

Intestinal permeability in healthy and allergic children before and after sodium-cromoglycate treatment assessed with different-sized polyethyleneglycols (PEG 400 and PEG 1000)

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Summary

Gastrointestinal permeability was investigated in twenty-two children on two occasions, before and after treatment with sodium cromoglycate. The children were between 8 and 10 years old; half of them were classified as allergic according to history and laboratory tests, and half of them as healthy. The 6-hr urinary recovery of different-sized polyethyleneglycols (PEG 400 and PEG 1000) in combination with a mathematical model was used to assess the intestinal permeability barrier.

No significant differences were seen in the first PEG test between healthy and allergic children, although those with gastrointestinal allergy showed a slightly lower, and those with other allergies a slightly higher recovery of the smaller PEGs than seen in the healthy individuals. After treatment with sodium cromoglycate, however, there was a significant decrease in uptake by allergic children, which could indicate that the permeability properties had returned to normal.

The PEG method offers a simple, harmless and reproducible method to measure intestinal permeability properties. The change in permeability observed after sodium cromoglycate corresponds well with the clinical experience of usefulness of the drug in some children with food allergy.

Introduction

A variety of symptoms have been attributed to absorption of allergens through the gut. A protective effect of sodium cromoglycate (SCG) in a considerable number of children with food allergy has been reported (Wraith, Young & Lee, 1979) but the mechanism is not yet completely understood (Altounyan, 1979).

The permeability has been studied by various methods. In man, absorption has been studied by sugars of different size (Menzies *et al.*, 1979), by absorption of

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ovalbumin (Dannaeus *et al.*, 1979), and by different-sized polyethyleneglycols (Chadwick, Phillips & Hofmann, 1977a, 1977b; Sundqvist *et al.*, 1980). In animal studies, the intestinal barrier has been studied by instilling a tracer, e.g. radiolabelled proteins, either in a tied loop or in an excised portion of the small intestine. Several studies have indicated the uptake of macromolecules (André *et al.*, 1974; Hemmings & Williams, 1978; Udall *et al.*, 1981) but the uptake of macromolecules radiolabelled with iodine has recently been shown to be overestimated due to dissociation of the radioactive label (Skogh, 1982).

The PEG 400 absorption test was first described by Chadwick *et al.* (1977 a,b) as a test to assess gastrointestinal permeability. It offers the advantage of giving detailed information of absorption of molecules of different size, from the gut (Sundqvist *et al.*, 1980, 1981).

Several studies in man (Heuman, Sjö Dahl & Tagesson, 1982; Jackson *et al.*, 1981; Sundqvist *et al.*, 1982) have indicated that a wider size range of probe molecules than supplied by PEG 400 would be more useful to examine the intestinal barrier. Therefore a mixture of PEG 400 and PEG 1000 (Magnusson, Serrander & Sundqvist, 1982), covering about 238–1250 daltons, was used. This also enables a more reliable mathematical assessment (Sundqvist *et al.*, 1980) of the permeability properties.

The aims of the present study were:

- 1 to apply the PEG absorption test to children and to evaluate the reproducibility and the effect of prolonged urinary collection time (from 6 to 24 hr);
- 2 to investigate intestinal permeability in allergic and healthy subjects; and
- 3 to study the effect of sodium cromoglycate on the intestinal permeability.

Using a mixture of PEG 400 and PEG 1000, it was found that the intestinal permeability was not significantly different in allergic and healthy children, but that allergic children responded with a reduced recovery of PEGs after treatment with SCG. The recovery of small PEGs was higher in the healthy children than in healthy adult volunteers, 18–54 years of age (Magnusson *et al.*, 1983).

Materials and methods

Subjects of investigation

Twenty-two children (twelve girls, ten boys), aged between 8 years and 1 month, and 9 years and 5 months, were included in the study. They were all members of a group of 140 children studied from birth (Kjellman & Johansson, 1976, 1979). They had been examined by family history, case history, clinical investigations and IgE determinations at birth and additionally five to eight times before the study.

