

Is Month of Birth a Risk Factor for Subsequent Development of Pollen Allergy in Adults?

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ABSTRACT

A comparison of the date of birth of 1501 adult patients with severe seasonal respiratory allergy (allergic rhinitis or bronchial asthma) due to parietaria, olive, and grass pollens with the expected births within 2,020,420 births in South Greece during the same period, was performed. The relative risk for developing respiratory allergy was characteristically increased in those born in a specific period of time different for each pollen. The relative risk for parietaria was increased (1.47) in those born in March; for olive it was 1.6 for May; 1.2 for April; and 1.4 for March, while the relative risk for grasses was 1.2 in those born in June and July. These findings are indicative of the importance of the month of birth; that is, the early exposure to pollens, for the development of respiratory allergy to certain pollens during adulthood. Because our findings do not directly correlate completely with the aerobiology studies on pollen calculation in Athens' atmosphere, we supposed that other environmental factors, e.g., the local intensity of the first pollination or the influence of weather conditions, may contribute to the final development of respiratory allergy as well. The most impressive finding was the significant influence of the month of birth in the development of respiratory allergy due to parietaria and olive pollens during adulthood. (Allergy and Asthma Proc 20:15-22, 1999)

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Presented at the Annual Meeting of the European Academy of Allergology and Clinical Immunology (EAACI), Rhodes, Greece, June 1-5, 1997

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The importance of prevention of allergic diseases is obvious. Therefore, there is a growing tendency to identify and specify risk factors relevant to the development of these diseases.

Exposure of humans to aeroallergens during the first 3 months after birth was considered as an important sensitization factor to these allergens.^{1,2} During this period, the immune system is immature and reduced levels of immunoglobulin A have been detected in the secretions, resulting in easier entrance of the allergens and thus potentially higher risk for sensitization.^{1,3,4} This is why many studies have been performed that correlate the month of birth with increased risk for sensitization to aeroallergens such as birch pollen, grass pollen and house dust mites mostly in patients under the age of 20 years.⁵⁻⁷ Some researchers reported a correlation between the month of birth and the sensitization to certain allergens¹⁰ (e.g., mites) and not to others (e.g., grasses), whereas others found no correlation at all.^{8,9}

It is a fact that the sensitization to allergens can take place in individuals with certain genetic predisposition during all periods of their life even during advanced age. This is the conclusion of studies performed on immigrants sensitized to new allergens in the places where they finally settled.

Also, low frequency of specific IgE against pollens, detected with skin or radioallergosorbent tests, in children aged less than 4 years, raises questions regarding the possibility of sensitization to pollens during neonatal age or infancy without evidence of sensitization when performing skin or radiollergosorbent tests. Schafer et al. found no correlation between sensitization and month of birth in children aged 5 to 6 years.¹¹

In the present study we evaluated a population of adults aged 20 to 35 years with severe allergic rhinitis or strictly seasonal asthma, sensitized to one or more of the three most

important pollens present in the Greek flora (grasses-olive-parietaria pollens).

Our belief was that, based on the existing literature, no such correlation between the month of birth and the disease may be evident, mainly because of the advanced age of the patients of our sample (mean age 28.2 years).^{5,12}

Nevertheless, certain findings of our study are impressive although difficult to interpret according to previous aerobiologic studies regarding the presence of pollens in the atmosphere of Athens.^{13,14}

The strict selection of patients with severe seasonal asthma or rhinitis sensitized to specific seasonal allergens, and not the simple sensitization as is the case in other studies, increases the importance of our findings.^{15,16}

MATERIALS AND METHODS

Patients

From the Departments of Allergy and Clinical Immunology of the Sotiria Hospital of Chest Diseases and the Air Forces General Hospital, patients with symptomatology of severe seasonal rhinitis or seasonal bronchial asthma for more than 2 years and strongly positive skin-prick tests ($>3+$) to one or more of the three most important aeroallergens of the Greek flora, that is, parietaria-olive-grass pollens, were selected to participate in this study.

Absolute prerequisites were the correlation of symptoms with the findings of skin testing and the absence of positive skin tests to house dust mites, molds, and pet fur. All patients were born between 1959 and 1974 (aged 20 to 35 years) in Athens or South Greece. A comparison of the frequency of births of patients per month was performed with the total births per month in South Greece during the 1959–1974 period (2,020,420 individuals). Data were derived from the National Statistical Service of Greece.

All patients underwent 20 skin tests to the most common allergens (Allergopharm, Germany) of the Greek flora with the prick method.

