

SPECIAL ARTICLE

Allergen injection immunotherapy (hyposensitization) on trial

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Introduction

In April 1988 immunotherapy (hyposensitization) was put on trial at the National Heart & Lung Institute, Brompton Hospital, London. The court was presided over by Professor ('Judge') Maurice Lessof. The counsel for the defence was Professor B. Weeke who called on Dr S. Dreborg as his chief witness. Counsel for the prosecution was headed by Dr R. Davies, nobly assisted by Dr J. Warner. The jury consisted of the 100 or so people attending the third international course on 'Basic Clinical Allergy'. The court heard a vigorous debate of the issues involved.

Synopsis

LESSOF. Ladies and gentlemen, you are going to be the jury and the case we have to consider today is 'is allergen injection immunotherapy (i.e. hyposensitization) a useful treatment in allergic disease?'. I call on Professor Weeke to defend this form of treatment in allergy practice.

WEEKE. Your honour, members of the jury. How many of you own a car? Nearly all of you I imagine. Do you realize that cars are very dangerous. They kill many people every year. We hear of road traffic accidents all the time. How do we respond? By selling our car because it is too dangerous. No! I find my car very convenient, I need it, but more importantly I have been taught to drive a car properly and I have a driving licence. When I was young, I often made some small mistakes with my driving but now I am experienced. I do not make these mistakes anymore. I have experience, I have education, and a licence. Furthermore, I never drive when I have been drinking and I never drive when I am tired. There are also other factors; traffic rules and traffic signs. Have any of you ever driven faster than 30 miles per hour in a built-up area? It can be very dangerous but you still do it. Is your car always in perfect condition? Are the brakes perfect? Finally, do you always need to drive? You could travel by bus, bicycle, walk or use the underground. There are some circumstances, however, where you need to take your car. You

work out the benefits for and against taking your car, or another form of transport.

What is the association between driving and immunotherapy? They are both potentially dangerous, but in skilled, educated hands the risks are minimal and the benefits considerable. I hear that you have been having major problems with immunotherapy here in the United Kingdom. How do you educate your doctors and nurses? Where and how do they learn the rules about immunotherapy? What about a licence to do immunotherapy? It is a very specialized procedure. How do you get a licence in the United Kingdom? It is not possible I am told. Perhaps this is one of the reasons why we are gathered here discussing this issue. You have been having serious problems here in Britain with immunotherapy, but allergy is not a specialty; no-one can get a licence. So what do you do—you criticize the treatment and say it is no good. What about experience? I am very experienced at driving my car. I am also experienced in immunotherapy because I have given thousands of allergy 'shots' in my professional career. Just as I am alert and prepared for the unexpected when I drive my car, it is the same when I treat my patients. Just as I obey the traffic rules and observe the traffic signs when I drive, so I obey the rules and observe the signs when I treat patients.

Finally, what about your car? Is it in good working order? If not it may kill people. Just as a bad allergy extract will sometimes kill people. What about the standardization of the extract? In some countries they are standardized, some companies standardize, some do not. Now I wish to call my first witness, Dr Dreborg, thank you for coming here today. How long have you been practising immunotherapy and allergology?

DREBORG. 28 years.

WEEKE. How many shots or injections have you given during that time?

DREBORG. Roughly 30 000 I think.

WEEKE. Thirty thousand, that is a lot of injections. Clearly you are very experienced. Also I know that you travel a great deal and that you are in contact with leading allergologists all over the world. How many publications have you in international journals?

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DREBORG. About 100.

WEEKE. About 100 publications in international journals. So we are standing in the presence of a person of a very high-standing, with considerable experience and who was educated in allergology in one of the most famous parts of the world, Sweden. First, would you give us information about deaths from immunotherapy. This seems to be the main reason for the present concern.

DREBORG. I would like to start with the United Kingdom. As most of you know there was a Committee on Safety of Medicines (CSM) update in the British Medical Journal in 1986, dealing with immunotherapy. Twenty-six deaths in 27 years were reported, approximately one death in 28 000 patients or one death in 1 300 000 injections. This should not have happened, but it did. Why? In nearly every case the injections were given by general practitioners. Apparently these doctors had no facilities or equipment for treating general anaphylaxis. Allergy is not a speciality in the United Kingdom. It appears that allergy is sometimes diagnosed on the basis of skin tests alone, by nurses, and that extracts are prepared on the basis of these tests. Some of the mixtures used were of low allergen potency, others had high potency, but they were not standardized.

