

# Increase in the Incidence of Allergy to Prosthetic Materials and Local Anesthetics: Immunophysiology and Laboratory Diagnostics of Intolerance

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**Abstract**—Combined analysis of drug sensitivity *in vitro* and *in vivo* is necessary for reliable diagnosis of the intolerance to prosthetic materials and local anesthetics as an intrinsic allergic reaction, especially in the cases of generally weak allergic reactions. Changes in peroxidase release from granulocytes in response to a corresponding substance is an effective *in vitro* test, and the provocative mucosal–gingival test (MGT) is used *in vivo*. During the past decade, a growth was observed in the population developing allergies to prosthetic materials and local anesthetics, which is expressed in an increased number of patients with intolerance to these materials against the background of increasing hyperresponsiveness to the drugs which have usually been tolerated well, as well as an increased proportion of patients with a polyvalent allergy to many prosthetic materials and anesthetics. At the same time, the amount of weak responses to drugs in the *in vitro* test has increased. Some of these patients exhibit a pathologic response to the given drug, which can be detected using the MGT. In most cases, polyvalent allergies to prosthetic materials or anesthetics and a pathological response accompanied by a weak *in vitro* reaction are found in patients with bronchial asthma and other chronic allergies, chronic candidosis of the oral cavity, and chronic *Helicobacter* and *Giardia lamblia* infections.

During the past two decades, the prevalence of various allergies has considerably increased in various regions of the world. This concerns both specific allergy and intrinsic allergy, which Russian researchers often call pseudoallergy [2–5].<sup>1</sup> Intolerance to various prosthetic materials [6, 7] and drugs, including anesthetics [8], are classified as allergic reactions. To date, there is much indirect evidence that their incidence in the population is increasing [6, 9, 10].

The ten-year experience of our lab indicates an increased prevalence of the intolerance to prosthetic materials and local anesthetics among patients (Fig. 1).

The clinical expressions of intolerance are various, but all of them are based on inflammation. The signs of intolerance to prosthetic materials are local and generalized eczema, urticaria, vasculites, and slow wound healing [6]. Denture materials are, in addition, characterized by local reactions: redness and swelling of mouth mucosae; ulcerations; sensations of burning in the mouth, soreness around the teeth, and scratchiness

in the throat; and disturbance of salivation [11, 12]. An intrinsic allergy to local anesthetics may be expressed as urticaria; angioneurotic edema; and anaphylactic reactions, sometimes to the degree of anaphylactic shock, fits of bronchial asthma, etc. [2, 13]. All of these reactions endanger life and health; therefore, attempts to determine their causes and mechanisms are constantly increasing in number [14].

The causes of the increase in the prevalence of allergies in the population remain unknown at present, except for the general considerations about ecological

<sup>1</sup> During an allergic reaction, specific IgE antibodies against an allergen are formed. Binding this allergen on the surface of mast cells and basophils, they induce the release of mediators (histamine, leukotrienes, etc.) triggering the allergic reaction, which gradually involves other immune components. In the case of intrinsic allergy, various drugs directly bind with receptors on basophils, mast cells, and other immunocompetent cells (these are probably *Toll*-like receptors (TLRs) [1]) and cause degranulation of these cells and the release of mediators (histamine and leukotrienes), which trigger the same allergic reaction as in the former case [2].

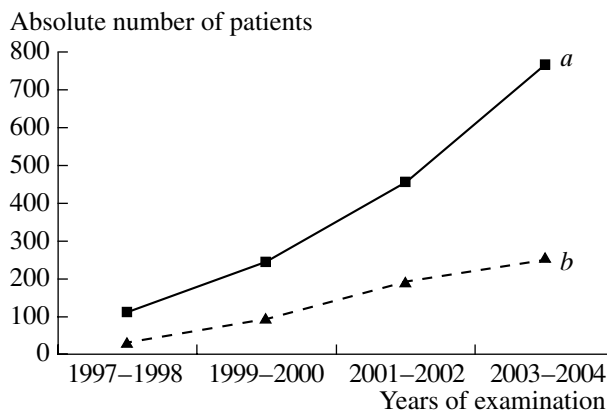


**Fig. 1.** Numbers of patients compromised with respect to (a) prosthetic materials and (b) local anesthetics who were examined in the lab in different years.

