Thymopentin treatment in severe atopic dermatitis—clinical and immunological evaluations

Kue-Hsiung Hsieh, Men-Fang Shaio, Tung-Nan Liao

Abstract

An open clinical trial of thymopentin was conducted on 16 children with severe atopic dermatitis. The patients were treated with injections three times a week of 50 mg thymopentin for six weeks. They were then divided randomly into two groups: group A continued thymopentin for an additional six weeks, and group B were treated with normal saline. Clinical parameters and immunological function were evaluated serially. The total severity score started to decline from baseline significantly three weeks after treatment, and continued throughout the study period in group A but began to flare up in group B two weeks after stopping thymopentin. All the eight patients in group A completed the trial but three out of eight in group B dropped out because of flaring up of skin lesion. In vitro production of interleukin-4 tended to decrease and that of interferon gamma tended to increase, but total serum IgE, in vitro IgE synthesis, and abnormally low CD8+ CD11b+ suppressor T cells remained unchanged. Histamine releasing factor (HRF), plasma histamine, and respiratory burst activities of polymorphonuclear leucocytes were appreciably decreased after thymopentin treatment.

It is concluded that the clinical efficacy of short term thymopentin treatment very possibly results from the decreased production of HRF and decreased release of polymorphonuclear leucocyte derived inflammatory mediators and may have no relation with antigen-IgE immune reaction.

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Atopic dermatitis is a chronic cutaneous inflammatory disease characterised by early age of onset, severe pruritus, typical morphology and distribution of skin rash, chronic relapsing course, and personal or family history of atopy.^{1 2} It is a common disease among infants and children with an incidence of 1·9% to 8·3% in white people^{3–6} and 1·24% in Chinese school-children.⁷ Chronic atopic dermatitis may result in significant morbidity, including hospitalisation for control of skin disease and infection, lost school days, psychological trauma from physical disfigurement, and occupational disability. The management of atopic dermatitis has been less than satisfactory. None of the currently available treatments are curative and treatment is empirical.⁶

Although the pathogenesis of atopic dermatitis

remains unclear, a number of immunological abnormalities have been described. They include:

- (i) Raised and sustained serum IgE concentrations,⁸
- (ii) Impaired T cell function,⁹
- (iii) Decreased natural killer cell activity,¹⁰
- (iv) Defective capacity to generate alloreactive cytotoxic T cells,¹¹
- (v) Impaired autologous mixed lymphocyte reaction due to defective CD4 responder T cells¹²
- (vi) Increased cell mediated cytotoxicity against skin fibroblasts,¹³
- (vii) Most importantly, immunological reconstitution after bone marrow transplantation results in the permanent resolution of eczema in Wiskott-Aldrich syndrome, a primary T cell immunodeficiency with raised serum IgE, providing in vivo evidence that immune defects predispose to the development of eczema.¹⁴

Thymopoietin is a polypeptide hormone of the thymus, originally isolated from bovine thymus extract by its effect on neuromuscular transmission.¹⁵ It is secreted by thymic epithelial cells and has been shown to influence both the differentiation of thymocytes¹⁶ and the function of mature T cells.^{17 18} Thymopentin (Timunox, Immunobiology Research Institute, Annandale, NJ) is the active pentapeptide (Arg-Lys-Asp-Val-Tyr) moiety corresponding to amino acids 32 to 36 of the linear 49 amino acid sequence of thymopoietin. The biological effects of thymopentin mimic those of thymopoietin in all systems in which it has been evaluated.^{18 19} It was marketed in Italy in 1985, in Belgium in 1987, and in Germany in 1988, and has been used in a number of diseases in which T cell deficiency may have a role.²⁰

Recent studies suggest that thymopentin influences IgE synthesis,²¹ and it might therefore influence the course of atopic diseases in man. Recently, clinical improvement with thymopentin that produced reductions in overall severity in patients with atopic dermatitis has been reported,^{22 23} but the working mechanisms have not been studied extensively. We present the clinical efficacy of an open trial of thymopentin in children with severe atopic dermatitis and correlate the clinical efficacy with the in vivo and in vitro immunological changes after thymopentin treatment.

Subjects and methods

SUBJECTS

Sixteen children, nine boys and seven girls, aged 3 to 14 years, were enrolled into this study.

