Eur. J. Epidemiol. 0392-2990
September 1991, p. 439-449

EUROPEAN JOURNAL OF EPIDEMIOLOGY

Vol. 7, No. 5

SOME NEW ASPECTS OF CJD EPIDEMIOLOGY IN SLOVAKIA

E. MITROVÁ

Institute of Preventive and Clinical Medicine - Bratislava - Czecho-Slovakia.

Key words: Creutzfeldt-Jakob disease - Genetic susceptibility - Environmental risk

Descriptive epidemiological and genealogical data obtained by prospective and retrospective studies on CJD in Slovakia and in patients emigrating from CJD clusters were analysed.

Observations contradictory to an exclusively genetic etiology of temporo-spatial accumulation of CJD are presented. Data indicating a genetically increased susceptibility to the disease and its coincidence with environmental risk in clustering patients are discussed.

INTRODUCTION

Subacute spongiform encephalopathies (SSE) are rare, lethal neurodegenerative disorders affecting humans and animals. They are at present the only known CNS disorders being both genetic and transmissible. Causative (infectious) agents of transmissible encephalopathies show atypical, unconventional biological properties, mainly a high resistance to chemical and physical procedures effective against typical viruses. Although transmissible, they are not contagious, and their natural spread is still unexplained. The most important human SSE is Creutzfeldt-Jakob disease (CJD) with a worldwide occurrence of about 0.5-1 case/year/mill. people. The first recognized and most widespread SSE in animals is scrapie in sheep and goats. The possibility of human infection from this zoonotic source has long been debated, and the recent epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom has given new impetus to the discussion. In this study,some new aspects of CJD epidemiology in Slovakia are presented. Besides the distribution of patients in time and space in the territory of Slovakia, their relationship to the occurrence and forms of CJD in other countries were investigated.

MATERIALS AND METHODS

Patients: Retrospective and prospective investigation of CJD in Slovakia has been carried out since 1971. In this study all notified CJD patients with their birthplace or last residence were analysed. In contrast to previous reports, this study comprises all probable and possible cases of CJD according to criteria proposed by Brown et al. (2) and Masters et al. (6), as well as neurohistopathologically verified patients.

Definitive diagnosis of CJD was confirmed (by neurohistopathology, and in a few cases also by experimental transmission to laboratory animals or by demonstration of SAF) in the National Reference Laboratory of Slow Virus Neuroinfections in Bratislava.

Epidemiological and genealogical data were obtained by personal interviews of patients, relatives, neighbours, and medical doctors, and from medical records, local and regional annals, and Annual statistic reports of CSFR.

RESULTS

Table 1 shows the annual distribution of male and female, (sporadic or familial) CJD patients in both

TABLE 1. - Annual distribution of notified focal and extrafocal CJD (1971-1991).

YEAR at DEATH	FOCUS 1 48.24 Km 2 55-74 Inh/Km 2 243 046 Inhab	FOCUS 2 36.30 Km 2 66-68 Inh/Km 2 142 000 Inhab	EXTRAFOCAL 42 041 Km 2 49-161 Inh/Km 2 5 000 000 Inhab
1971			M
1972	M		M
1973			M*
1974			F
1975	M* M F*		
1976	M	M*	
1977	F*		
1978	M		F F
1979	M M		M
1980	M F*		
1981		M F*	F
1982	F* F* F		M M F
1983	M*	M M F F* F*	M* M
1984		F F*	F F
1985	M*	M* M F*	F
1986	F*		M F F
1987		M* M M F* F* F* F F	M F
1988	F* F	F* M*	
1989		M* F	F F
1990	M	M* M F	F
1991	M*	F	F F F

M = MALE; F = FEMALE; * = FAMILIAL CJD.

areas of focal accumulation of cases and in the extrafocal territory of Slovakia during the years 1971-1991.

Areas in Km^2, number of inhabitants, and ranges of population density are presented for different regions of Slovakia. A predominance of cases (especially familial cases) in focal areas during the entire period is evident. There was no correlation between an increased occurrence of CJD and population density.

Table 2 compares the average annual occurrence of CJD/mill. inhabitants in focal and extrafocal areas thorought the entire period. The two CJD foci show a different time distribution of patients: in the southern Focus 1 the average annual occurrence of CJD is similar in both investigated decades, but in the northern Focus 2 there is a conspicuous outbreak of CJD patients appearing since 1981.

The geographical distribution of CJD cases according to their birth place and their last residence are shown in Figures 1 and 2. Using either criteria the two small rural CJD accumulations and a higher occurrence of cases in Central Slovakia, are evident. The cluster of CJD observed in Bratislava when the last residence of patients was used disappeared when the distribution of cases according to their birthplace was used. Mean age at death and distribution of patients in decades are shown in Table 3 a,b. Though there is no difference in the mean age at death between focal and extrafocal or familial CJD patients, death occurred in focal patients as early as the 3rd decade.

Table 4 presents the distribution of patients according to the duration of illness in focal and extrafocal patients. In both foci mean duration of clinically apparent CJD was must shorter than in the to extrafocal group of patients, where an unusually long clinically manifest stage of the disease (3-6 years) have also been observed.

In Table 5 parents of familial CJD patients with medical histories characteristic for CJD are presented. No autopsy was done in these patients, so they correspond to a diagnosis of "possible" CJD. They are the first notified CJD cases in Slovakia.

Table 6 compares the professional distribution of CJD patients to the general Slovak population. Conspicuous predominance of livestock farming as the only or additional job is evident in both groups of focal CJD cases. Besides this, a relatively high occurrence of health professions (5 nurses, 2 ambulance drivers) and teachers was found.

Figure 3 shows a genealogy of the only extrafocal familial occurrence of CJD, in which there were 2 definitive and 1 possible CJD cases.

Figure 4 shows an extrafocal case of sporadic CJD in a family with other neurological diseases.

In Figures 5-6 are genealogies of Family "Ku" (7) and Family "Sa", both representing focal familial occurrence of CJD with 2 definitive CJD patients, dying approximately at the same time.