For the purpose of the present investigation, clinical examination was performed and history of current allergic symptoms taken in half of the group by the doctor familiar with these children since their birth (MK). Only cases in which it was possible to classify the child definitely as allergic or non-allergic were accepted for the study. Of twenty-four such children, twenty-two accepted to participate. Blood samples were drawn for IgE (Phadebas IgE PRIST®) and RAST (Phadebas RAST®) to cow's milk, egg, fish, soy and wheat, and for serum creatinine.

Skin-prick test (SPT) was performed against cow's milk, soy, birch, timothy, mugwort, dog, cat, horse, mite and moulds (*Alternaria*, *Cladosporium*).

At the investigation, no child had signs of acute gastrointestinal disorder. No child showed signs of malnutrition. The children with gastrointestinal allergy were *not*

challenged with the offending food prior to the investigation. Children with seasonal allergy were investigated out of season.

Out of the twenty-two children, eleven were classified as healthy, having neither a case history nor clinical signs of allergic disease, and ten of them having no family history of allergy. The healthy children had normal IgE levels for age (Kjellman & Johansson, 1976). None of them had a positive SPT nor a positive RAST test. Five children were classified as having gastrointestinal allergy, and six as having other allergy (Table 1).

Measurement of intestinal permeability

The PEG test was performed at home. After an overnight fast and voiding, the child took 10 ml of an aqueous solution of 0.1 g PEG 400 and 2.5 PEG 1000 (molecular weight range 238–1250 daltons) (Macrogolum, Apoteksbolaget, Sweden), with a glass of water or lemonade. Another two or three glasses of beverage were taken during the 6-hr collection of urine.

All the children were investigated twice with at least 2 weeks interval. Before the second PEG test the children were treated with SCG, 100 mg four times daily before meals for a week. A quarter of an hour before the second PEG test they took 200 mg SCG. The SCG was dissolved in 20 ml of lukewarm water, and the mouth was rinsed with the solution before swallowing.

Three healthy children were investigated a third time at least 1 month after the second test. No pre-treatment was given, but the urine was collected over an extended period of time (0–6, 6–12 and 12–24 hr after drinking the PEG).

PEG analysis. Six-hr pooled samples of urine were analysed, and when the volume was under 500 ml, it was adjusted to 500 ml with water to average the PEG and other urinary constituents. Six ml was mixed on a Vortex mixer with 3.7 g Amberlite MB-3 anionic and cationic resin (BDH Ltd, England), inverted repeatedly for 30 min at 37°C, mixed with new resin and inverted for another 30 min at 37°C. A 2-ml sample was freeze-dried overnight, dissolved in methanol (42%) and water (58%), filtered through a 0.45 µm filter, and analysed in high-performance liquid chromatography (HPLC; HSRI 931, Tecator, Sweden, equipped with 20 cm (diam. 6.5 mm) reversed-phase C-8 column). The pressure was about 20 MPa and the flow rate (waste mode) around 40 ml/hr. A control urine was obtained by adding the same PEG mixture to urine to a concentration of 2 ml/l, which was treated in parallel with the other urine samples.

The amount of each PEG molecule-weight species was assayed from the height of the peaks (Fig. 1) as determined with an integrator (Supergrator 1, Columbia Science Instruments, Austin, Tx, U.S.A.). After measuring the recovery of the different-sized PEG molecules towards a five-point standard curve, the results were further analysed by curve-fitting to a mathematical filter function on a desk computer (ABC 800, Luxor, Motala, Sweden). The filter function, describing the intestinal filter (Sundqvist *et al.*, 1980, Sundqvist *et al.*, 1981) is:

$$F(k) = H_0 \left[(1 - H_4) + \frac{H_4}{1 + \left(\frac{k}{H_5} \right)^{H_6}} \right],$$

where $F(k)$ is the filter function, k the different molecular weights (dalton), H_0 is the recovery if there was no filtering (= recovery of small molecules), $1 - H_4$ the fraction

