

ON REPOSITORY THERAPY OF
GRASS HAY FEVER:
A SEVEN YEARS' EXPERIENCE

By

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Immunization against hay fever and hay asthma by means of repository injections of specific allergens was started and has grown widespread in U. S. A. *Loveless* first indicated the principles of the method in 1957. Soon *Brown* suggested fundamental technical improvements which made this method fit for the day to day practice of allergy. He tested it on a large number of patients claiming extremely satisfactory results. *Furstemberg* estimated in 1963 that more than 500 allergic clinics were testing this method in the U. S. A.

In Europe the repository method has never come into general practice. European reports on this matter are limited to those of *Frankland & Coll.* (1963 and 1964), *Evans* (1963), *Bruce Pearson* (1965), *Macaulay* (1965) and *Sanders* (1966), all in England, and of the present author (1962 and 1964) in Italy. The English authors' experience is a peculiar one in that they used depôt pollen vaccines with standard doses of 750 and 7500 Noon Units, which became commercially available in Great Britain in 1963. Conversely, emulsified vaccines used in my clinic were directly prepared according to the method advocated by *Brown*, with some modifications suggested by experience. A first pilot study was done in 1961. Since then, about 1500 patients were preseasonally treated with this method. It was thought that a report on these seven years' experience, with particular attention to the triennium 1965-1967 was of some interest.

MATERIALS AND METHODS

Emulsions are prepared with equal part of: a) grass aqueous non-glycerinated extract of chosen strength; b) incomplete Freund's adjuvant which is made of a mixture of Arlacel A (emulsifying agent) and Drakeol 6 VR (a light mineral oil for pharmaceutical use) at 35:65 ratio. The emulsion is formed by pumping alternately these materials through a couple of syringes connected by a double hubbed needle. An electro-mechanical device (Brown Emulsor®) provides regularity of rhythm and pressure for as many strokes as required for a full homogenization. Emulsions were found to be much more fine-grained and therefore much more stable, as underlined in a previous study (1964), when a Swinny unit filter containing a stainless steel grid screen, was inserted between the two syringes.

Emulsions containing respectively 2500, 5000 and 20,000 PNU per ml., as well as an inert emulsion of saline, are routinely prepared for *dépôt* therapy. The injection volume is of 1 to 1.25 ml. By loading a one ml. syringe with a given volume of pollen emulsion and bringing to the volume of one ml. with inert emulsion, any dose may be made available from 250 PNU (ml. 0.1 of 2500 PNU/ml. emulsion plus ml. 0.9 of inert emulsion) up to 25,000 PNU (ml. 1.25 of 20,000 PNU/ml. emulsion).

PATIENTS

The patients studied here are grass sufferers with cutaneous test repeatedly positive and classical hay fever and/or hay asthma history. They are divided into two groups:

- 1) Patients never previously treated except symptomatically, henceforth referred to as "new patients".
- 2) Patients previously treated with repository method for one or more subsequent years, henceforth referred to as "repeating patients". No patients having received in the past preseasonal traditional pollen injections was admitted to this study.

As pointed out elsewhere (1964), due to climatic factors which are favorable to the growth of grasses (*i.e.*, principally, high average temperature and frequent rainfalls), the grass season may be very long and severe in Northern Italy. Symptoms start between April 20 and the first days of May and, reaching a climax in mid-May, last very intensely till about June 10. Manifestations from moderate to severe may be observed far beyond this date, until the end of September or the first days of October. About one third of the patients studied had a long hay fever season, whereas the majority of them were symptomfree sometime in June.

DOSAGE AND ADMINISTRATION

New patients are usually given a first injection of 1000 PNU in January; a second one of 3000 to 4000 in February and a last one of 10,000 to 15,000 be-

tween the 15th of March and the 10th of April. Very exceptionally some new patients are given 2 or 4 injections instead of 3. Repeating patients have a first dose of 3000 to 5000 PNU between February and March and a last one of 10,000 to 25,000 PNU not after the 10th of April. A few repeating patients receive this last dose only.

All the injections are given deep subcutaneously in the deltoid region of the arm. The patient is asked to wait one hour in the surgery after each injection. No antiallergic pretreatment for an anaphylactoid reaction is routinely given. Only occasionally an antihistaminic tablet is administered, as a precaution, before discharging a particularly sensitive subject.