Statistical Analysis

A multivariate statistical analysis was performed. Initially, the χ^2 -test:

$$\chi^2 = \sum [(O - E)^2/E]$$

was applied as a “goodness of fit” criterion in order to determine whether the frequencies of births per month found in our patients were significantly different from the expected frequencies of births per month found in the population of 2,020,420 individuals born during the same period. Then, we identified the expected frequency of births per month according to the equation:

$$95\% \text{ confidence interval of } P = P \pm 1.96 P \cdot Q/N$$

In this way we defined the upper and lower limits of the expected births per month in each group of patients sensi-

tized to each allergen separately and compared the frequencies of births per month observed in the relative groups of our patients. The Bonferroni multicomparison procedure was used to control experiment type I error. Thus, results meeting the Bonferroni criterion were reported as “statistically significant.” Results failing to comply but having generalized $p < 0.05$ were reported as nonsignificant trends. We also calculated the relative risk of developing allergic asthma/rhinitis depending on the month of birth for each and every pollen and for all pollens with the following formula:

$$R = nm/n/Bm/B$$

where nm = the number of individuals allergic to certain allergens born during the month under examination, n = total sum of patients sensitized to this particular allergen, Bm = total number of births in South Greece during that month, and B = total sum of births annually for 1957–1974.

Aerobiology

Studies based on calculation of pollen grains in the atmosphere are available only for the area of Athens where environmental conditions differ from those existing in urban areas of South Greece. The findings of an interesting aerobiology study performed in Thessaloniki (in North Greece) are not applicable due to significant differences between the climatic conditions existing in comparison to South Greece.^{14,17}

From two studies,^{13,14} pollen circulation in the atmosphere of Athens is as follows:

1. Parietaria: from March to June, with peak concentrations during April and May;
2. Grasses: from April to August, with peak concentrations during late April and May;
3. Olive: from April 15 to June 15, with peak concentrations during May.

RESULTS

A total of 1501 patients with seasonal rhinitis or seasonal bronchial asthma participated in this study. Of those, 602 have been submitted or were under immunotherapy at that time. From the study population, 789 were men and 712 were women; 285 had positive skin tests to parietaria only; 283 had monosensitivity to grasses; 161 had monosensitivity to olive, and 772 had positive skin tests to two or three of the pollens studied. The mean age of patients was 28.2 years and the mean time of disease duration was 10.3 years for allergic rhinitis and 6.5 years for allergic asthma.

In our 1501 patients the distribution of births per month showed a statistical significant difference compared with the expected frequency in the 2,020,420 births at the same period with the application of the χ^2 -test as a “goodness of fit” criterion.

From the distribution of births per month in our 1501 patients and the expected frequencies per month after definition of the upper limit of expected births (ULEB) and the lower limit of expected births (LLEB) with a 95% confidence interval, significantly more births, 168 and 143 for March and June compared to the ULEB of 159 and 136, respectively (Tables I and II, Fig. 1), were recorded.

During these months (March–June), the relative risk for developing allergic rhinitis and asthma was 1.2 (base value: 1 (Table III).

The number of births during the first 6 months (January–June) was increased (801 compared to the mean expected frequency of 787) but not over the ULEB level, which was 824 (Table IV).

The number of births during the period from March to June, with the higher pollen concentration in the atmosphere, was significantly higher than the ULEB (554 births compared to 540 births of the ULEB) (Table V).

The statistical analysis was performed separately for the groups of patients with sensitivity to one pollen only; these findings have greater value because they are indicative of precise conclusions regarding the importance of a specific allergen on early sensitization and development of respiratory allergy during adulthood. The distribution of births per month in the 285 patients with monosensitivity to parietaria revealed a higher (statistically significant) frequency of births exclusively for March (39) that was much higher than the ULEB for the specific month (30). The relative risk for developing respiratory allergy due to parietaria for those born in March was 1.47. The distribution of births of allergic individuals sensitized to parietaria for the other months kept strikingly up with the expected frequencies (Table II, Fig. 2).

The distribution of births per month in the 283 patients with monosensitivity to grasses revealed a higher frequency of births during June and July (27 and 28 births, respectively; values higher than the ULEB of 26 and 27, respectively). Although this observation shows a nonsignificant trend using the Bonferroni multicomparison procedure, it is of interest because during these months, grass grains in the

atmosphere of Athens do not reach their peak; and patients allergic to grasses show, since mid-June, significant improvement of their symptoms (Table II, Fig. 3).