**Table 1.** Changes in the peroxidase activity in the culture medium after the incubation of peripheral blood cells in the presence of different substances. The female patient N. had a history of angioneurotic edema after the administration of Ubisthesine

| Substance        | Concentrations of the substance in a series of eight sequential tenfold dilutions | Mean $A_{450}$ in a series of eight dilutions | Significance of difference from the control ( $P$ ) |
|------------------|-----------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------|
| Control (saline) | Eight parallel samples                                                            | $0.367 \pm 0.009$                             |                                                     |
| Histamine        | $10^{-3}$ – $10^{-10}$ *                                                          | $0.257 \pm 0.027$                             | $\leq 0.01$                                         |
| Leukotriene B4   | $10^{-6}$ – $10^{-13}$ *                                                          | $0.492 \pm 0.032$                             | $\leq 0.01$                                         |
| Ubisthesine      | $10^{-3}$ – $10^{-10}$ **                                                         | $0.482 \pm 0.062$                             | $\leq 0.02$                                         |

\* The concentration is indicated in g/l.

\*\* The initial solution contained the substance at a therapeutic concentration.

degradation and the increased spectrum of synthetic drugs and materials [5–9].

We attempted to analyze our observations on intolerance in terms of estimating the general state of the patient's health, including the transition of inflammations into a chronic form, and to optimize the methods for diagnosing intolerance on the basis of the results obtained.

## METHODS

We examined 1349 patients aged 24–76 years with a history of intolerance to various prosthetic materials and 568 patients aged 14–62 years with a history of pathological responses to various local anesthetics (compromised patients). One hundred sixty-two patients that had never used dentures or were never administered local anesthetics constituted a separate group. These patients visited our lab to test their sensitivity to prosthetic materials or anesthetics that they were going to use for treatment (noncompromised patients). A control group comprised 112 healthy subjects aged 18–67 years that had a long contact with prosthetic materials or received various local anesthetics without any signs of pathology.

We tested the sensitivity to Procaine, Lidocaine, Ultracaine, Septanest, Scanodest, Mepivasthesine, and other local anesthetics. The prosthetic materials that the patients brought to test the intolerance to them were manufactured by different companies and were permitted for use to make dentures and implants. These were alloys of metals (mainly based on cobalt, chromium, nickel, titanium, silver, palladium, platinum, and gold), plastic (stained and unstained), and various ceramics. Thus, we determined the sensitivity to the drugs and materials that were officially approved for use after the

manufacturers had tested them for the absence of toxicity, at least at the doses permitted for clinical uses in humans. Therefore, we may presume that the intolerance to these drugs and materials was entirely determined by intrinsic allergic reactions to them.

We tested the sensitivity of each patient to one to six local anesthetics or 1–12 prosthetic materials in the course of selection; thus, in total, more than 1900 tests for the sensitivity to various local anesthetics and more than 4800 tests for the sensitivity to various prosthetic materials were performed in the lab.

The intolerance to anesthetics and prosthetic materials was detected by two methods, *in vitro* and *in vivo*.

The *in vitro* detection of the hypersensitivity of cells to a drug or material was performed by estimating the change in the release of peroxidase from granulocytes after blood cells were incubated in the presence of the given drug dissolved in the medium [15, 16]. The substances were used at concentrations that a priori could not be toxic to cells (usually, this corresponded to anesthetic concentrations of  $10^{-3}$  to  $10^{-5}$  therapeutic doses). The peroxidase activity in the reaction medium was estimated by the changes in the optic density after interaction with tetramethyl benzidine with the use of a plate photometer.

