

From the Bencard Allergy Service of Johann Wülfing, Neuss, W. Germany.

A MULTI-CENTRE TRIAL OF POLLEN-TYROSINE ADSORBATE

By

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Hyposensitisation using vaccines containing extracts of grass pollens has long been accepted as an effective form of treatment of hay fever (8). Such treatment involves a course of injections of allergenic extracts of increasing strength given so that the highest dose is reached prior to the onset of the hay fever season. The earlier vaccines were usually aqueous and had the disadvantage of requiring a large number of graded strength injections in order to overcome the risk of generalized reactions. Hyposensitisation was simplified by the introduction of alum-precipitated vaccines with a smaller number of injections and a lower incidence of side effects. The number of injections was reduced still further by the introduction of oil-emulsion vaccines but the severity of local reactions accompanying this vaccine was unacceptable. In 1974 Miller & Tees (9) reported the use of another adjuvant, L-tyrosine, which did not have this disadvantage of the oil-emulsion material. L-tyrosine is a fully metabolisable amino acid. It is sparingly soluble and has the property of adsorbing proteins from solution. It is slowly eliminated from the injection site allowing a gradual release of the allergens. Adsorption of the allergen onto L-tyrosine reduces its immediate bioavailability thereby increasing safety and permitting a lower dose and fewer incremental injections.

Johansson et al. (5) found that it was possible to increase the safety of pollen extracts even more by modification with

glutaraldehyde. This reagent reduces the ability of a pollen extract to cause an immediate allergic reaction but does not destroy its ability to induce IgG antibody capable of blocking the allergic response (10, 14). The tyrosine-adsorbed, glutaraldehyde-modified grass pollen vaccine (Tyrosin-Allergoid)* may therefore have the dual advantage of causing a lower incidence of systemic reactions and, since it consists of only three graduated doses which can be given at 1 to 2 weekly intervals, it enables the course to be started closer to the pollen season. Whereas common grass pollens are recognized as the principal allergens in hay fever as seen in Europe, cultivated rye pollen is considered to be an additional cause of symptoms particularly in Germany (3, 11) and for this reason cultivated rye pollen was incorporated into the vaccine in addition to the mixed grasses. The initial studies of the use of grass pollen tyrosine-adsorbates have so far involved relatively small numbers of patients. The object of the present study was to evaluate this material in a large number of patients in 11 widely separated centres throughout Germany. We report the results of this study here.

MATERIAL AND METHODS

Material

The material used in the study consisted of the Bencard B2 group of grass pollens: Bent (*Agrostis tenuis*), Brome (*Bromus spp*), Cocksfoot (*Dactylis glomerata*), Dogstail (*Cynosurus cristatus*), False Oat (*Arrhenatherum elatius*), Fescue (*Festuca pratensis*), Meadow Foxtail (*Alopecurus pratensis*), Rye Grass (*Lolium perenne*), Meadow Grass (*Poa pratensis*), Timothy (*Phleum pratense*), Sweet Vernal (*Anthoxanthum odoratum*), Yorkshire Fog (*Holcus lanatus*) together with Cultivated Rye (*Secale cereale*). Following glutaraldehyde modification, the pollens were adsorbed on to tyrosine, and individual syringes were prefilled with the material in a volume of 0.5 ml. Three strengths were prepared by dilution with the following allergenic potencies:

Injection No. 1: 300 Noon units (NU) per 0.5 ml.

Injection No. 2: 800 NU per 0.5 ml.

Injection No. 3: 2000 NU per 0.5 ml.

* A similar vaccine is available in other countries as Pollinex®, Polvac®, Pollagen® and Bencard Pollen.

Injections were administered subcutaneously into the upper arm at intervals of 1 to 2 weeks.

Patients

Patients were selected on the basis of a clearcut history of seasonal rhinitis or asthma associated with allergy to the pollens of grasses or cultivated rye. Patients with a history of allergic disorders other than pollinosis were not necessarily excluded from the study. Patients undergoing other forms of hyposensitisation, steroid therapy or treatment with antiallergic drugs other than antihistamines, were, however, excluded from the study.