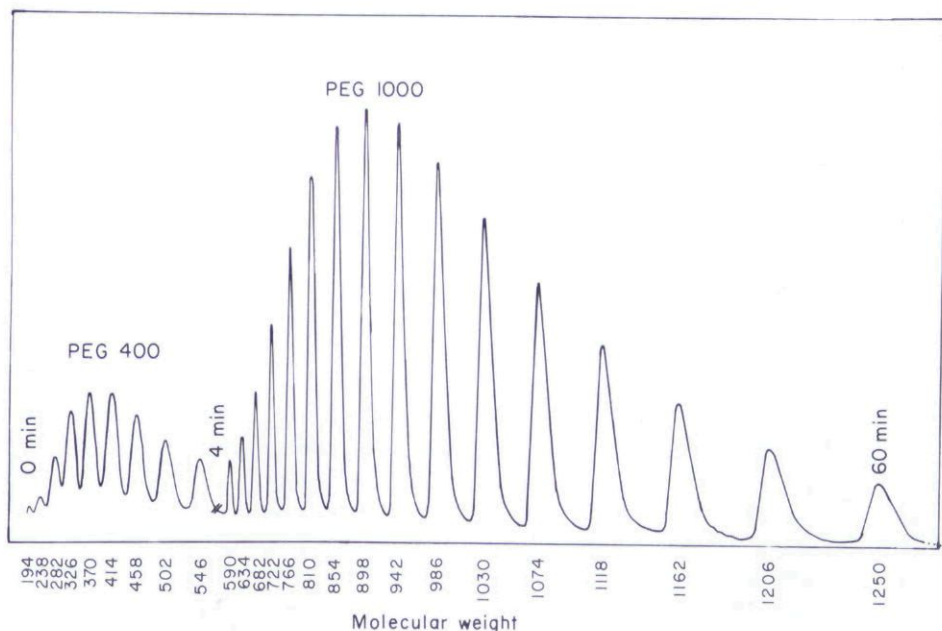


Fig. 1. A typical HPLC chromatogram showing the separation of the molecular-weight species of the mixture of polyethyleneglycols (PEG 400 and PEG 1000). The height of the peaks indicates the relative amount of each polymer.

that passes without filtering, H_4 the fraction that is filtered, H_5 the breakpoint, i.e. where 50% of filtering has occurred, H_6 the slope of the function where half of the filtering has occurred (i.e. inversely proportional to the molecular weight range where the filter operates).

Results

Clinical characteristics

The renal function, as measured by history and serum creatinine, was normal in all cases (40–90 $\mu\text{mol/l}$, reference value 30–115 $\mu\text{mol/l}$). There were no reports on gastrointestinal discomfort, diarrhoea or other side effects during the test or the following 24 hr. According to the case and family history, and the results of IgE, RAST and SPT, the children could be divided into the following groups, characterized by: (i) gastrointestinal allergy ($n=5$; IgE 125–2600 ku/l, median value 490 ku/l), (ii) other allergy (atopic dermatitis, allergic rhinoconjunctivitis and bronchial asthma ($n=6$; IgE 21–355 ku/l, median value 53 ku/l), and (iii) healthy ($n=11$; IgE 5–168 ku/l, median value 13). Further details on the allergic subjects are given in Table 1.

Urinary recovery of PEGs

The recovery of PEGs in 6-hr urine is shown in Fig. 2. It is seen that (i) the average uptake of small PEGs varies such that children with gastrointestinal allergy showed the smallest, those with other allergy the greatest, and the healthy children an intermediate uptake of probe molecules; and (ii) that SCG on average reduced the recovery of PEGs in all the three groups almost independently of the size of the probes. However, the

Table 1. Data on the children classified as allergic

Sex	Avoids	Clinical diagnosis*	ku/l	IgE cow's milk	RAST class				Skin prick test positive to	
					egg	fish	soy	wheat		
Gastrointestinal allergy (<i>n</i> = 5)										
Boy	Cow's milk, nuts, peas	AB, ARC, GI	2600	2	0	0	3	3	3	Timothy, alternaria
Girl	Cow's milk, fish, nuts	AB, ARC, GI	1000	2	2	3	1	2	2	Cow's milk, birch, cat
Boy	Fish	AB, ARC, GI	490	0	3	4	1	2	2	Birch, dog, cat, horse
Boy	Fish, nuts	AB, ARC, GI	135	0	0	2	0	1	1	Timothy
Girl	Peas, cucumber	AB, AD, GI	125	0	0	0	0	1	1	Birch, dog, cat, horse
Other allergy (<i>n</i> = 6)										
Boy		AB, ARC	355	0	0	0	0	0	0	Birch, dog, cat, horse
Girl	Nuts, apples	AD	105	0	0	0	0	0	0	Birch, timothy, dog, cat
Girl		AD	70	0	0	0	0	0	0	Horse
Boy	Carrots	AD, ARC	36	0	0	0	0	0	0	Birch, timothy, mugwort
Girl		AD, ARC	22	0	0	0	0	0	0	Birch, mugwort
Boy		AB	21	0	0	0	0	0	0	Mite