In this study, a closer attention was given to the new patients. One hundred and three of them had preseasonal depôt therapy in 1965, 93 in 1966 and 97 in 1967. A top final dose of at least 10,000 PNU was aimed at with these patients. If the two first injections had been well tolerated, a higher dose than 10,000 PNU was given, with a maximum of 15,000 PNU.

A comparison group of 20 new patients was treated in 1967 with preseasonal traditional therapy. These patients were assigned to the traditional treatment as they were referred to the clinic, starting from November 28, 1966, and until the number of 20 patients was filled. No other selection was made except for their having a grass pollenosis of more than average importance, *i.e.* of 60 days or more duration. Two patients out of 20 did not complete the treatment, so 18 patients remained on trial. The largest consistent dose with the patient's tolerance was given to these subjects. The average top dose was quite high.

Table 1 shows the various data regarding the number of treated patients, the absolute figure of systemic reactions encountered, the reaction rate per person and the average top dose for each group of repository new patients in 1965, 1966 and 1967, as well as for the group of the traditional patients in 1967.

Table 2 shows the same data for the repeating patients in 1965, 1966 and 1967.

RESULTS

The assessment of the result of each course of therapy was made by the patient himself. Each patient was given a symptom chart to be filled in with daily symptoms if present. Furthermore, the patient was requested to draw his final judgment about the effectiveness of the therapy according to the following terminology which was illustrated in a text printed on the reverse of the symptom chart.

The result could be classified as excellent, meaning that the patient had been free from symptoms or nearly so. Good when he had had an improvement of about 75 per cent in comparison

TABLE 1
New Patients.

	1965	Repository 1966	1967	3 years' total and averages	Traditional 1967
Cases n.	103	93	97	293	18
Injections total n.	303	276	288	877	269
Injections per person	3.03	2.96	2.96	2.99	16.5
Reactions total n.	13	15	32	60	13
Reactions per person	0.12	0.16	0.33	0.2	0.7
Average top-dose	13,150	14,100	12,200	13,200	15,800

TABLE 2
Repeating Patients—Repository only.

	1965	1966	1967	3 years' total and averages
Cases n.	185	174	188	547
Injections total n.	361	333	366	1060
Injections per person	1.91	1.94	1.94	1.92
Reactions total n.	9	6	8	23
Reactions per person	0.05	0.03	0.04	0.04
Average top-dose	17,300	17,250	16,600	17,000 ca.

to previous untreated year(s). Fair meant a 50 per cent and still satisfactory result. Any result considered unsatisfactory was classified as poor. Most patients sent their symptom chart and final subjective assessment at the end of the season, as requested. Some were reached by phone and asked to send it. In a few cases, a personal interview was accepted as a substitute for the lost symptom chart. All the unknown results were conventionally classified as unsatisfactory, although surely many of them were not.

Table 3 illustrates the results as declared by the new patients, following preseasonal depot therapy in 1965, 1966 and

TABLE 3
New Patients—Results for Preseasonal Treatments 1965-1967.

	1965 depôt	1966 depôt	1967 depôt	1967 aqueous
Average top-dose	13,150	14,100	12,200	15,800
Cases n.	103	93	97	18
Excellent	6	8	8	4
Good	43	37	34	8
Fair	31	28	34	6
Satisfactory total	80 (77.7%)	73 (78.5%)	76 (78.4%)	18 (100%)
Poor	13	13	15	none
Unknown	10	7	6	none
Unsatisfactory total	23 (22.3%)	20 (21.5%)	21 (21.6%)	none

1967, as well as the results of the control group traditionally treated in 1967.

Table 4 shows the results for the repeating patients in the same years.

SIDE EFFECTS

Anyone who is conversant with the practice of allergy knows that systemic and, more rarely, constitutional reactions may follow any pollen injection when, for some reason, the dose exceeds the patient's tolerance. No matter how accurate the technique and experienced the physician, treatment with effective doses will always result in a percentage of such reactions. According to calculations published in the past (1963), with the traditional method, in the present writer's hands, a reaction rate of about 4 per cent (*i.e.* four reactions out of 100 injections) has to be expected. With the control group of 18 new patients traditionally treated in 1967, the reactions were 13 of a total of 269 injections, which means a reaction rate of 4.8 per cent. Besides systemic reactions, local swellings, painful on occasions, are common after the injection of aqueous pollen extract. It is generally agreed that this type of reaction, too, may be a warning sign of overdosage.

