are less toxic. This is confirmed as well by prominent Soviet mycotoxicologists M.M. Pidoplichko and V.I. Bilay (1946), they believe millet and buckwheat that wintered under the snow to be most strongly affected by toxic fungi,wheat and rye being affected lesser. In appearance the wintered cereal grain, in particular millet, differ from normal grain by being "puny", friable and lighter, with a damaged germ. They mold rapidly and are covered with black spots. It is sometimes very difficult, however, to differentiate between the wintered and normally harvested grain without a laboratory analysis. The simplest technique is the germination test. The wintered toxic grain has a low germination power, if any at all. M.M. Pidoplichko and V.I. Bilay ascertain that 30-80% of millet grain retain the germination capacity after the wintering in stacks and shocks, 25-60% - when intact rooted millet wintered standing, and 3-1% and less - in swaths and heaps.

The experiments conducted by S.G. Mironov and A.Z. Ioffe (1947) on an experimental field with wintered millet revealed that the cereals acquired toxic properties only during the winter-spring season and manifest them with the thawing of snow. Our previous findings also confirm that the cereals obtained from under the snow before thawing failed to induce ATA after being eaten.

These findings have been confirmed by V.G. Geimberg, A.M. Baousenko and G.K. Shlygin on an experimental field in the area previously affected by ATA. Samples of millet cereals collected from the field in different winter and spring months failed to reveal any toxicity.

The ATA incidence was the highest among the individuals aged from 10 to 40. The female and male incidence was almost the same; infants contracted the disease only when fed the produce of the wintered grain. The disease never occurred in breast-fed infants.

The most widespread test for toxicity of wintered cereals is the test on rabbit skin. I.S. Pentman discovered in 1934 that the ether and alcohol extracts of the millet that wintered in the field, inducing ATA disease when eaten, caused a marked inflammatory reaction, resulting in necrosis when applied to the epilated rabbit skin. In 1942 this test was widely used by A.Kh. Sarkisov, and in 1943 - by V.V. Efremov to determine the toxicity of several samples of the wintered grain and the produce of its procession (groats, flour, etc.). This substantiated the official approval of the skin test as a toxicity criterion for the wintered cereals.

In experiments on swine in 1944 V.V. Efremov and L.S. Lyass obtained stable leukopenia and granulocytopenia by feeding the

animals with the toxic wintered millet. In 1945 A.Kh. Sarkisov et al. were the first to reproduce clinical symptoms of ATA on cats fed with the millet, contaminated with Fusarium sporotrichioides, Fusarium sporotrichiella toxic fungi.

These data were confirmed by Yu.I. Ruoinshtein in experiments on cats in 1946 and on monkeys in 1947. The disease, induced in the latter case was identical to human ATA both clinically and pathohistologically.

ATA etiology

The chemical nature of Fusarium sporotrichiella toxins was studied by L.E. Olifson et al. in 1965-1972. The toxin(s) was referred to the group of sterolactones. An amorphous white powder, called sporofusarin was obtained from the ethanol-chloroform extracts of the fat-free grain contaminated with F. sporotrichiella. This preparation contained two molecules of glucose and one - of ribose per one aglycone molecule; the melting point is 245-248°C, it is readily soluble in water, methyl and ethyl alcohols.

L.E. Olifson et al. (1971, 1972, 1974) revealed that sporofusarin administration to different animals (mice, cat, rabbit, frog) promoted a rapid development of toxemia, similar to that following the consumption of the grain, contaminated with Fusarium sporotrichiella. The cats exposed to 0.1 $DL_{100}$ of sporofusarin, developed characteristic ATA symptoms the next day after its administration.

Olifson et al. showed that the F. sporotrichiella metabolite - sporofusarin was apparently the cause of ATA. They proposed in 1975 a chromatographic method for the determination of the grain toxicity with a thin-layer chromatography and luminescent analysis. According to their data, sporofusarin is

a highly toxic substance; the $DL_{50}$ for mice in an intraperitoneal administration was 22.1 mg/kg. A higher dose of 25-30 mg/kg, was lethal for 100 per cent of the animals within 4-6 hours. Rabbits perished 30-60 min after an intravenous injection of 5 mg of the toxin.

