If a natural substance causes symptoms which do not involve the immune system, this is not an allergy or a side effect, but is known as intolerance. One example is the bronchial asthma and rhinitis which develops in some patients after administration of salicylates. Although salicylate intolerance has been known for more than 100 years, it is not adequately recognized in the relevant areas of medicine. The present article is intended to rectify this deficiency.

Methods

The literature search used the Medical Subject Heading (MeSH) and the Unified Medical Language System (UMLS) of the National Library of Medicine (NLM) for the period from 1970 to 2007. The key words were "eicosanoid," "leukotriene," "prostaglandin," "analgesic intolerance," "aspirin induced asthma," "nasal polyps," "inflammatory bowel disease," "urticaria," "adverse drug reaction," "allergy," and "tests." The search was performed in the databases of the National Center for Biotechnology Information (NCBI), the Infosystem of Erlangen-Nuremberg University (DBIS), science direct, web info science, Scobus, Current Contents Medicine (CC-Med), PubMed, and SciSearch. As there are hardly any randomized controlled trials in this area, the selection of literature was somewhat subjective. The literature search concentrated on possible clinical relevance.

Etiology and Pathogenesis

The focal point of the pathophysiology is the mechanism of arachidonic acid/eicosanoid metabolism, as clarified by the Nobel Prize winners Bergström (e1), Samuelson (e2), and Vane (e3). This is a system with complex elements (figure). Phospholipases break down phospholipids in cell membranes, giving arachidonic acid, the starting material for the eicosanoids. The main classes of eicosanoids – the leukotrienes (LT) and the prostaglandins (PG) and thromboxanes (TX) – are predominantly formed by the lipoxygenases (LOX) and the cyclooxygenases (COX). They are important mediators of inflammation and hypersensitivity in almost all cells and organs.

Salicylates and other analogues and anti-inflammatory drugs, particularly the non-steroidal anti-inflammatory drugs (NSAID) mainly used in rheumatology, inhibit cyclooxygenase, thus reducing prostaglandin synthesis (1). In intolerant individuals, there is also activation of basophiles and eosinophiles,
macrophages, mast cells, platelets, and lymphocytes. These cells play an essential role in the symptoms (2, 3, 4, 5, 6, e4, e5, e6, e7, e8, e9).

This stimulation of basophiles and mast cells leads to the secretion of pharmacologically active substances. It is not immunological and may be designated as a "pseudoallergy" or a "pseudoimmunopathy", analogous to cold urticaria. It has also been suggested that the trigger might be infectious agents (e6). The deficiency in enzyme function caused by administration of COX inhibitors may be regarded as intolerance. Thus salicylate intolerance combines features of pseudoallergy and intolerance (2, 7, 8). The pattern of symptoms may depend on the relative numbers of the responsible cells. Studies on the tissues and blood of the same persons are consistent with the symptoms found (4, 5, 9–12).

The effects of salicylates in food from plants or in industrially produced COX inhibitors are in principle the same. COX-2 inhibitors (so-called coxibs) cause fewer gastrointestinal symptoms and effects than COX-1 inhibitors (such as indometacin or ibuprofen) (2, 10, 13). In some cases, the most minor changes in chemical structure may cause substantial differences in the degree of intolerance (e4, 13).

### Classical symptoms

The classical symptoms are in the respiratory tract. These were first described by Hirschberg in Germany in 1902 (e11), later in France by Widal ("Widal's syndrome") (e12), and in the USA by Samter ("Samter's triad") (e9). The manifestations are rhinosinusitis, nasal and sinus polyps, or bronchial asthma (2, 8, e4, e6, e9). When polyposis and asthma occur together with analgesic intolerance, this is known as the "triad." Up to 2.5% of the European population is affected and about 10% of intrinsic asthmatics. The rate of chronic sinusitis with nasal polyps is even higher (table 1) and there are assumed to be many unrecognized cases (2, 8, e4, e5, e6, e9). The symptoms from salicylates in food are also often misinterpreted as allergies. Moreover, salicylates sometimes only trigger symptoms in the presence of independent allergies, as a type of "augmentation phenomenon" (e13). For these reasons, figures on frequency cover a wide range.