The change in peroxidase release from granulocytes after the incubation of blood cells in the presence of the causative allergen was largely determined by the effects of leukotrienes and histamine released from basophils, the former stimulating the release of enzymes, including peroxidase, and the latter inhibiting it (Table 1). The effect of these mediators on the release of enzymes from granulocytes was demonstrated by other researchers [17–19]. Because of this double effect of mediators, the peroxidase activity in the culture medium does not depend linearly on the allergen concentration in the culture medium. Instead, the activity oscillates, the oscillation pattern varying in different individuals. Probably, the cause of these oscillations is actually more complex, because numerous cellular and humoral components of the immune system, including T and B lymphocytes and various cytokines (Ld 10, TGF- $\beta$ , etc.), are involved in the reaction and different receptors, including the cell membrane receptors CD, 10, 63 and TLRs, are activated in the cases of both true allergy and intrinsic allergy [1, 14]. Depending on the concentration of the substance, the effects of different components become dominant, which determines the final result of the reaction. Therefore, we determined the cell response for at least eight subsequent tenfold dilutions of each drug.

Earlier, we demonstrated that the effectiveness of all methods for estimating cell sensitivity to various substances was considerably increased when the substance was used at eight to ten physiologically normal (nontoxic) dilutions. This finding is not unexpected, because indirect effects of various components of the immune

system on granulocytes played an important role in all of these tests [20, 21].

When estimating the results of the test for peroxidase release, we took into account not only the deviations of the mean optical density in the series of sequential dilutions of the solution of the substance tested to either side from the control values, but also the amplitudes of their variation. The result was estimated in percent from the mean control value of the parameter (the shift index).

A deviation from the control value by less than 10% was considered unsubstantial; it corresponded to the absence of sensitivity to the substance. This conclusion was substantiated by the results of this test with various prosthetic materials and local anesthetics in 77 healthy volunteers. The substances tested did not cause pathologic responses in the subjects during preliminary clinical trials.

Deviations by 11–25% corresponded to a low sensitivity to the substance, with most pathological signs being moderate and not expressed permanently. This conclusion was substantiated by the data on similar deviations in 19 patients that had constantly used dentures for a long time and 21 patients that had taken anesthetics a short time before the study. Eight out of the former 19 patients exhibited slight pathological reactions (occasional sensation of burning in the oral cavity and slight hyperemia), and 11 patients had no pathological reactions. Of the latter 21 patients, 12 had slight pathological reactions (complaints of slight dizziness, a small edema at the site of drug administration, etc.) and 9 had no pathological reactions. We termed this region a “gray zone.” To make a final conclusion on the possibility of using the tested drug or material in a patient, we estimated the response to it in the provocative MGT.

A deviation by more than 25% from the mean control value corresponded to an increased sensitivity of the patient to a given substance. This conclusion was substantiated by the finding of such deviations in 59 patients that had the aforementioned pathological signs after being fitted with dentures, with the manifestations of the pathology disappearing after the dentures were removed, as well as the results of testing the sensitivity to a local anesthetic in 31 patients that exhibited a strong reaction, sometimes even an angioneurotic edema, to the given drug shortly before the analysis.

We used the provocative MGT for studying the reaction to drugs and prosthetic materials *in vivo* [22, 23]. This test was performed when a patient exhibited a low sensitivity to the given allergen in the neutrophil damage reaction *in vitro* (i.e., when the parameter measured in this test fell into the gray zone).

The essence of this test is the estimation of the change in leukocyte migration into the oral cavity after the application of the material or solution of the drug behind the cheek. For analysis, we used a piece of material intended (or used) for a denture. Anesthetics

were used for testing in the form of a solution at a concentration that was certainly harmless to the patient ( $10^{-7}$  therapeutic dose): a lignin disk impregnated with the solution of the drug was put behind the cheek. The duration of application was 50 min. When the ratio between the number of leukocytes in the material washed from the oral cavity after and before the application of the substance behind the cheek was 0.8–2.0, this indicated an absence of pathological reactions to this substance. When the ratio between the numbers of leukocytes went beyond these limits, this finding was considered evidence of a pathological reaction.

To detect the infectious process caused by *Helicobacter pylori*, yeast of the genus *Candida*, or *Giardia lamblia*, we assayed specific IgG antibodies in the patients by means of ELISA with Chema-Medica, Vector Best, and Human kits.

