“ATA-test”: innovative *in vitro* test for prognosis, diagnosis and therapy monitoring of purulent-septic complications, intoxication, malignant tumors

Method is based on the detection of structural and functional abnormalities in **serum albumin (**the main carrier protein in the blood)

Intended use

- Prognosis, diagnostics and therapy monitoring of purulent-septic complications and intoxication
- Cancer diagnostics, monitoring of the course of the disease
- Quality control of albumin-containing solutions for infusion

Equipment:

LABORATORY ELECTRON PARAMAGNETIC RESONANCE ANALYZER "EPR AXM-09"

- Registration Certificate of Federal Service on Surveillance in Healthcare of Russian Federation (ROSZDARVNADZOR) no. FSZ 2012/12247 from June 01, 2012.
- Registration Certificate of Ministry of Health of the Republic of Belarus no. IM-7.98584 from February 02, 2012.

Reagents:

Sets of reagents for assessment of the albumin parameters in serum and plasma by the electron paramagnetic resonance method

- Registration Certificate of Federal Service on Surveillance in Healthcare of Russian Federation no. RZN 2013/377 from March 15, 2013.
- Registration Certificate of Ministry of Health of the Republic of Belarus no. IM-7.99443 from October 10, 2012.

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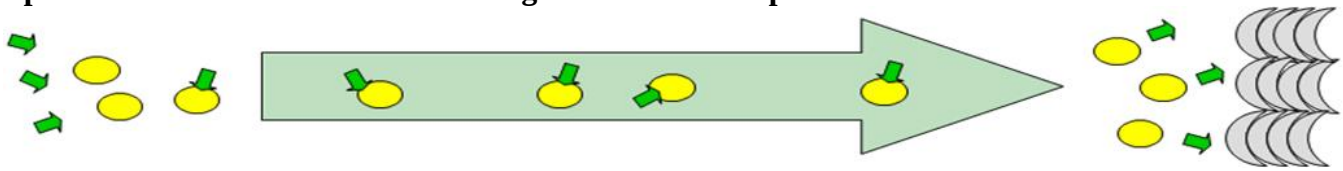
Principle of the method

Serum albumin is the main carrier protein in the blood that transports hydrophobic metabolites in the circulatory system. Albumin delivers fatty acids (cell nutrition), transfers multiple mediators and intermediates, provides binding of toxins and their uptake to hepatocytes, carriage of medical drugs – various hydrophobic compounds, which are toxic for the circulatory system and cannot be transferred in free state.

During the metabolite transport, the albumin molecules perform complex operations: at the beginning (1) efficiently bind metabolites; then, during the transfer in the circulatory system (2), strongly retain them in bound state; at destination (3) provide efficient dissociation and transfer to target cells.

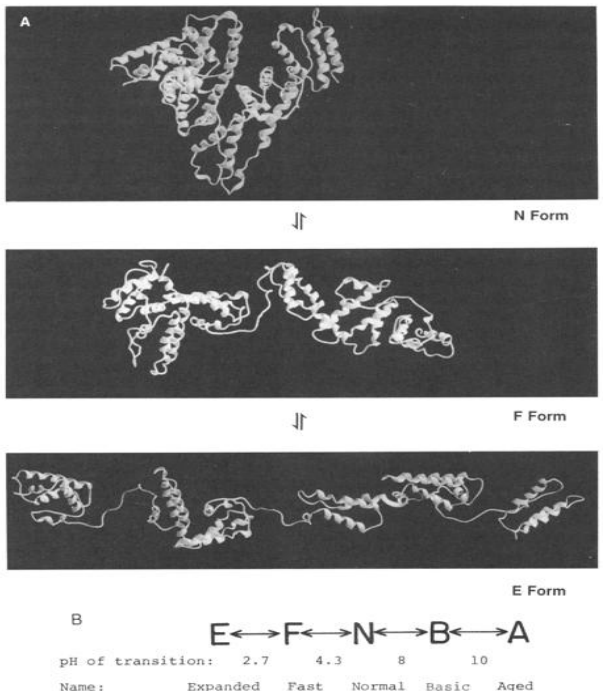
Operations of albumin molecule during metabolite transport:



(1) Binding *(2) Transport in the circulatory system* *(3) Transfer to target cells*

Variation of the albumin binding parameters during metabolite transport is based both on the conformational flexibility of albumin molecule and the strong allosteric interactions between its binding sites.