Figure 7 shows the genealogy of family "Go" (8) and demonstrates a focal familial CJD with numerous

TABLE 2. - Average annual incidence of focal and extrafocal CJD.

YEARS	SLOVAKIA	EXTRAF.	F 1	F 2	POLTAR	ZUBEREC
1971-1981	0.52	0.12	4.4	2.0	1000	66.6
1982-1991	0.96	0.36	4.0	17.3	3000	600
1971-1991	0.73	0.24	4.2	9.6	2000	333.3

Annual incidence of CJD / 1 Mill. Inhab..

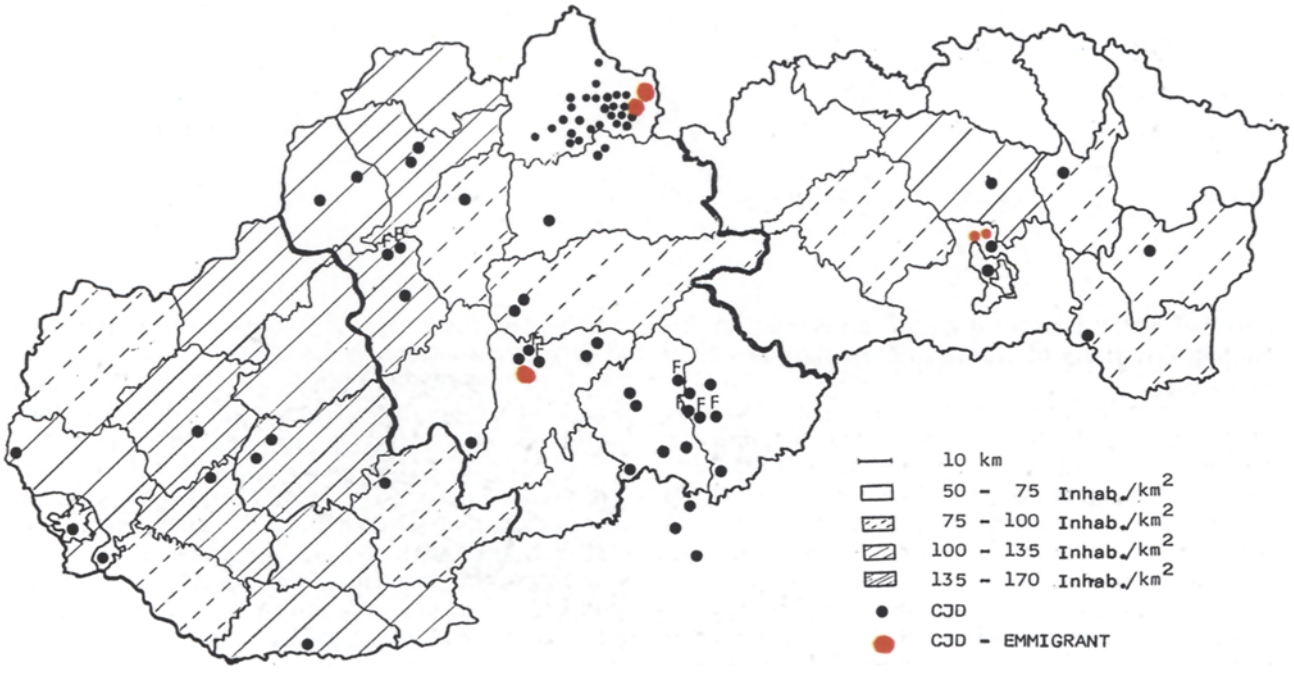

Figure 1. - Geographical distribution of CJD in Slovakia according to the birthplace of patients (1971-1991).

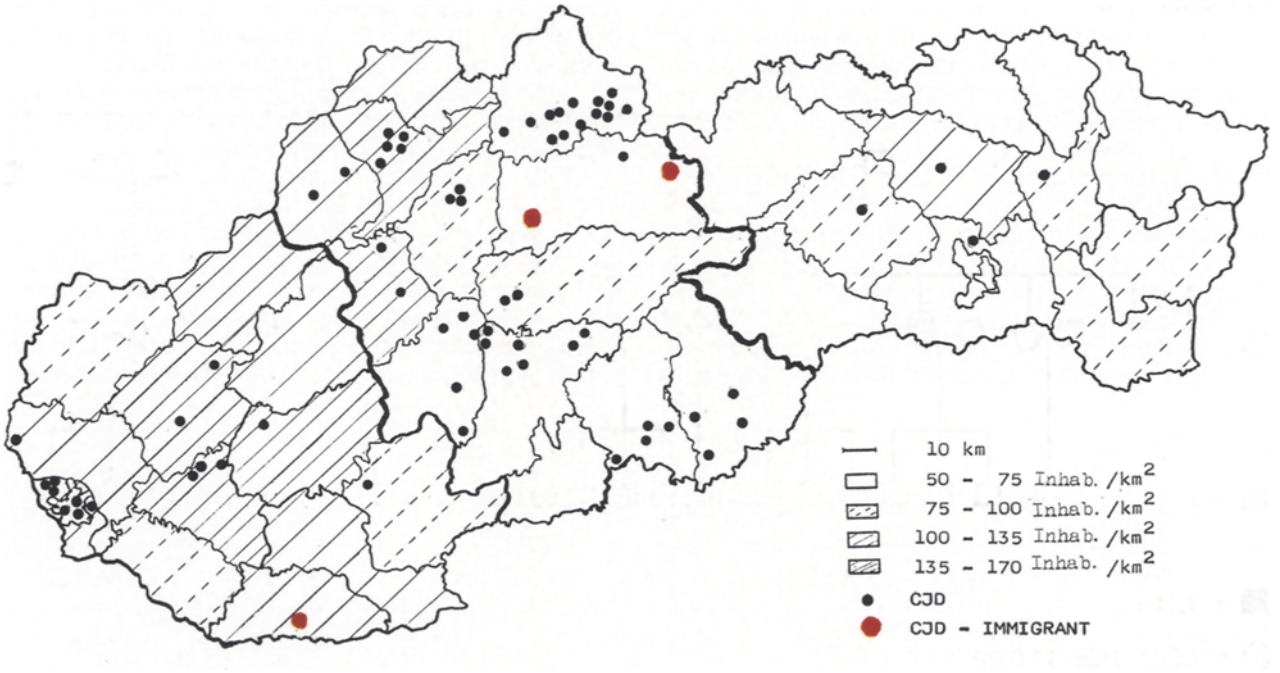

Figure 2. - Geographical distribution of CJD in Slovakia according to the last residence of patients (1971-1991).

