ade of CCK's action will not retard the development of morphine tolerance, the problem of tolerance may be mitigated by a reduction in the total amount of morphine needed to alleviate pain.

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7. The CCK receptor antagonists currently available are dibutyryl cyclic guanosine 5′-monophosphate [S. R. Peikin, C. L. Costenbader, J. D. Gardner, *J. Biol. Chem.* **254**, 5321 (1979)], benzocript, and proglumide [W. F. Hahne, R. T. Jensen, G. F. Lemp, J. D. Gardner, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 6304 (1981)]. Although these substances antagonize CCK receptors in pancreatic acinar cells, such receptors have been shown to be distinct from those in the brain [R. B. Innis and S. H. Snyder, *ibid.* **77**, 6917 (1980)]. While proglumide has been reported to inhibit the neuroexcitatory effects of CCK octapeptide on A10 dopaminergic neurons [L. A. Chiodo and B. S. Bunney, *Science* **219**, 1449 (1983)] and to potentiate morphine analgesia [J. Tang, J. Chou, M. J. Iadarola, H.-Y. T. Yang, E. Costa, *Soc. Neurosci. Abstr.* **9**, 288 (1983)], its mechanism of action is not known. N. D. Bui and M. Deschodt-Lanckman [*Arch. Int. Physiol. Biochim.* **90**, B5 (1982)] reported that the effect of proglumide on the activity of a CCK octapeptide–degrading brain aminopeptidase is not due to CCK receptor occupancy. Furthermore, it was recently reported that proglumide does not inhibit binding of [^{3}H]pentagastrin or [^{125}I]CCK octapeptide to brain CCK receptors [P. Gaudreau, R. Quirion, S. St.-Pierre, C. B. Pert, *Peptides* **4**, 755 (1984); R. Murphy, paper presented at the International Symposium on Endocoids, Fort Worth, 1984].
8. Because of the uncertainty of the mode of action and the specificity of pancreatic CCK receptor antagonists on other CCK receptors, including vagal CCK receptors, we chose to assess the function of endogenous CCK by sequestering peripherally circulating CCK with antibodies to this peptide. This method of antagonizing CCK action has been successful in studying the satiety-producing effects of CCK [C. A. Baile, C. L. McLaughlin, F. C. Buonomo, M. C. Boy, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **42** 392 (1983)]. In addition, we recently found that immunization against β-endorphin strongly antagonizes morphine analgesia. Compared to control values, analgesia in animals so immunized was reduced 24 percent ($P < 0.003$, paired *t*-test) and 29 percent ($P < 0.004$) 60 and 90 minutes after administration of morphine sulfate (10 mg/kg) (P. L. Faris *et al.*, in preparation). This finding supports the use of autoimmunization as an effective method for assessing the involvement of peripheral peptides in the modulation of nociception.
9. The BSA-immunized group controls for the antibodies developed in the CCK-immunized group against BSA as well as for a general stress effect of the immunization procedure.
10. Samples (10 μl) of serum from the tail vein or cerebrospinal fluid from the cisterna magna were incubated in Veronal buffer (*p*H 8.5) with [^{125}I]CCK octapeptide (10,000 count/min; New England Nuclear) for 48 hours. Bound radioactivity was precipitated with goat antibody to rat immunoglobulin G. Specific binding was calculated by subtracting nonspecific binding (that measured in normal rat serum) from total binding. The normal concentration of circulating CCK in rat is not known. However, resting values for dogs and humans are approximately 64 and 26 pg/ml, respectively [G. M. Fried *et al.*, *Gastroenterology* **85**, 1113 (1983); P. N. Maton, A. C. Selden, V. S. Chadwick, *Regul. Peptides* **4**, 251 (1982)]. Thus it is likely that the binding capacity of serum from our experimental animals (~50 pg/ml) was high enough to sequester a large percentage of the endogenously released CCK. It is also important to note that serum from our CCK-immunized rats could not have bound morphine, since this would have resulted in a decrease in free morphine and hence a decrease in analgesia rather than the observed potentiation.
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Incidence of Low Birth Weight Among Love Canal Residents