ATA pathogenesis

Local effect of the ATA toxin

Mycotoxin(s) Fusarium sporotrichiella present in the wintered cereals induces local and general effects when accidentally consumed by man. The local effect is expressed in the signs of irritation similar to those of a burn in a person with a normal reactivity. Alongside with an unusual bitter or insipid taste, the patient often has a burning sensation in the mouth, palate, fauces, esophagus and stomach, or a loss of taste, tongue numbness, nausea and vomiting. These symptoms disappear rather rapidly. Pathohistology following the application of the toxic grain extract on the epilated rabbit skin was described by A.I. Strukov in 1947. An inflammatory reaction with dominating exudative-proliferative symptoms and the accumulation of an enormous number of leukocytes were evident in this case without the general involvement of the whole organism. The effect on man is similar. The pathogenesis of the general effect of the wintered cereals toxin on man lies in a severe intoxication. There seems to be no total insusceptibility to the toxin; however, the degree of the body sensitivity to the toxin differs and is defined by many as yet undeciphered factors, among which the preceding qualitatively and quantitatively unbalanced nutrition is of paramount importance. Asthenic and dystrophic individuals were the first to contract the disease,

and its course was severe. The nutrition balanced as to biologically valuable proteins and vitamins, particularly of group B, and C (meat, milk, especially sour milk produce, eggs, vegetables and greens) may attenuate to a certain degree the effect of the toxin in the wintered cereals. The ATA toxin apparently possesses a cumulative effect. Those individuals who consumed products from the wintered grain at lengthy intervals still contracted the disease and developed all ATA stages. Further we shall see that early disturbances of cardiac activity can be also attributed to the toxin's cumulative effect.

ATA mycotoxin(s) which accidentally gets into the organism with food is absorbed in the gastrointestinal tract; accumulates in the organs and tissues and is then excreted with urine, and, to a lesser degree, with feces. The severity of the disease and its course are determined by the amount of the toxin and different reactive properties of different organs and tissues to this toxin. Fresh evidence has been obtained of late in respect to the damaging mechanism of the ATA mycotoxin on the subcellular structure membranes and its particularly harmful effect on the lysosomal membranes (L.A. Pokrovksky, V.A. Tutelyan, L.V. Kravchenko, 1976, and others). According to them the ATA mycotoxin is a typical toxin of lysosomal membranes.

General ATA toxin effect. Hematopoiesis disturbance

The organs of hemopoiesis and those controlling this process are the least resistant to mycotoxins of the wintered cereals. At the same time they are the main target of intoxication. This is reflected in the names of the disease in literature: alimentary agranulocytosis (M.A. Lyass, 1940), alimentary aleukia (I.V. Davydovsky and A.G. Kastner, 1935), alimentary

panhemoparesis (A.L. Myasnikov, 1935), cereal aplastic mesenchymopathy (M.A. Koza, 1944), acute myelotoxicosis (E.M. Manburg and E.A. Rakhalsky, 1947). Different levels of reactivity on the part of the bone marrow morphological elements can be traced by a detailed analysis of the hemopoietic organs affected by ATA. The involvement of the myeloid tissue results in irritation, which is followed by leukopoiesis inhibition manifested in the development of the agranulocytosis of the Schultz type and the diminishing absolute granulocytes count, followed by a more or less sharp inhibition of leukopoiesis, erythropoiesis and thrombopoiesis, resembling the onset of Frank type aleukia. However, these reactions are not stable; they are more or less individual not only in one and the same ATA outbreak, but also in different ATA outbreaks. This seems to be connected both with differences in the reactive capacity of patients and the amount of the toxin that penetrated into the organism. Some ATA investigators, M.A. Koza (1944) being among them, reported a serious bone marrow impairment in this disease in particular a reduced regenerative capacity and almost total arrest of hemopoiesis (panmyelophthisis); this allowing Koza to call the disease a "cereal aplastic mesenchymopathy", that is an areactive irreversible condition of the mesenchyma. As far as 1935 I.V. Davydovsky reported regenerative phenomena both in the erythroblastic and myeloid elements even in the aplastic bone marrow and emphasized that this points to the possibility of the reversibility, of the processes occurring in some cases rather soon. A valuable contribution to the study of the ATA pathogenesis was made by A.I. Strukov and M.A. Tishchenko (1944, 1947) who convincingly demonstrated that the hemopoiesis disturbance developed against the background of the viable bone marrow.