TABLE 3a. - Mean age at death of CJD patients.

CJD	FOCUS 1	FOCUS 2	EXTRAFOC.	TOTAL	ZUBEREC	POLTAR
SPORADIC + FAMILIAL	56.1 yr	55.9 yr	56.1 yr	56.1 yr	58.7 yr	57.8 yr
FAMILIAL	57.4 yr	54.9 yr	55.5 yr	55.9 yr		

TABLE 3b. - Age at death of CJD patients (Distribution in decades)

Decade	Focus 1	Focus 2	Extrafocal
Third		10.3%	
Fourth	24%	13.8%	15.5%
Fifth	38%	34.5%	53.8%
Sixth	38%	34.5%	30.7%

(3 definitive, 2 possible) CJD cases in 3 generations, in which 1 of the affected siblings emigrated to Belgium, where she lived for the rest of her life. Separation from relatives in Slovakia lasted more than 30 years.

Figure 8 shows a focal sporadic CJD in family "Kl", which originated in focus Orava and moved to the area of southern CJD accumulation.

In Figures 9-10, families with sporadic or familial occurrence of CJD in village ZUBEREC are presented. Intermarriages between members of affected families are demonstrated. Fig. 10 shows related, CJD affected families including that branch of family "Sh", which emigrated to USA in 1902. In this family 4 definitive CJD cases vere verified in the 1st and 1 case in the 2nd generation born in USA.

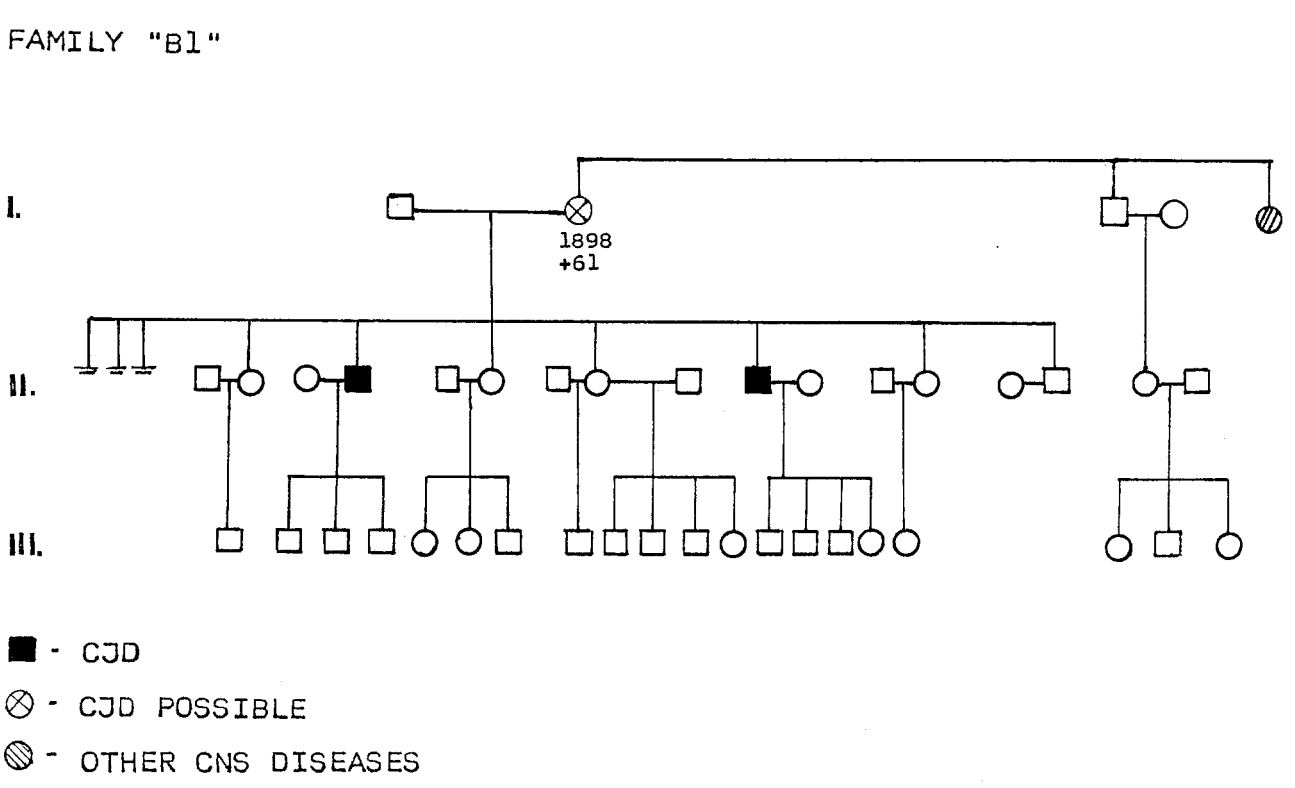

Figure 3. - Genealogies of CJD patients - Family "Bl".

