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A RANDOMIZED, DOUBLE-BLIND STUDY OF PHENYTOIN FOR THE PREVENTION OF POST-TRAUMATIC SEIZURES

NANCY R. TEMKIN, PH.D., SUREYYA S. DIKMEN, PH.D., ALAN J. WILENSKY, M.D., PH.D., JANE KEIHM, R.N., M.S., SHARON CHABAL, R.N., M.S., AND H. RICHARD WINN, M.D.

Abstract *Background.* Antiepileptic drugs are commonly used to prevent seizures that may follow head trauma. However, previous controlled studies of this practice have been inconclusive.

Methods. To study further the effectiveness of phenytoin (Dilantin) in preventing post-traumatic seizures, we randomly assigned 404 eligible patients with serious head trauma to treatment with phenytoin (n = 208) or placebo (n = 196) for one year in a double-blind fashion. An intravenous loading dose was given within 24 hours of injury. Serum levels of phenytoin were maintained in the high therapeutic range (3 to 6 μmol of free phenytoin per liter). Follow-up was continued for two years. The primary data analysis was performed according to the intention to treat.

Results. Between drug loading and day 7, 3.6 percent of the patients assigned to phenytoin had seizures, as compared with 14.2 percent of patients assigned to placebo ($P<0.001$; risk ratio, 0.27; 95 percent confidence interval, 0.12 to 0.62). Between day 8 and the end of year 1, 21.5 percent of the phenytoin group and 15.7 percent of the placebo group had seizures; at the end of year 2, the rates were 27.5 percent and 21.1 percent, respectively ($P>0.2$ for each comparison; risk ratio, 1.20; 95 percent confidence interval, 0.71 to 2.02). This lack of a late effect could not be attributed to differential mortality, low phenytoin levels, or treatment of some early seizures in patients assigned to the placebo group.

Conclusions. Phenytoin exerts a beneficial effect by reducing seizures only during the first week after severe head injury. (N Engl J Med 1990; 323:497-502.)

EACH year in the United States, approximately 420,000 patients are hospitalized with head injuries.[1] Five thousand to 30,000 of these patients have post-traumatic seizures,[2-5] which can be disabling and require lifelong treatment.

Antiepileptic drugs have been used for many years in an attempt to prevent the development of post-traumatic seizures. Early retrospective studies suggested that the prophylactic use of phenytoin was effective.[6-8] However, subsequent prospective, double-blind trials of treatment with phenytoin or a low dose of phenytoin combined with phenobarbital failed to show that such treatment had more benefit than placebo.[5,9-12] These latter studies have been criticized as inconclusive because the levels of phenytoin that were achieved were generally subtherapeutic and because they lacked statistical power to detect a clinically important effect. North et al.[13] performed a randomized study of phenytoin treatment as prophylaxis against seizures after supratentorial neurosurgery in 281 patients, 36 percent of whom underwent surgery because of trauma. These authors observed fewer seizures in the patients given phenytoin, and it had the most effect in the first few weeks.

We performed the present investigation to clarify the role of phenytoin in preventing early and late post-traumatic seizures. To overcome the deficiencies noted in the other studies, we conducted a double-blind placebo-controlled study in a population with head trauma that had a high rate of seizures, paying considerable attention to maintaining serum phenytoin levels in the high therapeutic range.

METHODS

Study Design

Between November 1983 and December 1987, all patients with a head injury who were admitted to Harborview Medical Center, a Level I trauma center, were evaluated for inclusion in the study. To be eligible, each patient had to meet at least one of the following criteria for severe injury: a cortical contusion visible on CT scanning, a subdural, epidural, or intracerebral hematoma, a depressed skull fracture, a penetrating head wound, a seizure within 24 hours of injury, or a score of 10 or less on the Glasgow Coma Scale[14] on admission. The Glasgow Coma Scale assesses the level of consciousness by grading verbal, motor, and eye-opening responses. If any of the criteria were met, the chance of seizure was estimated to be ≥20 percent.[14,15]

The criteria for exclusion from the study were an age of less than 16 years, an interval of more than 24 hours between injury and

From the Departments of Neurological Surgery (N.R.T., S.S.D., A.J.W., J.K., S.C., H.R.W.), Biostatistics (N.R.T.), Rehabilitation Medicine (S.S.D.), and Medicine (Neurology) (A.J.W.), University of Washington, Seattle. Address reprint requests to Dr. Temkin at the Epilepsy Center, University of Washington ZA-50, Seattle, WA 98104.