There were initially 433 patients admitted to the trial. Of these, 249 (57.5 per cent) were men and 184 (42.5 per cent) were women. Although a number of children over the age of 6 were included in the study, all were treated with the standard dosage.

Assessment of Patients' Symptoms

Patients were provided with diary cards starting in mid-April and ending in late July. In this they recorded their symptoms weekly and made a special note of any change in their environment involving differences in the amount of pollen in the atmosphere. At the end of the trial period the patients recorded their opinion of their overall symptoms compared with the previous year. After interviewing the patient the doctor graded their symptoms according to the following scale:

Very good	Symptom-free on average pollen exposure, slight symptoms on heavy pollen challenge. No symptomatic therapy required.
Good	Some symptoms on average exposure. No symptomatic therapy required.
Satisfactory	Moderate symptoms requiring additional therapy, and slight or infrequent reduction in capacity to work: (a) with improvement over 1974 season; (b) without improvement over 1974 season.
Unsatisfactory	Severe symptoms on average exposure. Increased need for symptomatic therapy and reduced work capacity.

Assessment of Effectiveness

Finally, each physician was asked to make an overall assessment of the effectiveness of treatment based on all the available data. Factors taken into account when considering the patients' symptoms included the pollen challenge, changes in environment and the need of symptomatic treatment.

Assessment of Side Effects

After each injection the patient was observed for 20 min. A special note was made of any untoward effect which followed treatment. These were divided into local and systemic reactions and were graded as shown:

Local reactions

- Mild** Local redness and swelling of up to 2 cm in diameter at the site of injection, with transient pain lasting at most 24 h.
- Moderate** Local redness and swelling of up to a hand's breadth accompanied by moderate pain lasting up to 3 days.
- Severe** Local redness and swelling covering an area greater than the palm of a hand accompanied by pain lasting more than 3 days.

Systemic reactions

- Mild** Reactions including exacerbations of the symptoms of pollinosis not severe enough to require treatment.
- Moderate** Reactions including exacerbations of symptoms of pollinosis requiring treatment.
- Severe** More marked reactions including those affecting organs not involved in pollinosis e.g. urticaria, or even anaphylactic shock.

RESULTS

Assessment of Patients' Symptoms

Of the 433 patients selected for inclusion in the trial, 406 patients completed the treatment and were included in the assessment of symptoms (Table 1). Therapy was discontinued in six patients, due to systemic side effects in five and a local reaction in one patient. A further 21 patients were excluded from this assessment either due to non-standard dosage or to incomplete data.

TABLE 1
Assessment of Patients' Symptoms in 1975.

Very good	33 (8.1 %)	} 299 (73.6 %)
Good	171 (42.1 %)	
Satisfactory—improved over 1974	95 (23.4 %)	
Satisfactory—not improved over 1974	44 (10.8 %)	} 107 (26.4 %)
Unsatisfactory	63 (15.5 %)	

Assessment of Effectiveness

An overall assessment of the effectiveness of the treatment was only possible in 378 of the 406 patients shown in Table 1.

In the remaining 28 cases unrelated environmental factors made this judgement impossible.

Treatment was assessed as effective in 276 (73.0 per cent) and non-effective in 102 (27.0 per cent).

The doctor's overall assessment of effectiveness was used in the consideration of other factors capable of affecting the outcome of treatment.

Age and sex. The age and sex of patients did not appear to influence the outcome of treatment (see Tables 2 and 3).

TABLE 2
Results of Treatment According to Age.

	Effective	Not effective	Total
Child (15 or less)	88 (73.9 %)	31 (26.1 %)	119
Adult	188 (72.6 %)	71 (27.4 %)	259
Total	276	102	378

$\chi^2 < 1$.

Not significant ($P > 0.05$).

TABLE 3
Results of Treatment According to Sex.

	Effective	Not effective	Total
Male	160 (73.7 %)	57 (26.3 %)	217
Female	116 (72.0 %)	45 (28.0 %)	161
Total	276	102	378

$\chi^2 < 1$.

Not significant ($P > 0.05$).