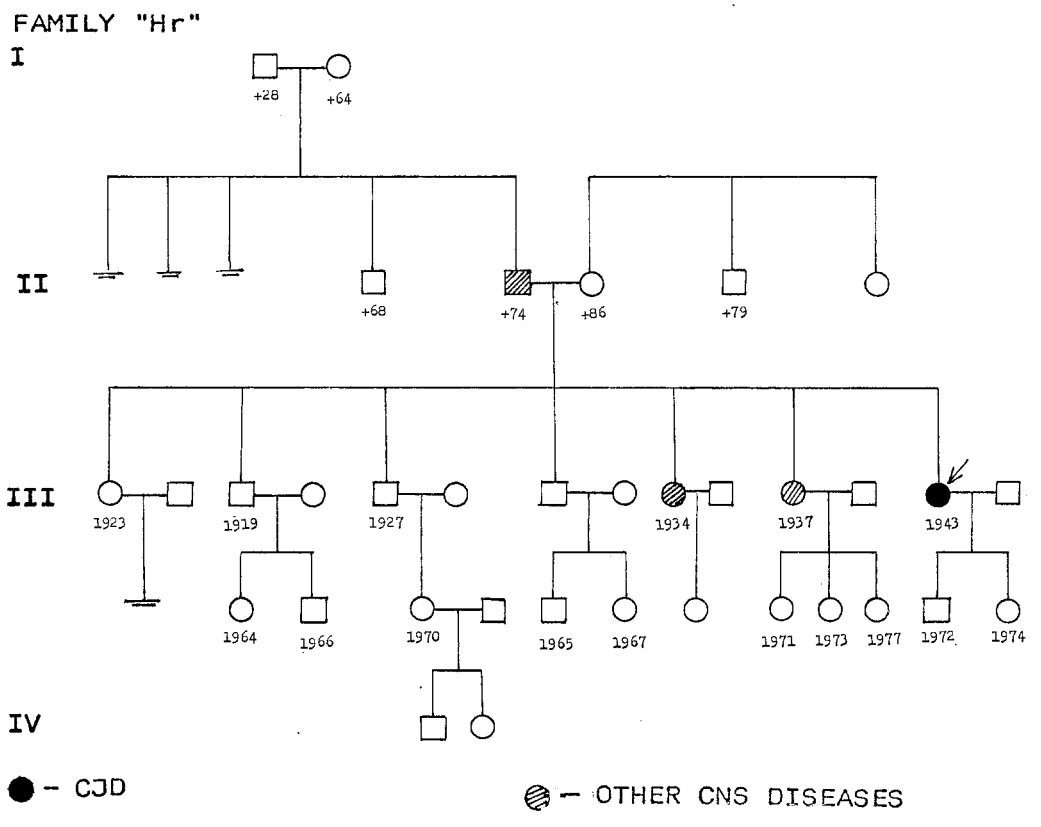

Figure 4. - Genealogies of CJD patients - Family "Hr".

TABLE 4. - Distribution of patients according to the duration of illness in focal and extrafocal CJD (months).

Duration months	Focus 1	Focus 2	Extrafocal	Total
1	5.0%	11.5%		5.5%
2-5	70.0%	63.4%	41.2%	58.2%
6-9	15.0%	11.5%	35.3%	20.6%
12-18	5.0%		5.9%	3.6%
24-36	5.0%	7.7%	5.9%	6.2%
48- <		5.9%	11.7%	5.9%
Mean value months	6.9	6.2	11.2	8.9

TABLE 5. - The first notified familial "possible" CJD cases in Slovakia.

Patient	Focus 1		Focus 2		Extrafocal
Sex	Male	Female	Male	Female	Female
Year of Birth	1885	1884	1896	1903	1898
Year of Death	1925	1932	1954	1964	1959
Age at Death	40	48	61	55	61

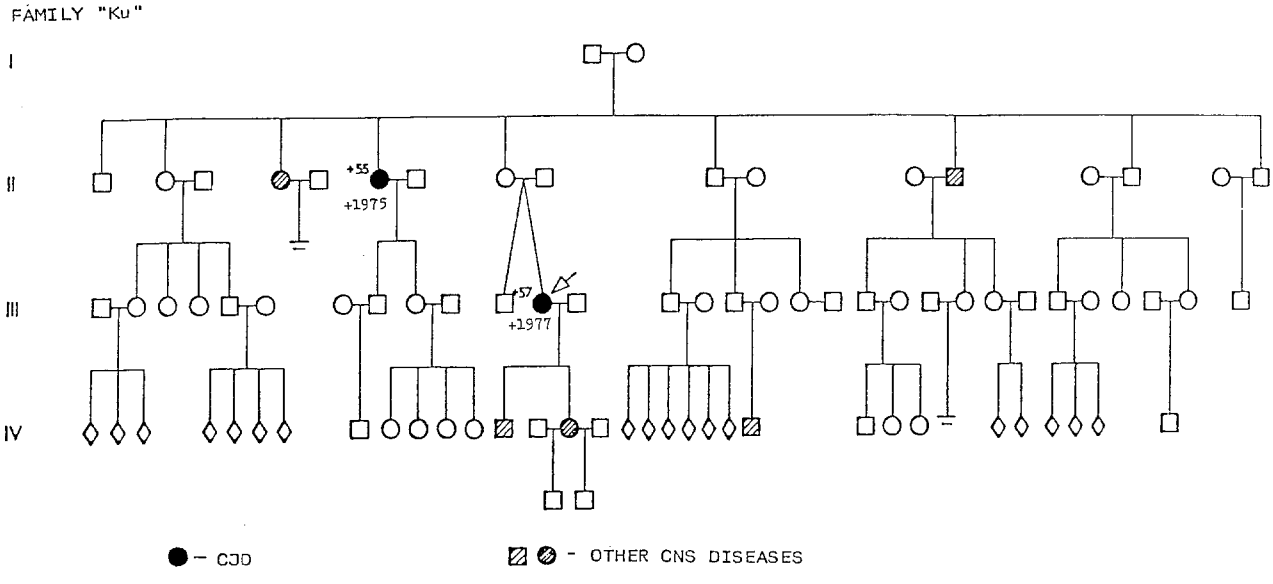

Figure 5. - Genealogies of CJD patients - Family "Ku".

