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].\(^1\) 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

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\(^1\) 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].

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**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.
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 $10^{-4}$ 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-β, 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 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). One hundred sixty-two patients aged 18–67 years that had a long contact with the substances were used in a series of eight subsequent tenfold dilutions.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentrations of the substance in a series of eight sequential tenfold dilutions</th>
<th>Mean $A_{450}$ in a series of eight dilutions</th>
<th>Significance of difference from the control ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (saline)</td>
<td>Eight parallel samples</td>
<td>0.367 ± 0.009</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>Histamine</td>
<td>$10^{-3}$–$10^{-10}$</td>
<td>0.257 ± 0.027</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>Leukotriene B4</td>
<td>$10^{-6}$–$10^{-13}$</td>
<td>0.492 ± 0.032</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>Ubistesine</td>
<td>$10^{-3}$–$10^{-10}$**</td>
<td>0.482 ± 0.062</td>
<td>$\leq 0.02$</td>
</tr>
</tbody>
</table>

* The concentration is indicated in $g/l$.
** The initial solution contained the substance at a therapeutic concentration.

$$
\text{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 Ubistesine.}
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