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loading of the study drug, pregnancy or lactation, inability to speak English, a history of severe alcoholism, a previous head injury, the occurrence of seizures before injury or the administration of antiseizure medication before study-drug loading, previous neurosurgery involving penetration of the dura, or another previous neurologic condition that might predispose the patient to seizures.

Eligible patients were randomly assigned to receive either phenytoin (Dilantin) or placebo under double-blind conditions. Both study medications were supplied by Warner-Lambert/Parke-Davis. The initial dose of medication (20 mg per kilogram of body weight) was administered intravenously within 24 hours of injury. Serum phenytoin levels were measured three times weekly in the intensive care unit, at least weekly in acute care units, and during clinic follow-up visits 1, 3, 6, 9, and 12 months after injury. Dosages were adjusted in the phenytoin group by an unblinded study-staff member to maintain levels in the high therapeutic range. Similar adjustments were made in the placebo group to ensure blinding. Serum drug levels were reevaluated 7 to 10 days after each dosage adjustment. The daily doses varied considerably over time and among patients: the doses given intravenously or orally ranged from 200 to 1200 mg, and the doses of suspension given through a nasogastric tube were as high as 2600 mg. Unless seizures or serious adverse reactions occurred, patients continued to receive their assigned drug for 12 months, after which the dose of phenytoin or placebo was tapered and the drug was stopped. All patients were followed for 24 months. Administration of the assigned drug was stopped if idiosyncratic reactions attributable to the drug occurred, and phenytoin was given in unblinded fashion if late seizures occurred (on day 8 or later); additional late seizures were treated as clinically indicated. Patients could also stop receiving the study drug by withdrawing their consent to the treatment, either at their physician's recommendation or for personal reasons. This option was exercised by 73 percent of the patients who had early seizures (5 patients given phenytoin and 19 given placebo and then phenytoin in unblinded fashion).

In all cases, patients were asked for their consent to participation in the study if they were able to give consent, or their relatives were asked. If neither the patient nor a relative was available, the study investigators had the approval of their institutional review board to proceed on the basis of deferred consent. The trial continued until its planned termination.

End Points

The primary end point of the study was the occurrence of seizures, which were classified as early (occurring from time of drug loading to day 7) or late (occurring on day 8 or later).[14] Patients and staff were instructed to call the study nurse if any event that might be a seizure occurred. Experienced clinicians blinded to the assigned treatment diagnosed seizures primarily on the basis of clinical manifestations, especially involuntary movements, alterations in consciousness, or abnormal motor, sensory, or psychosensory phenomena. Patients and care givers were trained to recognize subtle manifestations of seizures and were carefully questioned by study nurses when they called and at follow-up visits. Electroencephalographic findings were sometimes used as an adjunct in diagnosis. An event was considered to be a seizure only if the blinded neurologist had no doubt about the episode. Patients were included in the analysis of late seizures regardless of whether they had had early seizures.

Additional end points assessed were the possible adverse effects of phenytoin. Comprehensive neuropsychological testing, the results of which are not reported in this paper, was performed 1, 12, and 24 months after injury. Signs and symptoms thought to be associated with phenytoin were recorded at each follow-up visit. Rashes and abnormal laboratory findings were evaluated by both study investigators and treating clinicians. The treatment code was not broken unless phenytoin appeared to be responsible for the reaction and the patient's condition warranted such action.