Abstract. *The incidence of low birth weight among white live-born infants from 1940 through 1978 was studied in various sections of the Love Canal. A statistically significant excess was found in the historic swale area from 1940 through 1953, the period when various chemicals were dumped in this disposal site. Potential confounding factors such as medical-therapeutic histories, smoking, education, maternal age, birth order, length of gestation, and urban-rural difference did not appear to account for this observation. Low birth weight rates were comparable to those of upstate New York from 1954 through 1978, the period when there was no deposition of chemical wastes.*

Concern about adverse health effects that might be associated with hazardous chemicals dumped at sites such as the Love Canal has been growing. Over 200 chemicals have been found in the Love Canal dump site (*1*) and many, such as benzene (*2*) and lindane (*3*), have been shown to have toxic effects on man in industrial settings. The spectrum of human hazards that might be associated with other compounds isolated in the canal, such as certain isomers of dioxin (*4*), is not known.

Two major difficulties encountered in designing epidemiologic studies of chronic diseases in multichemical settings are the uncertainty in selecting appropriate end points and the long induction period between exposure and clinical diagnosis. Certain adverse reproductive events, however—low birth weight is an example—are objectively identifiable in a relatively short period of time. We analyzed data on the incidence of low birth weight among infants born in the Love Canal area from 1940 through 1978. This time span includes periods of active dumping at the site (1940 through 1953) and no formal dumping (1954 through 1978).

The study population included all people residing in single-family houses located in a series of parallel streets (97th Street through 103rd Street), bounded on the north and south respectively by two avenues (Colvin and Frontier) (*5*). Backyards of 99 houses on 97th and 99th streets directly abut the canal.

Because there are no historical environmental data on houses in the study area, we had to infer which subsets of the study population might have maximum exposure to chemicals. We reasoned that one group might be the families who lived on 97th and 99th streets directly adjacent to the chemical dump site. The accumulation of rain and ground water, facilitated by either natural or man-made activity, could have raised the level of chemical wastes to the topsoil layer, thus facilitating lateral migration. This slowly overflowing bathtub effect could result in the transport of waste products to adjacent backyards and basements.

Another possibility was that certain chemicals in the dump site might have spread preferentially to houses located on the natural drainage pathways in the area. Before the development of housing in this area, a number of natural shallow depressions traversed the area, some of

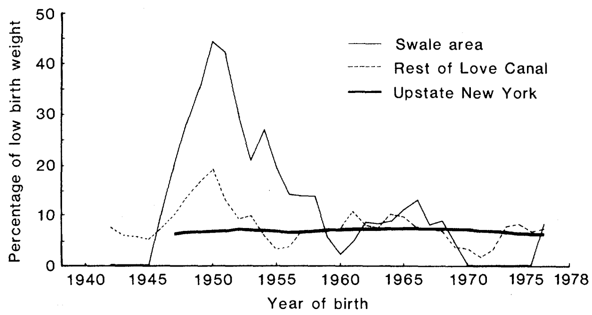

Fig. 1. The 5-year moving averages for percentages of low birth weights among infants born in the Love Canal swale area (n = 174), the rest of the Love Canal area (n = 443), and upstate New York.

which intersected the Love Canal itself. The locations of these depressions, commonly referred to as swales, were determined from aerial photographs taken in 1938, 1951, and 1966. The photographs were independently interpreted by a group at the Cornell University School of Civil and Environmental Engineering who had no knowledge of the hypotheses being tested. These depressions served as drainage ways and produced ponding in certain sections during times of high water. Additional verification of historical drainage pathways was obtained from interviews with area residents and review of their photographs and motion pictures. As the area was developed, the contour and extent of these swales was substantially modified. By 1956, the major swale which intersected the upper section of the canal was eliminated. The identification of houses located on these natural depressions was established from serial aerial photographs taken between 1938 and 1966. Still another possibility was that residents in the entire study area might have been exposed to toxic vapors emanating from the dump site. Accordingly, we hypothesized that there was an excessive incidence of low birth weight infants who were conceived and born in each of these areas.