In ATA it is not the bone marrow that is destroyed (panmyelophthisis), but only a temporary, quite reversible inhibition and disturbance of hemopoiesis occurs.These morphological data are confirmed by leukocytosis that replaces previous leukopenia when the ATA patients contract some intercurrent infection,for example, pneumonia. Infection seems to be a stimulant, lifting the temporary blockade of the bone marrow, A.I.Strukov (1947) and B.V. Alyoshin (1947) assumed that the toxin of the wintered cereals mainly affected not the bone marrow, but the extramedullary mechanisms of hemopoiesis regulation (the vegetative nervous and endocrine systems). We consider, however, that in the conditions of general and severe intoxication the toxin affects both the bone marrow and the extramedullary mechanisms, regulating hemopoiesis.

In ATA the activity of mesenchymal cells does not diminish. The reticuloendothelial system maintains its absorptive capacity even at the terminal stages of the disease; the compensatory hyperplasia of reticular elements is more intensive. This was also evidenced by B.A. Alyoshin in his experiments of aleukia reproduction in rabbits with benzene. He states that in this case there was no general involvement of the reticuloendothelial system, but only a selective transformation of the reticular tissue areas, located in the foci of hemopoiesis. A decreased body resistance in ATA is due not to the areactivity of the reticuloendothelial system, but to the disturbances of other body protective properties, for example, to the absence of neutrophils with phagocytic functions. As is rightly stated by A.I. Strukov and B.V. Alyoshin, the body remains biologically protected in ATA. Naturally, we back this opinion, as even in most severe conditions with the drop of the leuko-

cyte count to 300-200 per c.mm a sudden regenerative shift and rapid recovery were sometimes observed (V.V. Efremov, 1944, 1948). Similar evidence was obtained by Q.L. Gordon and L.M. Levitsky (1945). Thus, the opinion of Koza holding that the aplastic condition of the mesenchyma can be the basis for ATA pathogenesis, is erroneous. An aplastic condition, if any, is an exception.

General ATA toxin effect. Hemorrhagic diathesis

Another significant and a rather complicated problem of the ATA pathogenesis is the disclosure of hemorrhagic diathesis in this disease. Undoubtedly, the major role here is played by the disturbance of thrombocytopoiesis resulting in severe thrombocytopenia. It would be erroneous to assume that the thrombocytopoiesis disturbance is a comparatively late phenomenon. All depends on the individual resistance to the nature of the toxin. In some cases we encountered early disturbances of erythropoiesis and thrombocytopoiesis.

Hemorrhagic diathesis, however, can hardly be caused by the thrombocytopoiesis disturbance alone. A toxic destruction of capillaries resulting in hemorrhagic phenomena, also seem to be of some significance in this case. Decreased blood prothrombin and, hence, vitamin K deficiency, revealed by V.M. Karatigin and Z.I. Rozhnov (1947), can also play a certain role in this.

It is quite possible that a profound reconstruction of the functional capacities of body tissues under the effect of the wintered cereals toxin affects not only the bone marrow, but also the extramedullary apparatus, regulating hemopoietic

processes (vegetative nervous and endocrine systems) as A.I. Strukov and B.V. Alyoshin (1947) assumed. The same concerns the CNS whose functions are also disturbed in ATA, as can be seen below.

The damage of lysosomal membrane of the heomopoietic organs caused the destruction of the formed elements in the bone marrow with the symptoms of leukopenia, lymphopenia, thrombocytopenia and erythrocytopenia (A.A. Pokrovsky, V.A. Tulelyan, L.V. Kravchenko, 1976).

General ATA toxin effect. Neurotropism

In 1943 we assumed that the wintered cereals toxin is a neurotropic poison. The evidence collected by a number of neuropathologists (Z.A. Gurevich, 1944; M.M. Kovalev, 1944; A.S. Poznansky, 1947, and others) points to the fact that the nervous system is severely affected in ATA. They reported mainly the early vegetative changes, apparently induced by the disturbance of the vegetative centres of the hypothalamic area; acute encephalites, encephalic, meningeal, and meningoencephalic syndromes at the anginal stage. This was also confirmed by a whole number of phatoanatomists who identified morphological changes in the nervous system. M.A. Koza (1944), V.A. Zhukhin (1945) and others described destructive lesions of the brain neural elements in ATA. A.I. Strukov revealed pronounced lesions in the sympathetic nervous system, both in its trunk and in the ganglia of an acute ganglionitis type. Thus, the wintered cereals toxin is definitely a neurotropic poison.

