Colorado IDDM Registry
Incidence and Validation of IDDM in Children Aged 0–17 Yr

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The purpose of this study was to determine the incidence of insulin-dependent diabetes mellitus (IDDM) among children aged 0–17 yr for age, sex, season, and urban and rural residence of onset in Colorado. Retrospective registration of new-onset cases was conducted from 1978 to 1980, and then prospective registration continued through 1983 with the use of physician reporting with hospital validation. The annual incidence of IDDM was 15.2/100,000 per year (95% confidence interval [CI] 14.1, 16.3), with little difference between the sexes. The highest incidence was in the 10- to 14-yr age-group for both sexes. There was a seasonal peak of winter onset in those aged 10–17 yr, with similar patterns between sex and ethnic groups. No temporal trend over the 6 yr was seen, although an excess of cases was seen for 15- to 17-yr-old boys in 1980–1982. Rates were similar for urban and rural areas of the state. Case ascertainment was estimated to be 93.2% complete (95% CI 91.5, 95.5). Incidence was similar in Colorado to other populations in the United States at similar latitudes. These data serve as a baseline for evaluation of changes in incidence over time, by region, and for the identification of possible outbreaks. *Diabetes Care* 13:499–506, 1990

Insulin-dependent diabetes mellitus (IDDM) has only recently been studied in various populations around the world. Several IDDM registries were established that have identified a 17- to 60-fold difference in IDDM incidence worldwide among those <15 yr of age at onset (1–4). IDDM is a disease that presents challenges to investigators attempting to conduct a registry, especially one that is population based and maintains high case ascertainment. However, most of these registries have been established in predominantly urban areas and relied on hospitalized children with IDDM. The Colorado IDDM Registry was developed in 1981 to determine the incidence of IDDM on a statewide basis in a state that includes large urban centers and sparsely populated rural areas. In contrast to most registries, this registry relies primarily on physician surveillance to ascertain cases. Thus, it has the potential to identify children receiving only outpatient care at diagnosis. This study focuses on the incidence of IDDM among residents aged 0–17 yr, from January 1978 to December 1983, and on the results of validation.

RESEARCH DESIGN AND METHODS

Children who met the following criteria were eligible for inclusion in the registry: *1*) diagnosed with IDDM since 1 January 1978 and, for this study, through 31 December 1983; *2*) resident of Colorado at the time of diagnosis; *3*) <18 yr of age at diagnosis; *4*) placed on insulin within 2 wk of diagnosis; and *5*) diabetes not secondary to other conditions.

The registry identified incident cases of IDDM in Colorado, a geographic area of 103,598 sq miles located between latitude 37° and 41° N. The state was divided into five regions for analysis, which are shown in Fig. 1 and summarized in Table 1. The population of Col-

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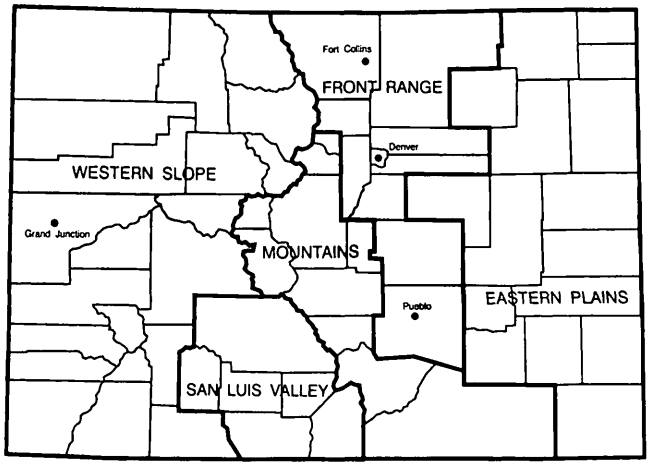

FIG. 1. Regions of Colorado that were used for analysis.

orado was 2.9 million, with 808,813 children aged 0–17 yr as of 1 April 1980 (5). Both passive and active surveillance and referrals from patient and voluntary organizations were used to identify cases. The registry was begun in 1981, with retrospective ascertainment of cases who were diagnosed from 1 January 1978 to mid-1981. Pediatricians, family and general practitioners, diabetologists, endocrinologists, and any physician reported to have cared for a person with IDDM were mailed information about the registry yearly along with a request for case notification with registry reporting cards. These cards contained the subject's name, address, telephone number, parent's name, eligibility criteria, ethnicity, and the physician's name, address, and permission to contact the family. Of all reported subjects, 99% had physician permission for contact.