Department of Paediatrics, National Taiwan University College of Medicine
Kue-Hsiung Hsieh
Tung-Nan Liao

Department of Parasitology and Tropical Medicine, National Defense Medical Center, Taipei, Taiwan, Republic of China
Men-Fang Shaio

Correspondence to:
Dr Kue-Hsiung Hsieh,
Department of Paediatrics,
National Taiwan University Hospital,
7 Chung-Shan S Road,
Taipei, 10016,
Taiwan,
Republic of China.

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The clinical trial was approved by the human research committee of this hospital and informed consent was obtained for each patient. All of the patients had severe pruritus, skin lesions of characteristic morphology and distribution, chronic relapsing course, and a history of atopy, which met the criteria for the diagnosis of atopic dermatitis.^{1,2} The age of onset ranged from 1 month to 1 year, the mean (SD) duration of atopic dermatitis was 8.6 (3.0) years, the serum IgE concentrations ranged from 224 to 5241 IU/ml (mean (SD) 2318 (1525) IU/ml), and the mean (SD) area of involved body surface was 81.5 (25.0)%. The severity was graded on a scale of 0–3 for each of the five parameters: erythema, pruritus, oedema/papulation, excoriation, and scaling/dryness. To be enrolled the patient had to have a severity score of 6 or higher (including a score of 2 or more for both erythema and pruritus). The mean (SD) total severity score before treatment was 14.4 (0.9) (range 12–15). Twenty healthy schoolchildren, aged 7 to 15 years, were included as controls for immunological study.

TREATMENT PROTOCOL

After enrolment the patients received three subcutaneous injections each week of 50 mg of thymopentin for a consecutive six weeks. The patients were then divided randomly into two groups. One group (group A) continued the thymopentin treatment for an additional six weeks, and the other group (group B) was injected with normal saline. Both groups were comparable regarding age, severity score, and serum IgE concentration. During the treatment patients were allowed to continue antihistamines and topical corticosteroids, but systemic corticosteroids were discontinued for at least four weeks before the study. No recommendation on food restriction and environmental control was made.

EVALUATION

The patients were seen every week by one author (KHH). Dermatological assessment, routine laboratory tests (blood chemistry, haematology, and urinalysis), and immunological tests were performed before and at the end of the third, sixth, and 12th week after treatment. The clinical response was evaluated by a dermatologist who did not know the treatment protocol, and adverse reactions were observed carefully. Parents' satisfaction was recorded.

IMMUNOLOGICAL TESTS

Enumeration of lymphocyte subpopulation

T cell subsets were enumerated by FACscan (Becton-Dickinson), using the monoclonal antibodies shown in table 1.

Preparations of sera and culture supernatants

Peripheral blood mononuclear cells (MNCs) were obtained by Ficoll/Hypaque gradient density centrifugation. MNCs at a concentra-

Table 1 Monoclonal antibodies used to enumerate lymphocyte subpopulations

CD3 (total T cells)
CD19 (total B cells)
CD3-CD16+CD56+ (natural killer cells)
CD4 (helper/inducer)
CD4+CD45RA+ (suppressor/inducer)
CD4+CD45R- (helper/inducer)
CD8+ (suppressor/cytotoxic)
CD8+CD11b+ (suppressor)
CD8+CD11b- (cytotoxic)
CD3+CD25+ (activated CD3)
CD4+CD25+ (activated CD4)
CD8+CD25+ (activated CD8)
CD3+HLA-DR+ (activated CD3)
CD4+HLA-DR+ (activated CD4)
CD8+HLA-DR+ (activated CD8)

tion of 2×10^6 cells/ml in complete culture medium (Roswell Park Memorial Institute-1640 supplemented with 10% heat inactivated fetal calf serum, antibiotics and L glutamine) were stimulated with 2 µg/ml phytohaemagglutinin (PHA) (Wellcome) for three days and the supernatants were collected by centrifugation and stored at -20°C until testing.^{24,25} The above mentioned culture conditions, including cell density, PHA concentration, and days of cultivation, were found to be optimal for cytokine production in our previous studies.²⁴⁻²⁶

Measurements of soluble interleukin (IL)-2R, CD4 molecule, and cytokines in supernatants