* AB = asthma bronchiale, ARC = allergic rhinoconjunctivitis, GI = gastrointestinal allergy, AD = atopic dermatitis.

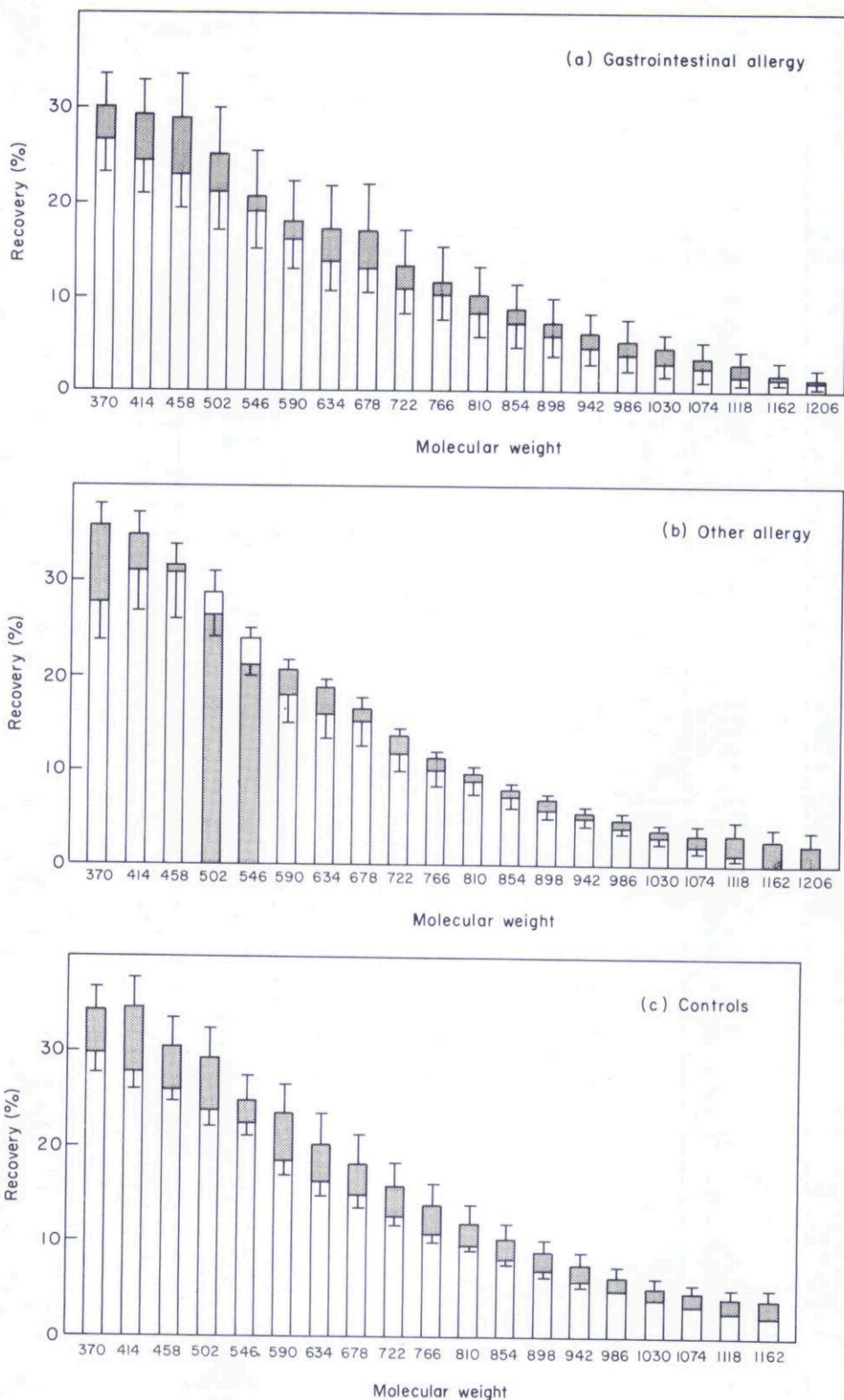


Fig. 2. Percent 6-hr urinary recovery ($\pm$ s.e.) of different sized polyethyleneglycols for (a) children with gastrointestinal allergy, (b) children with other allergy, and (c) healthy children. The shaded area depicts the reduction of the recovery after treatment with sodium cromoglycate (SCG), except for panel (b) and the PEG molecular weights of 502 and 546 daltons which appeared smaller before treatment.

variation within each group was large, and therefore the differences do not appear significant.

Table 2 shows the values of the filter constants characterizing the intestinal permeability barrier. The values were obtained after curve-fitting $F(k)$ to the recovery of PEGs in each subject before and after treatment with SCG. Table 2 also contains the values of the filter constants obtained after curve-fitting to the mean values of each PEG size. After treatment with SCG, almost all (ten of eleven), allergic children and six of eleven healthy children showed a reduction of H_0 , representing the recovery of a small PEG molecule not subjected to intestinal filtering (Table 3). The treatment with SCG did not alter significantly the mean values of the breakpoint (H_5), representing the molecular weights at which the intestinal barrier demonstrated 50% of its capacity (Table 2).