General ATA toxin effect. Necroses development

In the process of a profound body reconstruction in ATA even an insignificant stimulus is sufficient to cause necroses

with the tissue invasion by microbes, that are usually present on mucosa or the skin. A minor injury in the form of a scratch, abrasion, cut, pressure on bone prominences (sacrum and trochanters) in bed-ridden patients can be a trigger mechanism. Erosions and ulcers on the gastrointestinal tract mucosa can promote a deep necrosis. Concomitant infection by itself, can play an important role in case of abrupt changes in the reactive capacity of the body tissues. At the anginal-hemorrhagic stage of ATA the metabolites of pathogenic or conditionally pathogenic microbes, usually present on mucosa of the mouth, fauces, pharynx, etc. can trigger tissue necrosis. This was justly stated by M.A. Koza (1944). The effect of some drugs (sulfamide compounds penicillin, salvarsan, etc.) on necrotic angina and other pathological processes in ATA is apparently due to the bacteriostatic effect exerted on previously harmless microbes. Only in the body poisoned with the wintered cereals toxin did these microbes begin to play an active role in the development of necrosis.

ATA pathological anatomy

According to a number of works, pathoanatomical changes in ATA mainly concern the third, anginal-hemorrhagic stage, of the disease, and only partially, the fourth stage - that of the regeneration and possible complications. There is no evidence as to the pathomorphology of the first and second ATA stages in pertinent literature, which is only natural, since at these stages patients could die only by chance (accidents, intercurrent disease, etc.). The changes at the third ATA stage that were comprehensively described by I.V. Davydovsky and A.G. Kastner (1935) were substantially supplemented by

A.A. Koza (1944), A.I. Strukov and M.A. Pishchenko (1947) and others. They mainly consist of hemorrhagic diathesis, necrotic processes and bone marrow changes. I.S. Pentman (1935) found rigor mortis to begin earlier in the individuals who died as result of ATA; these corpses had a lower propensity to putrefaction, as compared to the corpses of those who died of other diseases. Such corpses had different degrees of hemorrhagic diathesis with punctate and diffuse hemorrhages both in the skin, the muscles and viscera. Necrotic processes begin from the surface in the areas of the greatest lymphoid tissue accumulation: at the root of the tongue, on the soft palate, in the pharynx, tonsils, and the gastrointestinal tract, penetrating deeply, with necrotic tissue decomposition. Microscopy fails to reveal usual inflammatory reaction around the necrotic foci. There are no leukocytes, but mainly alternative changes with histiocytes proliferation. Necroses can also occur at the sites of former hemorrhages. This is in favour of profound disturbances of the tissue trophism in ATA. The highest rick is presented by necrotic foci in the pharynx, larynx, bronchi, esophagus, stomach and intestine. Necrotic foci in the pharynx and larynx can lead to aspiration pneumonia and asphyxia due to edema and laryngeal occlusion by the gangrenous tissue masses or coagulated blood. Pneumonia as a complication of ATA is rather of frequent occurrence (50-60%), and is expressed as focal or confluent bronchopneumonia; gangrenous decomposition in the centre of a pneumonic focus is seen rather often. Necrotic foci in the esophagus, stomach and intestines can lead to severe hemorrhages. Esophageal necrosis with the symptoms of diphtheritic esophagitis is most incident; next in frequency is the gastric affection of the diphtheritic gastritis type, resembling a burn by caustic

agents. We have seen such gastrites at autopsy. Necrotic foci are present both in the small and large intestine.

The third major link in the ATA pathological anatomy is represented by the bone marrow changes - in the flat, not in the tubular bones. The microscopy reveals greater or lesser disappearance of the myeloid elements and their substitution by reticuloendothelial cells - hemocytoblasts. The changes in other organs are less characteristic: a moderate degree of organic parenchymatous degeneration and hepatic hemosiderosis. The spleen ic not enlarged. Sepsis is rare. The most frequent causes of death in ATA are general severe toxemia, asphyxia, severe hemorrhage, pneumonia. Although pathoanatomists had to deal with the most severe ATA cases, they (I.V. Davydovsky, 1935; A.I. Strukov and M.A. Tishchenko, 1947) stated quite explicitly that the pathological processes in this disease were reversible, and that recovery with proper treatment was possible.