### Additional symptoms

The skin and the gastrointestinal tract may also be affected by salicylate intolerance. As the cause is not recognized and the triggering substances continue to be taken, this can lead to chronic processes, such as urticaria (14, e4, e6, e9), colitis (15, e14), or diarrhea (e15). On the other hand, effects on the circulation, or even anaphylactoid (not anaphylactic!) shock, are very rare (e12). Interestingly enough, the symptoms tend to manifest themselves at interfaces – the skin, mucous membranes or (to stretch a point) the vascular system. Salicylate intolerance shares this feature with genuine IgE-mediated allergies.

Anomalies in the eicosanoid complex, sometimes with another background, are also found in other diseases. These include familial intestinal polyposis (e16), malignant processes in the gastrointestinal tract (e17), and some gastroduodenal ulcers (e18, e19).

### Diagnosis

Taking the history is of primary importance during the first visit to the doctor, who must attempt to establish the link between salicylate contact and the occurrence of the symptoms. This is only successful if they occur at close intervals. The doctor must therefore ask whether asthma, skin symptoms, swelling of the nasal mucous membrane, gastrointestinal symptoms or the (very rare) cardiovascular shock have occurred immediately after salicylate consumption. Polyps in the nose and nasal sinuses occur later and grow slowly; the decisive clue is then provided by their rapid and repeated recurrence after operative removal.

The accepted gold standard is the exposure or provocation test. However, these can only confirm or exclude the suspicion for rapid reactions such as

<table>
<thead>
<tr>
<th>Symptoms of salicylate intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Nasal polyps</td>
</tr>
<tr>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>Polyps with asthma</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Chronic intestinal inflammation</td>
</tr>
<tr>
<td>Urticaria/Quincke edema</td>
</tr>
</tbody>
</table>

(Sources: 2, 3, 8, 14)
asthma. Longterm developments such as polyps cannot be adequately followed.

Acetylsalicylic acid is normally administered orally or nasally (2, e4). This should only be done by persons familiar with these problems. Emergency precautions should be taken, as there may be violent reactions, such as asthma. This includes the possibility of observation in hospital and follow-up care. This diagnostic measure requires the proper equipment and is demanding for the personnel.

Fine tissue studies on biopsies can give valuable clues, particularly from eosinophilia (5, 9, 10, 11). This is an invasive approach, with the usual contraindications and risks.

Diagnosis can also be based on imaging techniques, including imaging procedures such as computed tomography (CT) for polyps and tests of lung functions to measure obstruction after exposure or provocation (2, 11, e6, e20). In individual cases, it may be necessary to perform endoscopy for local inspection and for the isolation of biopsies (9, 10, 11, 15, e14, e15, e17, e18).

Functional ex vivo tests are based on the detection of indicators in the patient’s tissues exposed to the test substances. Table 2 gives the sensitivity and specificity of functional in vitro tests and Table 3 summarizes the positive and negative predictive values. This procedure is derived from the techniques and methods used for “genuine allergies.” The following systems are currently commercially available:

- Measurement of the released quantity of LT from prepared basophiles (6, 16, e8). This corresponds to the LOX-dependent metabolic pathways.

- Measurement of the lysozyme-associated membrane protein CD63 by flow cytometry. This has been reported to occur on degranulating basophiles (6, 16, 17, 18). The measurement of enriched basophiles is a less suitable approach to diagnose salicylate intolerance (e21). The activation marker CD203 is a transmembrane metalloenzyme. Its activation by CD63 can be used as a consistent marker. This can be detected by flow cytometry for allergy diagnosis (19, e9).