However, the standard deviations were smaller after SCG treatment in all three groups (Table 2). Assuming, that the median value of H_5 in the healthy subjects (654 daltons) represents a 'normal' intestinal barrier, we investigated the change of H_5 in each subject on the SCG treatment, so as to determine whether the response to SCG could be described as a return to normal of the intestinal barrier properties (Table 4).

A change in H_5 was regarded as 'expected' if it differed from the median value of the healthy individuals by more than ± 44 daltons (= molecular weight of the oxyethylene unit) and changed towards the reference value with SCG. If it remained within the 44-dalton range of this value, it was regarded as an 'expected unchanged' value.

Table 2. Values of the filter constants (see text) characterizing the intestinal permeability barrier (mean $\pm$ s.d.) before and after treatment with SCG

Group	Gastrointestinal allergy (n=5)		Other allergy (n=6)		Healthy (n=11)	
	Before	After	Before	After	Before	After
H_0 (%)	33.2 $\pm$ 6.5	26.8 $\pm$ 8.2	38.4 $\pm$ 5.0	29.3 $\pm$ 8.4	35.7 $\pm$ 9.6	31.3 $\pm$ 7.9
$(1-H_4) \times 100$	2.5 $\pm$ 2.7	2.5 $\pm$ 4.1	1.8 $\pm$ 2.8	0.6 $\pm$ 1.2	4.9 $\pm$ 1.2	0.8 $\pm$ 1.2
H_5 (dalton)	625 $\pm$ 103	705 $\pm$ 99	628 $\pm$ 51	665 $\pm$ 20	669 $\pm$ 73	669 $\pm$ 54
H_6	4.6 $\pm$ 2.2	6.2 $\pm$ 1.1	4.6 $\pm$ 0.6	5.2 $\pm$ 0.7	5.5 $\pm$ 1.6	4.7 $\pm$ 1.3

Table 3. Number of children showing change in the maximum recovery parameter (H_0) after treatment with SCG

Group	Gastrointestinal allergy	Other allergy	Gastrointestinal + other allergy	Healthy
No. of children	5	6	11	11
Increase	1	0	1	5
Decrease	4	6	10	6
P value*	N.S.†	<0.05	<0.05	N.S.

* Determined with Wilcoxon's test (sign test).

† N.S. = not significant.