Because passive surveillance systems have been shown to result in incomplete ascertainment, we also used active surveillance techniques. As a reminder to report cases, we telephoned medical practices that reported at least three cases every 3 mo. Practices with fewer cases were telephoned twice a year.

To validate the completeness of case ascertainment between 1978 and 1983, we obtained permission to review records in 79 of 83 nonmilitary hospitals in Colorado (95%) in 1985–1986. Access to records in three military hospitals was denied. However, we estimated that only 3–4 cases would have occurred per year in the 25,280 military dependents aged 0–17 yr (Colorado Division of Local Government, unpublished observations). Discharge indexes were reviewed to identify patients admitted with diabetes in specified year-of-birth intervals, regardless of whether the subject was hospitalized at onset. This allowed the detection of subjects cared for as outpatients at onset, but who were later admitted to the hospital. These medical records were then reviewed to determine eligibility criteria and compared with existing registry records. Individuals not previously reported were registered.

The population in Colorado was estimated with the 1980 U.S. Census for Colorado, for children aged 0–17 yr, as of 1 April 1980 (5). For yearly rates, the intercensal estimates and postcensal projections as of 1 July of each year were obtained from the state demographer (R. Reynolds, unpublished observations). Annual incidence rates were estimated by assuming these denominators were midpoint populations at risk. Numerators were annual case counts. Average annual rates for 1978–1983 were estimated by pooling all cases and dividing by 6. Confidence intervals (CIs) were calculated with the Poisson distribution (6). Significance of cross tabulations was determined with χ^2-statistics (7). To determine statistically significant seasonal trends, the method of Jones et al. was used (8). Completeness of ascertainment was estimated with the capture-recapture method (9; Appendix 1). Age adjustment was determined by the direct method with the following age-specific weights as standards (3,10)

	Weight for direct adjustment (%)	
Age-group (yr)	Adjusted rate (0–14 yr)	Adjusted rate (0–17 yr)
0–4	33	27
5–9	33	27
10–14	34	28
15–17		18

RESULTS

Between 1978 and 1983, 738 subjects with incident IDDM who met all eligibility criteria were identified. The crude incidence rate was 15.2/100,000 per year (95% CI 14.1, 16.3). An additional 778 subjects were identified but were not eligible. Reasons for ineligibility included prevalent rather than incident cases (n = 470), nonresidents of the state at diagnosis (n = 117), age ineligible (n = 40), lack of treatment (n = 4), and combination of these reasons (n = 84). There were 63 subjects with data for one or more of the eligibility criteria missing who were also excluded from analyses.

To determine the completeness of the registry, we located missed cases and estimated the completeness of ascertainment. Table 2 shows that of 738 eligible cases, 121 (16.4%) were found only at hospital validation, whereas 617 (83.6%) had been reported voluntarily by physicians. Combining both sources of these cases, we estimated that ascertainment was 93.2% complete, with 95% CIs from 91.0 to 95.5 (Appendix 1).

Characteristics of subjects that were identified solely from validation were compared with those reported to the registry in Table 2. Those not previously reported were more likely to be older at diagnosis. Hispanics were less likely to have been reported than non-Hispanic Whites (76.3 vs. 86.1%). The year of diagnosis of subjects found in validation also differed from the year of diagnosis among those reported to the registry. The highest proportion of subjects was reported in 1981 (94.1%), with the lowest proportions in 1979 and 1983.

TABLE 1
Summary of regions of Colorado, 1980

Region	Percentage of population aged 0–17 yr by ethnic group			Area (sq miles)	Occupational characteristics*
	White	Hispanic	Black/other		
Front range	76	16	8	15,597	Urban: professional/technical services, retail trade, manufacturing, construction
Eastern plains	81	18	1	27,083	Rural: agriculture, professional/technical services, retail trade, educational services
San Luis Valley	49	50	1	8188	Rural: agriculture, professional/technical services, retail trade, construction
Western slope	88	9	3	39,414	Rural: retail trade, professional/technical services, construction, mining
Mountains	79	20	1	13,316	Rural: professional/technical services, retail trade, construction, manufacturing

*Based on first 4 occupational classes in region as determined by U.S. Census Bureau (36,37).