- An extended functional eicosanoid test (FET) can be used to measure the eicosanoids LT and PG released after exposure to salicylates or other substances (4). This gives a more quantitative measurement of the metabolic pathways of LOX and COX under both normal conditions and conditions equivalent to the disease, together with the dependence on symptoms such as polyposis, rhinitis, and others. These values from blood samples are naturally exceeded by those from the affected tissues – which are only rarely demanded. The FET is also capable of detecting other pathological features of eicosanoid metabolism, e.g., in gastroduodenal ulcer (e19), malignant processes in the intestinal tract (e17), sepsis, and “systemic inflammatory response syndrome” (SIRS) (e22). These are not cases of intolerance. Measurements are usually performed on blood samples (4, 7, 12, 14, 20, 21, 22, e17, e19, e22). As comparative studies have not been performed on the same patient, the value of the different tests cannot yet be rated. Only released substances, such as the eicosanoids, can be measured on tissues or biopsies (9, 10, 11). Flow cytometry cannot be used for this.

**Value of diagnosis**

These tests are limited by the technical possibilities and are mostly useful in recording the current situation. The newer functional tests are useful for unclear cases and when there is no close correlation in time between the symptoms and exposure or provocation. These tests are absolutely indispensable when exposure or provocation is unacceptable because of the circumstances and the patient’s expected reaction, or because of contraindications such as infection or bronchial asthma (2, 6, 23).

The doctor sends the patient’s blood for in vitro/ex vivo functional tests. Because of the biological character of these tests, sophisticated equipment and controls are necessary. Nevertheless, the analytical effort is justified and worthwhile, as the diagnosis is accelerated and improved, promising treatment can be

<table>
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<tr>
<th>Parameter</th>
<th>Released LT (17, 18, e7) SE</th>
<th>Released LT (17, 18, e7) SP</th>
<th>Released LT (17, 18, e7) n</th>
<th>CD63 (6, 18, 19, e9) SE</th>
<th>CD63 (6, 18, 19, e9) SP</th>
<th>CD63 (6, 18, 19, e9) n</th>
<th>FET (7, 14, 21, 22, e18, e19, e21, e22) SE</th>
<th>FET (7, 14, 21, 22, e18, e19, e21, e22) SP</th>
<th>FET (7, 14, 21, 22, e18, e19, e21, e22) n</th>
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<td>99</td>
<td>88</td>
<td>63</td>
<td>93</td>
<td>90</td>
<td>96</td>
<td>83</td>
<td>465</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>68</td>
<td>97</td>
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<td>60</td>
<td>93</td>
<td>50</td>
<td>96</td>
<td>89</td>
<td>407</td>
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<tr>
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<td>50</td>
<td>99</td>
<td>72</td>
<td>65</td>
<td>93</td>
<td>70</td>
<td>96</td>
<td>97</td>
<td>58</td>
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<tr>
<td>Stomach</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>98</td>
<td>90</td>
<td>102</td>
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<tr>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>64</td>
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<td>Respiratory tract/skin/intestine/stomach</td>
<td>--</td>
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<td>--</td>
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<td>--</td>
<td>90</td>
<td>82</td>
<td>699</td>
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</table>

SE, sensitivity in %; SP, specificity in %; n, size of the test group; LT, leukotrienes; CD, cluster of differentiation; FET, functional eicosanoid test
initiated, and the stress and risks for the patient can be avoided. Prices range from 60 to 230 euros, depending on the clinical problem, the required sensitivity and specificity, whether the patient is an inpatient or an outpatient, and whether the insurance is private or not.

**Therapy and prophylaxis**

**Interruption of treatment**
The most reliable form of prophylaxis and therapy is to interrupt treatment. It is particularly important to avoid COX-1 inhibitors. However, some patients react with the same symptoms to very high dosages of paracetamol, used as a substitute (2, e4). In these cases, low-dose buprenorphine or tramadol must be prescribed. If highly sensitive patients interrupt treatment, they must also avoid cosmetics and food with high salicylate content, particularly spices and industrially processed food; 1 g curry may contain up to 2 mg salicylate (e23) (table 4). Advisory teams from university hospitals and other specialized facilities provide tables and diet recommendations for this purpose.

**Surgery**
An operation may be necessary if there is massive tissue growth in the upper respiratory tract and inhibition of the runoff of secretion. There are nevertheless frequent recurrences in patients with salicylate intolerance (2, 4, 6, 8, e4, e5, e6), which greatly reduces inactivation or desensitization (21, e20).

