AN OUTBREAK OF THYROTOXICOSIS CAUSED BY THE CONSUMPTION OF BOVINE THYROID GLAND IN GROUND BEEF

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Abstract We report an outbreak of thyrotoxicosis without true hyperthyroidism that occurred between April 1984 and August 1985 among residents of southwestern Minnesota and adjacent areas of South Dakota and Iowa. One hundred twenty-one cases were identified through surveillance of medical clinics, laboratories, hospitals, and physicians' offices. Investigation of the outbreak demonstrated an association between the occurrence of thyrotoxicosis and the consumption of ground beef prepared from neck trimmings processed by a single slaughtering plant (odds ratio, 19.0; P = 0.0001). The cause was confirmed by the findings of bovine thyroid tissue in samples of these trimmings and high concentrations of thyroid hormone in implicated samples of ground beef and the demonstration of prompt increases in serum thyroid hormone concentrations in volunteers who ate the implicated ground beef.

Bovine thyroid tissue had been introduced into the neck trimmings inadvertently during the process of "gullet trimming," a procedure that harvests muscles from the bovine larynx. The outbreak resolved after this procedure was discontinued at the plant. The clinical features of the illness suggested the diagnosis of silent thyroiditis, and it is possible that sporadic cases — or even outbreaks — of thyrotoxicosis factitia caused by this mechanism may have occurred in the past but were not recognized. (N Engl J Med 1987; 316:993-8.)

OUTBREAKS of thyrotoxicosis, the clinical syndrome associated with thyroid hormone excess, have been identified as resulting from iodide supplementation in populations with iodine-deficient goiter (jodbasedow disease).[1,2] The cause of a nationwide epidemic of thyrotoxicosis that occurred in Denmark during World War II remains obscure,[3] whereas an outbreak in Poland was apparently associated with consumption of sausage that contained porcine thyroid tissue.[4] Between January and March 1984, an outbreak of thyrotoxicosis occurred in York County, Nebraska,[5] where 54 cases were documented. The initial report of this outbreak identified no common vehicle of transmission or etiologic agent.

We report the results of studies that revealed the cause of an outbreak of thyrotoxicosis that occurred in adjacent areas of Minnesota, South Dakota, and Iowa between April 1984 and August 1985. This outbreak was initially reported to public health authorities by one of us (J.M.M.), who recognized similarities between cases in the York County outbreak and several cases of "painless thyroiditis" in a South Dakota community with a population of 808. The patients in South Dakota had onset of illness between February and April 1985. Preliminary investigations in June 1985 revealed additional cases of a similar illness in nearby Minnesota communities.

We found that thyrotoxicosis was associated with the consumption of ground beef prepared from neck trimmings processed at a single slaughtering plant (Plant A). The trimmings contained bovine thyroid gland that was inadvertently harvested along with muscle from the larynx during a process called "gullet trimming." Hence, this investigation provided information that identified a common vehicle and confirmed the etiologic agent of this community outbreak of thyrotoxicosis, brought an end to the outbreak in the area, and resulted in the promulgation by the U.S. Department of Agriculture (USDA) of regulations that should prevent the occurrence of similar illness in the future.

METHODS

Case Surveillance

A case was defined as an illness characterized by the presence of one or more values for serum total thyroxine (T_4), free T_4, or triiodothyronine (T_3) that were at least 25 percent higher than the upper limit of normal in the laboratory in which the test was performed, and two or more of the following symptoms: sleeplessness, nervousness, headaches, increased heart rate or palpitations, shortness of breath, fatigue, excessive sweating, tremor, hyperdefecation, heat intolerance, or weight loss. Patients were excluded if they had Graves' disease or if they had received thyroid hormone replacement therapy during the two months before diagnosis. Analyses for T_4, free T_4, and T_3 concentrations were performed by radioimmunoassay in local laboratories using commercial kits.

