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The North American EPD Study

73 physicians participated in the study at different centers (multi-center) in the USA and Canada. Patients were selected randomly for this study in many or most instances. However, a quite significant percentage of these of patients were selected because they had previously failed on treatment with both medications and conventional immunotherapy.

EPD treatment was administered every two to three months, generally by one to five small (1/20 c.c.) intradermal (in the first layer of skin) injections which were generally administered in the skin of the inner aspect of the forearm.

Patients were evaluated by the use of initial and interim questionnaires. The initial questionnaires were completed by patients prior to receiving EPD, and the interim questionnaires were completed immediately prior to receiving each subsequent treatment. Patients evaluated how they responded to EPD "overall" and how they responded to each specific condition they had recorded. Overall and individual categories were evaluated for both the effect on the *frequency* of their symptoms and the effect upon *severity* of symptoms.

Patients were allowed to evaluate as few as one and as many as six conditions for which they were being treated. Patients were required to choose one of the following categories for both their "overall" response for each evaluation and their response to EPD treatment for each specific condition were evaluated:

Excellent

Very good

Good

Fair

Poor

Terrible (worse than the before starting treatment)

Patients also recorded their frequency of use of self-selected medications at the onset of treatment and for their evaluation after each treatment (over 600 medications were listed by patients).

EPD - Frequency of Treatment

EPD treatments were given every 2 to 3 months at first, then less often. Generally, patients with multiple problems were treated every two to three months for six to eight times. After that, treatments usually decreased to every four to six months and then less often as needed. Once therapy reached once yearly, treatments were often stretched to as little as once every 6-12 months. 68,428 treatments were given to 10,372 patients. Since "treatments" consisted of 1 to as many as 7 injections, the total number of actual injections given is not known exactly, but was between 175,000 and 179,000.

EPD - Conditions Treated

Over 60 conditions were treated with EPD in this study. The conditions treated are listed here

EPD - Complications and Adverse Reactions

There were 3 patients reported with possible complications to EPD to the IRB over the period of 1994-1999. None of these complications were serious or life threatening.

Results

The study evaluated 10,372 patients over 7 years. Of those patients, 60% (6261) were female and 40% (4111) were male. Average age of females was 45, and the average for males was 33.

Of the 10,372 patients enrolled in the study, 6030 were evaluated as to overall response, response as to improvement in frequency (see Table I below) and response as to improvement in severity (see Table II below). The "dropout" rate was 41% over the 7-year period of the study. This compares to 50% for much shorter-term studies of escalating dose immunotherapy, where only very few conditions (4 or less) were studied.

It has been established by previous studies that it may take up to three treatments with EPD to determine whether the therapy may be effective. Considering this, the 1160 patients who stopped treatment prior to three treatments were counted as dropouts, but really cannot be counted as treatment failures.

Responses were scored numerically by computer. For specific conditions evaluated, for the purposes of this paper, patients who reported a response of "excellent", "very good" or "good" were grouped together as "satisfactory"). Patients who reported "fair" results were classified as "fair", and patients who reported "poor" or "terrible" were reported as "no change" or "worse".

The "overall" response showed that 20% of patients reported excellent, 30% reported very good and 26% good, with an *overall* "satisfactory" response rate of 76%. Fourteen percent (14%) reported fair and 8% reported no change. Two percent (2%) of patients felt they were worse after receiving EPD than they had been prior to

starting EPD; most investigators suspected that many of these patients worsened despite EPD, rather than as a result of EPD, though this could not be determined.

Discussion

The American EPD Society study is the largest outcome-based study ever undertaken of any type of immunotherapy, with over 10,000 patients. We believe that this study demonstrated the significant clinical value of EPD as a treatment tool. We have listed a brief comparison of EPD immunotherapy to conventional immunotherapy in Table IV.