Any symptom other than local, of currently admitted allergic nature, occurring within 24 hours after the administration of the pollen injection was considered as systemic reaction.

As shown in Table 1, sixty such reactions were recorded among 293 new patients treated during 3 years with a total of 877 emulsified pollen injections. More than half of these reactions occurred in 1967, a year in which unusually frequent and long lasting local reactions were recorded, too. Since the technique of preparing the emulsions and of injecting them was rigorously the same as in previous years, it was supposed that the grass extract used that year was more potent than usual.

TABLE 4
*Repeating Patients—Results for Preseasonal Treatments 1965–1967.
Repository only.*

	1965	1966	1967
Average top-dose	17,300	17,250	16,600
Cases n.	185	174	188
Excellent	15	26	25
Good	90	89	88
Fair	44	33	42
Satisfactory total	149 (80.5%)	148 (85.0%)	155 (82.5%)
Poor	18	16	17
Unknown	18	10	16
Unsatisfactory total	36 (19.5%)	26 (15.0%)	33 (17.5%)

From the point of view of the severity, the reactions were classified as slight, moderate and severe.

The reaction was considered slight when either it needed no treatment and subsided spontaneously, or the patient managed to control it with his own means (namely a tablet of Triaminic® with which each patient was provided). The reaction was considered moderate when the patient had symptom relevant enough (or he felt they were) as to return to the surgery to be treated, but the reaction subsided promptly with usual antial-

lergic medication (Trimeton® 10 mg plus epinephrine 1 per mille, ml 0.5, subcutaneously or Hydrocortisone mg 25 intramuscularly). The reaction was considered as severe when acute symptoms, requiring very active medical care, were observed.

Out of the 60 reactions, 35 were classified as slight. Many of them were so irrelevant that they came to the light only after close questioning. Twenty-four more were moderate. Only one was potentially severe, and was recorded in 1967.

T. A., woman, aged 30, first seen on January of 1967, with an history of seasonal asthma and hay fever of two months' duration (May and June), begun in 1962 and never previously treated except symptomatically. Tests gave strong positive reactions for grasses. A first dose of 1000 PNU was given on February 2, 1967, without any apparent harmful effect. A second dose of 3000 PNU was given 15 days later. Forty-five minutes afterward, when the patient was still in surgery, a swelling of the eyelid appeared, which rapidly spread all over the face and neck, with intense flushing and itching. An injection of 75 mg of hydrocortisone was given intravenously. The bulk of the symptoms gradually subsided within 2 hours, after which a second injection of 50 mg of hydrocortisone was given intramuscularly and the patient discharged. A certain degree of oedema of the eyelids persisted till the evening. The morning after the patient had moderate wheezing, and all the third day nasal discharge. The fourth day she complained of stomach ache and had some diarrhoea. During those days she felt faint and unusually drowsy.

It is worth-while to notice that in all the 60 reactions recorded here by far the most prevalent symptom was urticaria. Asthma was noted in only 3 instances besides the case above described in detail.

A record was also kept of the time of onset of each reaction, with the aim of ascertaining if the practice of keeping the patient one hour in the surgery was a worth-while one. The only potentially severe reaction started, as told above, 45 minutes after the injection was given. Out of 24 reactions of moderate intensity, 13 started within the first hour; none arose after two hours. The average onset time was of 77 minutes. As regard slight reactions, the earliest ones (four) started at about 60 minutes and the latest one after 24 hours. The average onset time was of about 4 hours.

It clearly appears that the sooner a reaction takes place after the injection, the more severely is it likely to develop. According to this experience, as well as of the previous four years, no potentially severe reaction started after one hour, nor did a moderate reaction after two hours. Our practice of keeping the patient at hand for one hour seems therefore to be a valid one. It is also opportune to ask the patient coming from other towns not to leave till two hours have expired.

Out of 60 systemic reactions, 18 were recorded with the first injection of 1000 PNU, 24 with the second of 3-4000 PNU and 18 more with the last dose of 10-15,000 PNU. This calculation was intended to verify if the dose increment empirically adopted was in fact a reasonably safe one. According to the reported figures we ought to conclude that this schedule was acceptable, the number of reactions being roughly similar in each group. The slight prevalence of the number of reactions after the second dose of 3-4000 PNU could possibly suggest that 3000 PNU rather 4000 is the optimum second dose.