Length of history. No difference was found between groups of patients with a history of hay fever for more than 5 years compared with those with a history of 5 years or less (see Table 4).

TABLE 4
Results of Treatment According to Length of History.

	Effective	Not effective	Total
5 years or less	102 (76.7 %)	31 (23.3 %)	133
Over 5 years	153 (75.0 %)	51 (25.0 %)	204
Uncertain	21	20	41
Total	276	102	378

$\chi^2 < 1$.

Not significant ($P > 0.05$).

Previous hyposensitisation. A group of patients who had received a course of hyposensitisation to pollens in 1974 was compared with the other patients not so treated. There were no significant differences between these groups in their response to the 1975 course of vaccine (see Table 5).

TABLE 5
Results of Treatment According to Previous Hyposensitisation.

	Effective	Not effective	Total
Hyposensitised in 1974	89 (74.8 %)	30 (25.2 %)	119
Not hyposensitised in 1974	187 (72.2 %)	72 (27.8 %)	259
Total	276	102	378

$\chi^2 < 1$.

Not significant ($P > 0.05$).

Multiple allergies. 126 patients had a history of allergic diseases other than pollinosis. This did not appear to influence the outcome of treatment (see Table 6).

Side Effects

Local reactions. The number of local reactions which occurred is shown in Table 7. The majority of reactions were mild and short-lived. Only one patient discontinued treatment

as a result of a severe local reaction occurring 2 h after the second injection. The local reactions reported from the different centres were examined separately but did not differ greatly. The incidence of reactions was approximately similar for the first and second injection. There were significantly fewer reactions to the third injection. ($\chi^2 = 21.7$, $P < 0.001$).

TABLE 6
Results of Treatment According to Allergies.

	Effective	Not effective	Total
Multiple allergies	95 (75.4 %)	31 (24.6 %)	126
Pollinosis only	181 (71.8 %)	71 (28.2 %)	252
Total	276	102	378

$\chi^2 < 1$.

Not significant ($P > 0.05$).

TABLE 7
Local Reactions.

	Total injections administered	Details of reactions				Not known
		None	Mild	Moderate	Severe	
1st injection	433	103 (23.8 %)	194 (44.8 %)	100 (23.1 %)	36 (8.3 %)	
2nd injection	432	102 (23.6 %)	205 (47.5 %)	92 (21.3 %)	33 (7.6 %)	
3rd injection	426	152 (36.1 %)	164 (39.0 %)	67 (15.9 %)	38 (9.0 %)	5
Total all injections	1291	357 (27.8 %)	563 (43.8 %)	259 (20.1 %)	107 (8.3 %)	5

Systemic reactions. The total number of systemic reactions which occurred following treatment was 136 out of a total of 1291 injections given (10.5 per cent). Details of systemic reactions are given in Table 8. The majority of systemic reac-

tions were mild and consisted mainly of exacerbation of allergic symptoms such as rhinitis, conjunctivitis or bronchospasm. A few patients complained of symptoms possibly unrelated to the injections, for example headaches, tiredness and dizziness. Bronchitis which occurred in three patients was probably the result of intercurrent infection and in one of these patients it was necessary to discontinue the treatment.

Three patients developed severe generalised reactions characterised by such symptoms as dyspnoea, tachycardia, sweating, nausea and vomiting and one patient developed severe eczema. These four patients therefore represent truly allergic reactions necessitating discontinuation of treatment, an incidence of 0.9 per cent. None of these reactions can be classified as anaphylactic shock since they occurred many hours after injection.

TABLE 8
Systemic Reactions.

Type of reaction	Severity of reaction			Total injections causing reactions
	Mild	Moderate	Severe	
Exacerbation of allergic symptoms				
Rhinitis/Conjunctivitis	46	21	4	71
Bronchospasm	9	1	3	13
Bronchitis	2	2	—	4 (1)
Pruritus, urticaria, eczema	11	2	1	14 (1)
General systemic	—	—	3	3 (3)
Other	15	7	9	31
Total	83	33	20	136

Figures in parentheses indicate discontinuation of treatment.