**Drug treatment**
The most active drugs are corticosteroids, as one of their activities is to inhibit the catalysis of the formation of arachidonic acid by phospholipases, the precursor of the responsible eicosanoids (figure). Steroids treatment can be topical or systemic (2, 6, 22, e5).

**Biological methods**
Inactivation or desensitization is a possible biological approach. The term "desensitization" is widely used in the USA, but is somewhat misleading, as it implies the specific suppression of immunological genuine allergies. The treatment is based on the administration of increasing quantities of acetylsalicylic acid. There is no fixed scheme. The first dose is usually 5 mg. The single doses are then increased up to 100 to 300 mg, which must then be taken once daily on a longterm basis. Depending on the procedure and the patient's tolerance, this can last from a few days to two weeks (2, 22, 23). In about 80% of cases, improvements in nasal respiration, sense of smell and freedom from recurrent polyps are retained for two to three years (22, e20).

The effect can last for up to two weeks after salicylate administration has stopped. There are no consequences if a single dose is omitted or forgotten. If there are longer interruptions (as may be necessary before operations), the treatment must be restarted. As we know from first hand, this is always successful again.

It is better to perform the initial phase of treatment in hospital, as there is some risk of adverse reactions such as asthma or gastrointestinal symptoms, particularly in the phase of dose increase. This deactivation is only justified and permissible in patients with established salicylate intolerance.

The underlying principle is thought to be adaptive enzyme induction (2, 3, 4, 10). It is also possible that the irritable and partially responsible cells can be gradually shifted into a refractory state, in which the generation and metabolism of eicosanoids are arrested.

**Other consequences of shifted eicosanoid patterns**
Eicosanoid production may be abnormal even without exogenous factors. This influences vascular formation and apoptosis, as well as the formation and growth of tumors (e10, e11). In this context, familial accumulation of polypous and malignant processes in the gastrointestinal tract has long been known. This is reduced by COX inhibition, so that compounds of this group may be used for prophylactic therapy (e10, e24).
Interestingly enough, even nutrition can influence the eicosanoid complex. Because of the content of salicylates in plants, vegetarians exhibit increased serum concentrations (e24). This may be one of the reasons for their lower rate of cancer (e25). Increased consumption of unsaturated fatty acids leads to reduced de novo formation of arachidonic acid, coupled to decreased uptake from food. This inhibits inflammatory activity and also has an immunomodulatory effect (e26). This has been shown in gastroenterology (e27), rheumatology (e28), and neurology (e29). As however other triggering factors are important and other therapeutic approaches are available, diet alone cannot be more than an accompanying supportive measure.

Salicylate intolerance and the resulting eicosanoid shift is a specific systemic feature, accompanied by different individual manifestations and symptoms. It is necessary to think outside the box, e.g., by watching out for nasal polyps after protracted administration of COX inhibitors (24).

**Perspectives**

The systemic nature of the disturbance may hint at involvement in other diseases, such as Sudeck’s disease, eosinophilic organopathies or even the HELLP syndrome. Functional tests on blood or tissue would be capable of establishing this. They would also indicate whether, or to what extent, typical changes exist before the disease has broken out and who is at risk.

The eicosanoid complex and the actions of salicylates and fatty acids form a specific and interlocking theme in medicine. There is a wide variety of facets. Knowledge based on tests of function opens new approaches to diagnosis and therapy. Taken together with established options, these could help many more of those affected by these problems.

**Conflict of interest statement**

The author holds the patent to the test of eicosanoid function.

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Translated from the original German by Rodney A. Yeates, M.A., Ph.D.

**REFERENCES**


<table>
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<tr>
<th>Food</th>
<th>Salicylate content (mg/kg)</th>
<th>Spices</th>
<th>Salicylate content (mg/kg)</th>
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<td>2.7</td>
<td>Cayenne</td>
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<td>Bananas</td>
<td>0.1</td>
<td>Garlic</td>
<td>1</td>
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</table>

**TABLE 4**

Modified from (e22)


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For e-references please refer to:
www.aerzteblatt-international.de/ref0808
**Salicylate Intolerance**

**Pathophysiology, Clinical Spectrum, Diagnosis and Treatment**

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