Subjects with IDDM who lived outside the urbanized Front Range corridor of Colorado at diagnosis were also less likely to be reported by physicians to the registry.

Table 3 shows the number of eligible cases, population, and average annual incidence rates by sex and age-group at clinical diagnosis. There were 380 boys and 358 girls with IDDM identified. The highest incidence rates were in the 10- to 14-yr-old age-group in both sexes. Female rates were higher than male rates at 5–9 yr of age, the same at 10–14 yr, and lower at 15–17 yr. Age-adjusted rates for groups 0–14 yr of age and 0–17 yr of age are also shown. With an estimated completeness of ascertainment of 93.2%, actual incidence rates could be as high as 16.3/100,000 per year.

Table 4 summarizes the incidence of IDDM by geographic regions. There were no significant differences in incidence by region, although rates were lowest in San Luis Valley. The rate in this six-county region was only 6.8/100,000 per year (95% CI 2.2, 15.8). This area is an intermontane valley, situated on the Colorado-New Mexico border, where 50% of the population report Hispanic ethnicity (11). We have previously shown that IDDM incidence in Hispanics in Colorado is ~50% that of non-Hispanic Whites (3,4,12).

Incidence rates by year of diagnosis were examined to determine whether any short- or longer-term temporal trends had occurred in Colorado. No significant temporal trends were seen for all age-groups combined. Figure 2 shows year-specific results by sex and age-group. Male and female rates showed no significant temporal trends. However, in boys aged 15–17 yr at diagnosis, rates appeared to increase from 1980 to 1982 then decreased again. The lower limit of the 95% CIs for 1980–1982 excludes the 1978, 1979, and 1983 point estimates of male incidence rates. Rates for girls did not show this pattern, and they were also below the lower limit of the 95% CI for male rates for 1980–1982.

Figure 3 shows the percentage distribution of cases by month of diagnosis for boys and girls by age-group at diagnosis. There was a significant wintertime peak of diagnosis, with a weak but significant second midsummer peak in subjects 10–17 yr of age (8). There was no significant seasonal pattern in subjects aged 0–9 yr nor was there any difference in seasonal onset between boys and girls, or between Hispanics and non-Hispanic Whites.

DISCUSSION

The Colorado IDDM Registry is a statewide incidence registry that primarily uses physician surveillance with hospital validation. With the use of physician and hospital sources, we estimated that ~6.8% of the cases might have been missed. The use of the capture-recapture method to estimate the degree of ascertainment assumes that subjects have independent and equal probabilities of entering each source of ascertainment (9). Some subjects are treated as outpatients at onset. However, they have an equal chance of having a subsequent hospitalization compared with those who were hospitalized at onset. We reviewed hospital records at a sufficient time after onset to allow for a hospitalization to occur. Therefore, the use of the capture-recapture method appears appropriate as a way to estimate completeness. We used repeated mailings and telephone contacts with practitioners to increase reports of the number of subjects treated only in outpatient locations. If these subjects have a lower probability of subsequent hospitalization, then the completeness estimates reported here will be low. Most subjects who receive outpatient care at onset in Colorado do so at only two sites that are directed by registry collaborators (H.P.C. and G.J.K.). Because we conduct monthly reviews of new case registers, we believe underascertainment of this group is low. It seems impossible to estimate precisely the number of missed cases, given the realities of conducting a study such as this in a large geographic

TABLE 2
Characteristics of subjects aged 0–17 yr identified through validation compared with those reported to registry; Colorado, 1978–1983