Conformation of albumin molecule is very flexible. Figure on the right shows the pH depended albumin conformation forms.
(*Theodore Peters Jr., All about albumin, Academic Press, 1996*).



Ability of albumin molecule to change conformation and binding properties determines its capacity to perform the operations of metabolite transport (functional activity of albumin).

In the circulatory system, the albumin molecules are always loaded with carried metabolites. The content and amount of those depend on the organism condition. The conformation and binding properties of albumin can be altered by the pathological processes such as inflammation and malignation.

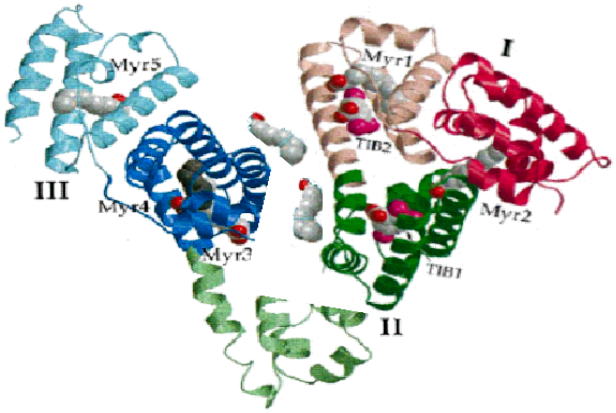
- **Pathological processes can lead to albumin functional activity deterioration**
- **Status of albumin conformation can serve as the marker of pathological process**

Analytical technique

Investigation of the serum albumin functionality is based on the method of Spin Probe EPR Spectroscopy (EPR = electron paramagnetic resonance).

- ***Spin Probe*** *– the molecule that contains stable free radical and is able to bind on other molecules. In ATA-test the spin probe (16-doxyl stearate) binds on serum albumin.*
- *Exposure to the high magnetic field and microwaves causes a resonance of the free radical in the spine probe. The resonance response of the spin probe is measured as EPR spectrum that reflexes the structure and the properties of the protein molecule on which the spin probe is bound.*
- ***EPR spectroscopy*** *– the technique for measurement and interpretation of EPR spectra.*
- *Initially, the method of EPR spectroscopy of serum albumin in vitro had been developed in Belorussian Research Institute of Oncology and Medical Radiology. Then, the method was being improved in cooperation with experts of Transfusion Medicine and Medical Physics Institutes of Leipzig University, University Clinic Charité (Berlin), Oregon Health University (USA) and others. Development of the laboratory diagnostic complex "ATA-test" was carried out under the leadership of Vladimir Muravsky.*

The ATA-test investigates the serum sample. For that the spin probe 16-doxyl stearic acid is added to the sample. The spin probe molecules are bound specifically on albumin in two basic positions: (1) in the primary binding sites located in the albumin domains I – III (in these sites their mobility is restricted), and (2) in the relatively wide hydrophobic area between the albumin domains in the interior of the protein globule. Those positions of the spin probe allow comprehensive assessment of the conformation of albumin molecule.



I, II and III - domains of albumin

Mobility of the albumin-bound spin probe is restricted. This becomes visible as the changes of EPR spectrum, which reflect features of the protein site where the spin probe molecule is located. The Analyzer "AXM-09" software provides analysis of the EPR spectrum and calculates parameters of the functional activity of albumin.