Conventional escalating dose immunotherapy is the immunotherapy most widely used in the United States. Most classically trained allergists employ this type of treatment in some form. It should be made clear, however, that this type of immunotherapy is effective for only a relatively few conditions. According to the medical literature, these conditions are fairly limited to seasonal hay fever, dust mite allergy, cat (and perhaps dog) allergy, and possibly seasonal asthma.

Most studies done of patients treated with conventional immunotherapy for classical pollen allergy claim an overall success rate of between about 60 and 80 percent for highly selected patients.

Although every condition evaluated in our study did not necessarily appear to respond dramatically to EPD immunotherapy, most responded quite favorably. Most importantly, a large number of conditions which do not respond at all to conventional immunotherapy, and many which do not respond well to *any*type of therapy - appear to have responded to EPD.

For example, there is no effective immunotherapy for angioedema, which consists of facial swelling, swelling of the lips or eyes or swelling of other parts of the body, primarily as a result of acute food allergy. 78% of 180 patients reported satisfactory (excellent, very good or good) results with EPD immunotherapy. Conventional therapy dictates treatment primarily with drugs.

Likewise, immediate food allergy, which includes anaphylaxis (a condition that is generally life-threatening) has no effective treatment except for emergency drug treatment and avoidance of the offending food or foods. This includes such potentially fatal problems as peanut and shrimp or shellfish allergy. In the group of 519 patients who had some type of immediate food allergy, EPD was effective in 72%. Conventional immunotherapy has no effect for anaphylaxis to foods or chemicals, and is in fact dangerous and contraindicated. The only exception is a type of immunotherapy (Rush desensitization) that has been employed for penicillin, bee sting and a few other problems.

Several conditions that are difficult to treat don't respond extremely well to drug therapy and cannot be treated with conventional immunotherapy. Yet many appeared to respond well to EPD in this study. The quite successful response (in regards to severity) of such conditions as perennial asthma, (732 patients with 75% success), headaches (1186 patients with 75% success), food intolerance - or food reactions, which in most cases was moderate to moderately severe (2857 patients with 74% success), chronic perennial rhinitis (2258 patients with 74% success), hyperactivity/attention deficit disorder (578 patients with 70% success) and eczema or severe dermatitis (669 patients with 69%

success), are just a few conditions that response to *any* type of immunotherapy should be considered dramatic.

Although the results of treatment with EPD of some of the autoimmune diseases studied here may not appear to be dramatic, treatment of these conditions with any type of immunotherapy has been extremely disappointing or has not been considered possible.

Results for certain autoimmune conditions varied from center to center, primarily as a result of specific treatment protocols employed by physicians that were used in addition to the fundamental study protocol. For example, in this study, 14 patients with ankylosing spondylitis (severe, debilitating arthritis of the spinal column) had a modest success rate of 64%. However, in one treatment center, likely as a result of the specific protocol chosen by the physician, all four patients treated for ankylosing spondylitis with EPD responded extremely well.

The same case can be made for rheumatoid arthritis. This is a typically debilitating and progressive disease for which the only available treatment is the employment of a specific regimen of drug therapy. For the 76 patients with rheumatoid arthritis in the study, most would consider a 57 percent rate of success - which means patients were satisfied with the results - remarkable. 79% of patients with rheumatoid arthritis in the study reported a decrease in the medications needed to treat symptoms.

Although the final statistics of this study have not yet been published, the considerably large numbers of patients in fairly well defined groups gives a strong indication that the conclusions are reliable. Also, the success rate of EPD (78%) for seasonal rhinitis (1361 patients) compares favorably to that of conventional immunotherapy.

The results for the treatment, listed by response to Frequency and Severity, appear below, sorted from greatest to least effect. Groups of patients with less than 20 individuals (N< 20) should not be considered accurate enough to be statistically significant.

A comparison of EPD immunotherapy and conventional immunotherapy appears in Table III.