No record was kept of minor local swellings and pains, since it was considered obvious that, if only because of the oily injection, a transient local nuisance was to be expected. Twelve injections in 1965, 17 in 1966 and 30 in 1967 were followed by a marked and sometimes painful local swelling which lasted for more than one day with a maximum of 6 days. Almost all such swelling were connected with the first or second injection. Paradoxically, the highest third dose seldom gave noticeable local reactions.

No abscesses were observed among the 293 new patients and the 547 repeating patients, nor were noticed with more than 4000 emulsified pollen injections administered since 1961. In 1967, however, a second injection of 4000 PNU was followed by redness, marked swelling, pain of all the deltoid region, and moderate fever. The whole symptomatology lasted for two weeks and slowly subsided under combined antibiotic and cortisone treatment.

Nodules and little cysts at the site of the injection are ob-

served in some patients given emulsion therapy. Nodules are more common than cysts. Both nodules and cysts seldom exceed the volume of a pea. Nodules always diminish with time although some may take one or more years to disappear completely. Cysts do not disappear, as far as I know, unless aspirated. Aspiration with a syringe yields one ml or less of greyish thick sterile pus. A personal predisposition must play a rôle in the genesis of the nodules: some subjects develop them with each injection, whereas most of the patients never do. Furthermore, nodules and cysts were more commonly observed with the less stable emulsions used in the early years of this experience (1961-1963). I am inclined to suggest that strong local reactions provoked by emulsions not thoroughly homogenized or simply by overdosage are a factor in giving rise to these delayed tissular lesions.

It is difficult to ascertain exactly the frequency of the nodules among the patients treated with the present technique. Before starting a further course of therapy, palpation of the deltoid area is regularly made. On the other hand, patients who failed to report again for treatment may carry unnoticed nodules and hardly any of the patients treated in 1967 have yet been re-examined from this point of view. Out of the 840 studied here, only in 6 patients were nodules observed and no cysts. One of the patients had four nodules following four injections in 1966 and 1967. We are probably not far from the truth in estimating that emulsion injections causes lasting local reactions in one to two per cent of the patients. They rarely worry about nodules, once they are reassured about their benignity. Our current policy is to transfer to the aqueous treatment any patient whose examination gives evidence of fibrosis on the site of previous year(s)' injections.

DISCUSSION AND CONCLUSIONS

Although optimum dosage in preseasonal therapy of pollinosis is still under debate, there is little reasonable doubt that large preseasonal doses of pollen extract are more effective than

small ones. *Frankland* demonstrated this fact as early as 1955 and *Bruce Pearson* confirmed it for repository therapy in 1965. Close examination of controlled studies which failed to find any statistical difference between patients given pollen or placebo injections (*Fontana et al.*, *Norman et al.*) reveals that many so-called treated patients were given very small top doses ranging from a few hundred to 2500 or 3000 PNU. One wonders whether such patients may be considered effectively treated patients.

Since we cannot believe that the injected pollen acts for its mere presence, independently from the dose, the most logical hypothesis is that, within the range of the human sensitiveness and tolerance, the protection varies according to the dose, whatever the mechanism, either specific or not, involved in affording this protection. Daily practice, as well as a number of statistical trials support this opinion. A point, therefore, which does not seem have been generally appreciated is that the comparison of observations from various sources concerning the results of the preseasonal therapy is meaningless if the magnitude of the top doses given to each group is not taken into account.

The general trend followed in treating the patients of this study has been of giving the highest tolerated dose. With this principle, 293 new patients and 547 repeating patients were preseasonally treated with repository injections during 3 years from 1965 to 1967, with a total of 840. These 840 courses of therapy required a total of 1937 injections. Eighty-three systemic reactions were recorded, one of which only was classified as severe. Most of them were very slight. To treat these 840 subjects with the conventional method *and corresponding average doses*, at least 10,000 injections should have been given instead of 1937, and at least 400 reactions should have been expected in lieu of 83. About five times fewer injections and reactions is, therefore, the most striking aspect of the repository treatment, as it was put into practice in this clinic, in comparison with the traditional one. The saving of time this method affords to the patients is obvious. The physician, too,

spends less of his time in giving injections and managing reactions, but an important part of the time thus saved has to be devoted in preparing and checking the emulsions. Everything considered, however, the saving of time still remains noteworthy for the physician, too. Furthermore, the work may be organized in a more orderly way when few visits are planned for each patient instead of 10 to 20 or more. To be weighed against these advantages are the local long lasting, but finally transient nodules induced by repository injection in a very small percentage of the patients. According to other authors' experience, the eventuality of an abscess must be taken into account, although none was observed among our patients.