There were also 161 patients with allergy to olive pollen only. The distribution of births revealed a higher (statistically significant) frequency, above ULEB during March (21 births with ULEB 17 births), April (16 births with ULEB 15 births) and May (21 births with ULEB 15 births) (Fig. 4). During the second semester (from July to December), the number of births per months was lower than the LLEB. The relative risk for developing a respiratory allergy due to olive pollen for patients born in March was 1.4, for April 1.20, and for May 1.60 (Table II).

It is obvious from these results that being born from March to May increases significantly the risk of developing allergic asthma or rhinitis due to olive pollen during adulthood. Therefore, it is important, especially when parents are allergic to pollens and olive in particular, to “schedule” the births at a time other than the March to May period (statistically significant risk for sensitization).

DISCUSSION

The results of many studies performed during the last 20 years show that the risk for developing respiratory allergy due to pollens is related to the month of birth; that is, the early exposure to allergens of pollen grains.^{1,2,5,18} The first 3 months after birth are considered as the critical period, with increased possibility of sensitization to allergens, because of the transient possible insufficiency of immunoglobulin A (IgA) in the secretions resulting in increased permeability of mucous membranes for allergens.¹⁹

Allergens present in the atmosphere for a limited period of time, as is the case for birch and olive pollens, are prone to such correlations compared to other allergens such as house dust which, despite the fluctuations in quantity, are present all year.^{14,21,22}

TABLE I

Classification per Month of the Births of 1501 (789 Men, 712 Women) Patients With Seasonal Rhinitis/Asthma Due to Pollens: Grasses-Olive-Parietaria, and the Expected Frequency With 95% Confidence Interval

Observed Frequency	JAN	FEB	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPT	OCT	NOV	DEC
	68*	61*	90*	57*	70*	80*	68*	64*	55*	61*	58*	57*
	60**	58**	78**	53**	63**	63**	65**	54**	55**	51**	60**	52**
Total 1501	128	119	168	110	133	143	133	118	110	112	118	109
Expected frequency with 95% CI Limits												
Upper	167	152	159	142	140	136	140	138	138	147	134	120
Mean	148	134	140	125	122	118	123	121	121	129	117	104
Lower	128	115	120	106	104	101	105	102	102	111	100	88

*men **women

CI = Confidence Interval

TABLE II

Relative Risk for Developing Seasonal Allergic Rhinitis and Seasonal Asthma Due to Pollens Parietaria-Grasses-Olive Depending on the Month of Birth

Pollen Species and Number of Patients	JAN	FEB	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPT	OCT	NOV	DEC
Parietaria <i>N</i> = 285	0.89	1.06	1.47	0.98	1.04	0.84	0.98	0.85	0.83	0.94	0.99	1.01
Grasses <i>N</i> = 283	0.54	0.91	1.06	1.11	0.83	1.20	1.20	1.09	0.82	1.06	1.12	1.07
Olive <i>N</i> = 161	0.94	1.11	1.40	1.20	1.60	1.10	0.84	0.92	0.57	0.72	0.63	0.80