Characteristic	Validation only		Reported		Total
	n	%	*n*	%	
Total	121	16.4	617	83.6	738
n (M/F)*	68/53	17.9/14.8	312/305	82.1/85.2	380/358
Age at diagnosis (yr)†					
0–4	9	8.4	98	91.6	107
5–9	28	12.4	197	87.6	225
10–14	52	17.2	250	82.8	302
15–17	32	30.8	72	69.2	104
Race/ethnic group‡					
White	83	13.9	515	86.1	598
Hispanic	18	23.7	58	76.3	76
Black	2	10.0	18	90.0	20
Other	3	30.0	7	70.0	10
Unknown	15	44.1	19	55.9	34
Year of diagnosis§					
1978	22	20.4	86	79.6	108
1979	24	20.5	93	79.5	117
1980	15	12.5	105	87.5	120
1981	8	5.9	128	94.1	136
1982	19	15.3	105	84.7	124
1983	33	24.8	100	75.2	133
Residence region at diagnosis‖					
Front range	79	14.6	463	85.4	542
Eastern plains	10	30.3	23	69.7	33
San Luis Valley	3	60.0	2	40.0	5
Western slope	15	20.8	57	79.2	72
Mountains	7	29.2	17	70.8	24
Unknown	7	11.3	55	88.7	62

*$\chi^2_1 = 1.28$, $P = 0.26$.
†$\chi^2_3 = 23.4$, $P < 0.0001$.
‡$\chi^2_4 = 25.6$, $P < 0.0001$. Ethnicity based on self-report of race and Hispanic origin (yes/no) for subjects with questionnaire ($n = 649$, 87.3%) and by physician report for remainder ($n = 55$, 8.1%) with ethnicity stated.
§$\chi^2_5 = 22.0$, $P < 0.001$.
‖$\chi^2_5 = 18.0$, $P = 0.003$.

area. Nonetheless, we think that completeness compares favorably with ascertainment rates reported from other registries not based on national insurance schemes (3,4), and was higher than unvalidated voluntary registries (13).

Our primary reason for establishing a physician-based reporting network was because IDDM is increasingly treated as an outpatient condition (14–19). In Colorado, 80 of 738 subjects (10.8%) with IDDM reported no hospitalization at onset. Of these 80 cases, 60 (75%) were identified through physician reporting and 15 were found both in validation and were reported by physicians, whereas 5 cases were identified from hospitalizations after disease onset. Thus, had we used only hospital reporting, we would not have known of 60 additional cases. Allen et al. (20) reported similar outpatient-only treatment proportions in central Wisconsin. In contrast, Green and Anderson (21) found that only 1.3% of Danish males with diabetes onset from 0 to 19 yr of age were not admitted to hospital at onset. The Oxford, England, registry found that 28% of cases were not hospitalized at onset (22). The authors concluded that hospital discharge data alone could no longer provide accurate incidence estimates. These studies show that there are wide regional and national differences in hospitalization practices at onset of diabetes. This suggests that there is no standard approach for reporting and case ascertainment validation that can be used for all registries.

Studies that rely only on hospital reporting systems may also lead to inaccurate results. At selected hospitals in Colorado we found incorrect discharge coding, missing individual records, and entire years of medical records that had been misplaced or destroyed. For example, of the 617 subjects who were reported to the registry by physicians, we attempted to verify reported hospitalizations. There were 111 subjects (18%) who reported a hospitalization that could not be verified.

TABLE 3
Number of cases of insulin-dependent diabetes mellitus, population, and average annual incidence/100,000 per year by age-group at diagnosis and sex; Colorado, 1978–1983

Sex	Age-group (yr)				Crude rate	Adjusted rate (yr)*	
	0–4	5–9	10–14	15–17		0–14	0–17
Males							
Cases (*n*)	61	101	153	65	380		
Population	110,954	108,961	115,145	78,210	413,270		
Rate/100,000/yr	9.2	15.4	22.1	13.9	15.3	15.6	15.3
95% confidence interval	7.1, 12.0	12.6, 18.8	18.8, 26.0	10.8, 17.9	13.8, 16.9	14.1, 17.3	13.8, 16.9
Females							
Cases (*n*)	46	124	149	39	358		
Population	150,541	104,174	111,002	74,826	395,543		
Rate/100,000/yr	7.3	19.8	22.4	8.7	15.1	16.6	15.2
95% confidence interval	5.3, 9.8	16.5, 23.8	19.0, 26.4	6.2, 11.8	13.6, 16.8	15.0, 18.4	13.7, 16.9
Total							
Cases (*n*)	107	225	302	104	738		
Population	216,495	213,135	226,147	153,036	808,813		
Rate/100,000/yr	8.2	17.6	22.3	11.3	15.2	16.1	15.2
95% confidence interval	6.7, 10.0	15.4, 20.1	19.9, 25.0	9.2, 13.8	14.1, 16.3	15.0, 17.3	14.1, 16.3

U.S. Census Bureau, Colorado, 1 April 1980.
*With direct method; standard population shown in RESEARCH DESIGN AND METHODS.

