

not need additional oxygen on the day of observation. One would expect much lower mean Spo_2 values in infants with cyanotic heart failure.⁷ Also, Lou's⁸ study on attention-deficit hyperactivity disorder describes infants with recurrent episodes of hypoxemia. Using the definition of hypoxemia given by Poets^{4,9} (i.e. oxygen saturation <80% for at least 4 seconds), none of our infants suffered from hypoxemia while being carried in the sling. Tin et al¹⁰ pointed out in their study that the saturation level in preterm infants is of only little influence on neurological outcome and on the development of retinopathy. Their study showed that the development of cerebral palsy in 296 preterm infants <28 gestational weeks did not correlate with the saturation level (target saturation level between minimum 70%–90% and maximum 88%–98%). Moreover, the percentage of threshold retinopathy in 1-year survivors increased with the saturation level.

As mentioned in our article, we only observed desaturation episodes (<88%) in preterm babies. We advised caution with the use of slings for carrying preterm infants before they reach term postconceptional age, although no desaturation below 80% was seen in our study, and the clinical relevance of desaturation to Spo_2 levels between 88% and 80% is unclear. We remain satisfied with our conclusion that term babies are not at risk of desaturation while being carried in the sling.

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Gelatin Allergy

To the Editor.—

We feel relieved after reading the paper by Pool et al and the VAERS Team¹ on the prevalence of gelatin allergy in the United States. They conducted a retrospective analysis after measles-mumps-rubella (MMR) vaccination. Among 26 cases of anaphylaxis, only 6 (27%) were positive for anti-gelatin IgE antibodies. The rate of anaphylactic reactions reported to the VAERS is 1.8 per 1 million doses, and no substantial increase in number of reported allergic events after MMR was observed since the introduction of

gelatin-containing diphtheria-tetanus-acellular pertussis vaccine (DTaP) in 1997. We reported that the cases of anaphylaxis or urticaria showed high positive rates of anti-gelatin IgE antibodies, and we speculated the causal relationship of the sensitization by gelatin-containing DTaP.² Discontinuation of gelatin-containing DTaP reduced the incidence of anaphylaxis after 1999,³ and we have no report of anaphylaxis after vaccination with live virus vaccines containing hydrolyzed porcine gelatin in the last few years. Thus, we were solicitous for the incidence of anaphylaxis in the United States, but they reported that the incidence of gelatin allergy was lower than that observed in Japan.

But we suppose the different prevalence of anti-gelatin IgE depends on sensitivity for the detection of IgE antibodies against gelatin and especially on the nature of antigen for the assay. The same was the reason why the sensitization against gelatin increased in Japan. Some vaccine manufactures used poorly hydrolyzed bovine gelatin in DTaP, and some used hydrolyzed porcine gelatin. A large number of patients with anaphylaxis had a history of having DTaP containing poorly hydrolyzed bovine gelatin. Poorly hydrolyzed bovine gelatin was immunogenic when administered with alum adjuvant. They did not mention the nature of gelatin in DTaP in the United States in their paper, and we suppose that it was probably highly hydrolyzed porcine gelatin (2–3 kDa). Although it is considered as less immunogenic, gelatin-free DTaP is desirable to avoid the possibility of unnecessary sensitization against gelatin.

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In Reply.—

Drs Nakayama and Kumagai note the difference in the prevalence of anti-gelatin IgE antibodies found in sera from patients suffering anaphylactic reactions to measles-mumps-rubella (MMR) vaccines in their study in Japan (93%)¹ and our study in the United States (27%).² They suggest that this difference may be due to differences in the sensitivity and specificity of tests to detect anti-gelatin IgE, which in turn may depend on the nature of gelatin used in the assay. The solid-phase allergen for the radioimmunoassay we used was made from a random lot of flavored sugared commercial gelatin (Jell-O) and thus not exactly the same gelatin that is present in MMR vaccines. It is not clear if the "bovine gelatin" used in their assay was the same as that used in vaccines manufactured in Japan. However, we believe that differences between the gelatin in the immunoassay and the gelatin in the vaccine are unlikely to be the primary explanation for the difference in prevalence of anti-gelatin IgE found in the Japanese and US studies. In the first case report describing gelatin allergy as a cause of anaphylaxis to MMR, inhibition immunoassays were performed.³ The patient's anti-gelatin IgE antibodies directed against gelatin (the same type of gelatin used in the assay in our present study) were inhibited not only by both bovine and porcine laboratory gelatins but also by the MMR vaccine itself containing