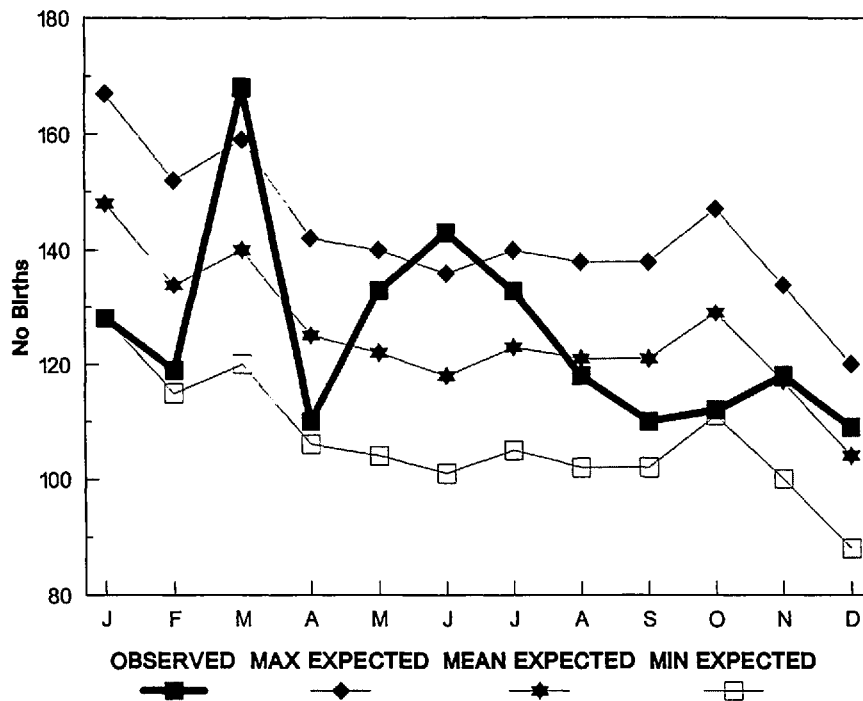


Figure 1. Distribution per month of birth of 1501 patients with seasonal rhinitis/asthma due to grass-olive-parietaria pollens and expected frequency with 95% confidence interval.

TABLE III

Relative Risk for Developing Seasonal Allergic Rhinitis and Seasonal Asthma Due to Pollens Parietaria-Grasses-Olive Depending on the Month of Birth

Pollen Species and Number of Patients	JAN	FEB	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPT	OCT	NOV	DEC
Grasses } (all three) Olive } <i>N</i> = 1501 Parietaria }	0.865	0.89	1.20	0.90	1.09	1.20	1.08	0.97	0.94	0.87	1.00	1.04
Parietaria (only) <i>N</i> = 285	0.89	1.06	1.47	0.98	1.04	0.84	0.98	0.85	0.83	0.94	0.99	1.01
Grasses (only) <i>N</i> = 283	0.54	0.91	1.06	1.11	0.83	1.20	1.20	1.09	0.82	1.06	1.12	1.07
Olive (only) <i>N</i> = 161	0.94	1.11	1.40	1.20	1.60	1.10	0.84	0.92	0.57	0.72	0.63	0.80

TABLE IV

Births per 6 Months in 1501 Patients with Rhinitis and Asthma Sensitized to Pollens (Olive, Parietaria, Grasses)

	Number of Births Per 6 Months		
	January–June	July–December	
1501 Allergic Patients			
Observed frequency	801	700	1501
Expected frequency	787	714	
$P = 0.524$; $Q = 0.4756$; $sEp = Q.P/N = 0.0129$			
95% Confidence Interval; $P = P \pm 1.96 sEp$			
95% Confidence Interval; $P = 0.524 \pm 0.02525$			
$= 0.5492 \Rightarrow 824 \text{ max}$			
$0.4987 \Rightarrow 749 \text{ min}$			

Bjorksen and Suoniemi showed that the risk for sensitization to birch pollen is increased over 28% to individuals born in between February and April, aged up to 20 years; no such correlation was found for the age group of 20–29 years.⁵

On the other hand, Schafer et al. in a recent study performed on children aged 5–6 years with positive skin tests, did not observe any increase in frequency of births for a specific month.¹¹ Other researchers such as Korsgaard and Dahl found that a correlation of month of birth with the development of asthma or rhinitis due to house dust does exist; this was not the case for grass pollen.⁹

The present study has certain peculiarities due mostly to the strict selection of the population sample:

1. Patients with severe allergic rhinitis or asthma and not individuals with only positive skin tests, as in the studies of Bjorksten and Schafer, were included.^{5,11,20}
2. Patients had positive skin tests exclusively to the most important pollens (olive, parietaria, grasses) of Greece, whereas those with positive tests to mites, molds, or pets were excluded from the study.
3. The age of patients was 20 to 35 years; that is, they belong to an age group for which even the most vocal

supporter of the correlation of month of birth and sensitization to pollens found no correlation,^{5,6} and

4. There were two groups of patients with allergy to olive and parietaria pollens, allergens for which there are no relevant studies in the international literature.

Although we were not expecting to find some form of correlation between the month of birth and the development of respiratory allergy due to specific pollens in this advanced age group, the results of our study were impressive^{5,6} and in the case of grass-induced allergy difficult to interpret. Also, it became obvious that the selection of patients sensitized to a single allergen is a necessary prerequisite for the extrapolation of correct conclusions.

In our study, when the month of birth was examined for all patients sensitive to pollens (1501 individuals), an increase in the relative risk of developing respiratory allergy (RRDRA), 1.2 for March and June, was found, whereas the situation was more clear in the groups of patients with monosensitivity to a specific pollen.