To identify patients who sought medical attention and who met the case definition and to determine the geographic distribution of the outbreak, we conducted the following surveys. Patient records from the medical clinics in the five referral communities in southwestern Minnesota, southeastern South Dakota, and northwestern Iowa were reviewed for the period February 1984 through July

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Supported in part by research grants (AM-07302, AM-18919, and AM-18416) from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, the Veterans Administration Medical Research Service, and the Joseph and Dorothy Benotti Iodine Research Fund.

Presented in part at the annual meeting of the Association of American Physicians, May 3–5, 1986, Washington, D.C.

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1985. A second record review was conducted in the same clinics for the period August through October 1985, after the cause of the outbreak had been identified and control measures instituted. Records pertaining to studies of thyroid radioactive-iodine uptake in the four departments of nuclear medicine in the major referral community were screened. Elevated thyroid hormone values observed in specimens analyzed at a large referral laboratory in the outbreak area were identified and patients were contacted. Physicians in eight counties in southwestern Minnesota and two in Iowa were surveyed by telephone and questioned about the occurrence of thyrotoxicosis in their patients between February and July 1985. In addition, all physicians in South Dakota and southwestern Minnesota were sent a letter describing the outbreak and requesting them to report suspected cases to their respective state health departments.

After the completion of two case–control studies and the identification of the cause of the outbreak, all persons whose illness met the case definition were interviewed again to determine their possible exposure to ground beef made from the implicated beef trimmings and the nature and duration of their symptoms. Subsequently, patients were considered to have had outbreak-associated cases if they recalled consuming ground beef prepared from neck trimmings processed at Plant A at the time of their illness.

Case–Control Studies

Two case–control studies were performed — the first between July 15 and August 1 and the second between August 4 and 12, 1985.

Case–Control Study I was initiated after our case surveillance had defined the approximate temporal and geographic boundaries of the outbreak. Patients were selected for the study if their illnesses fulfilled the case definition and if they had experienced onset of symptoms between February and July 1985. In households with more than one patient, only the family member with the earliest onset of symptoms was included in the study. The first 44 patients identified who met the study criteria were enrolled.

Control subjects were randomly selected from local telephone directories and were matched to cases according to the following criteria: the same sex and telephone exchange, and age within 10 years of the corresponding patient when the patient was 30 years old or older, and within 5 years when the patient was under 30.

Interviews were conducted in the homes of the patients and control subjects by investigators from the Minnesota and South Dakota Departments of Health and the Centers for Disease Control. All household members were interviewed. Information collected included the following: age; sex; occupation; recent illness; history of thyroid or other endocrine disorders; recent travel; exposure to animals; source and frequency of consumption of water, food, and beverages; and the use of diet pills, other medications, alcohol, and tobacco. Serum was collected from patients, control subjects, and family members of both groups whenever possible.

The results of Case–Control Study I suggested that the consumption of selected meat or poultry products was associated with illness. Therefore, Case–Control Study II was performed to define further the consumption of meat and poultry by patients and control subjects and to determine the sources of these products. In addition, managers of grocery stores where the patients and control subjects had purchased meat and poultry products were surveyed to determine the production source from which these foods had been obtained. If a grocery store had purchased products from a regional distributor, the distributor was contacted to identify the production source.

Data from the case–control studies were analyzed by standard univariate and multivariate methods.[6-8]

Investigations at Plant A

Two days after the recall of the implicated meat, 124 of 258 employees of Plant A were interviewed to determine whether they had purchased or consumed any of the meat processed at the plant and whether they had experienced symptoms compatible with thyrotoxicosis. Serum specimens were obtained both at the time of the interview and one week later, when the employees were interviewed again. Serum samples were analyzed for T_4 and the free T_4 index (the product of the serum T_4 concentration and the resin T_3 uptake).

Two 29-kg boxes of beef trimmings from Plant A and samples of ground beef derived from neck trimmings from Plant A were obtained from a local grocery store and examined visually and microscopically for the presence of thyroid tissue before the recall of the implicated meat. Subsequently, the proportion by weight of thyroid tissue was determined in 22 boxes (29 kg each) of beef trimmings produced at Plant A before the recall, and 4 boxes produced afterward were quantitatively examined for bovine thyroid tissue.