Cell free CD4 and IL-2 receptor tests kits were purchased from T Cell Sciences (Cambridge, MA), IL-2 and interferon gamma test kits from Genzyme (Boston, MA), and IL-4 and IL-6 test kits from R and D System (Minneapolis, MN). The principle of those tests was sandwich enzyme immunoassay (ELISA), using two monoclonal antibodies against different epitopes of the target molecule (CD4, IL-2, and IL-2R) or monoclonal antibody (first) followed by polyclonal antibody (IL-4, IL-6, and interferon gamma). The sensitivity of the ELISA was 50 pg/ml for IL-2, 50 U/ml for IL-2R, 12 U/ml for CD4, 3 pg/ml for IL-4, 3.5 pg/ml for IL-6, and 100 pg/ml for interferon gamma. The interassay variation of all tests were around 5–10% and a similar figure was found for intra-assay. All the samples of a single individual were run in duplicate simultaneously and at least one normal control was included in each experiment.

Measurement of histamine releasing factor (HRF) activity

HRF was measured as previously described.²⁷ MNCs (2×10^6 cells/ml) were stimulated with 2 µg/ml PHA for four hours, washed, and incubated for additional 20 hours. The supernatant was collected, concentrated 50-fold, using a YM-5 Amicon membrane. The HRF activity of the supernatant was measured by its capacity to release histamine from basophils obtained from a healthy high HRF responder and was expressed as percent of total cellular histamine released. The histamine was determined by using histamine radioimmunoassay kits (Immunotech, France). The sensitivity of the kit was 0.5 nmol/l.

Measurement of serum IgG, IgA, IgM, and IgE

The IgG, IgA, and IgM were measured by nephelometry (Beckman). In vitro production of IgE was done according to the method of Saryan *et al.*¹⁸ The IgE concentrations in sera and culture supernatants were measured by Phadebas IgE PRIST kits (Pharmacia).

Lucigenin amplified chemiluminescence assay

Chemiluminescence was assayed by the method of Gyllenhammar,²⁹ using a luminometer (model 1251, LKB, Bromma) and recorded as mV. Reaction mixtures contained 1×10^6 neutrophils, 0.1 mg lucigenin, and 40 ng phorbol myristate acetate (PMA) or 1 mg opsonised zymosan; and Hanks' balanced salt solution (HBSS) was added up to a final volume of 1 ml in each reaction. The readings were started two minutes after the addition of reagents and were monitored every eight minutes up to an hour.

MEASUREMENTS OF SUPEROXIDE AND HYDROGEN PEROXIDE PRODUCTIONS

Superoxide production was measured as superoxide dismutase inhibitable reduction of ferricytochrome *c* with PMA or opsonised zymosan as stimulant.³⁰ Quantitation of hydrogen peroxide is based on the horseradish peroxidase dependent oxidation of phenol red with PMA or opsonised zymosan as stimulant.³¹ For the superoxide assay the reaction mixture in each well consisted of ferricytochrome *c* (2 mg/ml), PMA (40 ng/ml), or opsonised zymosan (1 mg/ml) with neutrophils in the presence or absence of superoxide dismutase (300 U/ml). The microtitre plates were incubated and shaken at 37°C for one hour and absorbance was read at 550 nm on a Microelisa reader (MR 700, Dynatech Laboratories). For the hydrogen peroxide assay the reaction mixture in each well consisted of HBSS supplemented with 0.56 mM phenol red, 19 U/ml horseradish peroxidase, PMA (40 ng/ml) or opsonised zymosan (1 mg/ml), and neutrophils. The microtitre plates were incubated and shaken at 37°C for one hour and terminated with 10 µl of 1N sodium hydroxide. The absorbance was read at 600 nm. Conversion of absorbance to nanomoles of both superoxide and hydrogen peroxide was calculated by a standard method.³² The results were expressed as nmol of superoxide or hydrogen peroxide/60 minutes/mg of protein.

STATISTICS

All the data were expressed as mean (SEM) except T cell subsets which was expressed as mean (SD). Unpaired Student's *t* test was used for statistical analysis throughout the study except that the Wilcoxon signed rank test was used to analyse the immunoglobulin data. A *p* value of <0.05 was considered significant.