ATA clinical symptoms, Diagnosis of the disease

The anamnesis was thoroughly recorded at the initial examination of a patient, a suspect of ATA. Of utmost importance was whether the patient had ever eaten, even once, the grain (ears) collected in spring. What were these cereals? How much grain (ears), where and when did the patient gather it? Did he exchange this grain for normal one? If not, how many times did he and members of his family eat the toxic grain? How much grain had been eaten by his kin and in what form (gruel, pancakes, flat cakes, bread, etc.)? Did the patient eat the toxic grain alone or mixed with normal flour, and in what proportions? How much toxic grain has remained? Did any other of his

kin contract the disease? Had he and his kin gather grain of the wintered crop the previous years, did they eat this grain and did any of them contract ATA? If the patient did not gather the grain ears, where did he get the suspected grain - at the market or elsewhere?

Then the patient's temperature was measured. Among the complaints attention was primarily paid to such general symptoms as weakness, headache, "heaviness" in the head, and "mental fog" (stupefaction). The skin was examined for eruption. At the initial stage of the disease the rash is not easily discernible and resembles flea bites. Mouth and fauces were examined thoroughly with due attention paid to the mucous membranes, hyperemia and edema of the anterior palatine arches, suvula and the sublingual fold, as well as to the presence of punctate hemorrhages on the mucosa, the coated tongue, stomatitis with mucosal pallor, and to cell formation and their rejection. Tonsils were thoroughly examined for the catarrhal, follicular or necrotic angina; the soft palate and faucial lesions were looked for. Patient's complaints of irritation, burning sensation and pain in the mouth, pharynx and esophagus, pain in the stomach and intestine, nausea, vomiting, diarrhea or constipation, were duely noted. Special attention was paid to complaints and disturbances concerning the central and vegetative nervous systems and mental disorders: apathy, depression or hyperexcitability, insomnia or somnolence, mydriasis, hyperhydrosis or dryness of the skin. Early changes in the cardiovascular system were identified: techycardia, systolic murmur above the apex, hypotension. Blood was examined: leukocyte and erythrocyte count, differential leukocyte count, hemoglobin and the E.S.R.

Basing upon the pathogenesis ATA is divided into four stages:

the first is the stage of acute intoxication, the second - of latent development of the disease (leukopenic stage); the third - of clearly expressed clinical symptoms (anginal-hemorrhagic stage); and the fourth stage-that of recovery and possible complications.

The first ATA stage. Acute toxemia symptoms

Both local and general symptoms can develop immediately or several hours after eating a meal prepared of the toxic wintered grain. Local symptoms can be represented by a bitter or insipid taste in the mouth resulting in the full loss of taste, tongue numbness or swelling, a burning sensation in the mouth, fauces and pharyns, pain on swallowing. Mouth examination displayed mucosal hyperemia and edema, particularly of the anterior palatine arches, soft and hard palate, uvula and the sublingual fold. Individual punctate hemorrhages were encountered. In less acute cases focal or general mucosal pallor was registered; some areas had desquamation of the epithelium in the form of white membranes on the lips, gums, cheek mucosa, hard and soft palate, resembling a scald by boiling water, weak acid or alkali. Usually the tongue was whitish coated.
When no more toxic grain was eaten the above symptoms disappeared within 2 or 3 days, but they reappeared as soon as the patient started eating this grain again; one never gets accustomed to the toxin effect. Severe forms of ATA followed even a single toxic grain consumption. Cases with comparatively mild general toxemia were more frequent than acute forms. General toxemia was expressed in weakness, malaise, rheumatic-like pain, hyperhydrosis, a condition, resembling alcoholic intoxication, insomnia. These symptoms usually disappeared within

3 to 5 days.

Occasionally there were symptoms of acute food poisoning resulting in acute esophagitis, gastritis or gastroenteritis, accompanied by hypersalivation, nausea, vomiting, pain in the esophagus and stomach, diarrhea, and fever up to 39°C; there was also giddiness, headache, mydriasis, tachycardia, cyanosis, limb coldness, and sometimes convulsions. Hemorrhagic diathesis with skin and mucosal hemorrhages and epistaxis was also noted.