In an effort to identify and interview all individuals who resided in the study area at any time from 1940 through June 1978, the following sources were used: a review of all property records on file at the assessor's office in Niagara Falls, New York; city directories for all available years in the study period; calls to hot lines indicating individuals with prior residency in the area; and residents identified by those who lived in the area and were interviewed in 1978. Birth files from vital records at the New York State Department of Health were searched manually for all surnames identified through these sources, for the years 1940 through 1978. In addition, all available computerized vital record birth files (1958 through 1978) were surveyed to identify live births in the study area as a check on the other data. No additional births were found for the period. With use of a prepared questionnaire, adult residents (18 years of age and older) were interviewed about past medical, therapeutic, social (smoking, alcohol, and educational), and occupational histories. Pregnancy histories were obtained from all females. The same field investigators conducted the interviews throughout the study.

Of the 1295 adult females who were identified as having resided in the study area, 1201 (92.7 percent) were located and interviewed. Forty-one (3.2 percent) were located but refused to be interviewed, and 53 (4.1 percent) could not be located. There were 383 women who had a total of 617 children [612 (99 percent) white, 4 black, and 1 American Indian] born alive in the study area from January 1940 through June 1978. They had resided in the area an average of 11.0 years (range 1 to 30 years) during their reproductive period (15 through 44 years of age). Birth certificate information for all infants born to women who had lived in the area for at least 9 months before the time of the birth of the child was obtained from the State's Bureau of Vital Records. The address was reviewed and the birth weight shown on the certificate recorded. If the resident address on the birth certificate was not a study area address, the birth was not considered in the analysis. Infants who weighed 2500 g (5 pounds, 8 ounces) or less were considered low birth weight children.

The proportion of low birth weight infants among all live births was established for the entire study area, the swale area, and the area abutting the canal. The average proportion of all white infants of 2500 g or less at birth for upstate New York (that is, New York State, excluding New York City) from 1945 through 1978 (*6*) (5,088,556 live births, 351,682 $\leq$ 2500 g, 6.9 percent low birth weight) was used in comparisons to indicate whether there was an excess of low birth weight children in the various study areas. As another comparison, the proportion of low birth weight white children for all cities of population 25,000 or greater (1970 census) in upstate New York from 1953 through 1978 (*7*) was calculated (1,043,066 live births, 80,938 $\leq$ 2500 g, 7.8 percent low birth weight). Sex ratios (male rate divided by female rate) were calculated for each Love Canal study area, for upstate, and for the urban group. Binomial probabilities of the observed number or more of low birth weight children were established for each study area on the basis of these rates. Probabilities of differences between areas within the canal were also established by the normal approximation of the difference between two proportions (z test, one-tailed). This was also done for differences when smoking history of mothers and household education (highest number of years of school completed by either parent) were considered. An examination of the past medical, therapeutic, social, and occupational histories of adult females with live births did not reveal any unusual patterns, such as radiation therapy or known infection during pregnancy, in any of the areas studied.

The expected number of low birth

Table 1. Total live births and children born with low birth weights in the swale area compared with the rest of the Love Canal (that is abutting the canal and nonswale) and by the known smoking and educational histories. The P values are based on one-tailed z tests for two proportions. Numbers in parentheses are percentages.

History	Number of births: Swale, Live	Swale, Low birth weight	Rest of canal, Live	Rest of canal, Low birth weight	P
All live births	174	21 (12.1)	443	32 (7.2)	0.027
Smoking					
Never smoked	70	7 (10.0)	174	7 (4.0)	0.035
Smoked	102	13 (12.7)	265	25 (9.4)	0.175
Household education					
<12 years	41	6 (14.6)	105	3 (2.9)	0.004
12 to 15 years	124	14 (11.3)	285	24 (8.4)	0.179
≥16 years	7	1 (14.3)	44	0 (0.0)	

weight children by age of mother was determined from the proportion of low weight children in each age group in upstate New York and the number of live births by age of mother in each area. The probabilities of the differences were calculated (χ^2 test). The same analyses were done for birth order. Gestational age (under 37 weeks) of low birth weight children was examined for each area and for upstate New York. Finally, temporal trends in each study area were evaluated by calculating 5-year moving averages of the percentage of low birth weight children by year of birth.

Among the 617 children born in the entire study area, 53 (8.6 percent) had low birth weights. In the houses abutting the canal, there were 124 live births with 8 (6.5 percent) low birth weight infants, and among the 174 live born infants in the swale area, 21 (12.1 percent) had low birth weights.