As far as the clinical effectiveness of the procedure is concerned, it will be noted that the results of the emulsion therapy were very similar during the 3 years. A little less than 80 per cent of the new patients and a little more than 80 per cent of those who repeated the treatment felt that the treatment had been worthwhile and satisfactory. On the other hand all the 18 new patients with severe pollinosis traditionally treated in 1967 claimed a satisfactory result.

If a conclusion may be drawn from the experience here described, it is that repository therapy proved a very satisfactory immunizing procedure affording a good seasonal average protection with less expense of time and a lower incidence of side effects as compared with aqueous therapy. The conventional method, however, with its painstaking, time-consuming series of injections and higher rate of side effects, yields an even greater preseasonal protection when correspondingly high doses are used. Repository immunization, undoubtedly represents a satisfactory answer to the demand of the majority of pollen sufferers. It will be up to the physician trained in both methods to adopt the traditional one in cases which fail to respond to the other.

SUMMARY

A comprehensive report is given of the experience gathered with repository treatment of grass pollinosis during 7 years,

with particular attention to the triennium 1965-1967. During this last period 293 never previously treated patients and 547 re-treated patients had preseasonal depôt treatment with large final doses ranging from 10,000 to 25,000 PNU. The treatment on average required about 5 times fewer injections and elicited about 5 times fewer reactions than would have been expected with traditional methods. Although it seems that, doses being equal, multiple aqueous injections yield results slightly better, the repository method turned out to be a much quicker and safer immunizing procedure. Clinical results were considered satisfactory by about 80 per cent of the patients.

REFERENCES

1. *Brown, E. A.*: The Treatment of Pollinosis by Means of a Single Annual Injection of Emulsified Extract. *Ann. Allergy* 17, 34, 1959.
2. *Bruce Pearson, R. S.*: Depôt Injections in Treatment of Hay Fever and Pollen Asthma. *Brit. Med. J.* 2, 1148, 1965.
3. *Dal Bo, S.*: Traditional and Repository Emulsion Treatment of Grass Pollinosis—Proceedings of 5th European Congress of Allergy, Basel 1962 (Schwabe & Co).
4. *Dal Bo, S.*: La pollinosi da Graminacee nell'area di Milano. III. Reazioni in corso di cura prestagionale. *Folia Allerg.* 10, 326, 1963.
5. *Dal Bo, S.*: Experience with Repository Therapy of Pollinosis in Northern Italy. *Ann. Allergy* 22, 670, 1964.
6. *Evans, R. G.*: Indications for Hyposensitization in Upper Respiratory Allergy with Special Reference to Repository Injection Treatment. *Proc. Roy. Soc. Med.* 56, 213, 1963.
7. *Fontana, V. J., Holt, L. E. Jr. & Mainland, D.*: Effectiveness of Hyposensitization Therapy in Ragweed Hay Fever in Children. *J.A.M.A.* 195, 985, 1966.
8. *Frankland, A. W.*: High and Low Dosage Pollen Extract Treatment in Summer Hay Fever and Asthma. *Acta Allergol.* 9, 183, 1955.
9. *Frankland, A. W., Macaulay, D. B. & Evans, R. G.*: Hay Fever and Pollen Asthma Treated with Repository Injections. *Practitioner* 190, 505, 1963.
10. *Frankland, A. W., Evans, R. G., Macaulay, D. B. & Edwards, J. W.*: Hay Fever Treated by Repository Injections *Practitioner* 193, 71, 1964.
11. *Furstemberg, F. F.*: Reflexions on the Impact of Emulsion Therapy in the Practice of Allergy *Ann. Allergy* 21, 641, 1963.
12. *Loveless, M. H.*: Repository Immunization in Pollen Allergy. *J. Immunol.* 79, 68, 1957.

13. *Macaulay, D. B.*: Hyposensitisation with Emulsified Pollen Extracts in Britain. *Int. Arch. Allergy* 28, 12, 1965.
14. *Norman, P. S., Winkenswerder, W. L. & D'Lugoff, B. C.*: Controlled Evaluation of Repository Therapy in Ragweed Hay Fever. *J. Allergy* 39, 82, 1967.
15. *Sanders, S.*: The Treatment of Hay Fever and Asthma in Children. *Practitioner* 196, 811, 1966.

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