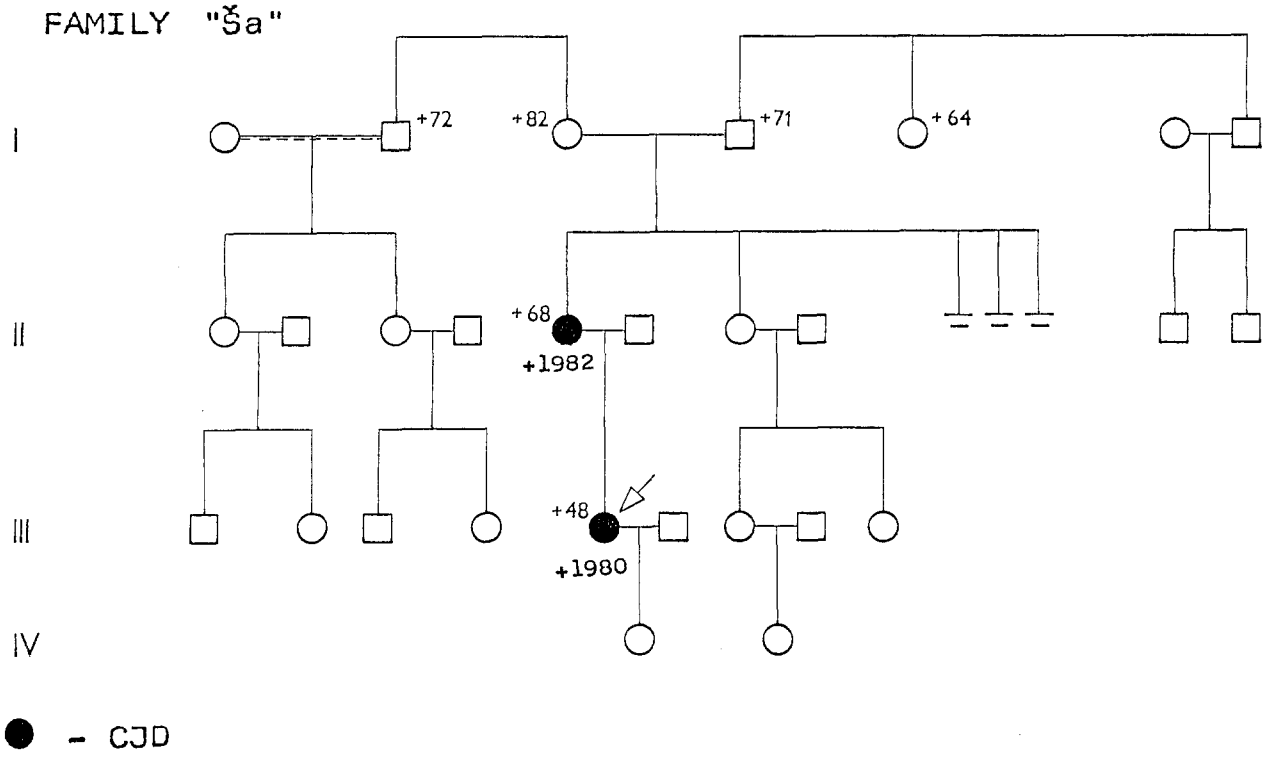

Figure 6. - Genealogies of CJD patients - Family "Ša".

TABLE 6. - Percentage frequencies of the professions of CJD patients compared to that of the general Slovak population.

Occupation	Slovakia Genr. Popul.	Focus 1	Focus 2 CJD Patients	Extrafocal	Total
Livestock farming	15.6	52.3	58.6	33.2	48.6
Meat processing	0.2	4.8	3.5	8.3	5.4
Forester	0.05	4.8	3.5		2.7
Health professions*	4.3		10.3	12.3	8.1
Teacher	6.4	14.3	13.8		9.5
White collars	3.4	19.0	10.3	37.5	20.5
House wife	1.6	4.8		8.3	4.0

*Health professions = nurses (5), ambulance drivers (2).

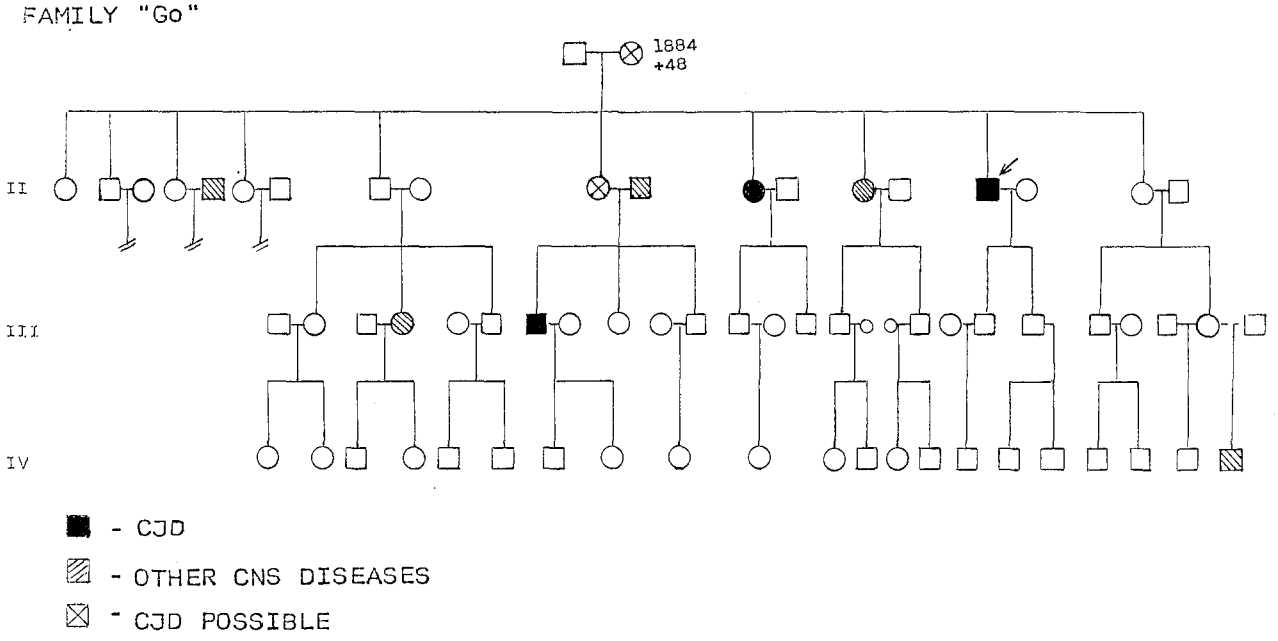

Figure 7. - Genealogies of CJD patients - Family "Go".