Test procedure: (1) venous blood sampling, (2) serum separation, (3) incubation of a serum sample with the reagent containing the spin probe on a shaker for 10 min at 37 °C, (4) drawing of the sample into capillary, (5) measurement of the sample on AXM-09 Analyzer, (6) EPR spectrum generation read out and analysis of the test result.
Whole test procedure takes 30 min per patient.

Investigated material: 50 µl of serum or plasma EDTA

Sample measurement time: 4 min (productivity of the analyzer is 15 samples per hour)

Evaluated parameters of albumin:

✓ **BE** - binding efficacy ✓ **RTQ** - transport efficacy	For quality control of transfusion materials
✓ **DTE** - detoxification efficacy	For diagnosis of intoxication and sepsis
✓ **DR** - index of albumin conformation	For cancer diagnostics and monitoring

INTERPRETATION OF "ATA-TEST" RESULTS

Diagnosis of intoxication and septic complications

- Parameter DTE higher than 40% indicates normal status of albumin transport function
- DTE lower than 40% indicates intoxications of different origin
- DTE lover than 9% is observed in patients with developing sepsis or SIRS
- DTE lower than 3% is observed in patients with septic shock

Diagnosis and monitoring of cancer

- Parameter DR higher than 1.0 indicates that patient does not have any active malignancy (no active growth of tumor)
- DR from 0 to 1.0 indicates in-between (borderline) state
- DR lower than 0 indicates the active growth of malignancy

Quality control of albumin-containing infusion solutions

- Parameter BE higher than 100% indicates that albumin has high binding constant and provides efficient binding of metabolites. Such infusion solutions are efficient for detoxification.
- BE lower than 65% indicates reduced binding efficiency of albumin. This can be a result of albumin conformation change due to either improper production and storage of the infusion solution or excessive concentration of stabilizers, or by other reason.
- Parameter RTQ in the normal range (60 – 100%) indicates that the albumin in the infusion solution has well balanced transport parameters that will support patient album transport system.
- RTQ lower than 60% indicates a disbalance of metabolites binding and release capacities of albumin.

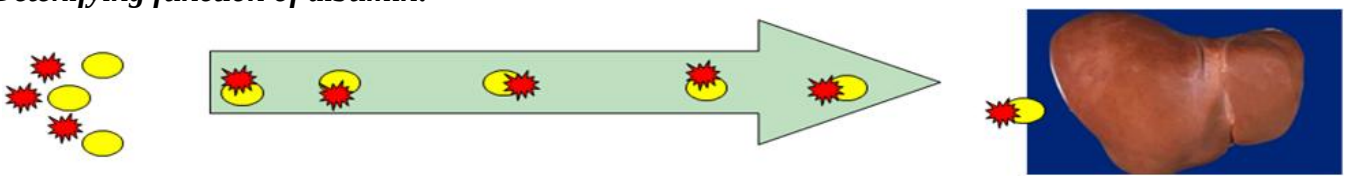
RESULTS OF CLINICAL INVESTIGATIONS

1. Early diagnostics of purulent-septic complications in post-surgery patients

Role of albumin in the pathogenesis of purulent-septic complications and intoxications

Serum albumin is the main protein providing binding of the toxic molecules of hydrophobic origin and their uptake to hepatocytes in the circulatory system. Albumin also takes part in binding of reaction-active hydrophilic toxins. The strength of binding and retaining of the toxins (i.e. binding constant) is the parameter determining the detoxification activity of albumin molecules.

Detoxifying function of albumin:



(1) **Binding** **(2) Transfer in the circulatory system** *Filtration in hepatocytes*

Binding of reactive ligand causes an allosteric modification of the albumin molecule that can result in reduced binding constants of other binding sites. Such albumin molecule may loose or significantly reduce ability to detoxify subsequent toxic molecules.

At normal condition, the concentration of toxins carried by albumin molecules is relatively low and most of the albumin molecules retain a high binding capacity. Permanent synthesis of new albumin and filtration of albumin molecules loaded with toxins (in the liver) maintain the functional activity of albumin in organism.