In patients with sensitivity to parietaria only, a characteristically and statistically significant increased RRDRA of 1.47, for those born exclusively in March was recorded, whereas for April and May the RRDRA was not high despite the high count of pollen grains calculated during that time. Perhaps other factors, such as viral infections and the vitiation of pollens because of the variation of weather conditions, may be responsible for the high RRDRA regarding parietaria exclusively in March.

The RRDRA for olive pollen was higher for those born in May (1.6), in March (1.4), and in April (1.2). In general, our findings regarding the development of allergy to olive pollen are in order with the theory of the early sensitization during the first trimester following birth. Olive has a limited blooming period (May) and in that respect is similar to birch. This fact is very important for the establishment of the influence of early exposure to this allergen in the development of respiratory allergy due to olive pollen during adulthood. Unfortunately, in contrast to birch, there are no studies focused on the development of allergy due to olive pollen. In our study we concluded that being born in March, April, or May increases significantly the risk of developing respiratory allergy due to olive pollen, while being born during June to December minimizes this risk.

TABLE V

Births Per 4 Months in 1501 Patients With Rhinitis and Asthma Sensitized to Pollens (Olive, Parietaria, Grasses)

1501 Allergic Patients	Number of Births Per 4 Months		
	March–June	July–October	November–February
Observed frequency	554	473	474
	max 540	max 510	max 510
Expected frequency	mean 505	mean 493	mean 503
	min 469	min 474	min 474

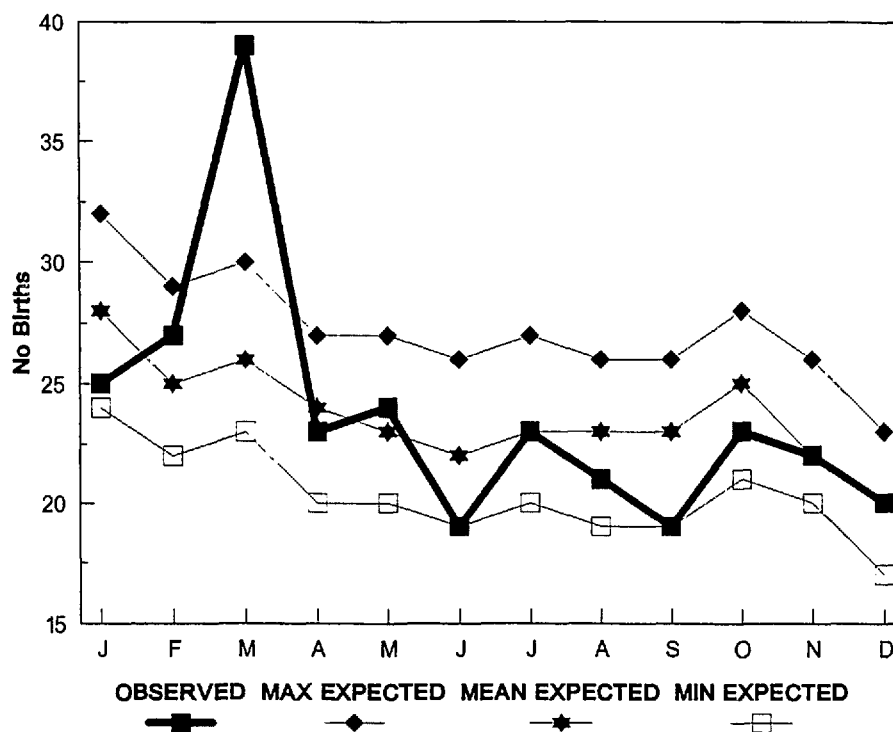


Figure 2. Observed frequency of births per month of seasonal asthma/rhinitis patients ($n = 285$) and monosensitivity to parietaria pollens.