Table I. American EPD Trial Outcome Results

Improvement in Frequency of Symptoms (Nov., 1993 - Nov., 2000)

Description	Patients	No response to question	Patients evaluated	Excellent, Very Good, Good	%	Fair	%	No change or worse	%
Repeated Ear Infections	281	15	266	236	89%	16	6%	14	5%
Secretory Otitis Media	39	9	30	26	87%	2	7%	2	7%
Repeated Chest Infections	251	13	238	192	81%	24	10%	22	9%
Asthma, seasonal only	210	3	207	163	79%	19	9%	25	12%
Angioedema	180	18	162	127	78%	12	7%	23	14%
Rhinitis, Seasonal	1361	67	1294	1011	78%	152	12%	131	10%
Allergic Conjunctivitis	1017	48	969	746	77%	125	13%	98	10%
Chronic Cough, not asthma	303	8	295	228	77%	37	13%	30	10%
Chronic Face ache	484	39	445	336	76%	61	14%	48	11%
Asthma	732	46	686	512	75%	91	13%	83	12%
Contact Dermatitis	176	11	165	124	75%	23	14%	18	11%
Headaches, Other	1186	89	1097	818	75%	149	14%	130	12%
Nasal Polyps	112	10	102	75	74%	13	13%	14	14%
Rhinitis, Perennial	2258	128	2130	1570	74%	297	14%	263	12%
Food Allergy, Other	2857	140	2717	1958	72%	399	15%	360	13%
Immediate Food Allergy	519	38	481	348	72%	59	12%	74	15%
Plugged Ears, moderately severe	402	14	388	276	71%	53	14%	59	15%
Chronic Anal Irritation	132	4	128	89	70%	20	16%	19	15%
Chronic Sinusitis	352	21	331	233	70%	49	15%	49	15%
Eczema	669	29	640	444	69%	91	14%	105	16%
Emotional/behavioral problems	488	15	473	327	69%	65	14%	81	17%
Irritable Bowel	613	38	575	397	69%	88	15%	90	16%
Candida-Related Complex	940	59	881	598	68%	156	18%	127	14%
Hyperactivity	578	34	544	372	68%	81	15%	91	17%
Mental confusion (brain "fog")	1650	77	1573	1065	68%	263	17%	245	16%
Migraine/Severe Headache	691	36	655	448	68%	85	13%	122	19%
Chronic severe post-nasal drip	561	5	556	374	67%	102	18%	80	14%
Pruritis	177	4	173	116	67%	25	14%	32	18%

Chemical Sensitivity	1413	83	1330	858	65%	252	19%	220	17%
Gut Fermentation	699	35	664	431	65%	124	19%	109	16%
Ankylosing spondylitis	14		11	9	64%	2	14%	3	21%
CFIDS	152	9	143	91	64%	24	17%	28	20%
Chronic Fatigue, Other	887	55	832	535	64%	163	20%	134	16%
Constipation	399	22	377	237	63%	68	18%	72	19%
Hypertension	109	6	103	65	63%	17	17%	21	20%
Depression, significant	452	8	444	276	62%	80	18%	88	20%
Epilepsy	45	3	40	26	62%	3	7%	13	31%
Psoriasis	65	4	61	38	62%	11	18%	12	20%
Arthritis, Non-Specific	689	43	646	393	61%	124	19%	129	20%
Chronic Vaginal Symptoms	179	8	171	103	60%	32	19%	36	21%
Muscle Pains	561	35	526	318	60%	117	22%	91	17%
Rheumatoid Arthritis	76	3	73	43	59%	13	18%	17	23%
Crohn's Disease	29	1	28	16	57%	6	21%	6	21%
Insomnia, moderately severe	423	9	414	225	54%	90	22%	99	24%
Autism	134	6	128	68	53%	31	24%	29	23%
Meniere's Disease	47		41	25	53%	11	23%	11	23%
Dermatographia, dermagraphia	17		12	8	47%	3	18%	6	35%
Sjogren's Syndrome	16		18	7	44%	4	25%	5	31%
Anosmia	116	5	111	48	43%	25	23%	38	34%
Multiple Sclerosis	5		4	1	25%	3	50%	1	25%