In the studies, it was established that in patients developing septic complications at an early stage (before the appearance of clinical symptoms), the functional activity of serum albumin is significantly reduced, down to 50% or lower compared to control group. In such patients, the clinical symptoms of sepsis appear later when the dysfunction of albumin is observed – albumin detoxifying activity is 2 - 9%.
Also, it was established that in the patients with purulent-septic complications the level of albumin functional activity correlated with the progress of the disease.

Data of several clinical studies are shown below.

Diagnostics of purulent-septic complications in the early postoperative period

1.1. The clinical study carried out in Blokhin ROSC, Moscow, 2006:

Study included 22 patients of ICU (99 samples), observed periodically after the surgery, beginning from the first day and up to the 30th day (for several patients):

- 8 patients with purulent-septic complications (5 died, 3 survived);
- 9 patients with peritonitis, pneumonia, empyema etc. (all survived);
- 5 patients without complications.

In addition to EPR-test following parameters were analyzed: white blood cells, neutrophils, amount of total protein, albumin, bilirubin, AST, ALT, amylase, procalcitonin, SOFA, APACHE II, SIRS.

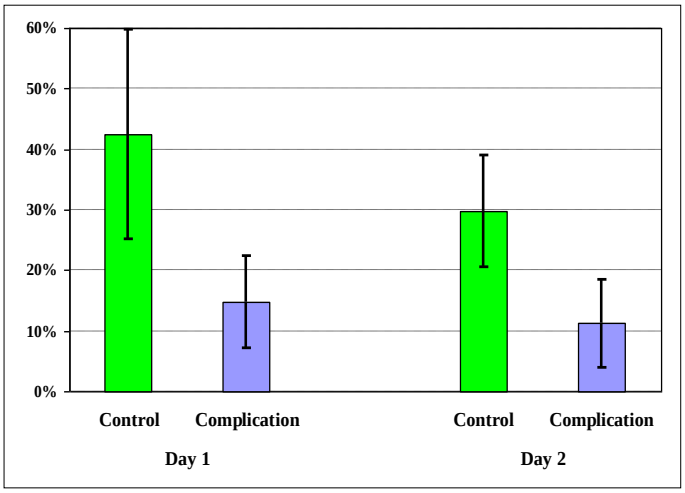
Conclusion:

- ✓ Reduction of the detoxifying capacity of serum albumin (DTE) on the first and second days after the surgery was observed in all postoperative patients:
  - down to 30 – 70% in the patients without complication;
  - down to 1 – 20% in the patients with purulent-septic complications.

  The observed difference was significant.
- ✓ Other laboratory indexes, including procalcitonin, did not show significant differences in the observed groups of patients.
- ✓ The EPR-test parameter reliably reflected the progression of the disease.

EPR-test demonstrated ability for diagnostics of purulent-septic complications in postoperative patients as early as 24 hours postsurgical, prior any other diagnostic biomarkers could be detected.

EPR-test (DTE):
significant different detoxification capacity of albumin ($p<0,01$) could be observed between control group and patients with septic complications



Diagnostics of purulent-septic complications in the early postoperative period

1.2. The clinical study carried out by Russian Society for Pharmaeconomics and Outcomes Research, Blokhin ROSC, Moscow, 2012-2013:

105 patients admitted in ICU after surgeries were observed beginning from 2 hours after the operation. Among them, 11 patients developed purulent-septic complications, and 94 patients were symptoms free. The patients with purulent-septic complications were:

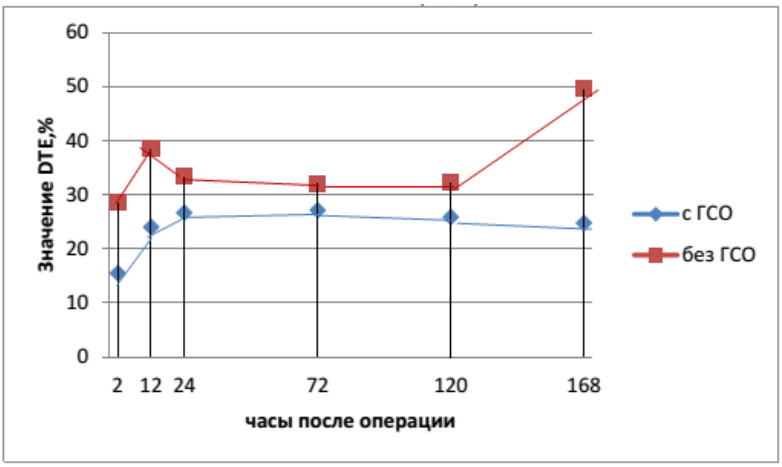
- 1 with sepsis (died);
- 1 with anastomotic leakage, mediastinitis (died);
- 1 with peritonitis, empyema;
- 1 with pancreatitis, septic shock;
- 1 with double-sided pneumonia, sepsis;
- 1 with bronchitis;
- 2 with festering wound;
- 3 with systemic inflammatory response.

Conclusion:

- ✓ the albumin index DTE was slightly reduced (mean 31.8%, median 30.3%, compared to the normal level of 40-175%) in the patients without septic complications (n = 94) first day after surgery and was back to normal level in 7 days.
- ✓ The albumin index DTE was significantly decreased (mean 22.1%, median 18%) in the patients with purulent-septic complications (n = 11) first day after surgery and remained low for further 7 days.
- ✓ DTE index can be used as the biomarker of the septic complications development.
- ✓ DTE index monitoring can be used to evaluate the effectiveness of the anti-septic therapy, in particular correct antibiotics choice.
- ✓ Value of DTE index can be used as the criteria for the choice of the antibiotic for prophylactic treatment.
- ✓ Clinical and economic analysis showed the total clinical expenses of 281752 rubles for a patient with purulent-septic complication, which was significantly higher than the clinical expenses of 95372 rubles for a patient without such complications.

The study demonstrated that ATA test predicts purulent-septic complications in patients as early as 2 hours after surgery.

Figure on the right: The course of DTE (Y-axis) in the subgroup of patients with purulent-septic complications (n = 11, blue line) and without those (n = 94, red line). X-axis shows hours after surgery.



2. Pre-clinical diagnosis of preeclampsia

The role of albumin in the pathogenesis of preeclampsia

According to actual knowledge, the preeclampsia (late toxemia of pregnancy) is not an independent disease but the syndrome that occurs only in pregnant women due to deterioration of the adaptation mechanisms of the mother to the needs of the developing fetus. Preeclampsia often leads to severe complications in mother and child.

Preeclampsia includes the disorders of the vascular system, hemostasis, hemodynamics, microcirculation and immune system, which then lead to the chronic hypoxia of tissues, changes in the composition of blood cells and plasma lipids, increased peroxidation of plasma proteins and disruption in the structure and function of plasma proteins. Latent development of the systemic abnormalities leads then to multiple organ failure and endogenous intoxication, known as toxemia.

Serum albumin is one of the key elements of the detoxification system in the organism. Albumin is the main protein that provides binding and evacuation of hydrophobic toxins in the circulatory system. Functional activity of albumin directly determines the capacity of the entire detoxification system and reflects the status of intoxication and detoxification processes in the body. Detoxifying capacity of the albumin is significantly reduced if the structure of the protein is perturbed, or albumin molecules are overloaded with external toxins due to hepatic failure.

In case of a significant reduction of albumin functional activity, the development of intoxication may be exacerbated by the so called "circulus vitiosus": insufficient detoxification leads to an increased concentration of toxins in the circulatory system that leads to further increase of "toxin loading" on albumin molecules causing a stronger reduction of albumin functional activity.