If we consider other parts of Europe, the story is different. In Sweden there has been one fatality in 20 years. I calculate that this is equivalent to roughly one death in 200 000 treatment years, or one death per 4 million injections (there are about 5000 patients a year receiving immunotherapy at present; it was 20 000 year until recently).

In Germany the figures are not readily available. In Italy and France it is about one death per year. In the U.S.A. there have been 46 fatalities in 40 years from either immunotherapy or intracutaneous tests. This is about one fatality in 6 million injections.

In Australia five deaths were reported in 1980, and this resulted in litigation. Again, all injections were given by general practitioners. An allergic diagnosis was made on the basis of skin tests. Materials were ordered by mail from the United Kingdom. The only knowledge the practitioners had about immunotherapy was from the package insert. No emergency equipment was available, in particular no adrenalin was immediately available and, in most instances no doctor was present or at hand. Injections were given during the pollen season to patients with symptoms of asthma.

So, members of the jury, lack of education led to errors by the doctor.

WEEKE. Dr Dreborg, how many people are treated with immunotherapy in Europe?

DREBORG. There are roughly 500 million people in Europe. About 50 million are allergic i.e. about 10%. In

Sweden about 30% of younger adults and adolescents have atopic allergy. 30 million of these consult doctors. According to the results of a recent questionnaire sent out by yourself Professor Weeke, about 1.5 million are given immunotherapy, i.e. about 20 million injections a year. There are about 10 deaths a year in Europe, i.e. one death in 150 000 treatment courses or 1 in 2 million injections. This is to be compared with 1 in 10 000 traffic victims annually in the United Kingdom and Scandinavia.

WEEKE. Then approximately 1000 times more people are killed in road traffic accidents compared with immunotherapy. Of course, one death is too many but this can be decreased to zero if we take care. But with human beings there is always human error. Is the treatment curative or just symptomatic? How long does it work for? Two, 3, 4 or 5 years? Can you give us some data on this Dr Dreborg?

DREBORG. It has been reported that the effects can last for at least 6 years after the termination of a course of immunotherapy.

WEEKE. That is good to know. Immunotherapy also reduces the need for drugs such as steroids. This is something to bear in mind. Dr Dreborg, can you tell us something about efficacy and cost benefits of immunotherapy?

DREBORG. Yes. We recently reviewed the world literature and found 26 controlled trials of IT in asthmatics, 19 showed efficacy as measured by symptoms scores and provocation tests. The cost benefit of immunotherapy for hay fever is certainly not formidable. In Sweden we usually confine treatment to patients with severe symptoms. It costs about £800 per patient per year.

WEEKE. So there is little doubt that immunotherapy works; should it be used more often? I would like to mention a report entitled 'Guide-lines for use in immunotherapy'. This was prepared for the Copenhagen meeting of the European Academy of Allergology and Clinical Immunology (EAACI) in June 1988. This report contains four sections:

- (1) indications for immunotherapy;
- (2) allergen extracts;
- (3) monitoring of treatment; and
- (4) practical information.

Dr Dreborg can you tell us, very briefly, some of the main points arising from this report?

DREBORG. Extracts and vaccines must be standardized, their contents characterized, their potency established and their efficacy proven. In Scandinavia we have the Nordic guide-lines and we recommend that these should be followed by all manufacturers. Patients should monitor treatment by self-evaluation. Although subjective this is useful for the allergist. Treatment should be evaluated

by the physician every year. Simple provocation tests, i.e. conjunctival provocation, are useful. Before treatment, it is important to obtain consent, inform patients of possible side-effects and instruct them regarding the procedure (in our Department we see patients in groups, they are then given an hour's talk on how the procedure is performed). Communication is essential and all questions should be thoughtfully answered and any complaints dealt with. In this way we gain the patients' confidence and allay their anxieties. Immunotherapy is given only if the patient requests it and are co-operative. The patient must be evaluated before and after each injection, i.e. when he attends follow-up treatment he should be asked how he felt after the last injection and whether he has had any symptoms (particularly asthma) within the last 3 days. If so no treatment is given. Also, before the patient leaves the clinic simple pulmonary function tests should be carried out, i.e. peak expiratory flow rate. We then investigate any reactions: when and why did they occur? The group in Copenhagen agreed that there were two main reasons for adverse reactions:

- (1) too high a dose given in error; and
- (2) complicating medical conditions, particularly asthma.

We also agreed that a specialist should start a course of immunotherapy and be responsible for providing structured information for the patient for monitoring immunotherapy.