Table II: American EPD Trial Outcome Results

Improvement in Severity of Symptoms (Nov., 1993 - Nov., 2000)

Description	Patients	No response to question	Patients evaluated	Excellent, Very Good, Good	%	Fair	%	No change or worse	%
Repeated Ear Infections	281	5	276	243	**88%**	18	**7%**	15	**5%**
Secretory Otitis Media	39	2	37	32	**86%**	3	**8%**	2	**5%**
Repeated Chest Infections	251	5	246	196	**80%**	22	**9%**	28	**11%**
Chronic Cough, not asthma	303	6	297	234	**79%**	33	**11%**	30	**10%**
Contact Dermatitis	176	3	173	135	**78%**	23	**13%**	13	**8%**
Rhinitis, Seasonal	1361	22	1339	1041	**78%**	162	**12%**	136	**10%**
Urticaria	230	6	224	175	**78%**	23	**10%**	26	**12%**
Allergic Conjunctivitis	1017	23	994	770	**77%**	126	**13%**	98	**10%**
Nasal Polyps	112	5	107	82	**77%**	11	**10%**	14	**13%**
Asthma, seasonal only	210	1	209	158	**76%**	22	**11%**	29	**14%**
Chronic Face ache	484	14	470	358	**76%**	61	**13%**	51	**11%**
Angioedema	180	9	171	128	**75%**	21	**12%**	22	**13%**
Asthma	732	17	715	539	**75%**	93	**13%**	83	**12%**
Headaches, Other	1186	24	1162	868	**75%**	154	**13%**	140	**12%**
Food Allergy, Other	2857	55	2802	2060	**74%**	385	**14%**	357	**13%**
Rhinitis, Perennial	2258	33	2225	1644	**74%**	307	**14%**	274	**12%**
Chronic Sinusitis	352	10	342	245	**72%**	47	**14%**	50	**15%**
Immediate Food Allergy	519	15	504	364	**72%**	65	**13%**	75	**15%**
Plugged Ears, moderately severe	402	7	395	281	**71%**	56	**14%**	58	**15%**
Hyperactivity	578	16	562	392	**70%**	84	**15%**	86	**15%**
Candida-Related Complex	940	30	910	630	**69%**	150	**16%**	130	**14%**
Eczema	669	10	659	457	**69%**	104	**16%**	98	**15%**
Emotional/behavioral problems	488	11	477	331	**69%**	61	**13%**	85	**18%**
Irritable Bowel	613	10	603	419	**69%**	96	**16%**	88	**15%**
Chronic Anal Irritation	132	3	129	88	**68%**	19	**15%**	22	**17%**
Migraine/Severe Headache	691	14	677	458	**68%**	83	**12%**	136	**20%**
Chronic severe post-nasal drip	561	6	555	370	**67%**	104	**19%**	81	**15%**