In the performed studies, it was established that "ATA test" of serum albumin functional activity can be used for preclinical diagnostics of preeclampsia. Significant decrease of the detoxifying activity of serum albumin (DTE index was below 30%) was observed in serum samples from pregnant women with preeclampsia, compared to control group (DTE values were 95 ± 8%).
After the efficient treatment of preeclampsia, the index of albumin detoxification activity recovered to normal range (DTE over 40%).

The clinical study carried out in Belarusian State Medical University, Minsk, 2012:

A total of 17 pregnant women at age of 21-28 years followed up in 5th City Hospital of Minsk were participating in the study. Six women were diagnosed with preeclampsia and 11 with normal pregnancy. For both cases, complicated by preeclampsia and normal, the terms pregnancy were 36-38 weeks.

Conclusion:

Significant reduction of albumin functional activity was observed in the serum samples of women, whose pregnancy was accompanied by preeclampsia, in comparison to women whose pregnancy was normal. No changes in functional activity of albumin were observed in women with normal pregnancy – the examined albumin parameters were in the range of healthy individuals.

In women with preeclampsia, the index of albumin detoxification activity (DTE) correlated with the clinical condition of the patient and the severity of preeclampsia. In case of mild preeclampsia the index DTE was reduced down to 30%, moderate severe preeclampsia reduced the index down to 22 - 28%. The efficient preeclampsia treatment increased the DTE index back to the normal range (43% and 46%).

Thus, these results suggest that new method for pre-clinical diagnostics and therapeutic monitoring of preeclampsia can be developed based on this test.

Results:

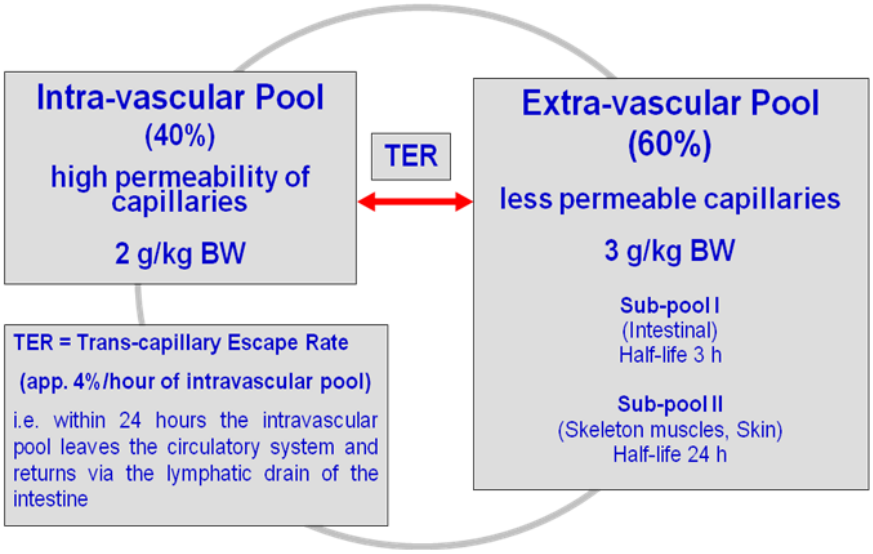
Group	**Index of albumin functional activity**
	DTE, %
Norm for healthy persons	*40-175*
Women with normal pregnancy	
(Control group, n=11:	**95 ±8**
Pregnant women with preeclampsia (n=6):	**32 ± 4**
1. Mild preeclampsia	**30**
2. Moderate severe preeclampsia	**22**
3. Monosemeiotic preeclampsia (pregnancy edema)	**24**
4. Monosemeiotic preeclampsia (pregnancy edema)	**28**
At the end of treatment:	
5. Mild preeclampsia at the end of treatment	**46**
6. Preeclampsia of moderate severity at the end of treatment	**43**