This was because the records were not available in the hospital 69% of the time. Hospital errors (5.4%), registry errors (20.7%) induced by differences in so many hospital record systems, and unknown reasons (4.5%) accounted for the remaining problems.

The use of physician reporting as a primary data source requires substantial effort, given the many potentially eligible practitioners. The Colorado IDDM Registry maintains a computerized file of ~1400 practitioners; however, only ~10% of them care for children with IDDM in Colorado. There was year-to-year variation in the completeness of physician reporting. This suggests that a uniform rate of reporting or a constant fraction of missed cases cannot be assumed, even over short time intervals. When examined by year, it appeared that voluntary reporting only missed 5.9% of cases in 1981, which might be used as a lower limit on the missed-cases proportion. However, voluntary physician reporting would identify only 75–90% of cases on average were it not supplemented with hospital record review.

The average annual incidence rate of IDDM in Colorado was 15.2/100,000 per year, with few differences between boys and girls. Taking into account underascertainment led to an estimate of crude incidence of 16.3/100,000 per year. Age-adjusted incidence rates for children 0–14 yr of age, including the Colorado population, have been reviewed (4). It appears that Colorado, like other populations in the U.S. at similar latitudes, has an intermediate IDDM risk (15.2/100,000 per year) between that of Japan (1.7/100,000 per year) and Finland (29.5/100,000 per year).

The observations of almost doubled incidence rates in 15- to 17-yr-old boys from 1980 to 1982 raises the possibility of a short-term alteration in etiologic factors, either recently or in the distant past. The number of cases was small and there was no a priori hypothesis of

TABLE 4
Average annual incidence of insulin-dependent diabetes mellitus per 100,000 among subjects aged 0–17 yr by region of Colorado, 1978–1983

Region	Cases (*n*)*	Population†	Incidence/100,000/yr	95% Confidence interval
Front range	592	647,637	15.2	14.0, 16.5
Eastern plains	36	41,328	14.5	10.1, 20.2
San Luis Valley	5	12,170	6.8	2.2, 15.8
Western slope	79	80,346	16.4	13.1, 20.5
Mountains	26	27,469	15.8	10.3, 23.2
Total	738	808,950	15.2	14.1, 16.3

$\chi^2_4 = 3.91$, $P = 0.42$.
*Sixty-two subjects with unknown region at onset were distributed like 573 subjects with known region at onset.
†Population estimates based on U.S. Census Bureau, 1 April 1980 county estimates, age 0–17 yr.