Table 4. Median value (in dalton) of the breakpoint, (H_5), before and after treatment with SCG, and the number of subjects showing a 'normalization'* of H_5

Group	Gastrointestinal allergy		Other allergy		Gastrointestinal + other allergy		Healthy	
	Before	After	Before	After	Before	After	Before	After
Median value of H_5	656	646	621	663	652	659	654	654
Subjects showing expected changed or unchanged value		4/5		6/6		10/11		9/10

*The median value in the healthy group was assigned normal (=reference value). A change of H_5 was regarded as "expected" if SCG changed the H_5 -value towards the reference value (654 dalton). If it remained unchanged within a 44-dalton range of the reference value it was described as an 'expected unchanged' value.

Ten of eleven allergic children showed an expected change, that is 'normalization' of barrier properties after SCG, and nine of eleven healthy children showed no change.

Prolonged urinary collection time

In the reinvestigation of the three healthy children with a prolonged urine collection time (in total 24 hr), less than 10% of the 6-hr recovery was added during the following 18 hr. Therefore, we performed no further extended collection of urine.

The coefficient of variation between the first and third occasion was less than $\pm 5\%$, independent of the size of the PEG, indicating that the test was not subject to uncontrollable changes.

Discussion

Different-sized polyethyleneglycols have been used in several studies in man to examine gastrointestinal permeability, in coeliac disease (Chadwick *et al.* 1977b), rheumatoid arthritis (Sundqvist *et al.*, 1982), Crohn's disease (Heuman *et al.*, 1982, Magnusson *et al.*, 1983, Skogh *et al.*, 1980) and infectious diarrhoeal diseases (Magnusson *et al.*, 1982).

Earlier studies (Jackson *et al.*, 1981) have indicated increased uptake of larger PEGs (600 and 4000) in atopic individuals, and also increased urinary excretion of larger molecules over an extended period (24 hr). In the present investigation, using a mixture of PEG 400 and PEG 1000, we found no significant difference between healthy and atopic subjects, including symptom-free children with a diagnosis of gastrointestinal allergy (Fig. 2). However, for almost all sizes of PEG, the atopic patients with eczema, asthma or hayfever showed greater absorption than the healthy individuals and those with gastrointestinal allergy; the latter group showed the smallest urinary recovery. Using the filter theory, neither the uptake of small molecules (proportional to H_0), nor of larger PEGs (proportional to $H_0 \times (1 - H_4)$) was significantly altered in the atopic subjects (Table 2). However, the children in our study were not considered clinically ill at the time of investigation, and they were not challenged with the incriminating food; the exclusion diet is stated in Table 1. The conflicting results may

also be due to the fact that the subjects were of different age in the two studies, or that slightly different methodology was used to determine the PEGs.

The tendency to a decreased uptake of PEGs in the subjects with gastrointestinal allergy, may reflect minute epithelial damage with villous atrophy, resulting in a reduced absorptive surface area, as has been shown in some cases of food allergy (Vitoria *et al.*, 1982). SCG has previously been shown to depress mast-cell degranulation (Pauwels & van der Straeten, 1979) and also reduces the uptake of food antigen (ovalbumin) in humans (Dannaeus *et al.*, 1979). According to the mean values for each PEG molecular-weight species in Fig. 2, SCG reduces the intestinal permeability in all the three groups, but only in the children with 'other allergy' does the change appear significant (Table 3). When analysing the data for each child, there seem to be groups of 'high' and 'low' or 'non' responders to SCG among the atopic subjects. This corresponds to clinical experience, when using SCG for treatment of patients with food allergy (Zanussi, 1982). The same pattern was seen also in half of the group of healthy subjects (Table 3).

As a point of discussion we propose that SCG exerts a 'normalization' of the permeability properties of the gut (Table 4), e.g. by inhibition of degranulation of mast cells in the gut and prevention of appearance of IgE-IgG complexes with antigen (Brostoff *et al.*, 1979).

To conclude, we think that the PEG absorption test in combination with the mathematical model is a reproducible and useful method to describe resorption and filtration of the different-sized molecules by the gut. The results indicate that there is a difference in the recovery between children and adults, with higher uptake among the children. The test is currently used in atopic children during food challenge, and in younger children to assess permeability changes due to age.

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