Phenytoin Levels

Total and free levels of serum phenytoin were determined by fluorescent polarization immunoassay (Abbott TDX).[16] The serum samples in which free phenytoin was measured were prepared with the Amicon ultrafiltration[16] system. All procedures were performed at room temperature. When these methods are used, the therapeutic range for total phenytoin is 40 to 80 μmol per liter (10 to 20 mg per liter) and that for free phenytoin is 3 to 6 μmol per liter (0.75 to 1.5 mg per liter).[17]

Statistical Analysis

In the primary data analysis, patients were evaluated according to the group to which they were initially assigned, regardless of whether their treatment deviated from the regimen for that group during the study period ("intention-to-treat" analysis). Categorical variables such as indexes of severity and the incidence of idiosyncratic reactions were compared by means of chi-square tests. The cumulative percentage of patients in each group who had seizures was represented as a Kaplan–Meier[18] "survival" curve; the percentage with seizures was calculated by subtracting from 100 the Kaplan–Meier estimate of the percentage free of seizures up to that time. Death and loss to follow-up were reasons for censoring. Statistical significance was determined by comparing differences in the estimates with the standard error of the differences at day 7 and one and two years after injury — times when the effect of phenytoin would be expected to be maximal. The estimated mortality in each treatment group was also represented by a Kaplan–Meier curve. In addition, Cox[19] regression models were fitted to obtain more powerful analyses that would control for the severity of injury. Control variables were selected in a stepwise fashion with the use of a log-linear model that did not account for interactions between variables. The variables considered were the Glasgow Coma Scale score on admission, the duration of coma, age, and the indexes of severity shown in Table 1. The estimate of relative risk associated with drug assignment and its confidence interval were obtained by exponential transformation from the coefficient for drug effect in this model.

Results

Of the 586 patients assigned to treatment, 404 met the eligibility requirements. Because drug loading had to occur within 24 hours of injury, some patients were assigned before complete information about them was available. A total of 85 patients assigned to phenytoin and 97 assigned to placebo were ineligible. Eligibility

Table 1. Characteristics of the Study Groups.

Characteristic	Phenytoin (N = 208)	Placebo (N = 196)
Demographic variables		
Mean age (±SD)	34±18	34±17
Sex (% male)	78	75
Marital status (% single)	74	75
Race (% white)	86	87
	percent of group	
External cause of injury		
Automobile	34	31
Motorcycle	18	19
Pedestrian	13	12
Fall	15	15
Assault, fight, suicide attempt	14	11
Other	6	11
	percent of group	
Severity of injury		
Glasgow Coma Scale score ≤10	60	67
Cortical contusion	49	49
Depressed skull fracture	17	16
Subdural hematoma	35	42
Epidural hematoma	18	16
Intracerebral hematoma	20	18
Penetrating head wound	8	7
Seizure within 24 hours	6	8

was determined jointly by a blinded study nurse and an unblinded statistician without knowledge of the treatment assignment of the patient. The reasons for ineligibility were late receipt of information that indicated an excluding condition (31 patients assigned to phenytoin and 48 assigned to placebo), a lack of confirmation of the severity of injury (26 phenytoin and 19 placebo), denial of consent (22 phenytoin and 14 placebo), delay in loading of the study drug (5 phenytoin and 12 placebo), and death before loading (1 phenytoin and 4 placebo). The exclusion of these patients did not affect the conclusions of the study.

A total of 208 eligible patients were randomly assigned to phenytoin and 196 to placebo. The treatment groups were well balanced in both demographic variables and the severity of head injury (Table 1).

Table 2. Number of Patients Stopping Assigned Drug, According to Study Period.

Period/Reason	Phenytoin (N = 208)	Placebo (N = 196)
	no. of patients	
Drug stopped during loading to day 7	46	62
Death	30	25
Seizures	5	19
Idiosyncratic reactions	1	0
Patient's request	8	13
Other	2	5
Patients taking drug on day 8	162	134
Drug stopped during day 8 to year 1	103	67
Death	9	6
Seizures	17	10
Idiosyncratic reactions	18	8
Patient's request	53	33
Other	6	10
Patients taking drug at year 1	59	67
Patients lost during year 2	1	2
Death	0	0
Patient's withdrawal	1	2
Patients completing year 2	58	65

Thirty percent of the patients met one of the entry criteria for severity, 40 percent met two, and 30 percent met three or more.