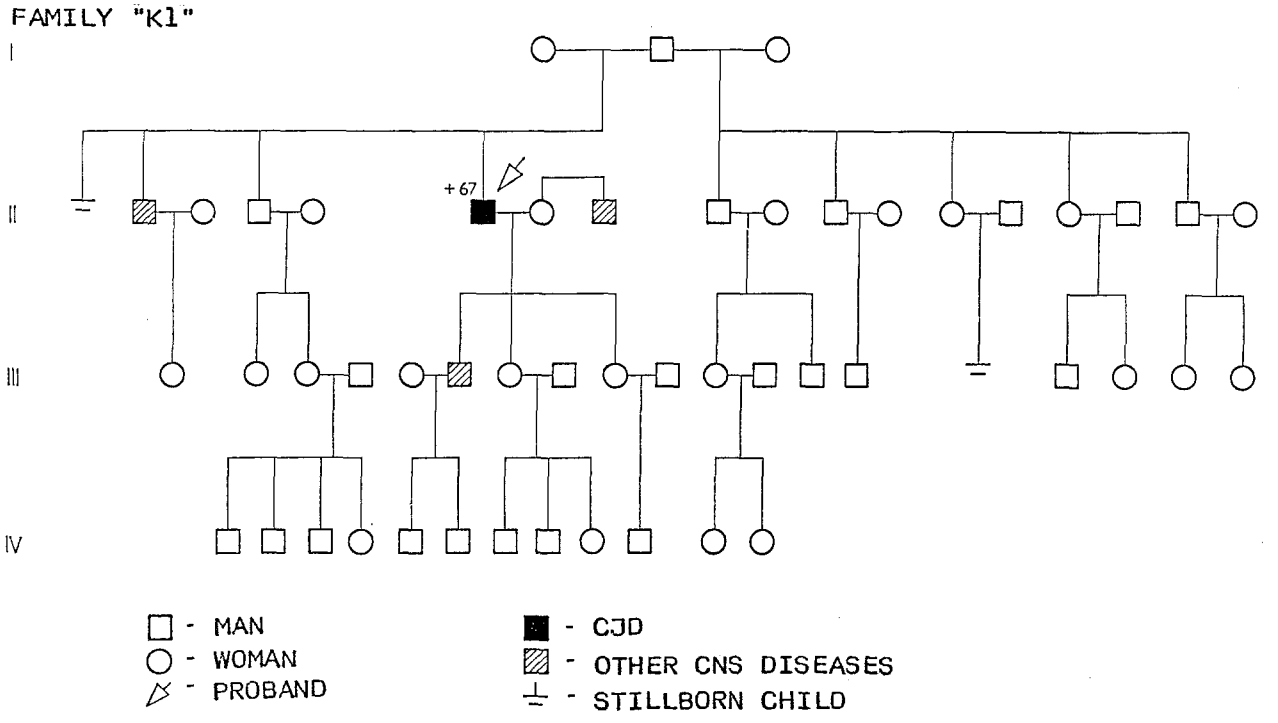

Figure 8. - Genealogies of CJD patients - Family "Kl".