3. Cancer diagnostics

Serum albumin - the molecular marker of pathological processes

Serum albumin is the main protein in the circulatory system that provides the transport of hydrophobic metabolites, including the products of cellular metabolism, mediators and intermediates of hydrophobic origin and other compounds, which together reflect the nature and intensity of physiological and pathological processes in the body. The binding of hydrophobic compounds by albumin prevents their toxic effect on blood vessels. Albumin binding of mediators and intermediates provides their prolonged activity due to their accumulation on the albumin for 6-12 hours. For comparison, hydrophilic metabolites are rapidly filtered in the kidney, where the entire volume of plasma is filtered in 25-30 minutes.

In the body, the albumin remains in two pools: in the circulatory system and in the extravascular space - in muscles, skin, intestines, etc. There is the permanent exchange of albumin between the intra- and extra-vascular volumes. The rate of exchange of intravascular part by the albumin from the extravascular volume is 12 hours.



Thus, the albumin molecules circulating in the large vessels carry the low molecular weight markers which have been produced in the body tissues several hours ago. Therefore, the serum albumin serves as a carrier of a variety of low molecular weight markers. Binding of specific molecules causes a conformational change of the albumin molecule, that can be used as the markers of pathological process.

Performed studies found that in patients with different types of malignancies the specific conformational change of albumin molecules was observed, which allows early diagnosis of tumors with approx. 90% specificity and sensitivity. The changes of the molecular state of albumin correlate with tumor activity and presumably depend on the rate of metabolites secretion into the circulatory system by tumor cells.

Monitoring of patients during treatment showed a clear correlation between the degree of albumin modification and the clinical condition of the patients.

3.1. Study carried out in State Institution "Aleksandrov Republican Scientific and Practical Center of Oncology and Medical Radiology", Minsk, 1990-1999:

Extensive clinical studies included 1824 patients:

- 745 with lung cancer,
- 373 with gastric cancer,
- 294 with colon cancer,
- 412 with various chronic diseases (control group).

More than 40 biochemical indexes, including EPR test of serum albumin, were analyzed in order to identify the most informative biomarkers or complexes of biomarkers for early diagnosis of cancer.

Results:

- Most of the studied biochemical parameters showed significant differences between the studied groups, but the diagnostic accuracy of each individual biochemical index was low and did not exceed 69%, with the exception for the tumor antigens.
- Higher accuracy of cancer diagnosis was shown by the tumor-associated antigens and EPR test of serum albumin, but the diagnostic utility of the EPR test of albumin was higher.

For example, the results obtained for the group of lung cancer patients were following:

Lung cancer diagnosis	Sensitivity	Specificity	Diagnostic precision
Cancer embryonic antigen	**87%**	**63%**	**75%**
Neuron specific enolase	**89%**	**59%**	**74%**
EPR test of albumin ***(Evaluation of EPR test potential)***	**95%**	**91%**	**93%**

3.2. Studies performed in German clinics, 2000-2005:

The purpose of these studies was to evaluate the clinical utility of the EPR test of serum albumin in the diagnosis of malignant tumors of different locations.

Conclusion of the investigations:

- Studies of more than 2000 patients with various types of cancer have shown the specific changes of albumin conformation in cancer patients, which allows early diagnosis of tumors with approx. 90% specificity and sensitivity.
- Monitoring of patients whose blood samples were serially collected during the treatment showed the clear correlation between the degree of albumin modification and the clinical condition of the patients.
- The change of the molecular state of albumin correlated with the tumor activity and probably is determined by the tumor cells secreted metabolites in the bloodstream.
- EPR spectroscopy of albumin is the non-invasive method that demonstrates the diagnostic potential for cancer identification and allows the monitoring of therapy.

Results of the EPR test of serum albumin in cancer patients observed before treatment:

Blind samples of serum / plasma of 1267 patients were studied:

- 585 healthy individuals (blood and plasma donors, volunteers);
- 128 patients with chronic non-malignant diseases;
- 554 cancer patients before treatment.