In such cases the blood count can show hemopoiesis shifts as soon as in 1-4 days: the leukocyte count could fall; to 2,000 per c.mm. This was accompanied by neutropenia and relative lymphocytosis, thrombocytopenia and some E.S.R. acceleration (V.I. Chilikin, 1945; E.M. Manburg, 1947). The disappearance of the above symptoms and the regeneration of the blood took place rather slowly, during one-three weeks. The acute poisoning by toxic grain can be due to (1) marked changes of the body reactive capacity (unbalanced nutrition with a considerable deficiency in biologically valuable proteins and vitamins, in particular of vitamin C and group B vitamins, and general low caloria content of food; (2) high grain toxicity; (3) great quantity of the consumed grain. At the initial stage the differential diagnosis of an acute poisoning was facilitated by an adequate anamnesis.

Second ATA stage. Leukopenia.

With the subsequent consumption of the toxic grain the disease progresses and within several days enters the second stage. Local symptoms can recur, as there is no habituation to the toxic product. The patients either pay no attention to

the changes in the mouth, or try to somewhat alleviate pain. A comprehensive study of the leukopenic stage was of primary significance for physicians, since it was at this stage that the institution of therapeutic measures guaranteed maximum success. However, this period is the least luscident with regard to the clinical symptoms, pathological physiology and morphology.

The duration of the ATA leukopenic stage was different: sometimes it lasted 2-3 weeks or could go on for 6-8 weeks and even 3-4 months, depending on the patient's reactive capacity on the toxicity and the amount of the wintered grain eaten. At this stage the clinical symptoms were not clearly manifested and were, thus, often overlooked. Clinically, the leukopenic stage developed with the domination of the central and vegetative nervous systems symptoms (V.V. Efremov, 1944, 1945, 1948). The patients complained of weakness, spathy, fatiguability, vertigo, headache, poor sleep or, on the contrary, somnolence tachycardia developed even under minor physical strain. In a number of cases they had an inversed Ashner's symptom - the pressure exerted on the eyeball failed to reduce the pulse-rate. The patients' skin was pale, dry, with an earthly colour and the symptoms of late dermographism; mydriasis was vividly pronounced. Some of the patients had a lowered blood pressure and diminished heart sounds. The ECG revealed changes in the T-wave which became diphasic in all the three leads (Z.I. Malkin, N.N. Odelevskaya, 1945). Subfebrile conditions lasted 2-3 days and then disappeared. The hemopoiesis disturbance began several days after eating the wintered grain products and slowly developed into the progressive inhibition of leukopoiesis, erythropoiesis and thrombocytopoiesis. Leukopenia, neutropenia and relative lymphocytosis

gradually increased. At the same time the erythrocyte and thrombocyte count dropped. In certain cases hemoglobin lowered parallel with the erythrocyte count. In other cases, however, it persisted at a relatively high level for a long time, progressive anemia acquiring a hyperchromic nature in this case. The leukocyte count differed essentially during the second ATA stage. There were discrepancies, between the patients' subjective complaints and the peripheral blood leukocyte count. Sometimes these patients having 3,000-2,000 c.mm leukocytes and even less continued to walk and to work, until the symptoms of hemorrhagic diathesis, fever and progressive weakness forced them to become bedridden.

When timely and adequately treated the leukopenic stage was usually followed by recovery.

Third ATA stage. Manifest clinical symptoms (anginal-hemorrhagic stage)

In case due measures (hospitalization, etc.) had not been taken in time the disease progressed into its third stage, usually within two or three(rarely six or eight) weeks after the wintered grain had been eaten. The third ATA stage is characterized by acute symptoms: rash, hemorrhages, necrotic angina, high temperature and tachycardia. At the end of the leukopenic stage the patients discovered petechial rash of scarlet or dark cherry colour on the breast, the internal surfaces of the brachial part of the upper extremities, the lateral abdominal areas, the internal femoural and innominate regions
The rash had nothing to do with the hair follicles of the skin and this differed it from petechial rash of scurvy; it was polymorphic and labile. At first the rach spots were rather