Mental confusion (brain "fog")	1650	27	1623	1095	**67%**	286	**18%**	242	**15%**
Chemical Intolerance	1413	28	1385	918	**66%**	240	**17%**	227	**16%**
Gut Fermentation	699	20	679	450	**66%**	116	**17%**	113	**17%**
Urinary Tract Symptoms	152	6	146	96	**66%**	20	**14%**	30	**21%**
Constipation	399	9	390	252	**65%**	62	**16%**	76	**19%**
Pruritis	177	2	175	114	**65%**	31	**18%**	30	**17%**
Ankylosing spondylitis	14		14	9	**64%**	1	**18%**	4	**36%**
Chronic Fatigue, Other	887	21	866	554	**64%**	168	**19%**	144	**17%**
Depression, significant	452	6	446	286	**64%**	67	**15%**	93	**21%**
Hypertension	109	3	106	67	**63%**	17	**16%**	22	**21%**
Arthritis, Non-Specific	689	21	668	413	**62%**	121	**18%**	134	**20%**
CFIDS	152	5	147	89	**61%**	29	**20%**	29	**20%**
Chronic Vaginal Symptoms	179	1	178	108	**61%**	34	**19%**	36	**20%**
Muscle Pains	561	10	551	333	**60%**	130	**24%**	88	**16%**
Crohn's Disease	29		29	17	**59%**	6	**21%**	5	**17%**
Psoriasis	65	5	60	35	**58%**	13	**22%**	12	**20%**
Ulcerative Colitis	40		40	23	**58%**	8	**20%**	9	**23%**
Meniere's Disease	47	1	46	26	**57%**	10	**17%**	10	**14%**
Rheumatoid Arthritis	76	2	74	42	**57%**	15	**20%**	17	**23%**
Insomnia, moderately severe	423	8	415	232	**56%**	89	**21%**	94	**23%**
Autism	134	7	127	70	**55%**	31	**24%**	26	**20%**
Epilepsy	45	6	39	21	**54%**	2	**4%**	16	**36%**
Dermatographia, dermagraphia	17		17	9	**53%**	3	**50%**	5	**29%**
Multiple Sclerosis	5		5	2	**40%**	1	**0%**	2	**100%**
Sjogren's Syndrome	16		16	6	**38%**	4	**33%**	4	**22%**

Table III: Comparison of EPD Immunotherapy to Conventional Immunotherapy

	Conventional Immunotherapy	**EPD Immunotherapy**
Strength (dosage) at start of therapy	1:10,000	1:1,000,000,000,000,000 (quadrillion) to 1:1,000,000
Strength (dosage) at maintenance (highest)	1:10 to 1:100 (approx.)	1:1,000,000
Conditions treatable	Limited	Diverse
Autoimmune disease	Not treatable	Often treatable
Life-threatening food allergy (peanut, shellfish, others)	Not treatable, and immunization is contraindicated	Treatable (success rate of 72% of 519 patients)
Frequency of treatment	Twice weekly, usually for 6 months, then once every 1-2 weeks, then less often	Every 2 months for 12 months, then every 2-24 months
Ability to stop therapy	Often not possible	Half of all patients can stop after 16-18 treatments
Drug Usage	Very little changed	Considerably decreased, 50% of patients were able to stop medications
Cost	Moderate - long term	30-60% less than conventional
Safety	Fatalities recorded due to high dosages needed	safe; no fatalities ever recorded
Efficacy	Proven for certain pollen and other limited types of allergy. Not satisfactory for patients with allergy to multiple inhalants. Ineffective for patients with autoimmune diseases, food allergy and intolerance and most others. Efficacy said to be approx. 80% for *treatable* allergy.	Effective for all types of allergy and intolerance to inhalants, foods and chemicals. Effective for some types of autoimmune diseases. The *only*immunotherapy available for treatment of anaphylaxis to foods. Virtually all patients with allergy treatable. Overall efficacy for *all conditions treated* (approx. 60 diverse conditions, American EPD Study) was 75%.

Conclusions

At the end of this 7-year study of 10,372 patients who received at least 175,000 injections of EPD, the physicians who participated in this study concluded that the healing and health potential of EPD for use to treat allergy and autoimmune disease is significant.

As a result of the findings of this study, and in comparison to conventional immunotherapy, we must conclude that EPD:

Is extremely safe, without incidence of fatality or serious side effects

Is virtually the only option available to actually prevent the occurrence of life-threatening reactions or death as a result of acute food allergy

Is as successful as conventional immunotherapy for the very limited conditions for which conventional immunotherapy is used to treat.

Can be used to successfully treat a vastly greater number of conditions, and is more convenient than conventional immunotherapy (i.e. treatment every 2 weeks)

Reduces the amount and/or number of drugs required to be taken by patients by at least 50 percent on the average.

Has several major advantages over conventional escalating dose immunotherapy:

- is 30-60% more cost-effective
- is administered far less frequently with an earlier and more complete endpoint
- can be discontinued without complete relapse of symptoms, or treatments can be extended to very long intervals of a year or more