More patients in the group assigned to phenytoin stopped taking the drug between day 8 and year 1, primarily because of idiosyncratic reactions or at the patient's request (Table 2). Many patients who stopped taking their assigned drug were still followed. About 22 percent of all patients died, and 24 percent were lost to follow-up (Table 3). Of the 97 patients lost to follow-up, 6 had reached the end point of late seizures before they were lost, 24 were known to be alive two years after they entered the study, and 2 died after they were lost to follow-up, according to a search of death records (King County Vital Statistics).

Early Seizures (Drug Loading to Day 7)

Figure 1 shows the estimates of the percentage of patients with early seizures in the treatment groups. The phenytoin group had a cumulative (±SE) seizure rate of 3.6±1.3 percent at the end of the first week, as compared with 14.2±2.6 percent in the placebo group ($P<0.001$). Phenytoin treatment was associated with a decrease of 73 percent in the risk of seizures in the first week (by Cox regression analysis; 95 percent confidence interval, a decrease of 88 percent to 38 percent).

Table 3. Follow-up of Patients after Randomization.

Event	Phenytoin (N = 208)	Placebo (N = 196)
	no. of patients	
Lost during week 1	38	43
Death	30	29
Lost to follow-up	8	14
Observed through day 8	170	153
Lost during year 1	51	41
Death	15	11
Lost to follow-up	36	30
Observed through year 1	119	112
Lost during year 2	7	7
Death	4	1
Lost to follow-up	3	6
Followed to end of year 2	112	105

Late Seizures (Day 8 to Year 2)

Estimates of the percentages of patients with late seizures in the two groups are shown in Figure 2. By year 1, 21.5±3.6 percent of the phenytoin group and 15.7±3.2 percent of the placebo group had had late seizures; by year 2, the differences were similar — 27.5±4.0 percent and 21.1±3.7 percent, respectively. The differences between the groups were not statistically significant ($P>0.2$ for each comparison). The Cox regression analysis demonstrated with 95 percent confidence that phenytoin treatment was associated with between a 29 percent decrease and a 102 percent increase in late seizures, with a point estimate of a 20 percent increase (risk ratio, 1.20; 95 percent confidence interval, 0.71 to 2.02).

Since the primary (intention-to-treat) analysis may have obscured the effectiveness of phenytoin because

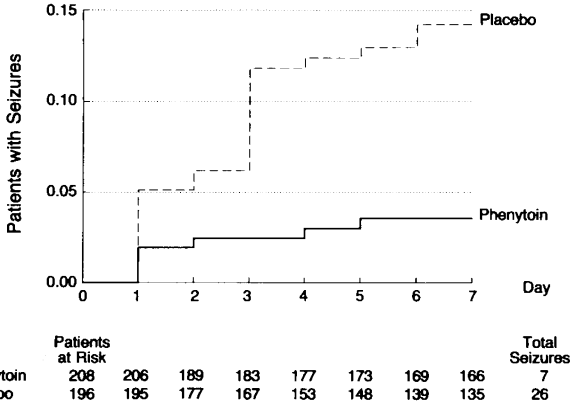

Figure 1. Cumulative Fraction of Patients with Early Seizures (between Drug Loading and Day 7).

The number of patients observed and at risk for seizures and the total number of seizures are shown at the bottom of the figure. The seizure rate was significantly lower in the phenytoin group ($P<0.001$).

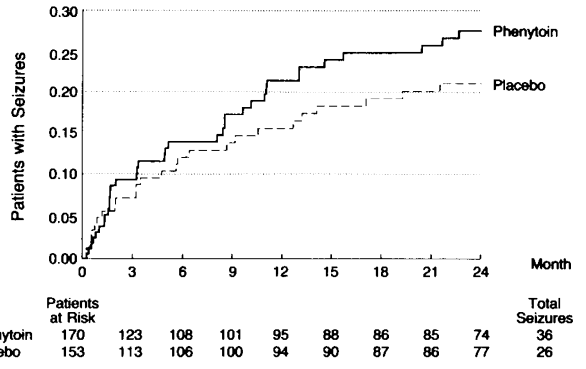

Figure 2. Cumulative Fraction of Patients with Late Seizures (after Day 8).

