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HYPOSENSITISATION IN GRASS POLLEN HAY FEVER

*A double blind Trial of Alum precipitated Pollen Extract
and Depot Emulsion Pollen
Extract compared with Placebo Injections*

By

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INTRODUCTION

It is now generally accepted that hyposensitisation treatment is effective in the treatment of pollen allergy. Success rates ranging from 30-90 per cent have been reported in uncontrolled trials using aqueous extracts, depot emulsions and alum precipitated vaccines of pollen (*Fuchs & Strauss* 1959, *Feinberg et al.* 1960, *Brown* 1962, *Gaillard* 1963, *Arbesman & Reisman* 1964, *Frankland et al.* 1963 and 1964). The varying success rates of these may be due, at least in part, to the difficulty of eliminating bias in assessing symptoms in uncontrolled trials where the investigator is aware of the treatments prescribed.

There have been three trials undertaken in which control groups have been incorporated and which have been double blind. *Frankland & Augustin* (1954) obtained higher success rates with aqueous pollen than with placebo, while *Pearson* (1965) found that aqueous pollen extracts were less effective than depot emulsions, and *Frankland & Noelpp* found that aqueous extracts were also less effective than alum precipitated pollen.

There has, however, been no direct comparison of depot emulsion with alum precipitated pollen, nor has there been any double blind trial comparing either of them with a placebo.

Results of treatment of hay fever are difficult to assess with any degree of confidence owing to the impossibility of obtaining any objective evidence of improvement. Subjective improvement is influenced by placebo responses which in allergic diase may be as high as 30-45 per cent. Success rates have to be calculated on an arbitrary standard, no proper numerical value can be put upon them and they consequently vary in different hands.

The present trial attempts to make a more accurate assessment of the relative values of the two most popular forms of pollen hyposensitisation by the following methods:-

1. A very rigid protocol for selection of patients, with special regard to accurate allergic diagnosis.
2. Random allocation of treatment and the inclusion of a placebo series.
3. Double-blind prescription and administration of treatments.
4. Daily written records of symptom severity with clearly defined terms for the entries.
5. Statistical analysis of the results taken only from the written records and based on a numerical code for symptom severity.

METHODS AND MATERIALS

Patients attending the Allergy Clinic at University College Hospital between November and February 1966-67 were admitted to the trial if they were between the ages of 12 and 60 years and if symptoms of hay fever had been present for at least two previous years.

Positive immediate whealing skin reactions were present on prick testing with grass pollen extract, but other positive skin reactions were ignored if symptoms were not referable to them.

Patients were excluded if symptoms occurred outside the months of May, June and July, if other clinical allergies were present, if they were taking oral corti-

TABLE 1

Details of Initial Comparability of Patients with Hay Fever of at least 2 Years' Duration who were Admitted to the Trial.

	Alum precipitated extract 47 patients	Depot emulsion 40 patients	Placebo 23 patients
Males	22 (47 %)	16 (40 %)	12 (52 %)
Females	25 (53 %)	24 (60 %)	11 (48 %)
Mean age	25 yrs.	28 yrs.	26 yrs.
Mean length of history	13 yrs.	15 yrs.	11 yrs.
Number of patients with severe symptoms	31 (72 %)	24 (60 %)	15 (65 %)
Number of patients with asthma	14 (30 %)	13 (32 %)	8 (35 %)
Number of patients previously treated with hyposensitisation	18 (38 %)	14 (35 %)	8 (35 %)
Number of patients not previously treated with hyposensitisation	29 (62 %)	26 (65 %)	15 (65 %)

costeroids, or if they had previously responded satisfactorily to antihistamine drugs.

Each patient was given one of three preparations: alum precipitated pollen extract, depot emulsion pollen extract, or a placebo injection. The alum precipitated pollen extract ("Allpyral G") contained the pollens of five grasses and was given in a dosage of 50 P. N. U. (protein nitrogen units) rising to 10,000 P. N. U. as a course of nine weekly injections. The depot emulsion pollen extract ("D-Vac") contained the pollens of 12 grasses (including the five in "Allpyral"). It was given in a dosage of 750 Noon units followed by 3,500 Noon units and 7,500 Noon units as a course of three injections at intervals of four weeks (10 P. N. U. is roughly equivalent to 17 Noon units). The placebo material was normal saline and was given as a course of three injections of 1 ml at four-weekly intervals.