Results

CLINICAL RESPONSE

All eight patients in group A who received 12 weeks of continuous thymopentin injections

Figure 1 Total severity score during treatment with 50 mg thymopentin. Group A had 12 weeks continuous treatment with thymopentin and group B had six weeks of thymopentin followed by six weeks of normal saline injections. Vertical bar represents the SEM; **p* < 0.03, compared with baseline; ***p* < 0.0001, comparison between groups A and B at 12 weeks.

completed the clinical trial. Three out of eight patients in group B who received thymopentin injections for the first six weeks and then switched to normal saline injections during the later half of clinical trial, however, dropped out because of flare up of skin lesions to a degree comparable with the period before thymopentin four weeks after stopping thymopentin. No difference in the total severity score was observed between two groups before and during thymopentin treatment, but the total severity score of group B was much higher than that of group A at 12 weeks (*p* < 0.0001, fig 1). In both groups a therapeutic effect became evident after one week of treatment (*p* < 0.03). The results of evaluation by parents matched very well with that of the physician (data not shown).

LABORATORY CHANGES

Figure 2 demonstrates, as an example, that in case 6 the maculopapulovesicles and lichenification over the neck and antecubital areas (left panel) were much improved after three weeks of thymopentin treatment (right panel). In general, erythema and pruritus were the parameters that were improved most quickly and noticeably among the five clinical parameters evaluated, whereas the improvement in scaling/dryness was much less impressive.

Figure 3 shows the in vitro productions of soluble CD4, IL-2R, and cytokines during the course of treatment. the patients produced a greater amount of soluble CD4 (*p* < 0.001), IL-2R (*p* < 0.01), IL-2 (*p* < 0.001), and IL-4 (*p* < 0.001), but less interferon gamma (*p* < 0.01) than normal controls. After treatment, in vitro production of soluble CD4, IL-2R, IL-2, and IL-4 tended to decrease, but only the decrease in IL-2 (*p* < 0.01) and IL-4 (*p* < 0.01) reached a

Figure 2 The papulovesicles and lichenification of diseased skin before treatment (left panel) and after three weeks of treatment (right panel).

Figure 3 In vitro productions of soluble CD4, IL-2R, and cytokines during thymopentin treatment. For CD4, *** $p < 0.001$; for IL-2, *** $p < 0.001$, ** $p < 0.01$; for IL-2R, ** $p < 0.01$; for IL-4, *** $p < 0.001$, * $p < 0.01$; for IFN- γ , ** $p < 0.01$, * $p < 0.05$. Data are expressed as mean (SEM).

significant degree. In vitro production of IFN- γ was increased ($p<0.05$). No change in IL-6 production was found. Again, those changes were reversed after stopping treatment (group B).

The effect of thymopentin on the distributions of T cell subsets is shown in table 2. When compared with normal controls, the patients

with atopic dermatitis had a normal number (%) of total T cells (CD3+), B cells (CD19+), natural killer cells (CD3- CD16+CD56+), suppressor inducer T cells (CD4+CD45RA+), helper inducer T cells (CD4+CD45RA-), cytotoxic T cells (CD8+CD11b-), CD25+, and HLA-DR+ activated CD3 and CD4 cells. However, suppressor T cells (CD8+CD11b+), and CD25+ and HLA-DR+ activated suppressor/cytotoxic T cells (CD8+) were appreciably decreased in patients. After thymopentin treatment the suppressor T cells (CD8+CD11b+) and CD25+ activated CD8+ cells remained very low even at the end of 12 weeks of thymopentin treatment (table 2).

The changes of serum immunoglobulin concentrations were followed up serially after thymopentin treatment. IgG and IgM tended to decrease after six weeks of treatment, but not to a significant degree. No change was found for IgA, IgE, and in vitro IgE production throughout the course of trial (table 3).

Figure 4 demonstrates that both plasma histamine and HRF activity were much higher in patients than in normal controls ($p<0.001$ for the former and $p<0.001$ for the latter). After thymopentin treatment, both plasma histamine and HRF were decreased significantly. The decrease persisted in group A but reversed to pretreatment value in group at the 12th week (A v B, $p<0.01$).