We used Student's *t* test and the Kolmogorov–Smirnov method (after testing whether the data variation parameters allowed the use of parametric criteria) for statistical treatment.

## RESULTS AND DISCUSSION

Most of our patients were compromised; i.e., they had a history of clinical signs of intolerance to a prosthetic material or a local anesthetic. We attempted to find a material (or drug) to which each given patient had no pathologic reaction. For this purpose, we sequentially tested different materials and anesthetics. In this group of patients, the proportion of persons with intolerance to the first substance tested was 63.2%; i.e., it was extremely high. In the group of noncompromised patients, the prevalence of intolerance to the first substance tested was only 8.6%. We did not find a significance variation of these parameters in different years.

The number of patients that visited our lab to select a prosthetic material or local anesthetic because they had a history of intolerance to these substances has increased constantly during the past eight years (Fig. 1). Certainly, the results obtained cannot be considered exclusively in terms of the increase in the absolute number of persons with intolerance. Other factors may have played a role, such as a wider use of local anesthetics in dentistry [24]; an increase in the mean age of the population, which leads to a larger number of persons that need dentures; and, finally, the fact that our lab has gradually become known to a larger number of dentists in Moscow. In any event, the increase in the number of patients that need testing for increased sensitivity to various prosthetic materials and anesthetics still indicates that the proportion of persons with intolerance to these substances is increasing.

In the same period of time, the compromised patients exhibited an increased frequency of pathological reactions to local anesthetics and prosthetic materials to which intolerance had been rarely observed before (Fig. 2). Examples are Ultracaine and titanium

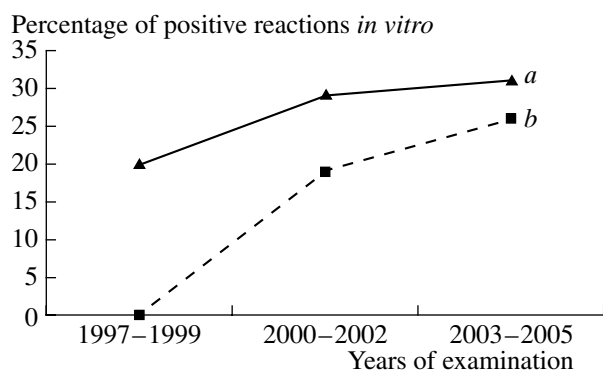


**Fig. 2.** Changes in the numbers of patients (%) with an increased sensitivity to (a) Ultracaine and (b) titanium alloys as estimated in the *in vitro* test in the group of compromised patients examined over a period of eight years.

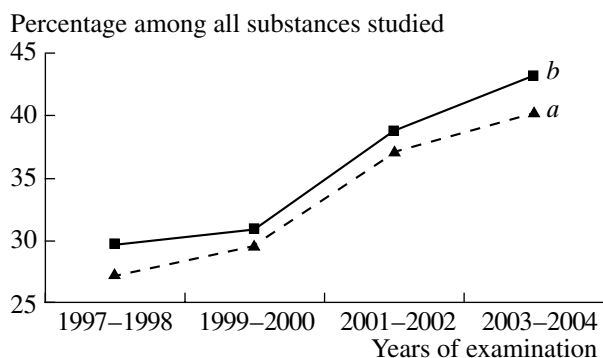


**Fig. 3.** Changes in the percentage of patients (%) for which (a) a proper prosthetic material or (b) a proper local anesthetic was selected after testing more than three samples of substances over a period of eight years.

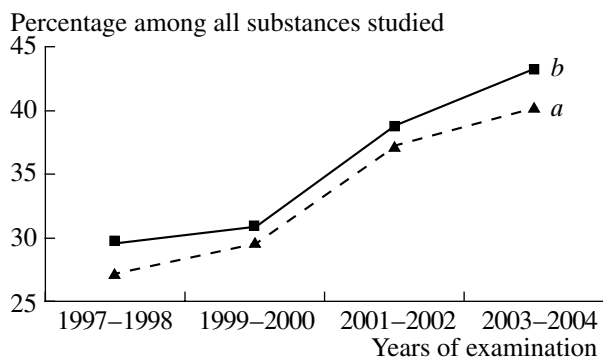


**Fig. 4.** Changes in the number of patients (%) with a low sensitivity to the (a) prosthetic materials and (b) local anesthetics studied as estimated in the *in vitro* test (corresponding to the gray zone) over a period of eight years.

alloys; until recently, it was assumed that these substances never cause intolerance [25, 26]. These data also indicate that the prevalence of allergies in the population is increasing.