Operational procedures employed at Plant A during the three years before the investigation were reviewed with plant officials and line employees.

Concentration and Bioavailability of Hormones in Ground Beef

We obtained ground-beef samples prepared from the implicated trimmings that had been returned to Plant A by patients, employees, and grocery stores. In addition, ground-beef samples were collected from local grocery stores after the recall, from residents of the outbreak area who had had their own animals slaughtered on site, and from grocery stores in California, Georgia, Iowa, Massachusetts, Michigan, North Dakota, and South Dakota. These samples were analyzed for total iodine by the method of Benotti et al.[9] Concentrations of T_4 and T_3 in the ground beef were measured by a method previously used for the analysis of rat thyroids.[10]

With the approval of the Human Subjects Institutional Review Committee at the University of Massachusetts Medical School, test samples of the implicated ground beef were eaten by four normal adult volunteers. Before they were administered, all samples were cultured to exclude the presence of salmonella, shigella, and campylobacter. Well-cooked 227-g (0.5-lb) portions were eaten by the volunteers after they had fasted overnight. Blood samples for thyroid-related hormone analyses were obtained before ingestion and at 4, 8, 12, and 24 hours, as well as 2, 4, 7, 10, 14, 17, and 24 days, after ingestion. All samples were assayed in duplicate in the same assay run.

Results

Case Surveillance

A total of 121 outbreak-associated cases of thyrotoxicosis were identified through surveillance methods among residents of nine counties in Minnesota, South Dakota, and Iowa. The highest incidence (34 cases per 10,000 person-years) was found in the county where Plant A is located. The incidence in surrounding counties ranged from less than 1 to 12 per 10,000 person-years. Only two patients were identified in Sioux Falls, the major population center in the area, which is 40 km from the center of the outbreak. Onsets of illness occurred between April 1984 and August 1985 (Fig. 1). No patients whose illness began before April 1984 or after August 1985 were identified. The median age of the patients was 41 years (range, 5 to 84); 62 (51 percent) were male. The distribution of patients by age and sex is shown in Table 1.

Forty-one patients (34 percent) were examined for goiter by at least one of us (J.M.M., D.B.F., L.E.B., or S.H.I.); only three patients (7 percent), all of whom had a history of thyroid disease, had an enlarged thyroid gland. A review of the clinical records of the remaining patients revealed that a specific description of the thyroid was available for only 16 (20 percent), and in only 3 (19 percent) of them was the thyroid noted to be palpable or slightly enlarged.

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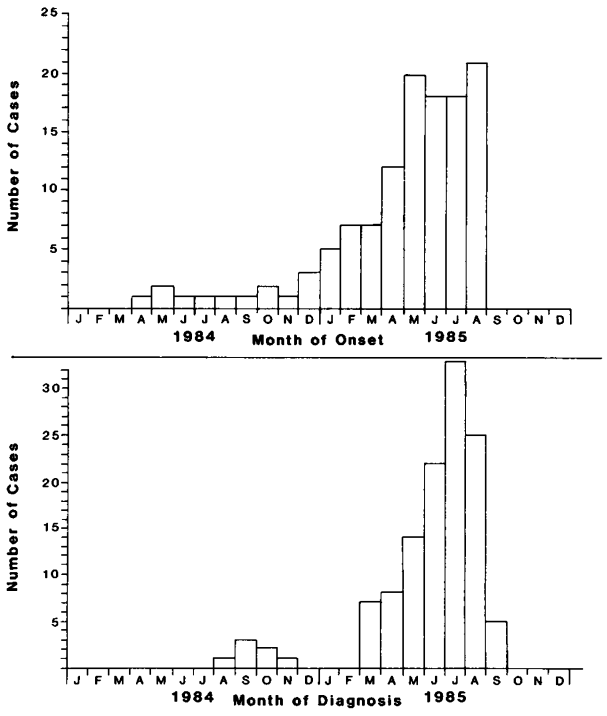

Figure 1. The Month of Onset of Symptoms and the Month of Diagnosis in 121 Cases of Thyrotoxicosis Factitia Due to the Ingestion of Ground Beef Containing Thyroid Tissue.