The number of patients at risk for seizures and the total number of seizures are shown at the bottom of the figure. The seizure rates were similar in the phenytoin and placebo groups.

this analysis included 15 patients assigned to placebo who actually received phenytoin after they had early seizures, we performed a secondary (worst-case) analysis, in which each of these patients was assumed to have had a late seizure on day 8. Under this overly pessimistic assumption about the occurrence of seizures during placebo administration, the seizure rate at the start of the study period was artificially high. The curves for the rates began to converge almost at once, and the worst-case cumulative seizure rates with placebo were no higher than those actually observed with phenytoin from 11 months to the end of the study at two years.

Any Seizures (during Administration of Assigned Drug)

An additional secondary analysis compared the probability of any seizures (early or late) among patients who continued to take their assigned drug while blinded, 70 percent of whom had therapeutic levels of phenytoin. The curves diverged early, reflecting the effect of phenytoin during the first week, but by 12 months the cumulative probability of seizures was identical in both groups (22 percent) and it remained similar thereafter.

Mortality

The survival curves for the two treatment groups were similar. Forty-nine patients given phenytoin and 41 given placebo died during the follow-up period: 14 and 15 percent, respectively, by day 8; 19 percent in each group by month 1; 22 and 20 percent, respectively, by year 1; and 24 and 21 percent, respectively, by the end of year 2.

Serum Phenytoin Levels

The free-phenytoin levels are shown in Table 4. The initial loading dose quickly produced therapeutic levels. At one week, the levels were considerably lower, probably because of the hypermetabolic state of the patients.[20] At one month, therapeutic levels had been reattained. At the scheduled outpatient visits, levels were at least therapeutic in 70 percent of the group (Table 4). Phenytoin levels also were determined in patients who had a seizure while in the hospital or who came to the hospital immediately after a seizure. On the day of the first late seizure, the levels were at least therapeutic in three quarters of the patients for whom phenytoin measurements were available (Table 5).

Idiosyncratic Reactions

Rashes were the most common idiosyncratic reaction; 25 patients in the phenytoin group and 17 in the placebo group reported that they had rashes, which caused 17 given phenytoin and 4 given placebo to stop taking their assigned medication ($P<0.01$ for stopping treatment because of a rash). Other reactions, including leukopenia and elevation of liver enzyme levels, occurred about equally in the phenytoin and placebo groups (12 and 8 patients, respectively).

Discussion

This randomized, double-blind study provides convincing evidence of the effectiveness of phenytoin in preventing seizures during the first week after serious head injury. As compared with placebo, treatment with phenytoin was associated with a 73 percent decrease in the risk of seizures in the first week. However, no significant protective effect was detected between day 8 and the end of the second year of study.

An assumption of prophylaxis for seizures following head injuries is that treating patients early will prevent eventual post-traumatic epilepsy. The early but not the late effect of phenytoin lends support to the idea that this drug has an early suppressive effect but not a true prophylactic effect.

This study used intention to treat as a basis for analyzing the results — that is, all patients, including those assigned to phenytoin who stopped taking it because of idiosyncratic reactions and those assigned to placebo who had early seizures and were treated with phenytoin, were still evaluated as members of their assigned groups. There is a risk that this type of analysis could mask the true effectiveness of a treatment by decreasing the differences between the experimental and control groups. Secondary analyses of efficacy were performed to minimize that risk. No sug-

Table 4. Distribution of Serum Levels of Free Phenytoin in Patients Initially Assigned to Phenytoin Treatment, According to Time of Observation.