A considerable proportion of the compromised patients exhibited an increased sensitivity to several local anesthetics or prosthetic materials with various compositions; i.e., they had polyvalent allergies. We assigned to this group the patients for which we managed to find a safe prosthetic material or anesthetic after testing more than three substances for intolerance. In recent years, we observed a significant increase in the proportion of persons with a polyvalent allergy among all compromised patients visiting our lab (Fig. 3).

Summarizing the data reported above, we may conclude that the proportion of persons with intolerance to prosthetic materials and local anesthetics in the population of the Moscow region has increased in recent years.

The increase in the number of patients with intolerance was accounted for by an increase in the number of not only persons highly sensitive to the materials and drugs tested, but also those exhibiting a low sensitivity to these substances in *in vitro* tests (falling within the gray zone) (Fig. 4). In many patients with a polyvalent allergy, blood cells had a low sensitivity to the substances tested. To determine what the low sensitivity to the substance in the *in vitro* test meant, we examined these patients in more detail.

The results of the MGT showed pathological reactions to the application of either material or drug solution in 43.8% of these patients; the remaining patients exhibited a normal reaction in the *in vivo* test. This low sensitivity of blood cells to the substance may be regarded as an initial stage of the development of an intrinsic allergy, when a general pathological reaction of the body may be absent. In any event, the patients in which the results of testing blood cells for the sensitivity to a material or drug fell within the gray zone but the results of the MGT did not show pathological reactions used this substance afterwards for treatment without any clinical manifestations of pathology.

Thus, the increase in the proportion of patients with weak reactions in the *in vitro* test indicates that it is necessary to perform not only *in vitro* tests, but also innocuous *in vivo* tests (e.g., the MGT used in this study) in labs carrying out the diagnosis of prosthetic materials and drugs.

We recorded detailed anamneses of the patients that exhibited polyvalent allergic reactions to various drugs or materials with parameters falling within the gray zone and tested their blood for antibodies against *Helicobacter pylori*, yeasts from the genus *Candida*, and *Giardia lamblia*.

Chronic inflammatory diseases were found in the majority of the patients from this group (Table 2). The most frequent infections were candidosis of the oral cavity mucosa (mainly in the cases of a polyvalent allergy to prosthetic materials) and *Helicobacter* infection. Bronchial asthma was mainly diagnosed in patients with polyvalent allergies to local anesthetics.

**Table 2.** Chronic inflammatory diseases and infections in patients with polyvalent allergic reactions to prosthetic materials and local anesthetics

| Detected chronic diseases and infections | Patients with intolerance to prosthetic materials (N = 34) |      | Patients with intolerance to local anesthetics (N = 60) |      |
|------------------------------------------|------------------------------------------------------------|------|---------------------------------------------------------|------|
|                                          | number of patients                                         | %    | number of patients                                      | %    |
| Bronchial asthma                         | 5                                                          | 14.7 | 14                                                      | 23.7 |
| Candidosis of the mouth mucosa           | 11                                                         | 32.4 | 11                                                      | 18.6 |
| Helicobacter pylori infection            | 7                                                          | 20.6 | 16                                                      | 27.1 |
| Giardia lamblia infection                | 6                                                          | 17.6 | 5                                                       | 8.5  |
| Combined infection                       | 4                                                          | 11.8 | 9                                                       | 15.3 |

Note that only a few of these patients had distinct clinical signs of candidosis of the oral cavity, *Giardia lamblia* infection, or gastrointestinal diseases (only 25 out of 140 patients with diagnostically significant titers of specific antibodies (17.8%) had marked clinical manifestations of the infection). In other words, these infections had subclinical manifestations in most cases.