The thyroid 24-hour radioiodine uptake (normal range, 10 to 35 percent) had been measured in 25 patients (21 percent). The median value was 2 percent, and the value was less than 10 percent in 23 of the 25.

Case–Control Studies

Case–Control Study I revealed that two factors were associated with illness — consumption of commercially processed chicken (odds ratio, 2.3; P = 0.03) and consumption of ground beef prepared from neck trimmings from Plant A (odds ratio, 1.9; P = 0.05). We were aware, however, that patients and control subjects had not been questioned uniformly about the production source of all beef and poultry they had consumed; therefore, Case–Control Study II was performed. The study participants were not aware of the results of Case–Control Study I when we conducted the second study.

In Case–Control Study II, we found that 32 patients (73 percent) and 14 control subjects (32 percent) recalled consuming ground-beef patties prepared from beef trimmings from Plant A (odds ratio, 19.0; P = 0.0001). However, patients and control subjects who had consumed ground beef prepared from trimmings processed at Plant A had eaten an average of 13 and 10 servings of the ground beef per month (P>0.2). Four patients (9 percent) and 15 control subjects (34 percent) had consumed ground beef prepared from privately slaughtered local animals (odds ratio, 0.08; P = 0.005). Consumption of meat products other than ground beef originating in Plant A was not associated with illness.

Multivariate analysis revealed no difference between patients and control subjects with respect to the consumption of other brands of ground beef, steak, roast beef, roast pork, sausages, or specific brands of chicken. Most patients (82 percent) and control subjects (70 percent) preferred to eat ground beef that was well cooked (P>0.2).

Investigations at Plant A

Sixty-five of the 124 employees of Plant A (52 percent) who were interviewed had consumed ground beef produced from the implicated trimmings in the 14 days before the first interview. Seven of these employees (11 percent) had a free T_4 index that was at least 25 percent above the upper normal limit of 9.5 (≥11.8), as compared with only 1 of the 59 employees (2 percent) who had not consumed the implicated ground beef (odds ratio, 7.0; P = 0.042). One week later, the free T_4 index was within normal limits in six of the seven exposed employees who had an initially elevated free T_4 index; a decrease in free T_4 index from 27.4 to 12.0 was observed in the remaining employee. Four of the seven employees experienced symptoms of thyrotoxicosis and were considered to have had outbreak-associated cases, whereas three remained asymptomatic. The one unexposed employee with an initially elevated free T_4 index continued to have an elevated free T_4 index in serum collected one and two weeks later. He was referred for consultation, was found to have an elevated radioactive-iodine uptake, and was treated for Graves' disease.

Two work shifts per day operated at Plant A, and approximately 800 animals were slaughtered and dressed during each shift. Before April 1983 thyroid glands were selectively removed and sold for use in the manufacture of thyroid extract. After that time, "gullet trimming" was employed to harvest muscle from the bovine larynx. In this procedure, the larynx was placed vertically on a peg 1 m above the floor. The sternothyroid and sternohyoid muscles were removed from the larynx with a downward slicing

Table 1. Age and Sex of 121 Patients with Thyrotoxicosis in Minnesota, South Dakota, and Iowa — February 1984 through September 1985.

Age	Male	Female	Total
yr	*no. of patients*		*no. (%)*
0–9	1	1	2 (2)
10–19	3	5	8 (7)
20–29	7	8	15 (12)
30–39	15	14	29 (24)
40–49	8	10	18 (15)
50–59	16	6	22 (18)
60–69	9	5	14 (12)
≥70	3	10	13 (11)
Total	62	59	121 (100)

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motion performed on both the left and right ventral surfaces. This motion allowed portions of both lobes of the thyroid gland to be inadvertently included in the muscle trimming. Since thyroid and muscle tissue harvested in this manner had similar colors and general appearance, close inspection was required to distinguish them. Although the process of gullet trimming was performed by a limited number of employees, the presence of thyroid tissue in the neck trimmings could not be attributed to any one employee.