The respiratory burst activities of polymorphonuclear leucocytes after stimulation with PMA are shown in fig 5. The production of superoxide ($p<0.001$) and hydrogen peroxide ($p<0.001$) before thymopentin treatment was much higher than normal controls and the

Table 2 Changes of distributions of T cell subsets during thymopentin treatment. Results are mean (SD)%

T cell subset	Treatment period (n=10)			Controls (n=20)
	0	3 Weeks	6 Weeks	
CD3+	68.0 (8.7)	66.8 (8.4)	68.3 (6.3)	67.1 (8.2)
CD19+	14.1 (4.8)	17.4 (4.9)	16.6 (7.0)	16.2 (4.9)
CD3-CD16+CD56+	17.3 (9.0)	17.1 (7.5)	16.3 (5.3)	18.3 (9.0)
CD4+	31.9 (8.4)	32.0 (8.1)	33.8 (5.8)	34.8 (6.1)
CD4-CD45RA+	10.7 (3.6)	10.8 (3.9)	11.8 (3.0)	11.9 (3.9)
CD4+CD45RA-	24.7 (5.3)	25.4 (6.8)	24.4 (6.6)	26.7 (7.3)
CD8+	28.5 (5.6)	26.3 (5.9)	29.2 (9.8)	26.7 (9.8)
CD8+CD11b+	5.0 (2.4)*	3.5 (2.1)	5.6 (2.7)	11.9 (3.9)*
CD8+CD11b-	24.2 (5.2)	24.8 (4.8)	26.1 (5.7)	20.0 (9.9)
CD3+CD25+	5.0 (5.1)	4.5 (0.9)	4.1 (1.4)	5.1 (2.8)
CD4+CD25+	5.2 (2.9)	5.6 (2.4)	5.0 (2.3)	6.6 (2.8)
CD8+CD25+	0.7 (1.3)**	0.2 (0.4)	0.2 (0.4)	3.0 (1.9)**
CD3+HLA-DR+	8.2 (5.8)	12.1 (4.4)	15.1 (8.7)	11.3 (4.1)
CD4+HLA-DR+	3.8 (0.9)	6.7 (2.6)	7.4 (2.6)	3.6 (1.3)
CD8+HLA-DR+	4.5 (3.0)***	7.8 (3.5)	8.5 (4.8)	10.3 (4.5)***

* $p=0.0001$, ** $p<0.005$, *** $p<0.002$.

Table 3 Serum immunoglobulins and in vitro IgE synthesis during thymopentin treatment. Results are mean (SD)

Immunoglobulin	Treatment period (n=10)		
	0	3 Weeks	6 Weeks
IgG (g/l)	10.24 (3.43)*	9.91 (3.32)	8.28 (1.37)
IgA (g/l)	1.52 (0.60)	1.52 (0.56)	1.48 (0.38)
IgM (g/l)	1.49 (0.72)	1.49 (0.74)	1.19 (0.39)
IgE (IU/ml)	3283.2 (1666.7)	2862.1 (1653.2)	3026.8 (1388.8)
In vitro IgE synthesis (pg/ml)	1714.5 (3004.2)	2117.6 (2578.3)	1335.8 (1447.6)

* $p<0.05$ (Wilcoxon signed rank test).

Figure 4 Plasma histamine and HRF activity during thymopentin treatment. For plasma histamine, *** $p<0.001$, ** $p<0.01$; for HRF activity, *** $p<0.01$, ** $p<0.01$. Data are expressed as mean (SEM).

Figure 5 Respiratory burst activities of polymorphonuclear leucocytes stimulated by PMA. For chemiluminescence, *** $p < 0.001$, *** $p < 0.001$; for superoxide production, *** $p < 0.001$, *** $p < 0.001$; for hydrogen peroxide production, *** $p < 0.001$, *** $p < 0.001$. Data are expressed as mean (SEM).

Figure 6 Respiratory burst activities of polymorphonuclear leucocytes stimulated by serum opsonised zymosan. For superoxide production, *** $p < 0.001$, *** $p < 0.001$; for hydrogen peroxide production, *** $p < 0.001$, *** $p < 0.01$. Data are expressed as mean (SEM).

heightened activity decreased to normal after treatment. A similar tendency was found when polymorphonuclear leucocytes were stimulated with opsonised zymosan (fig 6); their enhanced activation returned after discontinuation of thymopentin (group B).