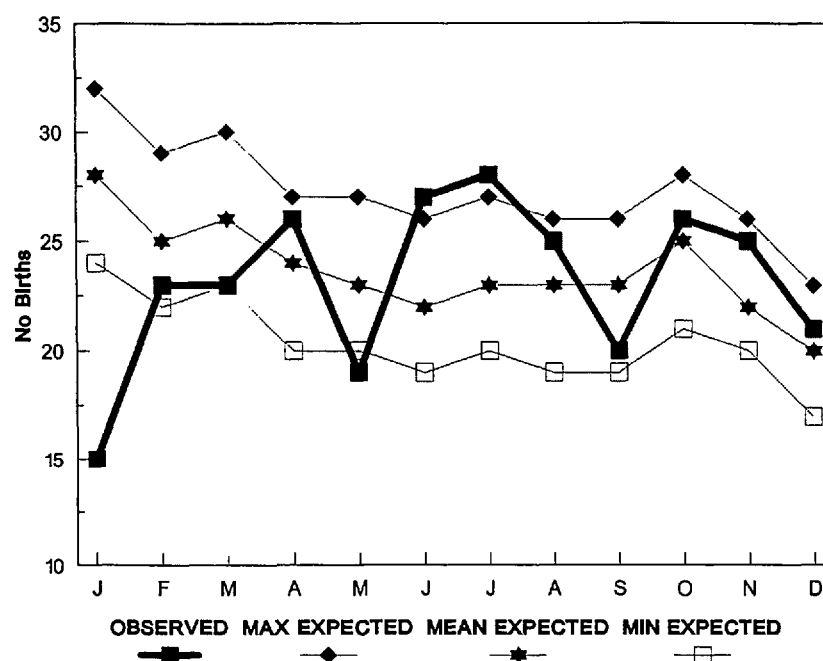


Figure 3. Observed frequency of births per month of seasonal asthma/rhinitis patients ($n = 283$) and monosensitivity to grass pollens.

Our results regarding the month of birth for the development of allergy to grasses during adulthood are difficult to interpret. The period with the higher concentrations of pollens in the atmosphere starts within the last 15 days of April and continues during May and June. Therefore, we should have had increased frequency of births during April to May and not only in June (RRDRA: 1.2) and in July (1.2), found in our study.

In the study by Korsgaard et al. of 336 patients with allergic rhinitis or asthma and positive skin tests to grasses, there was no increase in the number of births for a specific month.⁹ On the contrary, Kemp found an increased number of births during the blooming period of grasses, whereas Pearson et al. observed high risk of sensitization to grasses in individuals born between December and February.^{15,21} In recent studies, Businco reported an increased number of

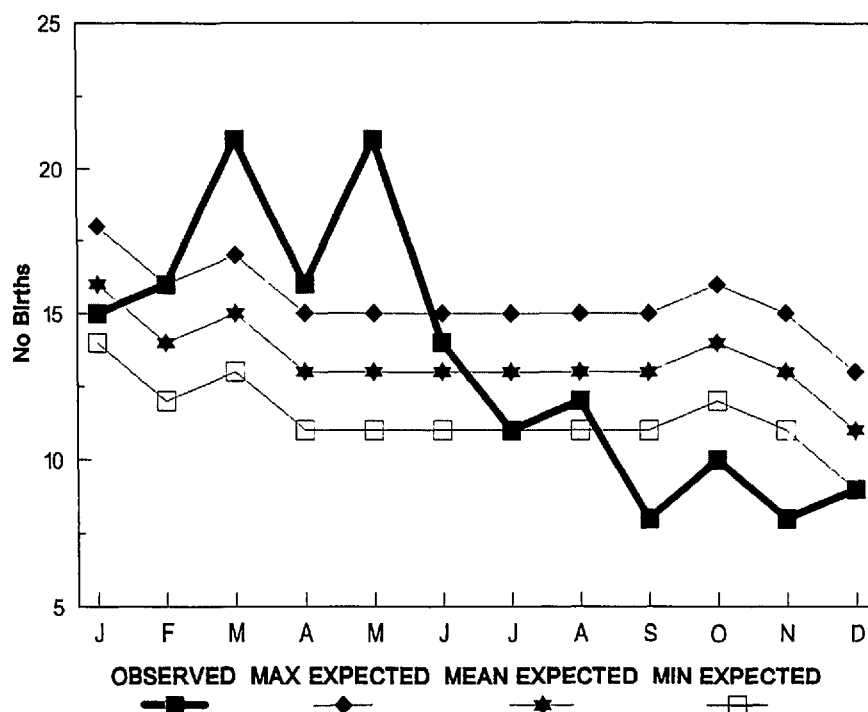


Figure 4. Observed frequency of births per month of seasonal asthma/rhinitis patients ($n = 151$) and monosensitivity to olive pollens.

births from March to June in children with positive skin tests to grasses.²²

In our study, the increased RRDRA for grasses (1.2) in those being born in June and July is difficult to explain. During this period there is a small number of grass pollens in Athens' atmosphere, according to existing aerobiology data. Nevertheless, it is possible that the majority of our patients aged 20–35 years were born in urban parts of Greece, where aerobiologic studies do not exist.^{13,14,17} It is well known that in most of the urban territories, grasses do not dry out because of the constant watering of the crops, thus producing pollens all summer. This may explain the nonsignificant trends for sensitization to grasses during June and July.