DISCUSSION

There have been several reports of clinical trials using Pollinex (4, 12, 13), and in this trial, using a similar preparation, we have confirmed the results of these earlier studies. If one

takes the most meaningful parameter of efficacy of treatment to be the physician's final overall assessment, we have reported a 73.0 per cent effectiveness for the vaccine used in this trial. This relates very well to the figure of 73.6 per cent as being the number of patients improved in comparison with 1974.

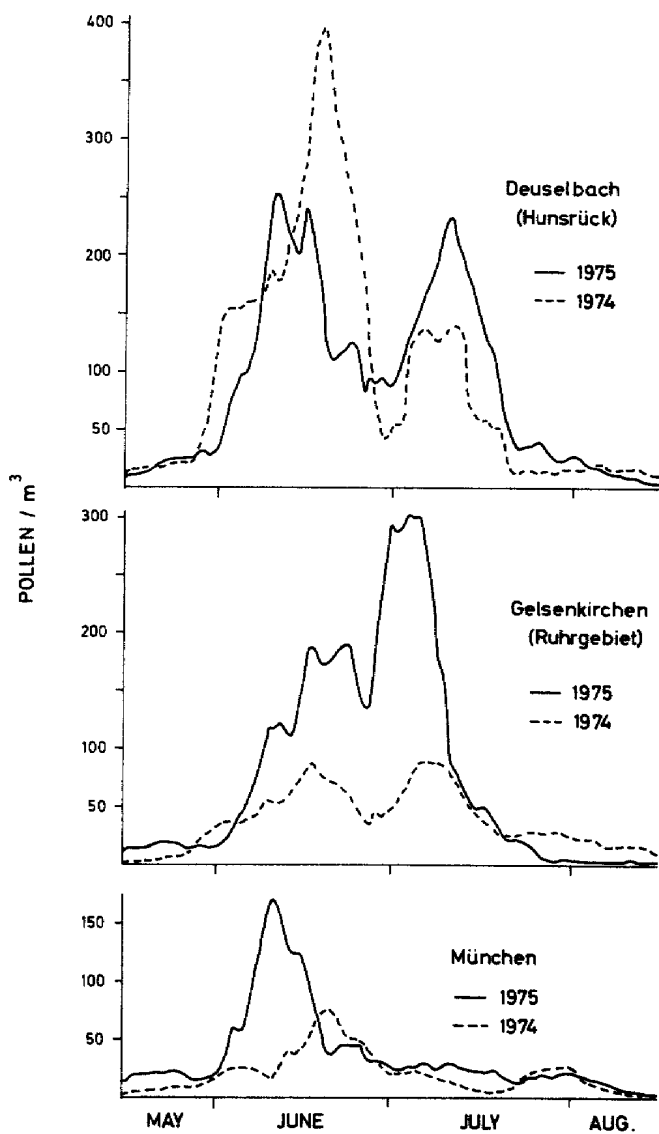
In the large study reported here on over 400 patients, there was a great similarity between the results obtained by the various trialists, and these results compare favourably with the smaller clinical trials already mentioned. Johansson et al. (5) reported 83 per cent clinical success where Verstraeten et al. (13) reported a success of 70 per cent, Girard & Huguenin-Dumittan (4) reported 79 per cent and Purser (12) 73 per cent success.

These results of treatment with a similar vaccine incorporating cultivated rye compare very favourably with the well-established standards accepted for alum-precipitated vaccines where, for instance, it was demonstrated by Kerr et al. (6) in a placebo-controlled trial using a pyridine-extracted alum-precipitated vaccine that one could expect success rates for treatment of 80 per cent. Similar vaccines have been variously reported by other workers to give favourable response in 82.5 per cent (1) and 62 per cent (7) of patients. The aqueous vaccines are known also to give results of a similar order (2).

Fig. 1.

Grass pollen counts in three test areas in Germany in the years 1974 and 1975. The pollen content in 1975 was clearly higher than in 1974 particularly in the two urban areas of Munich and Gelsenkirchen. (Kindly supplied by Umweltbundesamt, Berlin (3)).