WEEKE. Thank you very much. Your honour, I think Dr Dreborg has given very strong evidence to exonerate immunotherapy. I would now like a few more minutes and I wish the jury to join me in an experiment.

LESSOF. Permission granted.

WEEKE. Please sit back in your chair and relax. Close your eyes and listen to me. It is summer, you are in the countryside, you can smell the flowers, you can feel the warmth of the sun, you can feel the wind, you can smell the grass, you are at peace with the world. Unfortunately there is one thing wrong—you are allergic to pollen! Now imagine that you need to use drugs six to eight times a day for your eyes and nose and that you even have breathing difficulties. You are using many drugs and medicines but your symptoms are still very troublesome, so you ask your doctor to help you. An experienced allergist offers you immunotherapy. He explains the side-effects and discusses the pro's and con's of the treatment. Fully informed, it is now up to you to make the decision. The doctor will supervise the treatment and after the induction course you will need monthly maintenance injections for 3, 4 or possibly 5 years. You may be among the 80–90% who will improve. You will be aware that the side-effects are minimal as long as you and your doctor are

working together, and that the allergen extract will be of the finest quality. Now come out of the trance back to reality and make a decision as to whether or not you would decide on immunotherapy. Thank you your honour.

LESSOF. Thank you Professor Weeke, thank you Dr Dreborg. I now call upon Dr Davies to speak for the prosecution.

DAVIES. I expect that you all enjoyed the last few moments of Professor Weeke's talk as much as I did. Let me tell you at the outset that hypnotherapy is as successful as hyposensitization! It improves allergic symptoms in seven out of 10 people, as we know from the very earliest studies done in this country. Also we know from the first controlled studies with hay fever that 70% of people got better with placebos. The more Professor Weeke spoke the more obvious it was to me that immunotherapy is now obsolete. We (the British) gave the world hyposensitization in 1911; now it is time to take it away from you. You have enjoyed playing with it but we have found it does not work. Now the questions I am going to raise with you are:

- (1) does immunotherapy work?
- (2) is it safe?, and
- (3) how does it compare with other forms of treatment?

But first what about cost? I was amazed to hear that in Sweden it costs £800 to treat hay fever. In this country we could get a kidney transplant with that sum of money. In the United Kingdom it costs £21.60 to treat hay fever effectively. That is the price for regular topical corticosteroids and modern selective H_1 antihistamines. How does immunotherapy work? There is no doubt from the Frankland and Augustin study and others that there was clear improvement in symptoms in rhinitis. The evidence that there were changes in responsiveness to provoking allergen is much weaker, especially as assessed by measurements of nasal resistance.

Nevertheless I concede that, as far as grass pollens are concerned, active preparations have been superior to placebo. The situation with house dust mite extracts is far less convincing. Here there does not seem to be a clear relationship between the results of symptoms scores and nasal provocation.

I was recently involved in a British-Italian study of house dust mite hyposensitizations. There were 60 subjects, 30 from Italy and 30 from England. In general, the subjects who received the mite preparations tolerated high doses of allergen in nasal provocation, but at 5 months symptomatic improvement was similar in both the active and placebo group. At 15 months there were some differences in favour of the active compound in nasal blockage, but not in sneezing or runny nose. This

seemed to us to be a very large amount of time and energy for such a small improvement.

The next question is, is it safe? Of course it is not, and it is not only mortality but morbidity. Generalized allergic reactions requiring adrenaline are common, as are large local reactions and sometimes widespread urticaria. Even the most experienced allergist is regularly confronted with these problems. For example, 60 patients were recently treated with a very well characterized house dust mite preparation. Generalized allergic reactions requiring adrenaline occurred in 15%. I will not labour the question of fatalities, but only emphasize that, although rare, deaths from hyposensitization injections are appreciable, whereas deaths from allergic rhinitis are zero. If injection immunotherapy was extremely effective and we could tell the patient confidently that it would work then perhaps we could accept the risks better. But it is not. Antihistamines and topical corticosteroids, on the other hand, are clearly effective. The cost for all the summer months—£21.60. I rest my case on that.

LESSOF. Thank you Dr Davies. I believe that your colleague Dr Warner will now raise other points in support of your argument. Dr Warner.

WARNER. My Lord, learned colleagues. Professor Weeke made you think of the summer, and the sun, the wind on your cheeks, the bees and the pollens. I now want you to think of the winter. The 5-cm weal on your arm after your immunotherapy injection, waiting around for hours in the doctor's surgery, the resuscitation trolley and the syringe of adrenaline just to remind you how hazardous the procedure can be; and when the summer comes you will still have to take your medicines because even the best trials have shown that you only *reduce* the requirements for anti-allergic drugs—you cannot do away with them completely.