***Clinical utility of the EPR test of albumin**:*

Patient group	Number	Specificity of the EPR test of albumin
Healthy individuals	585	*98%*
Patients with chronic non-malignant diseases	128	*73%*

Patient group	Number	Sensitivity of the EPR test of albumin
Cancer patients, in total	554	*90%*
Gastrointestinal tumors	*84*	*93%*
Lung cancer	*26*	*96%*
Breast cancer	*31*	*87%*
Prostate cancer	*82*	*90%*
Non-Hodgkin's lymphoma	*39*	*95%*
Malignant lymphomas	*23*	*91%*
Plasmacytoma	*34*	*97%*
Leukemia	*31*	*87%*
Other cancers	*204*	*88%*

4. Quality control of transfusion solutions

Albumin is the major component of the blood transport system that provides the transport of fatty acids, tryptophan, bilirubin, calcium, steroid hormones and many other important compounds, toxin binding and transfer to detoxifying organs, delivery of drugs. Providing transport of such compounds, albumin supports the functioning of organs and body systems.
The albumin functionality is determined by metabolite binding capacity, strength of retention during the transfer in the circulatory system, and efficiency of the dissociation during delivery to the target cells.
Utility of the quality control of albumin solutions and plasma products is determined by the fact that a variety of factors, such as aggregation of albumin molecules with toxins and drugs, denaturation or polymerization, can cause the irreversible abnormality of the protein conformation resulting in the inability of albumin to perform the transport.
In the industrial production of the transfusion media, there are processes of filtering, virus inactivation, pasteurization, the addition of stabilizers and other chemical exposures applied, which also may affect the functionality of albumin.

It is advisable to evaluate the albumin functionality in the solutions for transfusion in order **to predict the oncoming therapeutic effect**, for example:
- Albumin solutions with high binding capacity and reduced efficiency of dissociation are suitable for detoxification;
- Albumin solutions with binding and dissociation parameters balanced to normal physiological level are suitable for support for the blood transport system;
- Preparations with reduced functionality of albumin should be used with caution. Such preparations can help to maintain oncotic pressure, but they may contain an excessive concentration of the stabilizer (sodium caprylate), which may cause hepatic toxicity.

The investigation had been carried out in Institute of Transfusion Medicine Suhl, Germany, 2002.

Plasma preparations obtained using 4 different filter systems (FFP1-FFP4), and the albumin preparations of 6 different manufacturers (ALB1-ALB6) were investigated.

Figure: Detoxification activity of albumin (DTEff) in the investigated specimens measured by EPR.

(G.Matthes, G.Seibt, V.Muravsky at al. Albumin transport analysis of different collected and processed plasma products, by electron spin resonance spectroscopy. Transfusion and Apheresis Science, 2002, 27, p. 129-135)

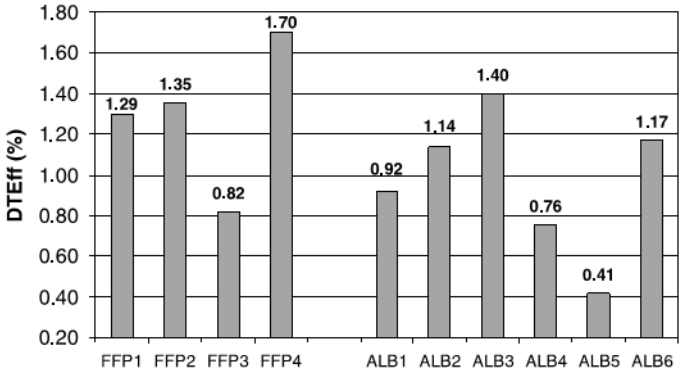


Fig. 4. DTEff of unfiltered and filtered plasma units FFP 1–4 in comparison to DTEff in albumin solutions (ALB1–ALB6), normal native serum = 1.0.

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