pharmaceutical gelatin. This suggests that common IgE-binding gelatin epitopes are present on a wide variety of animal gelatins regardless of source or use. We also note that the prevalence of anti-gelatin IgE we found in US recipients of MMR suffering anaphylaxis (27%) is remarkably similar to that found in a study from Finland (28%) using different immunoassay techniques.⁴ We believe a possibly more likely explanation for the difference in Japanese and US prevalence has been proposed by Dr Kumagai himself in a report describing a strong association between gelatin allergy and HLA-DR9, which is unique to Asians, in which he concludes that this association would "seem to provide a key answer to the question why there are so many reports of gelatin allergy in Japan compared to other countries."⁵

Drs Nakayama and Kumagai note that the addition of poorly hydrolyzed gelatin to diphtheria-tetanus-acellular pertussis (DTaP) vaccines in Japan may have contributed to sensitization to gelatin in some children, resulting in increased risk of anaphylaxis on subsequent MMR vaccination.¹ Removal of the gelatin from DTaP vaccines in Japan was followed by a decline in reports of anaphylaxis to subsequently administered MMR vaccines.⁶ However, the nature of the gelatin in the MMR vaccine was also changed to a more thoroughly hydrolyzed material at the same time. Either or both of these changes could have contributed to the decline in reactions.⁶ We do not believe that gelatin containing DTaP is a likely contributor to reactions to MMR in the United States, however. During a time when DTaP vaccines that contained traces of hydrolyzed gelatin became widely used, we did not observe an increase in allergic reactions to subsequently administered gelatin-containing MMR or varicella vaccines.²

Certainly we share with Drs Nakayama and Kumagai the conclusion that gelatin is responsible for a noticeable proportion of anaphylactic reactions to gelatin-containing vaccines, although the rates may differ in different countries (as discussed above).

Persons with a history of anaphylaxis after MMR or other gelatin-containing vaccine are likely at increased risk of similar reactions to subsequent doses of other gelatin-containing vaccines such as varicella and some brands of influenza. Therefore, for these persons we continue to recommend an allergy evaluation including assessment of anti-gelatin IgE by skin testing or now commercially available in vitro testing prior to such immunization.

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Is Obesity Associated With Early Sexual Maturation?

To the Editor.—

I read with interest the article by Dr Wang¹ and would like to share with you our experience in a different population, performing a close follow-up study.² We analyzed in detail the auxology and the appearance and size of pubertal signs compared to weight and skinfolds in boys and girls with simple obesity between the 10 and 16 years old.

All were Israeli-born Jews referred and followed because of simple obesity. The group consisted of 136 boys, 41 girls, and 48 age-matched, randomly selected, healthy boys and 48 healthy girls. Our main statistically significant findings were as follows: At all ages, the obese boys were taller and their bone age more advanced than the controls up to age 14 ($P < .01$ and $.001$). There was no difference between the two male groups in the time of appearance and development of axillary or pubic hair, moustache, beard, acne or breaking of the voice, testicular volume, and penile size. The mean overall pubertal score and age of first ejaculation³ were also similar.

The obese girls were taller than the controls up to age 14, with a statistically significant difference between 11 and 13 ($P < .001$). The bone age was significantly advanced between 9 and 11 years ($P < .01$), but there was no significant difference in the age of appearance and development of the breasts, pubic hair, genitalia, or age at menarche. There were two additional small groups of obese girls: 8 with obesity and tall stature but without sexual precocity and 12 obese girls with precocious puberty. The degree of obesity in these girls was not different from those with so-called simple obesity, and therefore we concluded that these developmental characteristics were hereditary.

An additional finding was that parents of the obese children were significantly overweight ($P < .01$) compared with the parents of the controls, supporting the opinion of Schwarz⁴ that obesity is a hereditary disorder with familial faulty dietary habits. We concluded that our data do not support the hypotheses of a "critical weight factor" determining sexual maturation.

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