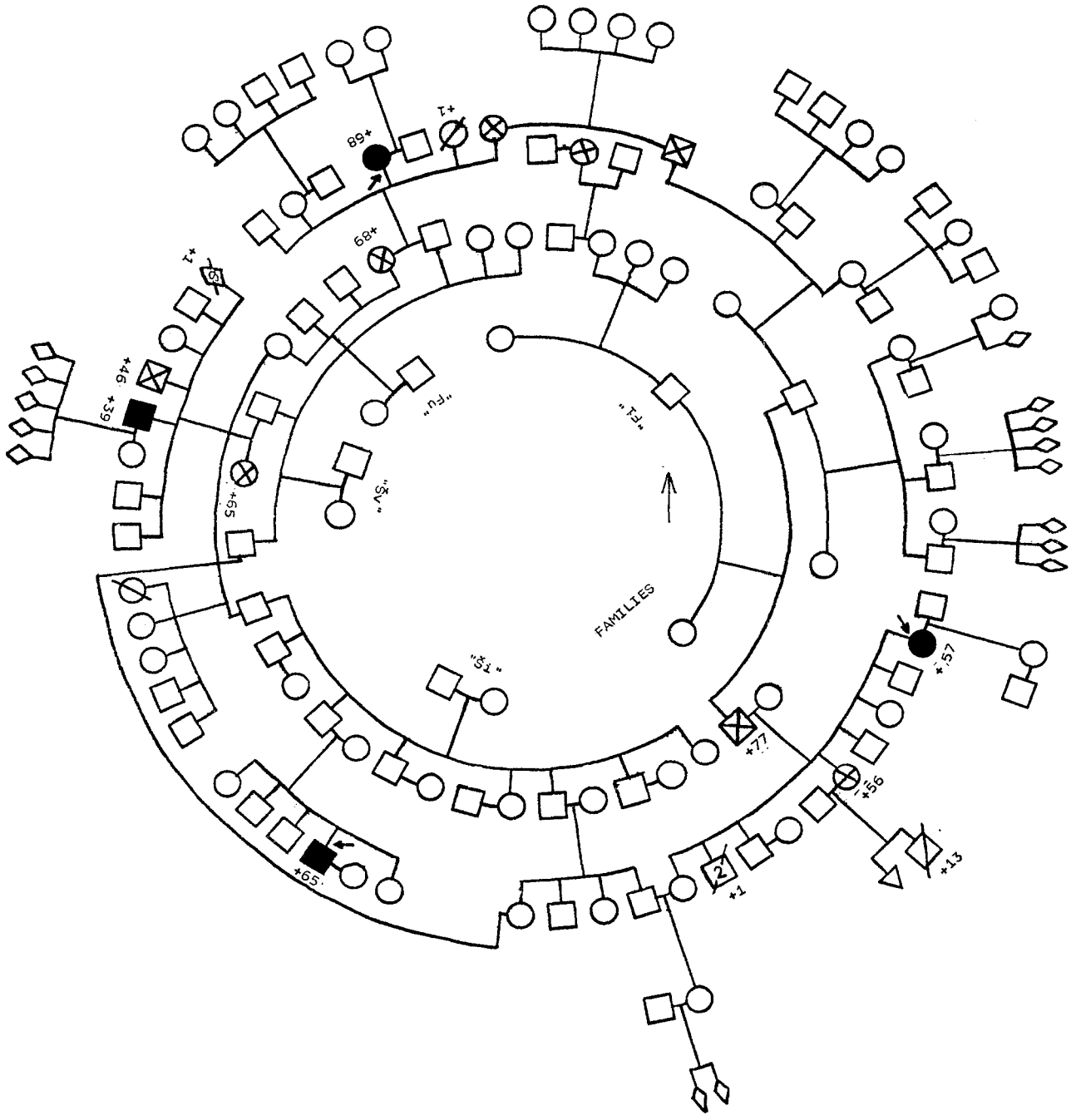

Figure 9. - CJD families in Zuberec.

DISCUSSION

A number of studies have addressed temporo-spatial accumulations of CJD. Epidemiological investigations and statistical analysis of CJD in England and Wales (12), and France (3) demonstrated regional variations of CJD without evidence of CJD clusters. An ethnic (and familial) clustering was observed among Libyan immigrants to Israel (11) and familial clustering was identified in Chile (1).

The only accumulation of CJD with a statistically significant temporo-spatial relationship was identified in Slovakia (9). There are two areas of increased occurrence of CJD in southern (Focus 1) and northern (Focus 2) parts of Central Slovakia. Both are rural clusters with an increased percentage of familial CJD. All tested focal patients have a mutation at codon 200 of the prion protein gene (4, 5). Although a

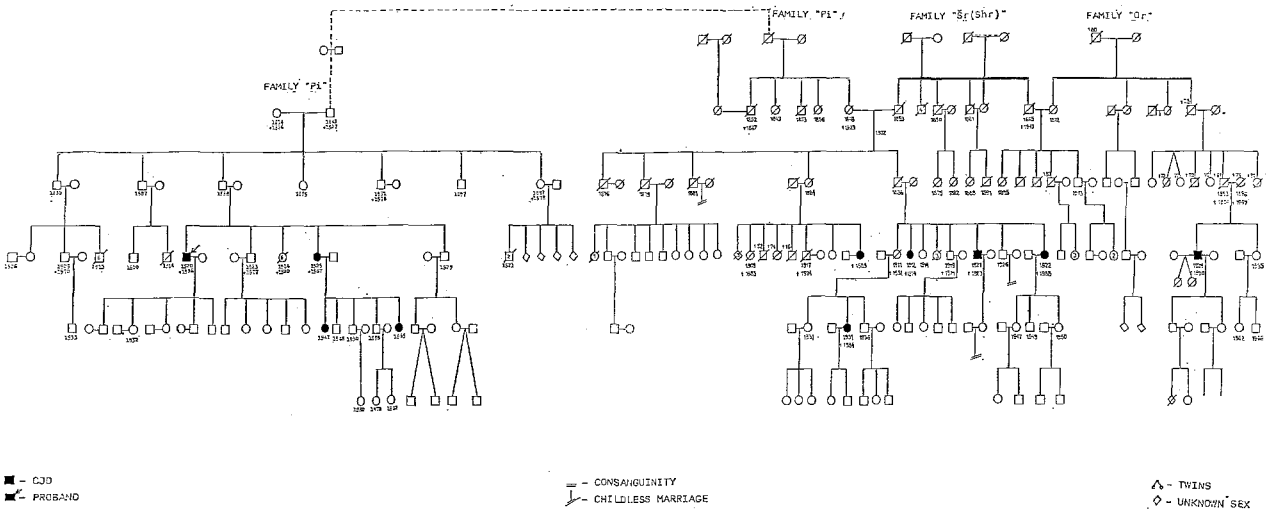

Figure 10. - Families "Pi", "Sr" and "Or".

high percentage of livestock farming in affected patients in both clusters indicates a possibility of professional risk of CJD, the etiology of Slovak CJD clusters has still to be explained.

Well documented high occurrence of familial cases, numerous cases of consanguinities, and a disease associated mutation at codon 200 of the prion protein gene strongly support the involvement of genetic mechanisms in the origin of CJD clusters. According to Goldfarb et al. (5) familial CJD in Slovak cluster is primarily a genetic disease, without any contributing role played by local environmental factors.

The genetic hypothesis of CJD clustering cannot account for the presence of the mutation without evidence of CJD in Orava at least as far back as 1902. Furthermore, despite the fact that the first possible CJD cases occurred in 1930-1940, they remained rare until the Seventhies. In that time, since the extensive migration throughout the country at the end of the World war II., genetic isolates, including those in Orava, started to disappear.

An autosomal-dominant mode of inheritance with a low degree of disease penetrance does not fully explain:

- the onset of CJD in affected family members approximately at the same time and not at the same age;
- the occurrence of the disease - associated mutation in healthy CJD relatives over the age of CJD onset (69-76 years) in Slovak clusters;
- the significant difference in temporal accumulation of patients in two clusters (earlier, gradually accumulating cases in the Focus 1 and an epidemic-like outbreak of CJD in Focus 2) consisting of a genetically identical population, as far as the mutation is concerned.