The binomial probabilities of the numbers of low birth weight children observed for the entire study area as well as for the area abutting the canal were within chance variation ($P > 0.05$ for all) when compared with upstate New York or the urban areas. The χ^2 probabilities of the distributions by maternal age and by birth order when compared with upstate New York were also within chance variation ($P > 0.05$ for both). However, the number of low birth weight infants born in the swale area was significantly more than both upstate New York (binomial, $P = 0.009$) and the urban area group (binomial, $P = 0.029$) (*8*). When the data were analyzed by age of mother and by birth order, the number observed in this area was also significantly more than upstate New York for each [respectively, $\chi^2(1) = 7.0514$, $P = 0.008$; $\chi^2(1) = 6.7438$, $P = 0.009$].

Swale area residents had significantly more low weight children than did the residents of the rest of the canal ($P = 0.027$) (Table 1). This was also true among women who had never smoked ($P = 0.035$). Results for educational level are also shown in Table 1. The proportions of low birth weight children for whom gestational periods were under 37 weeks were similar in the swale area and the rest of the canal: 52.4 and 53.1 percent, respectively. The percentages in both areas were consistent with that of upstate New York (48.9 percent) ($P > 0.05$ for both).

The sex distributions for all live births and low birth weight children in the swale area and the rest of the canal were all within chance variation (z test, two-tailed, $P > 0.05$ for each) when compared to those of upstate New York and the urban areas. The average length of residence for all women with live births was 10.8 years for the swale area and 10.3 years for the rest of the canal. For women who had a low weight child the averages were 10.9 years for swale area residents and 11.4 years for residents of the rest of the canal. For those without a low weight child the average residence was 10.8 years for swale residents and 10.2 years for the rest of the Canal. None of the differences between areas, or within area by weight of child, was statistically significant ($P > 0.05$ for all).

The 5-year moving average of the percentage of low birth weights indicated that in the swale area there was a marked excess of these births starting in 1946 and ending in 1958 (Fig. 1), peaking in 1950 (8 of 18 infants, 44.4 percent). The rest of the canal area also showed a peak in 1950, but the magnitude was not as large (4 of 21 infants, 19.0 percent) and the time span, 1947 to 1953, was shorter. For the period of active dumping (that is, prior to 1954), the swale area's percentage of low weight births was higher than in upstate New York (z test, $P < 0.0001$) and the rest of the canal (z test, $P < 0.012$). Low birth weights in the rest of the canal were not significantly higher than in upstate New York ($P > 0.05$).

It is important to emphasize that the low birth weight data used for all analyses were obtained from birth records and not through interview. There are several major difficulties in study design that limit the interpretation of results. It is not certain that all infants born in the area during the study period were included in this investigation. Although it is clear that human exposure to a specific toxic agent can result in an adverse reproductive outcome (*9, 10*), it is exceedingly difficult to define exposure in multichemical settings such as the Love Canal. In addition, the evidence associating low birth weight with toxic chemical exposure is limited (*11*). Other variables, for which there are no objective data, can influence the frequency of the end point. Although we found no convincing evidence that educational level, smoking, occupation, past medical or therapeutic histories influenced the results, most of these data were obtained from interviews and are, therefore, subject to recall bias. In addition, it was impossible to examine other important variables such as alcohol ingestion before and during the pregnancies included in this study.

Despite these limitations, our findings suggest that a real excess of low birth weights occurred in the swale area during a time period when there was active dumping at the Love Canal. Whether other objective health end points, such as congenital defects, will show similar results is not yet known. In any event, our study also suggests that infants born alive in the Love Canal study area between 1960 and 1978 were at no greater risk of low birth weight than were those born in upstate New York.

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8. Stillbirths were excluded from our analysis because there were only a total of seven among residents of the Love Canal area during the study period. Four were born to residents of the swale area of which two were low birth weight. Of the three born to residents of the rest of the canal, one was low birth weight, one was not, and the status of the third was not known. In order to determine whether their exclusion could significantly distort the frequency of low birth weight infants in one or more of the study areas, we analyzed total births (including stillbirths) and found that our findings were not altered ($P = 0.008$ for the period of active dumping in the historical swale area compared to the rest of the canal).
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