In November 1984 two changes occurred in plant operations that may have contributed to the occurrence of the outbreak. First, the kosher killing operations were discontinued. Before this, one shift had used a kosher killing process exclusively. Employees indicated that the thyroid gland from animals killed in this manner was less likely to be included with the muscle during the trimming process, since the thyroids were pale after exsanguination.

The second change was that the work area in which the trimmings were produced was moved to the second floor. As a result, the trimmer allowed several gullets to accumulate while he tended to other responsibilities. The accumulated gullets were then trimmed rapidly, and the trimmings were added to a tub containing neck muscle. The tubs were then emptied, without additional mixing, into a chute from which boxes were filled on the first floor. This procedure resulted in great variability of thyroid content in each box. Among the 22 boxes of beef trimmings produced before the recall that were examined, thyroid tissue was found in all, and it constituted 0.04 percent (10 g) to 2.6 percent (715 g) of the total weight (27 kg) (mean, 0.8 percent, or 22.5 g). No thyroid tissue was found in four boxes produced after gullet trimming was discontinued. Thyroid tissue was also identified by gross examination in two boxes of beef trimmings from Plant A and by histologic examination in samples of ground beef that were obtained from a local grocery store before the recall of the implicated meat.

Concentration and Bioavailability of Hormones in Ground Beef

Ground beef from beef trimmings produced at Plant A before product recall and from households with a patient had significantly higher mean (±SD) concentrations of iodine (87.44±31.7 μg per gram; n = 20) than samples of ground beef also produced from Plant A neck trimmings but obtained from households without a patient (17.1±4.5 μg per gram; n = 22; $P<0.05$ by Student's two-tailed t-test). Sixteen samples of ground beef obtained from local grocery stores after the recall and from other areas of the country had undetectable iodine concentrations (<0.1 μg per gram).

Nine samples of implicated ground beef with a mean iodine concentration of 43.7±8.4 μg per gram had a mean T_4 concentration of 11.4±2.1 μg per gram and a mean T_3 concentration of 0.67±0.15 μg per gram. From these values, it can be calculated that an average 114-g (0.25-lb) hamburger would contain approximately 1300 μg of T_4 and 76 μg of T_3. These values can be compared with the average daily maintenance doses of T_4 (100 μg) or T_3 (50 μg) that are used in the treatment of myxedema. T_4 and T_3 were not detected in samples of ground beef obtained from other areas of the country.

The iodine concentration in the samples of implicated ground beef eaten by the human volunteers ranged from 24 to 66 μg per gram, with T_4 and T_3 concentrations ranging from 6 to 21 and 0.3 to 0.9 μg per gram. The T_4 and T_3 concentrations in the samples after they had been well cooked ranged from 9 to 27 and 0.7 to 1.7 μg per gram. Mean serum T_4 concentrations in the volunteers increased from a control value of 6.8±1.4 μg per deciliter to a peak value of 15.7±6.3 at 8 to 12 hours. The values then declined but did not reach normal levels until 7 to 10 days later. Mean serum T_3 concentrations increased from 168±19 ng per deciliter to a peak value of 573±140 at four to eight hours. Normal values were achieved 4 to 10 days later. Serum concentrations of thyroid-stimulating hormone averaged 2.4±0.9 μU per milliliter in control serum, decreased or became undetectable (<0.5 μU per milliliter) during the next 4 to 17 days, and then returned to base-line values. Findings in a typical volunteer are shown in Figure 2. All volunteers remained asymptomatic.