The origin of the codon 200 mutation in Spain and spread by migration of expelled Sephardic Jews was suggested (5). Sephardic Jewish merchants and slavetraders were described in historical documents in the territory of present Slovakia since the 12th century. They came through present Austria or Bohemia and wandered across the country either to present Poland or Hungary. There is historical evidence of periods of their special privileges as well as persecutions and both legitimate and illegitimate descendants betwen the local inhabitants. However, there is no explanation for an absence of the mutation in other non-focal regions of Slovakia.

Data concerning the spread of the mutation from Orava to the territory of Slovakia and to abroad are available. Massive migration from Orava started in 18th century after an unproductive "hungry" year (1717). The second wave came in the last half of the 19th century, after cholera. At that time people emigrated mainly to the USA, less to Canada. Later, between the two World wars the main aim of emigration became France and Belgium. Our findings correlate well with these data; most CJD patients were among Slovak emigrants to USA (6 cases), less in Canada (2 cases), 1 in Belgium and 1 CJD patient born to Slovak emmigrants in France returning home were notified. Besides the last, extrafocal case, all had CJD associated mutation (5).

Clustering familial CJD, both emigrated as well as found in Slovakia could be differentiated to two types:

- Families with a small number, mainly two affected members, usually in two generations, dying approximately at the same time.
- Families with numerous CJD cases in 2 or 3 generations; affected family members dying either approximately at the same time or at the same age.

The first, more frequent type of familial CJD is

suggestive of a common source of infection, whereas in the second type (emigrant family Shr), the genetic risk appears to play a decisive role.

These findings, together with data suggesting a professional risk in both foci, an epidemic-like outbreak of CJD since 1987 in Orava with unchanged occurrence of CJD in the southern focus, confirmation of scrapie in Orava region (10), temporal dissociation between the occurrence of the CJD associated mutation and CJD clustering, all indicate that the etiology of Slovak CJD clusters involves both, genetic and environmental factors.

Considering scrapie to be a hypothetical environmental risk, temporal differences between the two clusters could be explained. Inhabitants in Orava were extremely poor, their traditional food was potatoes, cabbage, cheese and milk. Meat consumption was rare and exceptional. A considerably higher standard of living occurred in the area of the southern cluster, where consumption of meat was more common. Originally, Valaska breed sheep of poor quality were raised in both focal regions. At the end of the 19th century sheep with better qualities of wool or meat were imported, earlier to the more rich and progressive southern focus. Since with imported sheep, scrapie was also known to be imported (13), the infected flocks in the southern focus could not be excluded.

An improved standard of living, associated with new dietary customs appeared in Orava in the early 1950s. A delay in better life style in Orava could possibly be a reason for a later occurrence of CJD accumulation in relations with a genetically similar backround.

We conclude that the mutation predisposes to CJD, but is not able to induce the disease without an additional, probably environmental influence.

Acknowledgement

The author thanks Mariann Meriova, Katrin Gunisova and Edith Mrvkova for their excellent technical assistance.

REFERENCES

1. *Araya G., Galvez S., Cartier L.* and *Gajdusek D.C.* (1983): A spatio temporal clustering of Creutzfeldt-Jakob disease in Chile - Rev. Chil. Neuropsiquiqt. *21:* 291-195.
2. *Brown P.* and *Cathala F.* (1979): Creutzfeldt-Jakob disease in France. In: Prusiner S., Hadlow W. - Eds. Slow transmissible diseases of the nervous system - Vol. 1. NY Acad Press, 213-227.
3. *Brown P., Cathala F., Raubertas R.* et al. (1987) : The epidemiology of Creutzfeldt-Jakob disease: conclusion of a 15-year investigation in France - Neurology, *37:* 895-904.
4. *Goldfarb L., Mitrova E., Brown P., Toh B.* and *Gajdusek D.* (1990): Mutation in codon 200 of scrapie amyloid protein gene in two clusters of Creutzfeldt-Jakob disease in Slovakia - Lancet, *33:* 514.
5. *Goldfarb L., Brown P., Mitrova E., Cervenakova L.* et al. (1991): Creutzfeldt-Jakob disease with the PRNP codon 200 Lys mutation : an analysis of 45 families. Europ. J. Epidemiol. This issue.
6. *Masters C., Harris J., Gajdusek D.C.* et al. (1979): Creutzfeldt-Jakob disease: pattern of worldwide occurrence and the significance of familial and sporadic clustering - Ann Neurol. *5:* 177-188.
7. *Mitrova E.* and *Mayer V.* (1981): Inherited susceptibility, Ovine brain consumption and Creutzfeldt-Jakob disease - J. Neurol. *226:* 219-220.
8. *Mitrova E., Lowenthal A.* and *Appeal B.* (1990): Familial Creutzfeldt-Jakob disease with temporal and spatial separation of affected members - Europ. J. Epidemiol. *6:* 3 233-238.
9. *Mitrova E.* and *Bronis M.* (1991): Cluster of CJD in Slovakia: The first statistically significant temporo-spatial accumulation of patients - Europ J. Epidemiol., This issue.
10. *Mitrova E., Huncaga S., Hocman G., Nyitrayova O., Tatara M.* and *Cervenakova L.* (1991): Cluster of CJD in Slovakia: The first laboratory evidence of scrapie - Europ. J. Epidemiol., This issue.
11. *Neugut R., Neugut A., Kahana E* et al. (1979): Creutzfeldt-Jakob disease: familial clustering among Libyan-born Israelis - Neurology *29:* 225-231.
12. *Will R., Mathews W., Smith P.* et al. (1986): A retrospctive study of Creutzfeldt-Jakob disease in England and Wales 1970-1979 - J. Neurol. Neurosur. Psych., *49:* 749-755.
13. *Zlamal V.* (1987): Allatkor es gyogytan - Budapest, Atheneum Kiado, pp. 285.