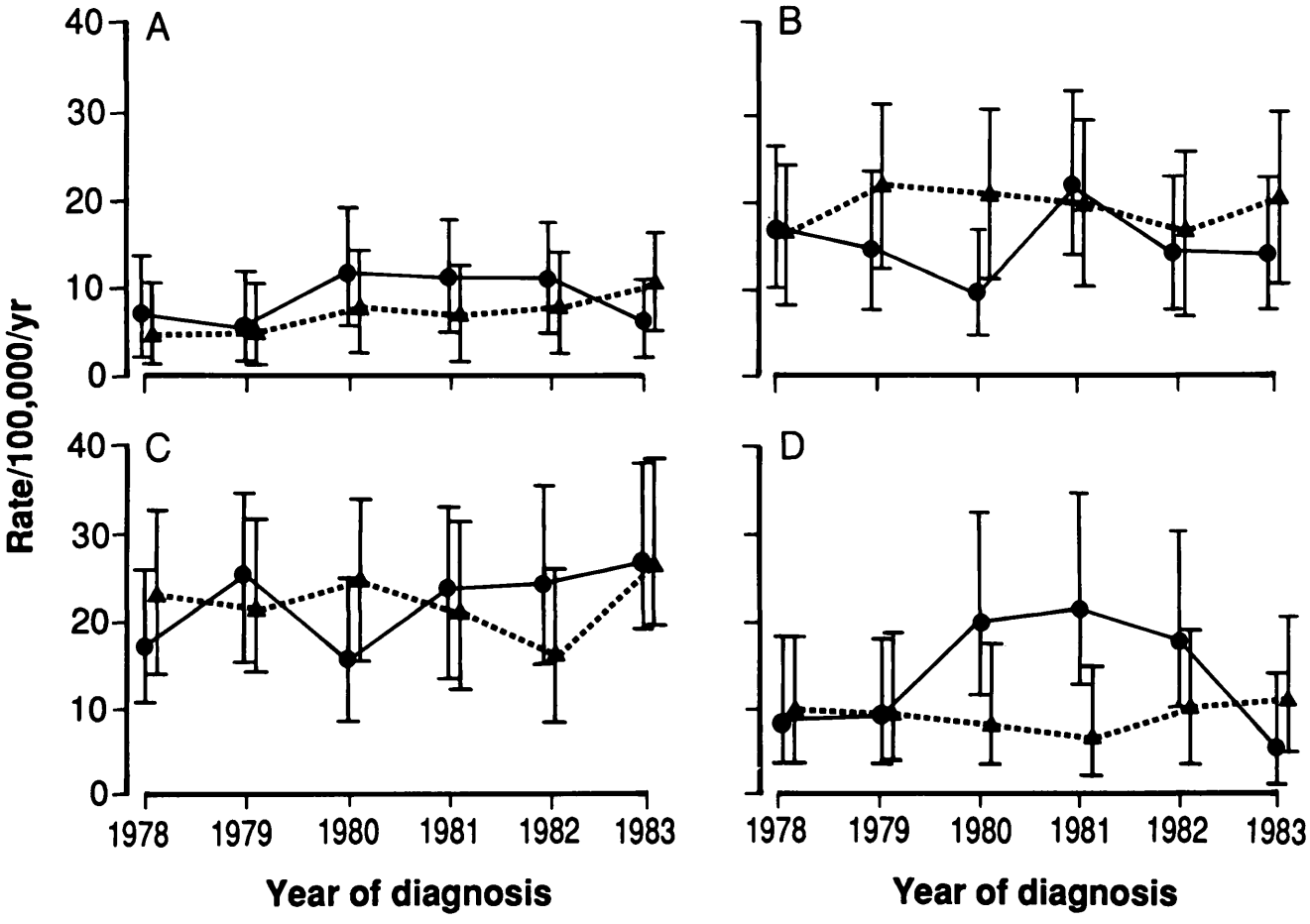

FIG. 2. Average annual incidence of insulin-dependent diabetes mellitus per 100,000 by age-group (0–4 yr, *A*; 5–9 yr, *B*; 10–14 yr, *C*; 15–17 yr, *D*), sex (●, male; ▲, female), and year of clinical diagnosis in Colorado, 1978–1983. *Bars*, 95% Poisson confidence intervals.

an epidemic for this subgroup, so caution is required in interpretation. Reports of short-term increases in incidence rates have occurred more often as additional registries examine onset patterns. Possible outbreaks have been reported from Florida (23), Poland (24), Scotland (25), Finland (26), and Sweden (27). Data from New Zealand (28), Pittsburgh (29), Norway (30), and England (31) suggested increases in incidence up to 1982–1985.

Colorado data encompass only 6 yr, so examination of temporal trends has limited power. No statistically significant increase in rates over this time span was found. Examination of rates over the next 5–10 yr will be more informative. Comparison of temporal trends from other registries have been presented (29–32). There is evidence of a longer term temporal increase in incidence in northern Europe, although not in France (3). There are limited amounts of older data with which to make long-term comparisons such as these. The only U.S. study to suggest such an increase may have had differential case ascertainment over time (33).

The onset of IDDM is distinctly seasonal, although the variability is not large. We noted a peak from November to February and a weaker one in midsummer, with no differences between males and females or Hispanics and non-Hispanic Whites (8). Seasonal patterns suggest that the environment influences either onset or etiology but they provide little help with tests of specific hypotheses about individual agents.