Discussion

All patients responded to thymopentin treatment. The itching, scratching, and erythema decreased appreciably three weeks after treatment (fig 1), and the improved skin texture due to subsidence of papulovesicles and lichenifica-

tion usually occurred later (fig 2). The improvement continued in those patients (group A) who received thymopentin treatment throughout the 12 week period, however, the eczema flared up in all patients of group B four weeks after discontinuation of thymopentin (fig 1). The use of topical steroids and antihistamines could be reduced and no serious side effects were observed except transient pain at the injection site. The beneficial clinical response was largely similar to that reported by Kang *et al*²² and Leung *et al*.²³

The immunological mechanism(s) responsible for the clinical efficacy of thymopentin has not been well studied. Cooper *et al* reported that

thymopentin could influence the in vivo and in vitro production by atopic dermatitis MNCs.²¹ The same group further described increased CD8+ (suppressor/cytotoxic) cells after six weeks of thymopentin administration.²² The results obtained in our study could not confirm their hypothesis: (i) total serum IgE and in vitro IgE production were not changed after treatment, and (ii) the CD8+CD11b+ suppressor T cells, but not the total number of CD8+ suppressor/cytotoxic T cells, were decreased in patients with atopic dermatitis, and thymopentin treatment failed to increase the CD8+CD11b+ suppressor and CD8+CD25+ activated T cells. Recent studies have demonstrated that peripheral blood MNCs from patients with atopic dermatitis produced increased concentrations of IL-4,³³ a cytokine that induces IgE synthesis, and decreased concentrations of interferon gamma³⁷ a cytokine that inhibits IL-4 dependent IgE synthesis.^{34–36} Our results confirm those reports,^{33–37} and furthermore this study showed that thymopentin treatment tended to suppress the production of IL-4 and enhanced the production of interferon gamma in vitro. However, Li *et al* recently reported that the total serum IgE and specific IgE antibodies were not decreased in patients with allergic rhinitis after receiving interferon gamma treatment in both periods of off season and during season.³⁸ Vercelli *et al* also found that anti-IL-4 and interferon gamma were unable to suppress the in vitro spontaneous IgE synthesis in patients with hyper-IgE syndrome,³⁹ and no significant difference in mitogen induced productions of IL-4 and interferon gamma was detected between HIE patients and normal controls. Thus, mechanisms other than antigen-IgE immune reaction may account for the rather quick appearance of clinical benefit of short term thymopentin administration in the treatment of atopic dermatitis.

It is important to note that HRF and plasma histamine concentrations were decreased after thymopentin treatment (fig 4). Furthermore, the augmented activation of polymorphonuclear leucocytes was also suppressed, as evidenced by the lessened respiratory burst activities (fig 5 and 6). Sampson *et al* recently reported that patients with atopic dermatitis caused by food allergy produced significantly less HRF after the offending food allergen was eliminated from the diet for an extended period.⁴⁰ Our recent study also demonstrated decreased production of and responsiveness to HRF in asthmatic patients benefited by successful immunotherapy.²⁷ Thus, the decreased production of HRF and decreased release of polymorphonuclear leucocytes derived inflammatory mediators may account partly for the clinical efficacy of thymopentin treatment in patients with atopic dermatitis.

One of the shortcomings of this paper is lack of immunohistological studies of diseased skin before and after thymopentin treatment. Such studies would provide the most direct information that could be used to explain the clinical efficacy of thymopentin. Unfortunately, we are unable to obtain consents from parents to do skin biopsies.

Finally as no serious side effects are

encountered during the 12 week period of treatment and there is still no satisfactory management for severe atopic dermatitis, thymopentin may be used in those patients with atopic dermatitis who are refractory to traditional treatment. Studies with longer duration and larger number of patients are needed before the rationale for such kind of treatment can be justified.