small; later they assumed the size of lentil or haricot beans, their colour turning into dark violet, or nearly black. The rash, the first and an obligatory symptom of the anginal-hemorrhagic stage, the first and an obligatory symptom of the anginal-hemorrhagic stage, usually preceded angina. The leukocyte count continued to drop. Granulopenia, neutropenia and relative lymphocytosis increased to 80% and higher; the toxic granularity of the remaining granulocytes was almost 100%. The E.S.R. mounted to 40 mm/h. The erythrocyte count dropped to 2.5-2.0 million, and hemoglobin - below 40%, followed by the development of micro- and macroanisocytosis and poikilocytosis. The plateled count decreased to 80,000-20,000 per c.mm and lower. Hemorrhages occurred with the platelet count of 50,000 per c.mm; the bleeding time increased and the blood coagulability was delayed. The clot retraction time increased. The Rumpel-Leede (rubber bandage) and Mozer (pinch) tests were positive in approximately half of the cases, as opposed to scurvy.

There were hemorrhages from the nose, pharynx, esophagus, intestine, kidney, urinary bladder and uterus. Being one of the gravest ATA symptoms hemorrhages can be prolonged; they are rather difficult to arrest and very often result in severe anemization and even death. Nasal, pharyngeal (most frequent), esophageal, gastric and intestinal hemorrhages are particularly dangerous. The sternal puncture is an important criterion for assessing the condition of the hemopoietic organs.

The study of bone marrow punctates at the third ATA stage showed (V.L. Chilikin, 1947) complete bone marrow aplasia to be relatively rare. More frequent is the depletion of formed elements and "embryonization" of the bone marrow (replacement by young, poorly differentiated cells of myeloid series

and lymphoid cells).

Several days after the appearance of rash the patients develop angina which in severe cases can be necrotic or gangrenous, and catarrhal or follicular in mild ones. The swollen red mucosa in the fauces was covered in the area of one or both tonsils, first with greyish-white, then dirty yellow, and finally dirty brown coat that was difficult to remove. The forced removal left a deep bleeding defect without an evident surrounding inflammatory reaction. In moderate cases the demarcation occurred within 5-7 days, with the further rejection of the gangrenous area and the subsequent filling of the defect with the granulation tissue. In severe cases necrotic foci were transformed into gangrenous masses involving both tonsils, anterior and posterior arches, soft palate, woula, pharynx, posterior pharyngeal wall and lingual tonsil. Necrotic process penetrated deep into the pharyngeal ring, transforming all tissues into fetid masses of green-yellow-brownish colour. The complete decomposition of the tonsils was accompanied by acute edema of the laryngeal vestubule and occlusion within 3-8 days with necrotic masses and blood clots. This resulted in asphyxia and aphonia and rather often caused death at the third ATA stage. The gangrenous process further spread to the soft palate, gums, tongue, lips, cheeks, ala nasae, which in turn led to the loss of teeth, and cheek perforation of the noma type. These symptoms were most frequent among the individuals with unbalanced nutrition and in children. In severe cases of the third ATA stage lethality was high, death occurring within 1-2 weeks after the development of the anginal process. However, the favourable course of the disease resulted in patients' recovery within the same period. Severe anginal

symptoms were accompanied by the intensification of the hemorrhagic diathesis. The size of the rash elements could be that of a 10-15 kopecks coin, merging into spots and stripes and forming blood blisters. Hemorrhages at this stage are caused by thrombocytopoiesis disorder, decreased blood prothrombin level, toxic damage of the capillaries, as well as by the destruction of the vascular walls in the necrotic foci of the nasopharynx, lungs, stomach, intestine, etc. In this period the leukocyte count can drop to 300-200-100 per c.mm and even lower. Neutrophils and eosinophils fully disappear. The platelet count drops to several thousand per cubic millimetre. The erythrocyte count decreases to one million and less and hemoglobin drops to 20, 10% and even lower. The E.S.R. elevates to 70-90 mm/h. All these symptoms were accompanied by fever: 38-39°C in the morning, and 39-40°C and higher in the evening. The pulse rate exceeded 100 per min and was highly labile; the blood pressure dropped essentially, respiration was greatly accelerated. Anoxia and anoxemia, aspiration bronchiopneumonia, and pulmonary abscesses developed along with general toxemia.