The confounding results obtained from the international bibliography regarding the influence of the month of birth on the risk of developing atopic disease may be due to differences in the design of the studies and inappropriate selection of the population, which sometimes aims only to increase the sample population.

The choice of patients suffering from a specific allergic disease (asthma or rhinitis) and sensitivity to a single allergen, present in the atmosphere for a specific period of time, may help in resolving the problem.

In conclusion, our results regarding olive pollen are both clear and expected based on the theory of early sensitization. It seems that those born from March to May experience RRDRA for olive pollen >1.4 during adulthood. Being born in March is accompanied by high RRDRA for parietaria pollen (1.47) during adulthood. It is possible that other factors (viral infections, weather conditions) may affect this finding as well. The high but nonsignificant trends

of RRDRA for grasses (1.2) for those born in June and July are difficult to interpret based on the existing aerobiology studies for the Athens area.^{13,14,17} From a practical point of view, since pollination in Greece is from March to June (with overlapping of pollination regarding olive, parietaria, and grasses) it could be argued to schedule births, especially when parents are atopic, away from this period, resulting in decreased sensitization to pollens.

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THE SAFETY AND EFFICACY OF LEVOFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)

In immature rats and dogs, the oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY in full Prescribing Information.)

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See PRECAUTIONS: General, Information for Patients, Drug Interactions and ADVERSE REACTIONS.)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See PRECAUTIONS and ADVERSE REACTIONS.)

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome), vasculitis, arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See ADVERSE REACTIONS.)

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

PRECAUTIONS

General:

Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES. (See DOSAGE AND ADMINISTRATION.)

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance ≤ 80 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See WARNINGS and Drug Interactions.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately. (See Drug Interactions and ADVERSE REACTIONS.)

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See WARNINGS and ADVERSE REACTIONS.)

Information for Patients:

Patients should be advised:

- to drink fluids liberally;
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See WARNINGS and ADVERSE REACTIONS);
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, lightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See WARNINGS and ADVERSE REACTIONS);
- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs;
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician. (See PRECAUTIONS: General and Drug Interactions.)
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.
- that if therapy with oral levofloxacin is initiated, then (1) antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx® (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution should be taken at least two hours before or two hours after levofloxacin administration. (See Drug Interactions); and (2) oral levofloxacin can be taken without regard to meals.

Drug Interactions:

Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN Injection: There are no data concerning an interaction of intravenous quinolones with oral antacids, sucralfate, multivitamins, Videx®, (Didanosine), or metal cations. However, no quinolones should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See DOSAGE AND ADMINISTRATION.)

LEVAQUIN Tablets: While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of LEVAQUIN Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx®, (Didanosine) chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

Theophylline: No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient

population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels. (See WARNINGS and PRECAUTIONS: General.)

Warfarin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S-warfarin was detected in a clinical study involving healthy volunteers. No significant change in prothrombin time was noted in the presence of levofloxacin. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, since some quinolones have been reported to enhance the effects of oral anticoagulant warfarin or its derivatives in the patient population, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Cyclosporine: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and K_e were slightly lower while t_{max} and $t_{1/2}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine: No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{1/2}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and Cl_R were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See WARNINGS and PRECAUTIONS: General.)
Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration for 2 years; the highest dose was 2 or 10 times the recommended human dose based on surface area or body weight, respectively. Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the *in vitro* chromosomal aberration (CHO cell line) and sister chromatid exchange (CHL/AU cell line) assays. Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day (2124 mg/m²), corresponding to 3.0 or 18 times the recommended maximum human dose based on surface area or body weight, respectively, and intravenous doses as high as 100 mg/kg/day (590 mg/m²), corresponding to 1.0 or 5 times the recommended maximum human dose based on surface area or body weight, respectively.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day (4775 mg/m²), which corresponds to 14 or 82 times the recommended maximum human dose based on surface area or body weight, respectively, or at intravenous doses as high as 160 mg/kg/day (944 mg/m²) corresponding to 2.7 or 16 times the recommended maximum human dose based on surface area or body weight, respectively. Doses equivalent to 25 or 81 times the recommended maximum human dose of levofloxacin (based on surface area or body weight, respectively) caused decreased fetal body weight and increased fetal mortality in rats when administered orally at 810 mg/kg/day (8910 mg/m²). No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day (550 mg/m²) which corresponds to 1.6 or 5.0 times the recommended maximum human dose based on surface area or body weight, respectively, or when dosed intravenously as high as 25 mg/kg/day (275 mg/m²), corresponding to 0.8 or 2.5 times the maximum recommended human dose based on surface area or body weight, respectively. There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

Nursing Mothers:

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See WARNINGS.)