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- Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980;92 (suppl):44–7.
- Hanifin JM. Basic and clinical aspects of atopic dermatitis. *Ann Allergy* 1984;54:386–93.
- Halpern SR, Sellars WA, Johnson RB, *et al*. Development of child allergy in infants fed breast, soy or cow's milk. *J Allergy Clin Immunol* 1973;66:465–71.
- Kjellman N-JM. Atopic disease in seven-year-old children. *Acta Paediatr Scand* 1977;66:465–71.
- Walker RB, Warin RP. Incidence of eczema in early childhood. *Br J Dermatol* 1956;68:182–3.
- Hanifin JM. Atopic dermatitis. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. *Allergy principles and practice*. 3rd Ed. St Louis: CV Mosby, 1988: 1403–28.
- Hsieh KH, Shen JC. Prevalence of childhood asthma in Taipei, Taiwan, and other Asian Pacific countries. *J Asthma* 1988;25:73–82.
- Johnson E, Irons J, Patterson R, Roberts M. Serum IgE concentration in atopic dermatitis. *J Allergy Clin Immunol* 1974;54:94–9.
- Leung DYM, Geha RS. Immunoregulatory abnormalities in atopic dermatitis. *Clin Rev Allergy* 1986;4:67–86.
- Chiarelli F, Canfora G, Verrotti A, Amerio P, Morgese G. Humoral and cellular immunity in children with active and quiescent atopic dermatitis. *Br J Dermatol* 1987;116: 651–60.
- Leung DYM, Wood N, Dubey D, Rhodes AR, Geha RS. Cellular basis of defective cell-mediated lympholysis in atopic dermatitis. *J Immunol* 1983;130:1678–82.
- Leung DYM, Saryan JA, Frankel R, Lareau M, Geha RS. Impairment of the autologous mixed lymphocyte reaction in atopic dermatitis. *J Clin Invest* 1983;72:1482–6.
- Leung DYM, Parkman R, Feller J, Wood N, Geha RS. Cell-mediated cytotoxicity against skin fibroblasts in atopic dermatitis. *J Immunol* 1982;128:1736–41.
- Saurat JH. Eczema in primary immune deficiencies: clues to the pathogenesis of atopic dermatitis with special reference to Wiskott-Aldrich syndrome. *Acta Derm Venereol (Stockh)* 1985;114:125–8.
- Goldstein G, Audhya TK. Thymopoietin to thymopentin: experimental studies. *Survey of Immunological Research* 1985;4 (suppl):1–10.
- Scheid MP, Goldstein G, Boyse EA. The generation and regulation of lymphocyte populations: evidence from differentiative induction systems in vitro. *J Exp Med* 1978; 147:1727–43.
- Meroni PL, Barcellini W, Frasea D, *et al*. In vivo immunopotentiating activity of thymopentin in aging human: increase of IL-2 production. *Clin Immunol Immunopathol* 1987;42:151–9.
- Diezel W, Waschke SR, Forner K. Induction and augmentation of mitogen-induced immune interferon production in human lymphocytes by a synthetic thymopoietin pentapeptide. *Biomed Biochim Acta* 1984;43:9–12.
- Goldstein G, Scheid MP, Boyse EA, *et al*. A synthetic pentapeptide with biologic activity characteristics of the thymic hormone thymopoietin. *Science* 1979;204:1309–10.
- Sundal E, Bolla K. Therapy with thymopentin: a clinical overview. In: Malaise MG, ed. *Immune regulation by characterized polypeptides*. New York: Alan R. Liss 1987:121–36.
- Cooper KD, Kang K, Hanifin JM. Effects of thymopoietin pentapeptide (TP-5) on in vitro and in vivo IgE production by atopic dermatitis cell subsets. *Diagnostic Immunology* 1983;1:211–5.
- Kang K, Cooper KD, Hanifin JM. Thymopentin pentapeptide (TP-5) improves clinical parameters and lymphocyte subpopulations in atopic dermatitis. *J Am Acad Dermatol* 1983;8:372–7.
- Leung DYM, Hirsch RL, Schneider L, *et al*. Thymopentin therapy reduces the clinical severity of atopic dermatitis. *J Allergy Clin Immunol* 1990;85:927–33.
- Hsieh KH. Altered interleukin-2 production and responsiveness after hyposensitization to house dust. *J Allergy Clin Immunol* 1985;76:188–94.
- Hsieh KH. Decreased production of interleukin-2 receptors after immunotherapy to house dust. *J Clin Immunol* 1988; 8:171–7.
- Hsieh KH. Decreased production of CD8 (T8) antigen after immunotherapy. *J Clin Immunol* 1989;9:111–8.
- Liao TN, Hsieh KH. Decreased production of and responsiveness to histamine releasing factor after immunotherapy in asthmatic children. *J Allergy Clin Immunol* 1990;86: 894–901.