Acute parenchymatous hepatitis without or with mild jaundice almost always occurred at the third ATA stage. The liver was somewhat enlarged, whereas the spleen was normal. There was microhematuria and, less frequently, hematuria. The urine contained a small amount of protein and cylinders. In spite of serious conditions the patients were fully conscious, suffered from thirst, had hypohydrosis, but their appetite was normal. Sharply enhanced neuropsychic disorders developed into apathico-abulic syndrome (P.N. Serafimov, 1946) connected both with cerebral asthenia and the affection of the frontal lobes of the brain cortex, rather sensitive to the ATA

toxin. All this affected the behaviour of those patients who developed evening and nocturnal hallucinations; the mentioned disorders were reversible and disappeared in several days. As to the digestive tract - constipation was the rule, but diarrhea occurred in the severest cases. All these symptoms began to subside in several days. Necrotic foci cleared; fever dropped lytically and the patients recovered from acute toxemia rather rapidly. Even in grave cases a sudden change for the better and even recovery within 1-2 weeks are quite possible

In the gravest cases death resulted from heart paralysis, uncontrollable hemorrhages, asphyxia, pneumonia with a pulmonary abscess and gangrene

Fourth ATA stage (recovery and possible complications)

When pathogenetic therapy was provided the disease progressed into the fourth stage lasting 10-14 days. During this period the necrotic foci began to heal and hemorrhages subsided; a lytid drop of fever indicated the recovery from acute toxemia. However, residual toxic symptoms (tachycardia, hypotension, systolic murmur at the apex, heart dilatation to the left, dyspnea, weakness, vertigo, gastritis, gastroenteritis, hepatitis, central and vegetative nervous systems disorders) persisted for a long time. The evidence concerning hemopoiesis regeneration was controversial: sometimes the leukocyte count increased 5-10-fold in several days, or the normalization of blood composition was slower and took one to one and a half months. Erythropoiesis regenerated more rapidly than thrombopoiesis, the latter reaching the normal value only in four and a half

to six months. The E.S.R. normalized within one to one and a half months. All the hemopoietic regeneration processes were rapid and complete in children.

Late ATA sequelae

An expedition of the Institute of Nutrition of the Academy of Medical Sciences, USSR (V.V. Efremov, L.S. Lyass, 1945) examined 94 individuals for residual affects one year after the recovery from APA of diverse severity. Nine (30%) of 27 patients who sustained severe ATA had leukopenia (2,000-3,000 leukocytes per c.mm); in the rest the count was 3,000-4,000 cells, without granulopenia. About 50% of this group had thrombocytopenia down to 50,000 c.mm and hypochromic anemia. Sternal punctate revealed an increase in immature myeloid elements and lowered neutrophil count, poor erythropoiesis or the embryonic type of hemopoiesis, with megaloblasts. A group of patients who had ATA of moderate severity (49 individuals) a year earlier and mild (18 individuals) had only relative thrombocytopenia and anemia that was not marked. This indicates that after the toxin elimination processes the body regeneration could last for a relatively long period.

ATA treatment

The therapeutic measures at the first stage of the disease are aimed at excluding from nutrition different wintered grain products and flour, and systematic blood check: leukocyte, erythrocyte, platelet and leukocyte differential count.

The therapeutic measures at the second stage envisage balanced nutrition, in particular containing biologically valuable proteins and vitamins: ascorbic acid, thiamine, riboflavine, niacin, vitamin $B_6$, folacin, vitamin E. Food should

include milk, preferably sour milk produce, among them "kefir", "acidophyllin", "airan", "matsoni", "kumys" "equine sour milk), "shubat" (camel sour milk). Constant medical supervision with systematic blood check is compulsory. If the leukocyte count drops below - 3,000 c.mm the patient should be hospitalized. General and hemopoiesis-stimulating means and drugs are required.

At the third stage of the disease the patient should be immediately hospitalized, and put on a balanced diet, which, in case of necessity, can be administered enterally. The required measures include early prescription of large doses of sulfamide compounds and adequate antibiotics, the use of general and hemopoiesis stimulants: blood transfusion and autohemotherapy, the application of hemostatic, detoxicating and cardiovascular activity-stimulating agents, the local treatment of the necrotic foci.

Medical measures at the fourth AFA stage should be aimed at elevating the body reactive capacity by general bracing and hemopoiesis stimulation, as well as at eliminating the toxic residual effects with detoxicating drugs.

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