The three treatments were equalised for every ten patients in a 4:4:2 proportion, the smaller group being given the placebo. All injections were given pre-seasonally from February to April and were allocated according to a pre-arranged schedule. Neither the physician, nor the patient knew the identity of the treatment until after the results were assessed. Injections were given by nurses or general practitioners. Records were kept by the patients during the following pollen season.

110 patients were admitted to the trial and details of the initial comparability of the treatment groups are given in Table 1. Only insignificant differences were found in respect of age, sex, length of history, severity of symptoms, presence or absence of asthma, and of previous treatment by hyposensitisation. None of the patients had asthma in the absence of rhinitis.

Results were not obtained in 16 patients who either failed to attend for interview or did not complete their records adequately. Five of these were receiving alum precipitated extract, eight were receiving depot emulsion and three were receiving placebo. Treatment was withdrawn in three other patients who developed a generalised urticarial reaction following one of the injections. One of these was having alum precipitated extract and two were having depot emulsion pollen extract. These 19 patients are included in the first analysis as failures of treatment.

Daily records were kept by the patients on a printed chart for symptom severity. Each day an entry was made; "O" for clear of symptoms all day; "A" for minor symptoms not needing tablets or nasal decongestants; "B" for moderate symptoms which were defined as needing tablets or decongestants but symptoms were controlled by them; "C" for severe symptoms which were not controlled by tablets or decongestants. Patients also recorded at the end of the season whether they considered that treatment had been "satisfactory" or "unsatisfactory". For the purpose of analysis "points" were allocated for symptom severity: O = 0 points; A = 1 point; B = 2 points; C = 3 points. It will be appreciated that a high "points" count will therefore indicate a patient with severe symptoms.

The points were counted for 50 days from 1st June. This period includes the whole time in which the atmospheric grass pollen is at a high level in England.

RESULTS

Results were assessed in three ways; by comparing for each treatment the overall subjective success rate, the number of days for which patients remained clear of symptoms or virtually so (Categories "O" and "A") and the individual points counts for each treatment. (Table 2 and 3).

A higher proportion of patients who had received both active treatments considered that their treatment had been successful in the control of rhinitis than did those who received placebo. 30 (75 per cent) of the 40 patients receiving alum precipitated pollen extract and 21 (68 per cent) of the 31 patients receiving depot emulsion pollen extract considered their treatment successful compared with 7 (35 per cent) of the patients receiving placebo. (These differences were un-

TABLE 2

Overall Subjective Success Rates in Patients with Grass Pollen Rhinitis and Asthma Treated by Hyposensitising Injections.

	Rhinitis		Asthma Number of successful results in all patients
	Number of successful results in all patients	Number of successful results in patients completing records	
Alum precipitated extract	30 (63 %)	30 (75 %)	9 (64 %)
Depot emulsion extract	21 (40 %)	21 (68 %)	8 (62 %)
Placebo	7 (30 %)	7 (35 %)	2 (25 %)

Successful result = patients' written opinion as to the success of the treatment.

Number of successful results in patients completing records. (*Chi square test*).

Alum precipitated extract v. placebo $P = 0.01$.

Depot emulsion v. placebo $P = 0.046$.

likely to be due to chance ($P = 0.01$ and $P = 0.046$, respectively).

When the 16 patients who failed to complete the records were included as failures of treatment, the success rates fell to 63 per cent for the alum precipitated pollen extract, to 40 per cent for the depot emulsion pollen extract and to 30 per cent for the placebo. The improvement in patients with asthmatic symptoms was similar to that in patients who had rhinitis alone.

Those patients receiving alum precipitated pollen extract or depot emulsion pollen extract had a higher proportion of symptom-free days than did those given control injections, (Table 3). The difference was greater for the depot emulsion pollen extract and was unlikely to be due to chance ($P = 0.038$), but for the alum precipitated pollen extract was statistically insignificant ($P = 0.087$).

When the total points counts were considered, they were highest (indicating poor results) in the control group and

TABLE 3

Results of Treatment Assessed from Written Daily Records in Patients with Hay Fever Receiving Hyposensitising Injections.