PHENYTOIN* (μMOL/LITER)	OBSERVATION TIME POINT (NO. OF OBSERVATIONS)						
	1 DAY (155)	1 WK (159)	1 MO (142)	3 MO (98)	6 MO (69)	9 MO (63)	12 MO (63)
	percent of values						
≤1.4	1	14	1	11	9	6	10
1.5–2.9	2	28	12	11	12	6	13
3.0–4.4	8	21	16	14	30	24	25
4.5–5.9	33	13	18	25	15	32	20
6.0–7.9	40	11	19	24	20	16	24
8.0–9.9	14	4	16	9	10	10	6
≥10	2	8	18	6	4	6	2

*Range of therapeutic levels, 3.0 to 5.9 μmol per liter.

Table 5. Distribution of Serum Levels of Free Phenytoin on the Day of or within the Month before the First Seizure.

Free Phenytoin (μmol/liter)	Early Seizures — Same Day	Late Seizures	
		Same day	Within previous month
		no. of patients	
<1.4	0	1	1
1.5–2.9	0	1	0
3.0–4.4	1	3	2
4.5–5.9	2	0	2
6.0–7.9	1	1	1
8.0–9.9	1	3	1
≥10	0	0	0

gestion that phenytoin had efficacy against late seizures emerged from either the analysis that assumed that late seizures occurred in patients assigned to placebo who later received phenytoin after they had early seizures or the analysis that evaluated the course of patients only while they were receiving their assigned treatment. In addition, the finding of therapeutic levels of phenytoin in three quarters of the patients in whom levels were measured on the day of their first late seizure also gives no indication of efficacy with respect to late seizures.

Attaining and maintaining high therapeutic serum levels of phenytoin was a priority in this study. The nurses kept in close contact with the patients, emphasizing the importance of taking the medication to both patients and care givers. Behavioral techniques to aid patients in remembering to take their medication were developed when appropriate. Doses were changed 7 or more times in half the patients to maintain adequate serum levels, with 15 or more changes being common. This effort is considerably in excess of that likely in a routine neurosurgical practice. With these measures, about 70 percent of the patients had therapeutic levels during routine visits while taking their assigned drug. By comparison, 19 to 50 percent of patients with confirmed epilepsy have subtherapeutic levels.[21]

With negative results such as these, one must be concerned whether the study lacked the power to detect a beneficial effect. Four communications discussing the power of prophylaxis studies[12,22-24] have defined a minimal effect of interest as a decrease of 33 to 67 percent. Our study rules out even these minimal levels of effectiveness with about 95 percent confidence. Thus, we believe that this study shows that the clinical policy of intention to treat with phenytoin fails to decrease late post-traumatic seizures by a worthwhile degree.

Despite some difference in interpretation, our findings concerning prophylaxis are consistent with those of other randomized studies using phenytoin for prophylaxis against seizures. Two trials examined the effect of phenytoin in preventing early seizures.[5,13] Young et al.[5] detected no early prophylactic effect; however, because of the low seizure rate (3.7 percent), their 95 percent confidence interval extended from a 73 percent reduction to a 276 percent increase in the seizure rate with phenytoin. This interval overlaps the more precise 95 percent confidence interval calculated from our larger sample — from an 88 percent reduction to a 38 percent reduction. The study of North et al.[13] included all patients undergoing supratentorial surgery — 36 percent for head trauma. By day 7, the seizure rates were 2.9 percent in the phenytoin group and 10.0 percent in the placebo group — almost the same percentages of reduction in seizures as found in our study. In terms of late seizures, previous randomized studies reported a lack of effect of phenytoin,[9,10,12] in agreement with our findings. The observations of Young et al.[9] left open the possibility that high doses of phenytoin might be effective, in that none of their 11 patients taking phenytoin who had recently had a seizure had a total phenytoin concentration above 48 μmol per liter. This possibility is not supported by our findings, since four of nine patients in whom phenytoin was measured on the day of their seizure had levels above this value. The combined data on early and late seizures presented by North et al.[13] are consistent with ours, but those authors conclude that the protection of phenytoin "seems to start at the 7th postoperative day, and continues until about Day 72." Although the cumulative percentages of patients with seizures differed significantly for that entire period, the rates of new seizures in the phenytoin and placebo groups were the same after day 12.[13] The difference between the two groups at the later times mainly resulted from a difference in early seizure rates. Thus, we think that, in fact, their data support our conclusions.