Most of you own a car. How many of you drove here today to this venue in Central London? Three or four of you I see. Why did you do that? You have added to the pollution, created a hazard to pedestrians by parking in the streets, but more importantly you could have used the safe route and come here today by public transport. It is the same with immunotherapy. You take an unnecessary risk when there are alternative (and more effective) methods.

Our Scandinavian colleagues tell us that soon there will be vaccines that have a greater efficacy and are of proven value. But we are talking about today, ladies and gentlemen, and today I do not think we have any preparations that really are safe or effective.

What about the clinical trials? Is it good enough just to show that a treatment is marginally better than placebo. And indeed just how good is placebo? Has not the allergist thrived and flourished for too long on this

placebo response? How do we give this treatment (which I prefer to call hyposensitization)? Some people still give drops under the tongue, squirt solutions into the nose or lungs with increasing doses of essentially uncharacterized substances. Some of these preparations are immunogenic in their own right. Treatment is given at varying intervals, for an undefined period of time in an attempt to reduce allergic reactions to these substances. Supposing allergen injection immunotherapy had just been discovered and we were trying to get a product licence from the CSM or FDA. How do you think they would react to a form of treatment that was marginally better than placebo and where the optimal dose was unknown, the length of time to give was unclear, general anaphylaxis was a likely side-effect and where it was impossible to predict how many patients would respond.

Let me spend a moment addressing some difficulties of clinical trials in allergy. There are three main headings under which difficulties arise.

Patient selection. Patients have to be uniform and selected in the same way.

The allergy diagnosis. Skin tests alone are not sufficient. Provocation tests under standardized conditions are also required.

Objective evaluation. You must have appropriate measurements. You must be prepared for the unexpected. We conducted an oral immunotherapy trial a few years ago; several patients moved home; some lost their diary cards; some did not re-appear at clinics; one family had a fire in their apartment which melted the peak flow meter and burnt the diary cards; another patient suggested that their diary cards were stolen from a briefcase. There was a railway strike in the middle of the trial and several patients could not come for their routine evaluations. Many of the children got intercurrent infections during the winter months which of course confounded the observations about the effects of the treatment. Several patients went on summer vacations or had examinations at the height of the pollen season—the time when we were wanting to do our evaluations. Two families acquired a cat during the middle of the trial to which they were allergic. Several patients broke their peak flow meters. The number who actually completed the study was very much less than those who started and meant that the value of the study was substantially diminished.

I think I must conclude that immunotherapy remains a mysterious and chaotically applied treatment for allergy. Carefully conducted trials are still required to identify its place amongst the highly effective and safe pharmacotherapies currently available. At the present time this erratic and occasionally dangerous form of therapy cannot be recommended.

LESSOF. Is there anyone else who would like to give

evidence before the court?

AMERICAN ALLERGIST. Yes your honour, I would.

LESSOF. Where are you from?

AMERICAN ALLERGIST. I come from the United States.

LESSOF. Professor Weeke, your witness.

WEEKE. What is your experience of hyposensitization, how many allergy injections have you given?

AMERICAN ALLERGIST. I have given about 5000 allergy injections over a period of 10 years.

WEEKE. Do you feel it works?

AMERICAN ALLERGIST. I would say that I am now confused and I have been frightened today by these British doctors. Before hearing them, I had the impression that in some individuals you could accomplish some improvement and that symptoms did improve. Now I am not so sure. We always give the patients other medicines as well, bronchodilators or corticosteroids. You cannot tell if the improvement is due to the immunotherapy or to the drugs.

WEEKE. Asthma is a more severe problem. What about rhinitis or venom therapy?

AMERICAN ALLERGIST. I do not have any particular experience with venom therapy. My main expertise is with asthma.

WEEKE. Do patients ask for immunotherapy or do you offer it?

AMERICAN ALLERGIST. In the United States, one is under pressure because patients ask for allergy 'shots', but I am the one who makes the final decision in all cases.

WEEKE. Have you met a patient who has said that he is afraid of taking steroids? Has he asked you if you can be certain that by using sprays to the nose and bronchi, he will be all right in 10 to 20 years time?