	Alum precipitated extract (40 patients)	Depot emulsion (31 patients)	Placebo (20 patients)
Mean number of days symptom free	35	38.5	28.5
Mean points count	54	49	72
Number of patients with more than 35 symptom free days	19 (48 %)	16 (52 %)	6 (30 %)
Number of patients with more than 35 days of only mild symptoms	27 (68 %)	23 (72 %)	11 (57 %)

Number of clear days. (Mann Whitney U Test).

Alum precipitated extract v. placebo $P = 0.087$.

Depot emulsion v. placebo $P = 0.038$.

Total points. (Mann Whitney U. Test).

Alum precipitated extract v. placebo $P = 0.074$.

Depot emulsion v. placebo $P = 0.054$.

Number of patients with more than 35 clear days (Chi square test).

Alum precipitated extract v. placebo $P = >0.2$.

Depot emulsion v. placebo $P = >0.2$.

In each of the above parameters the differences between alum precipitated extract and depot emulsion were not significant.

lowest for the depot emulsion pollen extract, with the alum precipitated extract intermediate but the differences from the control were statistically insignificant ($P = 0.074$ and $P = 0.054$, respectively).

Although the results on the recorded symptom charts were better for depot emulsion pollen extract than for alum precipitated pollen extract than for depot emulsion pollen extract, when the two active treatments were compared all of the differences could have been due to chance in the numbers studied.

If all patients who had moderate or severe symptoms on

TABLE 4

*Treatment Failures.**Patients with Grass Pollen Hay Fever Treated by Hyposensitising Injections.*

	Alum precipitated extract (40 patients)	Depot emulsion extract (31 patients)	Placebo (20 patients)
Number of patients with 14 or more moderate or severe days of Hay Fever	21 (52 %)	14 (48 %)	14 (70 %)
Number of patients with 7 or more extremely severe days	9 (22 %)	6 (19 %)	3 (15 %)

14 or more days are arbitrarily considered as treatment failures, (Table 4), then 52 per cent of the alum precipitated pollen extract group, 48 per cent of the depot emulsion pollen extract group and 70 per cent of the controls failed to respond. Within these failures there were 18 patients who had very severe symptoms for at least seven days. They formed 9 (22 per cent) of the alum precipitated group, 6 (19 per cent) of the depot emulsion pollen extract group and 3 (15 per cent) of the controls. Thus, in spite of receiving a full course of active hyposensitisation, approximately 20 per cent of the patients continued to have very severe symptoms. Severe asthmatic symptoms were recorded in about half of these patients.

As it was thought that previous hyposensitisation might have influenced the results, a separate assessment was made (Table 5). Those patients who had had previous treatment had all had depot emulsion pollen extract for two previous years. There was no consistent pattern whereby one could say that these patients did better or worse than those receiving treatment for the first time.

Side effects from the treatment were few. One patient receiving alum precipitated pollen extract and two patients receiving depot emulsion pollen extract developed generalised

TABLE 5

Effect of Previous Treatment with Hyposensitisation on Present Results.

	Alum precipitated extract	Depot emulsion extract	Placebo
Number of patients			
previously treated	15	11	6
not previously treated	25	20	14
Mean points count			
previously treated	60	33	49
not previously treated	50	52	83
Success rate on points			
previously treated	47 %	64 %	33 %
not previously treated	48 %	40 %	23 %
Overall subjective success rate			
previously treated	66 %	55 %	50 %
not previously treated	75 %	80 %	23 %

urticaria within one hour of one of the injections. Following subcutaneous adrenaline and oral antihistamine the symptoms disappeared and did not recur. Nine patients developed asthma and rhinitis after about 12 hours, (eight of these were receiving alum precipitated pollen extract and the other one had depot emulsion pollen extract) but the symptoms were not severe in any case. Small persistent nodules developed at the injection site in ten patients receiving depot emulsion pollen extract but there were no local abscesses or sinuses. No other side effects of any kind were observed.

DISCUSSION

Previous trials with hyposensitisation treatment in pollen hay fever have based their results almost entirely upon the combined overall assessment of physician and patient. Most of the figures quoted have been in the region of 70-90 per cent successful results and are considerably higher than those of the present series.