On the basis of both the intention-to-treat analysis and the secondary analyses of efficacy, we conclude that phenytoin reduces the incidence of seizures in the first week after injury, but not thereafter.

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EXPOSURE TO HOUSE-DUST MITE ALLERGEN (*Der p* I) AND THE DEVELOPMENT OF ASTHMA IN CHILDHOOD

A Prospective Study

RICHARD SPORIK, M.R.C.P., STEPHEN T. HOLGATE, M.D., F.R.C.P.,
THOMAS A.E. PLATTS-MILLS, M.D., PH.D., AND JEREMY J. COGSWELL, M.D., F.R.C.P.

Abstract *Background and Methods.* Children with asthma commonly have positive skin tests for inhaled allergens, and in the United Kingdom the majority of older children with asthma are sensitized to the house-dust mite. In a cohort of British children at risk for allergic disease because of family history, we investigated prospectively from 1978 to 1989 the relation between exposure to the house-dust mite allergen (*Der p* I) and the development of sensitization and asthma.

Results. Of the 67 children studied in 1989, 35 were atopic (positive skin tests), and 32 were nonatopic. Of the 17 with active asthma, 16 were atopic ($P<0.005$), all of whom were sensitized to the house-dust mite, as judged by positive skin tests and levels of specific IgE antibodies ($P<0.001$). For house-dust samples collected from the homes of 59 of the children in 1979 and from 65 homes in 1989, the geometric means for the highest *Der p* I exposure were, respectively, 16.1 and 16.8 μg per gram of sieved dust. There was a trend toward an increasing degree of sensitization at the age of 11 with greater exposure at the age of 1 ($P = 0.062$). All but one of the children with asthma at the age of 11 had been exposed at 1 year of age to more than 10 μg of *Der p* I per gram of dust; for this exposure, the relative risk of asthma was 4.8 ($P = 0.05$). The age at which the first episode of wheezing occurred was inversely related to the level of exposure at the age of 1 for all children ($P = 0.015$), but especially for the atopic children ($r = -0.66$, $P = 0.001$).

Conclusions. In addition to genetic factors, exposure in early childhood to house-dust mite allergens is an important determinant of the subsequent development of asthma. (N Engl J Med 1990; 323:502-7.)

MOST asthma in children and young adults is found in association with immediate hypersensitivity to inhaled allergens and is associated with a familial tendency toward various forms of hypersensitivity, a condition known as atopy.[1,2] The clear evidence that atopy is inherited, its correlation with HLA types,[3,4] and its tentative localization[5] to the long arm of chromosome 11 emphasize the importance of genetic factors in predisposing people to allergic disease. However, the expression of atopy and allergic disease are dependent on exposure. Aeroallergens derived from the house-dust mite are powerful inducers of allergic responses in children.[6] *Dermatophagoides pteronyssinus* is the predominant house-dust mite in the United Kingdom and many other parts of the world. The most important allergen of this mite is a protein with a molecular weight of 24,000, *Der p* I, derived from its gastrointestinal tract.[7,8] This protein has recently been cloned[9] and identified as a cysteine proteinase. *Der p* I can be measured in house dust to give an index of the concentration of mite antigen, and levels of exposure that represent a risk for the development of asthma have recently been proposed.[10,11]

The majority of schoolchildren with asthma in the United Kingdom are sensitized to the house-dust

From the Department of Paediatrics, Poole General Hospital, Poole, Dorset, United Kingdom (R.S., J.J.C.); the Immunopharmacology Group, Medicine 1, Southampton General Hospital, Southampton, Hants, United Kingdom (R.S., S.T.H.); and the Division of Allergy and Clinical Immunology, University of Virginia, Charlottesville (R.S., T.A.E.P.-M.). Address reprint requests to Dr. Cogswell at the Department of Paediatrics, Poole General Hospital, Longfleet Rd., Poole, Dorset BH15 2JB, United Kingdom.

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