Graspollengehalt der Luft in der Bundesrepublik in den Jahren 1974 und 1975 nach täglichen Messungen mit Burkardfallen in einem landwirtschaftlich genutzten Gebiet (Deuselbach, Hunsrück) und in den Städten Gelsenkirchen und München. Angaben in Graspollen/m³ Luft, übergreifende Mittel von 10 Tagen. Diese Graphik wurde uns freundlicherweise vom Umweltbundesamt zur Verfügung gestellt. Sie ist teilweise in der Dissertation von K. Fuckerieder 1976 enthalten.



We have therefore shown that with a vaccine of only three injections, clinical results can be obtained which are comparable to those obtained in longer courses.

In 1975 there were very high pollen counts reported from German Centres compared with the lower counts of 1974 (see Fig. 1). Assessment of efficacy was made by comparing the patients' symptoms in 1975 (when they received the vaccine treatment) with those of 1974 whatever the treatment in that year. This comparison of symptoms can be regarded as very fair since the 1975 season was one in which symptoms could reasonably be expected to be worse than in the previous milder hay fever season.

In this study we have shown an unusually high incidence of local reactions, 72.2 per cent of all injections caused some reaction, although the majority of these were mild and it was only felt necessary to discontinue the injections in one patient. The incidence of systemic reactions was 10.5 per cent of all injections given. However, it was only necessary to discontinue treatment as a result of truly allergic systemic reactions in a relatively small number of these patients (four out of the 433 patients treated (0.9 per cent)) and none could be classified as anaphylactic shock. It should be pointed out that in this study side effects of a local and general nature were being specifically sought. Despite this, although the reaction rate of local reactions appears high, the incidence of severe reactions is relatively small. However, it is worth noting that there is remarkable consistency in the data obtained from all participants in this trial in contrast to the data from the previously mentioned trials which ranged in incidence from the 4 per cent reactions of any kind reported by Purser (12) to the incidence of 50 per cent of the injections causing some form of local reaction as reported by Girard & Huguenin-Dumittan (4).

It is not easy to correlate data from a multi-centre study of this sort where the individual clinician's assessment of both side effects and efficacy of treatment will vary considerably. However, the best way to assess new treatments is by the use of large number of patients as has been done in this study. We

would conclude that this study confirms previous reports that the use of glutaraldehyde-modified pollen-tyrosine adsorbate for the treatment of pollinosis is safe, convenient and effective and that further trials, preferably of a comparative nature, are desirable, either with placebo control or against a preparation of proven efficacy.

SUMMARY

We report the results of a multi-centre trial involving 433 hay fever patients treated in 1975 with a 3-injection tyrosine-adsorbed vaccine containing glutaraldehyde-modified grass pollens and cultivated rye. Despite the high pollen counts recorded in Germany in 1975, treatment was considered to be effective in 73 per cent of the patients, irrespective of their age, sex or past history. Side effects were normally mild although the incidence of local reactions was relatively high. Only six patients discontinued treatment due to untoward reactions and there were no cases of anaphylactic shock. This paper adds further evidence to support the view that this vaccine offers a safe, effective and convenient method of treatment for grass pollen allergy.

ZUSAMMENFASSUNG

Im Rahmen einer im Jahre 1975 durchgeführten Multicenter-Studie wurden 433 „Heufieber“-Patienten mit einem an Tyrosin adsorbierten, glutaraldehydmodifizierten Gräser- und Roggenpollen enthaltenden Extrakt behandelt, der in drei aufeinanderfolgenden Injektionen verabreicht wurde. Trotz des im Jahre 1975 in Deutschland gemessenen hohen Pollengehalts war diese Behandlung in 73 Prozent erfolgreich. Lebensalter, Geschlecht oder Vorgeschichte beeinflussten das Ergebnis nicht signifikant. Bei 6 Patienten musste die Behandlung wegen ernster Nebenwirkungen abgebrochen werden. Ein anaphylaktischer Schock wurde nicht beobachtet. Insgesamt werden die Therapiemöglichkeiten der Allergopathia pollinosa

durch eine sichere, wirkungsvolle und wenig aufwendige Behandlung bereichert.

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