ABSTRACT. Diabetes mellitus Type 1 (T1D) is an autoimmune disorder attributed to both genetic and environmental factors. The aim of this study was to identify certain stressful conditions potentially associated with the pathogenesis and/or expression of T1D. The study group included 107 children with diabetes (CD) and 153 controls of comparable age and gender distribution at diagnosis of T1D (10.73±3.62 yr vs 9.59 ±3.42 yr, respectively). The parents of both groups completed a questionnaire on socioeconomic status and stressful life events or adverse situations at home and school. Results: Lower social class was more prevalent among the mothers of CD (p=0.002) in comparison with the controls. Stressful life events (parental death, divorce, parental job loss), problems at home (parental abuse, parental dispute) and at school (poor performance) were more frequently observed in the CD group than in the controls (parental death: p=0.05, job loss: p=0.05, parental abuse: p=0.002, quarrels between parents: p=0.05, and among siblings p=0.002, poor school performance: p=0.037). A stepwise logistic regression analysis indicated that lower maternal social class [odds ratio (OR): 3.86, 95% confidence interval (CI): 1.37,10.9], parental dispute or divorce (OR: 2.78, 95%CI: 0.97,7.95), body mass index (OR: 0.87, 95%CI: 0.78,0.97), increasing age (OR: 1.14, 95%CI: 1.02,1.27) were the factors potentially influencing the occurrence of T1D, while the 2-yr period prior to diabetes occurrence emerged as the most important one (OR: 2.49, 95%CI: 1.14,5.42). Conclusion: Children with diabetes seem to experience certain stressful conditions with significantly increased frequency compared to controls, especially during the 2 yr preceding the diagnosis of T1D, with a higher clustering in those of lower social class. The resultant stress possibly contributes to the development of T1D in genetically susceptible individuals.

INTRODUCTION
Type 1 diabetes (T1D) is caused by an autoimmune destruction of pancreatic β-cells in genetically susceptible individuals. The autoimmune process is possibly triggered by certain environmental factors, such as the presence of viral infections (1) or their lower frequency during the first years of life (the hygiene hypothesis) (2), rapid somatic growth (the accelerator hypothesis) (3) and β-cell stress (4). The accelerator hypothesis (3) predicts earlier onset of T1D or Type 2 diabetes (T2D) in people who had rapid somatic growth during the first year of life and views T1D and T2D as the same disorder of insulin resistance in people with specific genetic background. The β-cell stress hypothesis (4), which is an extension of the accelerator hypothesis, suggests that a number of different factors (such as psychological stress or rapid weight gain) could cause an increase in insulin demand, leading to β-cell stress, which may lead to an autoimmune reaction in genetically susceptible individuals. During the past 15 yr, psychological stress has been considered as a factor facilitating or precipitating β-cell destruction (5-11), while recently Sepa et al. (4) showed that maternal stress is associated with the development of diabetes related autoimmunity [glutamic acid de-
carboxylase antibodies (GADA), tyrosine phosphatase antibodies (IA-2A) in infants. Moreover, there are some confounding factors for the development of T1D, such as dietary factors (12), increased maternal age at delivery (13) and low socioeconomic status (9). Psychological stress is defined as a particular relationship between the person and the environment, the person considering the stressful event as exceeding his/her resources and endangering his/her well-being (14). The process of stress implicates 4 factors: 1) the presence of an event; 2) the modification of the person’s psychological and physiological equilibrium by the event; 3) the reflection of disequilibrium in a state of arousal marked by neurophysiological, cognitive, and emotional consequences for the individual; 4) the disruption of the person’s adaptability by the changes involved (15). Stressful life events are life experiences or events that may result in changes in a person’s life and that necessitate varying degrees of coping and adaptation, without taking into account the person’s reaction (16).

The psychological impact of stressful events depends on their duration and frequency (chronic or intermittent), the severity of the threat imposed on the individual, as well as the ability of the individual to cope with them (6). On the basis of timing, stress may be classified into 4 types (17): a) acute, b) sequential (one stress initiates the other), c) chronic intermittent (e.g. conflicts with relatives) or d) chronic (physical disability). All these types of stresses are likely to act via a common pathophysiological pathway (17).