- 28 Saryan JA, Leung DYM, Geha RS. Induction of human IgE synthesis by a factor derived from T cells of patients with hyper-IgE status. *J Immunol* 1983;130:242-7.
- 29 Gyllenhammar H. Lucigenin chemiluminescence in the assessment of neutrophil superoxide production. *J Immunol Methods* 1987;97:209-13.
- 30 Rosen H, Klebanoff SJ. Chemiluminescence and superoxide production by myeloperoxidase-deficient leukocytes. *J Clin Invest* 1976;58:50-60.
- 31 Pick E, Keisari Y. A simple colorimetric method for the measurement of hydrogen peroxide produced by cells in culture. *J Immunol Methods* 1980;38:161-70.
- 32 Pick E, Mizel D. Rapid microassays for the measurement of superoxide and hydrogen peroxide production by macrophages in culture using an automatic enzyme immunoassay reader. *J Immunol Methods* 1981;46:211-26.
- 33 Brown MA, Li SH, Chan SC, Hanifin J. Interleukin-4 mRNA expression by normal and atopic T lymphocytes. *Clin Res* 1989;37:229a.
- 34 Pene J, Rousset F, Briere F, et al. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons gamma and alpha and prostaglandin E. *Proc Natl Acad Sci USA* 1988;85:6880-4.
- 35 Del Prete G, Maggi E, Parronchi P, et al. IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. *J Immunol* 1988;140:4193-8.
- 36 Jabara HH, Ackerman SJ, Vercelli D, et al. Induction of interleukin-4-dependent IgE synthesis and interleukin-5-dependent eosinophil differentiation by supernatants of a human helper T-cell clone. *J Clin Immunol* 1988;8:437-46.
- 37 Reinhold U, Pawelec G, Wehrman W, et al. Immunoglobulin E and immunoglobulin G subclass distribution in vivo and relationship to in vitro generation of interferon-gamma and neopterin in patients with severe atopic dermatitis. *Int Arch Allergy Appl Immunol* 1988;87:120-6.
- 38 Li JTC, Yunginger JW, Reed CE, Jaffe HS, Nelson DR, Gleich GJ. Lack of suppression of IgE production by recombinant interferon gamma: a controlled trial in patients with allergic rhinitis. *J Allergy Clin Immunol* 1990;85:934-40.
- 39 Vercelli D, Jabara HH, Cunningham-Rundles C, et al. Regulation of immunoglobulin (Ig) E synthesis in the hyper-IgE syndrome. *J Clin Invest* 1990;85:1666-71.
- 40 Sampson HA, Broadbent HR, Bernhisel-Broadbent J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 1989;321:228-32.

Maths and mumps

Given two different vaccines for the same disease, one more effective but with a higher complication rate than the other, which is it best to use? This problem is posed by the existence of two mumps vaccines, the Urabe Am 9 and the Jeryl Lynn strains. The former has an estimated protective efficacy of about 98% and the latter about 94% whereas the estimated complication rates are one in between 62 and 400 thousand for the Urabe Am 9 strain and one in between 250 and 1800 thousand for the Jeryl Lynn strain. D J Nokes and R M Anderson (*Lancet* 1991;338:1309-12) have applied a mathematical model to the available data in order to calculate the number of complications, from either the natural disease or the vaccine, to be expected over a period of 20 years after the introduction of a vaccination programme with either of the two vaccines. Incorporated within their calculations is an estimate of the degree of persistence of the natural disease at various levels of vaccine uptake within the population. Thus at 70% uptake the natural disease is still prevalent whereas at over 80% uptake the natural transmission of infection virtually ceases. Their model predicts that at the lower level of vaccine uptake (70%) the vaccine strain with greater efficacy and higher complication rate (Urabe Am 9) is associated with fewer complications overall as most of the complications at this level of vaccination are produced by the natural disease. On the other hand, at 80 to 90% uptake most of the complications are caused by the vaccine as the natural disease becomes uncommon, and the safer vaccine (Jeryl Lynn) is to be preferred.

So the answer is, if you can guarantee a high acceptance of the vaccine in your population use the safer vaccine, but if you can't, use the more effective one.

If you can achieve high immunisation rates you automatically create an interesting problem in ethics. The natural disease is now rare and most complications arise from the vaccine. So why not cheat? Why not encourage everybody else to have their babies immunised but leave yours alone? It would have to be secret, of course, because, if everybody else tumbled to the same ruse your baby would finish up at high risk of the disease again. Why should we be concerned about the welfare of others? You may have a theology based explanation but non-theological ethicists seem to debate the matter endlessly without coming to any satisfactory conclusion.¹

ARCHIVIST

1 Warnock M. *Ethics since 1900*. 3rd Ed. Oxford: Oxford University Press, 1978. (Reprinted 1990.)