There are at least two possible reasons for this. Firstly, the more rigid standards of assessment in this trial may have resulted in a lower success rate than has been generally accepted, as patients who needed to take other treatment were not accepted as successful. The effect of antihistamine drugs did not therefore confuse the issue. Secondly, the materials used in this trial may perhaps have had a low potency. It is known that the strength of pollen extracts will vary from year to year, but there is no reason to believe that the materials used in this trial were poor, particularly as they came from two entirely independent sources.

Results reported in terms of percentage success are based on arbitrary standards which will vary from trial to trial according to the standard which is accepted as a successful result. In the present trial the overall subjective success rate was based on the patients' written opinion and gave figures comparable to those previously reported (75 per cent and 68 per cent for alum precipitated pollen extract and depot emulsion pollen extract, respectively). But when an attempt was made to place a proper numerical value on the symptom severity, the success rates were much lower (48 per cent and 52 per cent) and were not better than the success rate for placebo (30 per cent). If a low standard for successful treatment were applied to the results in this trial by including as successful those patients who needed to take antihistamine treatment, the success rates would rise to approximately 70 per cent for both active treatments and 57 per cent for the placebo (Table 3).

These figures demonstrate the arbitrary nature of putting a numerical value on results which are not objective. One can only say that a treatment of this kind is the same, or better, or worse than another treatment – and that is all that this trial claims to do.

It is concluded that both alum precipitated pollen extract and depot emulsion pollen extract are effective in the treatment of grass pollen hay fever and asthma. There is no difference between the results of the two methods and both are

better than placebo injections. It is not possible to put a percentage success rate to the treatments on any accurate basis.

SUMMARY

A double blind controlled trial on 110 patients with severe grass pollen hay fever is reported.

A direct comparison is made between the two most popular methods of pre-seasonal hyposensitisation and a placebo. These methods of treatment have not previously been compared in a controlled trial.

It is concluded that both alum precipitated pollen extract and depot emulsion pollen extract are equally effective in one season's treatment and are better than placebo. The success rates of the treatments are impossible to determine on any accurate basis, but this trial has approximate success rates of 50-70 per cent for both active treatments and a placebo response rate which varied from 25 per cent to 57 per cent according to the parameter which was measured.

A small series who had received hyposensitisation treatment in previous years did not have a significantly better response than those receiving treatment for the first time.

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REFERENCES

- Arbesman, C. E. & Reisman, R. E.: Hyposensitization Therapy Including Repository: A Double-Blind Study. J. Allergy 35, 12, 1964.*
Brown, E. A.: Ragweed Pollinosis. Opsiphylactic Treatment of Inhalant Allergy. XXI. Ann. Allergy 20, 397, 1962.

- Feinberg, A. R., Feinberg, S. M. & Fisherman, E. W.*: Repository Antigen Injections. *J. Allergy* 31, 433, 1960.
- Frankland, A. W. & Augustin, R.*: Prophylaxis of Summer Hay-Fever and Asthma. A Controlled Trial Comparing Crude Grass-Pollen Extracts with the Isolated Main Protein Component. *Lancet*. 1954.
- Frankland, A. W., Macaulay, D. B. & Evans, R. G.*: Hay-Fever and Pollen Asthma Treated by Repository Injections. *Practitioner* 190, 505, 1963.
- Frankland, A. W., Evans, R. G., Macaulay, D. B. & Edwards, J. W.*: Hay-Fever Treated by Repository Injections. *Practitioner* 193, 71, 1964.
- Frankland, A. W. & Noelpp, B.*: Summer Hay-Fever Treated with Aqueous and Alum-Precipitated Pyridine Extracts. *Practitioner* 196, 766, 1966.
- Fuchs, A. M. & Strauss, M. B.*: The Clinical Evaluation and the Preparation and Standardization of Suspensions of a new Water-Soluble whole Ragweed Pollen Complex. *J. Allergy* 30, 66, 1959.
- Gaillard, G. E., Schellin, R. & Meyers, R. A.*: A Comparative Study of a New Alum-Precipitated Pyridine-Linked Ragweed Pollen Extract in Saline with an Emulsified Ragweed Pollen Extract. *Ann. Allergy* 21, 145, 1963.
- Pearson, R. S. B.*: Depot Injections in Treatment of Hay-Fever and Pollen Asthma. *Brit. Med. J.* 2, 1145, 1965.

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