Three different time periods seem to be important in the pathogenesis of T1D: 1) the time when the body learns to distinguish its own proteins from foreign proteins (0-24 months of age) (18); 2) the time at which the autoimmune process is initiated (up to 8 yr before the clinical onset of T1D) (19); 3) the time close to the clinical onset of T1D (20).

The aim of the study was to assess the prevalence of potential stressful events or conditions at home and at school, during the various periods of their life, as outlined above, in children newly diagnosed with T1D.

MATERIALS AND METHODS

Study population

The study group included all children with diabetes, aged 1.24-15.62 yr (mean±SD: 10.73±3.62 yr), diagnosed in two Pediatric Hospitals in Athens, Greece over a period of 2 yr. Our study population was unselected, as almost all children with serious conditions from central and southern Greece visit the two major Paediatric Hospitals in Athens. The CD were evaluated within a month after the diagnosis of T1D. The diagnosis of T1D was established according to the World Health Organization criteria (21), while there was no case of T2D among our study population. The control population included children who were examined in the Hospital for a temporary problem (i.e. hernia, acute appendicitis, pneumonia, gastroenteritis, etc.) and did not have a chronic disease. The sex distribution was comparable in the 2 groups.

Methodology

A psychologically stressful condition was derived from the use of the Coddington and Hurme questionnaire (22, 23). This scale has been used in previous studies in Greece on children with alopecia, recurrent abdominal pain, and headaches (24, 25). The events were recorded as follows: 1) independently of their timing in the child’s entire life period; 2) according to specific life period: (a) fetal life, (b) the first 2 yr of life, (c) the 2 yr prior to T1D presentation, and (d) the interval, if present, between the age of 2 yr and the beginning of period (c). For reasons of convenience, we call this last period the intermediate period.

The questionnaire was completed by the parents (mother and/or father) in the presence of the child (Table 1). However, as the majority of the children were under 10 yr, in most of the cases the recorded answers were in fact those of the parents. In the few cases of adolescents, an average score of the parental and adolescents’ answers was recorded. The questionnaire requested information concerning both socioeconomic and other family characteristics (e.g. parental age, education, and occupation status, marital status) and personal history.

Stress events were defined as problems in the family related to the relationship of the child with other family members, to living conditions, to parental occupation, as well as to the occurrence of serious illness or death of first degree relatives. Quarrels were classified on the basis of their intensity in the expression of disagreements. Households reporting heated argument and shouting were classified as having intense disagreement. If disagreements involved hitting or throwing, even rarely, the household was categorized as having violent disagreements (26). Stressful events at school included poor school performance, change of school, behavioral problems (27). School performance was classified as “poor”, “good”, “very good” or “excellent”, according to parental report. Some events or conditions could be inter-correlated (i.e. quarrels between parents and separation or divorce, parental job loss and financial difficulties, serious illness and death). For this reason, the recorded life events were grouped into 7 general categories: 1) everyday problems, 2) parental disputes or divorce, 3) parental abuse or frequent scolding, 4) occupational problems of a parent, 5) car accident or another shock event, 6) serious illness or death in the family, 7) problems at school.

The statistical analysis was planned as follows: initially we studied the potential association between the occurrence of at least one stressful event and T1D presentation, ignoring the time period of its occurrence. Time was taken into account at a second stage by defining the most intense “burden period” during a child’s lifetime, depending on the clustering of the particular event: a) no stressful events (burden period=0); b) most intense burden period, being either at fetal life, or the first 2 yr of life, or the intermediate period (burden period=1); c) the most intense burden period was during the 2 yr prior to diabetes diagnosis (burden period=2); d) uniform distribution of stressful events in the entire lifetime (burden period=3). The number of stressful events that a child had experienced was also examined, distinguishing between no problem, 1 or 2 problems, and 3 or more problems.