We examined regional differences to determine whether rural subjects had different patterns of risk. There were few differences across the state, except for lower rates in the heavily Hispanic San Luis Valley. These data, although ecological, lend little support to a hypothesis that etiologic factors differ in urban versus rural locations in Colorado. A nonsignificant excess in urban areas was noted in Wisconsin (20), and a significant excess prevalence was reported in urban Tasmania (34). In contrast, regional variation in incidence was reported to be higher in rural areas of Scotland (35). The underlying hypotheses being indirectly examined include *1*) population density (and thereby a transmissible agent hypothesis); *2*) exposures associated with rural life, i.e., chemical or animal viral exposures or dietary differences; and *3*) genetic differences. Care must be used in such ecological comparisons, given the marked differences between populations in the regions examined in these countries.

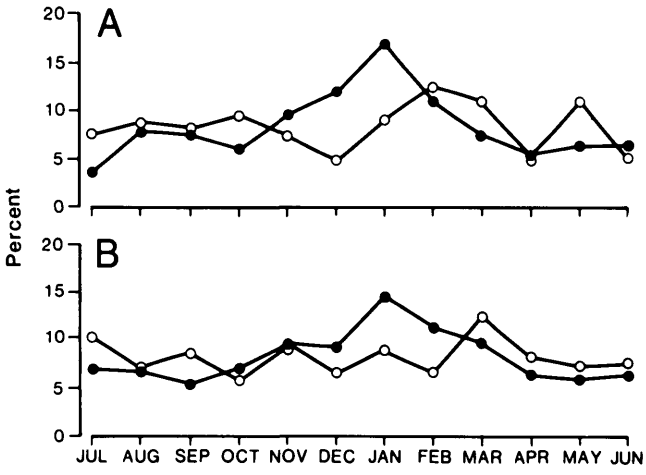

FIG. 3. Percentage of cases identified by month of clinical onset, sex (male, *A*; female, *B*), and age-group (●, 10–17 yr; ○, 0–9 yr) for subjects aged 0–17 yr at onset in Colorado, 1978–1983.

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APPENDIX: CALCULATIONS FOR CAPTURE-RECAPTURE METHOD

The determination of completeness of case ascertainment was performed as follows (9). Assume two sources of cases, i.e., physician and hospital reporting. It must be assumed that cases have an equal probability of being identified in each source. There were subjects who were not hospitalized at onset but had an equal chance of having a subsequent hospitalization as did subjects hospitalized at onset, and therefore an equal chance of being identified in validation. These cases can be represented as

		Reported by physician (method 1)	
		Yes	No
Found at hospital (method 2)	Yes	*a*	*b*
	No	*c*	*x*

where x is the number of cases not found by either method (unknown) and $N = a + b + c + x$, then

$$\begin{aligned}
\Pr(\text{not 1 + not 2}) &= x/N \approx [1 - \Pr(1)][1 - \Pr(2)] \\
x/N &= [1 - (a + c)/N][1 - (a + b)/N] \\
&= [(a + b + c + x)/N - (a + b)/N] \\
&\quad \times [(a + b + c + x)/N - (a + c)/N] \\
&= [(c + x)/N][(b + x)/N] \\
&= [(b + x)(c + x)/N^2] \\
x &= [(b + x)(c + x)/N] \\
xN &= x^2 + bx + cx + bc \\
0 &= x^2 + bx + cx + bc - xN \\
&= x(x + b + c - N) + bc \\
bc &= x(N - b - c - x) \\
bc &= x(a) \\
x &= bc/a
\end{aligned}$$

The completeness of methods 1 and 2 = $(a + b + c)/N$. Because N is unknown due to x being unknown, we can substitute for x

$$(a + b + c)/(a + b + c + bc/a)$$

then the completeness of ascertainment = $a(a + b + c)/(a + c)(b + a)$.

For this analysis there were 738 subjects. Thus, a = 428, b = 190, c = 120, and completeness = 0.932. Measured crude rate = 15.2/100,000 per year, and estimated rate = (15.2/100,000 per year)/0.932 = 16.3/100,000 per year. Pr, probability; not 1, not in method 1; not 2, not in method 2.

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