Twelve patients from the gray zone that exhibited pathological reactions to denture materials in the MGT and had one of the aforementioned infections received the corresponding treatment. One month after the end of treatment and disappearance of significant titers of antibodies, the MGT for the same prosthetic material was repeated in these patients. There was no pathological reaction to the tested materials in eight of these patients. Afterwards, dentures made from these materials were fitted and used successfully. The positive reaction in the MGT to the prosthetic materials to which these patients exhibited strong *in vitro* reactions was retained even after the treatment for chronic inflammatory disorders.

The elimination of intolerance to prosthetic materials after treating chronic inflammation indicates an important role of chronic infections in intrinsic allergic reactions. On the other hand, the intolerance to a drug or material was eliminated only in the patients that were assigned to the gray zone according to the results of the *in vitro* test for this substance. This indirectly confirms the above notion that a low sensitivity to a substance reflects the initial stage of an intrinsic allergic reaction to it.

In summary, these data indicate that chronic infections play a substantial role in the intolerance to prosthetic materials and local anesthetics, including polyvalent allergies.

In clinical practice, it is important that tests for *Candida*, *Helicobacter pylori*, and *Giardia lamblia* infections be performed, together with tests for increased sensitivity and pathological reaction, in compromised patients tested for intolerance to prosthetic materials, especially in patients that have used removable dentures for a long time, because these infections, espe-

cially candidosis of the oral cavity, are especially frequent in them [27, 28].

Our data are confirmed by the results of other studies where the development of various intrinsic allergies was found to be related to *Candida* and *Helicobacter pylori* infections, activation of *Giardia lamblia*, and other infectious diseases [2, 9, 12, 29]. There are also data that intrinsic allergies are more frequent in patients with bronchial asthma, lichen acuminatus, and some chronic infections [30].

Numerous studies published in recent years indicate an increasing prevalence of various chronic inflammatory diseases in the population, including diseases of the oral cavity and the alimentary canal [31–34]. Taking into account the important role chronic inflammations in the development of intrinsic allergies, it is reasonable to assume that the increase in the prevalence of these allergies is largely determined by the growth of chronic inflammatory diseases.

At present, we can understand, at least partly, the mechanisms of the stimulation of intrinsic allergic reactions to materials and drugs. The finding of TLRs on human immune cells forced researchers to revise the role of natural immunity in the protection from infections and the development of immune pathologies in the case of hyperresponsiveness of these receptors [1]. Membrane TLR activation has been found to accompany chronic inflammations [35, 36].

At the same time, many components of microorganisms, including lipopolysaccharides, release histamine via degranulation of mast cells and basophils [37], which also may favor the expression of pathology in the case of a weak intrinsic allergic reaction to the substance. This circumstance may account for the cessation of the pathological reaction to the substance after patients with a low sensitivity to the given substance (a weak intrinsic allergic reaction) have been cured from chronic inflammatory disease.

Taking into account the important role of TLRs as a component of natural (native) immunity in the development of allergies, mainly intrinsic allergic reactions, the term intrinsic allergy, i.e., inherent allergy, something belonging naturally to the body, seems appropriate,

because it allows the differentiation between this form of allergy and a true allergy, which is based on the disturbance of adaptive immune reactions.

## CONCLUSIONS

The prevalence of allergies to various denture materials and local anesthetics in the population of the Moscow region has been growing, with the proportion of persons with polyvalent allergies among them increasing. The increase in the proportion of persons with intolerance to various substances is largely determined by a high prevalence of various chronic inflammatory diseases in the population, mainly diseases of the alimentary canal and respiratory pathways. Evidently, timely and effective treatment for these diseases can stop the increase in the prevalence of allergies.

The diagnosis of intolerance to various substances should be based on the integrated estimation of cell sensitivity to these substances in *in vitro* tests and the response to them *in vivo*. When an allergy to many substances is diagnosed, chronic inflammation foci should be located, and the patient should be tested for the presence of infections that may cause inflammation on mucous membranes in the oral cavity, alimentary canal, and respiratory pathways. Adequate treatment often eliminates pathological reactions to those materials to which the given patient is especially sensitive.

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