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.2%. Among patients receiving levofloxacin therapy, 3.4% discontinued levofloxacin therapy due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:

nausea 1.3%, diarrhea 1.1%, vaginitis 0.7%, pruritus 0.5%, abdominal pain 0.4%, dizziness 0.4%, flatulence 0.4%, rash 0.4%, dyspnea 0.3%, genital moniliasis 0.3%, insomnia 0.3%, taste perversion 0.2%, vomiting 0.2%, anorexia 0.1%, anxiety 0.1%, constipation 0.1%, edema 0.1%, fatigue 0.1%, fungal infection 0.1%, headache 0.1%, increased sweating 0.1%, leukorrhea 0.1%, malaise 0.1%, nervousness 0.1%, sleep disorders 0.1%, tremor 0.1%, urticaria 0.1%.

In clinical trials, the following events occurred in >3% of patients regardless of drug relationship:

nausea 7.1%, headache 6.4%, diarrhea 5.6%, injection site reaction 5.6%, insomnia 4.0%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

constipation 2.9%, dizziness 2.9%, injection site pain 2.7%, abdominal pain 2.6%, dyspepsia 2.5%, vomiting 2.2%, rash 1.7%, flatulence 1.6%, vaginitis 1.6%, pruritus 1.5%, fatigue 1.3%, injection site inflammation 1.5%, back pain 1.2%, pain 1.2%, chest pain 1.1%, pharyngitis 1.1%, rhinitis 1.1%, taste perversion 1.0%.

In clinical trials, the following events occurred in 0.5 to less than 1% of patients, regardless of drug relationship:

anorexia, anxiety, arthralgia, coughing, dry mouth, dyspnea, ear disorder (not otherwise specified), edema, fever, fungal infection, genital pruritus, increased sweating, skin disorder, somnolence.

In clinical trials, the following events, of potential medical importance, occurred at a rate of less than 0.5% regardless of drug relationship: abnormal coordination, abnormal dreaming, abnormal hepatic function, abnormal platelets, abnormal renal function, abnormal vision, acute renal failure, aggravated diabetes mellitus, aggressive reaction, agitation, anemia, angina pectoris, ARDS, arrhythmia, arthritis, arthrosis, asthma, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure, carcinoma, cerebrovascular disorder, cholelithiasis, circulatory failure, coma, confusion, conjunctivitis, convulsions (seizures), coronary thrombosis, dehydration, delirium, depression, diplopia, dysphagia, ejaculation failure, embolism (blood clot), emotional lability, epistaxis, erythema nodosum, face edema, gastroenteritis, genital moniliasis, G.I. hemorrhage, granulocytopenia, haematuria, haemophysis, hallucination, heart block, hepatic coma, hyperglycemia, hypokalemia, hyperkinesia, hypokinesia, hypoaesthesia, hypoglycemia, hypokalemia, hypotension, hypoxia, impaired concentration, impotence, increased LDH, involuntary muscle contractions, jaundice, leukocytosis, leukopenia, lymphadenopathy, malaise, manic reaction, mental deficiency, muscle weakness, myalgia, myocardial infarction, nervousness, palpitation, pancreatitis, paresthesia, paralysis, paronychia, periorbital edema, phlebitis, pleural effusion, postural hypotension, pseudomembranous colitis, purpura, respiratory insufficiency, rhabdomyolysis, rigors, skin exfoliation, skin ulceration, sleep disorders, speech disorder, stupor, sublethal chest pain, supraventricular tachycardia, syncope, synovitis, tachycardia, tendinitis, thrombocytopenia, tinnitus, tongue edema, tremor, urticaria, ventricular fibrillation, vertigo, weight decrease, WBC abnormal (not otherwise specified), withdrawal syndrome.

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established. Crystalluria and cylindruria have been reported with other quinolones.

The following laboratory abnormalities appeared in 2.1 to 2.3% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Blood Chemistry: decreased glucose

Hematology: decreased lymphocytes

Post-Marketing Adverse Reactions:

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include:

allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, Stevens-Johnson Syndrome, tendon rupture, vasodilation.

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U.S. Patent No. 4,382,892 and U.S. Patent No. 5,053,407.

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Revised August 1998

633-10-811-38

635-10-287-38

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