AMERICAN ALLERGIST. Definitely. Patients are frightened by steroids. I do not know about Britain but in the United States there are many articles talking about the evil effects of steroids. Patients are indeed very frightened. Obviously you have to tell them that there are obvious risks in the use of oral steroids, but you also have to inform them of the benefits. I personally make an effort to inform the patient about the benefits and risks in using steroids.

LESSOF. Dr Davies do you have any questions to put to the witness?

DAVIES. Do you use topical corticosteroid sprays? Are people in the United States worried about the dangers of inhaled corticosteroids or corticosteroids applied to the nose?

AMERICAN ALLERGIST. In general they are not. There is some concern about the propellant.

DAVIES. Do you use inhaled steroids quite a lot?

AMERICAN ALLERGIST. Definitely. It is a very useful treatment. However, I do recognize a group of patients that perhaps will be helped with immunotherapy.

DAVIES. What kind of anti-histamines do you use in the United States? Are you using the newer non-sedating ones?

AMERICAN ALLERGIST. Yes, definitely. We now live in a climate of liability in the United States so we are constantly under pressure to explain to the patient the risks of taking anti-histamines and driving. This is solving the problem.

DAVIES. How do you see your practice going over the next 5 years in terms of injections and topical steroids? Which do you think is going to become the major part of your practice perhaps?

AMERICAN ALLERGIST. I must say that I am frightened.

DAVIES. By what?

AMERICAN ALLERGIST. By you. I do not mean you personally, but frightened by your sense of drama. Your speech was very dramatic. I would say that besides being an eloquent speaker you are also a very persuasive one.

DAVIES. Thank you very much, you are a very perceptive man.

LESSOF. Is there anyone else who would like to give evidence for us on this highly charged and important topic?

MR DYER. May I ask Professor Weeke, is there any chance that immunotherapy will compromise the immune system? Are there any long-term side-effects?

WEEKE. There is no such evidence. I would like to make the point that hyposensitization is an immunologically precise form of treatment and in this sense very elegant. In theory, one should get high dose tolerance to the offending allergens.

LESSOF. Any other witnesses please?

RESEARCH WORKER. As a basic researcher I am getting the impression from this debate that immunotherapy probably works and that if it is supervised by specialists safety is probably not a major problem. There is still a lack of data on how it works. It presumably produces some form of immunological tolerance. This is one of the most fascinating and important areas of immunology today. However, we really have no hard facts on the mode of action of immunotherapy and this is disappointing.

WEEKE. Can you drive a car?

RESEARCH WORKER. Yes, and I have a licence and a lot of experience.

WEEKE. Do you know how the engine works?

RESEARCH WORKER. Probably about as much as you do.

DAVIES. Correct. Neither of us know enough about how the car works. But that does not prevent us from driving. Do you think that doctors should only use drugs if they know how they work?

RESEARCH WORKER. They should at least try to understand.

DAVIES. Do you think we know anything about how

immunotherapy works?

RESEARCH WORKER. I did not learn anything about how immunotherapy works this afternoon.

LESSOF. I will now call on the defence and prosecution to sum-up. First Professor Weeke.

WEEKE. As far as immunotherapy is concerned, time seems to have stood still in the United Kingdom, at least for about 30 years or so. You seem to know very little about modern immunotherapy, the recent well-conducted clinical trials and the considerable advances in allergen standardization. You have had tragic experiences, but this was not all that surprising if you do not have allergy as a speciality and you do not obey the rules. The principle and practice of safe and effective immunotherapy are to be found in the guide-lines of the immunotherapy sub-committee of the European Academy of Allergology and Clinical Immunology. What you need here in the United Kingdom is a little more education.

DAVIES. I do not know whether immunotherapy works. In general and with a few exceptions, I do not think it does. On the other hand I think that immunotherapy probably

has an important and exciting future. But that is not the point. The point is that at the moment it is unhelpful and sometimes very dangerous. We have heard today of the total lack of comparative studies which would really support present immunotherapy. I was delighted to hear from a colleague that because of my presentation he is going to forego all the money he could make out of allergy 'shots' and be like us 'poor doctors'. But at least we are happy in the knowledge that we are giving the patients the best treatment, at by far the lowest cost, and in the safest way.

LESSOF. Thank you Dr Davies. Members of the jury have you considered your verdict? Is allergen injection immunotherapy (hyposensitization) a useful treatment in allergic disease? Teller, please count.

Verdict

The official verdict was 47 *for* immunotherapy and 50 *against* immunotherapy. But three members of the jury had to leave early to rescue their cars from parking meters. Asked afterwards, all of them said they would have voted '*for*'! Thus the final verdict was a tie—50:50.

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