Discussion

The inadvertent introduction of thyroid gland into bovine neck trimmings produced at Plant A resulted in an unusual outbreak of thyrotoxicosis factitia. We confirmed this with the following five findings. First, Case–Control Study II revealed a significant association between consumption of ground beef prepared from the trimmings and the occurrence of illness. Second, after discontinuation of gullet trimming, ingestion of ground beef originating at Plant A was no longer associated with illness. Third, in plant employees who had recently consumed the implicated ground beef and who were found to have elevated serum free T_4 indexes, the values were in the normal range or substantially lower a week later. Fourth, our analyses revealed high concentrations of total iodine, T_4, and T_3 in ground beef prepared from gullet trimmings produced in Plant A but not in ground beef obtained from other widely dispersed areas of the country. Finally, volunteers who ate the implicated ground beef had marked, acute increases in serum T_4 and T_3 concentrations. Similar marked elevations in T_3 and T_4 concentrations and decreases in serum concentrations of thyroid-stimulating hormone were observed in rats fed raw implicated ground beef for two days (data not shown).

Three aspects of the operational procedures at Plant A may have contributed to the timing and severity of the outbreak. First, until April 1983 thyroid glands were collected specifically for use in the prepa-

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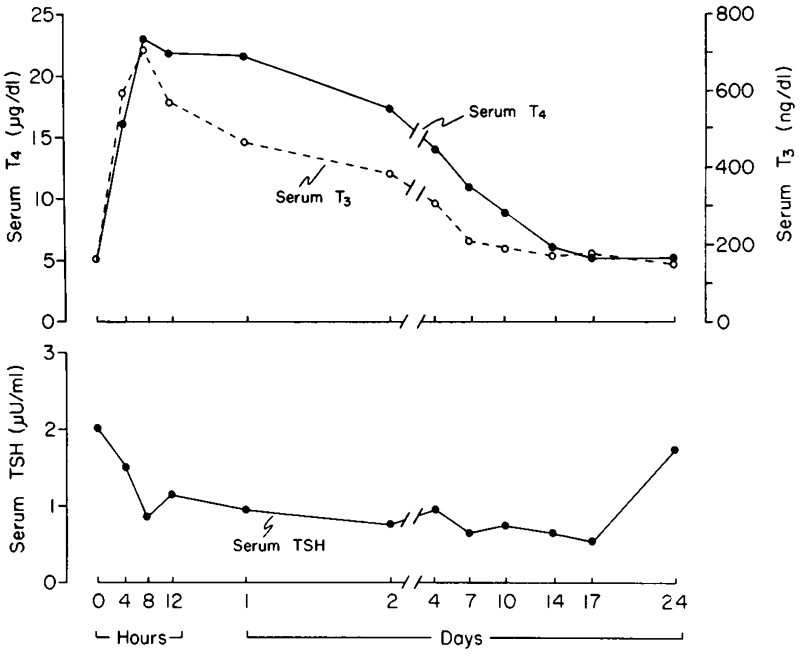

Figure 2. Serum Concentrations of T_4, T_3, and Thyroid-Stimulating Hormone (TSH) in a Normal Volunteer before and after the Ingestion of a Well-Cooked 227-g (0.5-lb) Hamburger Prepared from Ground Beef Obtained from the Freezer of a Patient.

Similar patterns of response were observed in three other normal volunteers who ate samples of the implicated ground beef.

ration of thyroid extracts. Second, in November 1984 the kosher killing process was discontinued. The third factor was the concomitant relocation of gullet trimming to the second floor of the plant. These changes probably resulted in the increased harvest of thyroid glands during gullet trimming and the increased variability of thyroid content in each box, leading to the presence of high concentrations of thyroid tissue in some boxes of neck trimmings. Therefore, the concentration of thyroid hormones in the ground beef consumed was significantly associated with the occurrence of illness, whereas the frequency of consumption of ground beef was not.

The prevalence of gullet trimming in all plants inspected by the USDA that slaughtered beef or pork before the present outbreak is unknown. However, owing to the low yield of muscles from the larynx, gullet trimming is only economically feasible in small slaughtering plants where the employees who perform this procedure are also able to accomplish other tasks. The absence of detectable iodine in a limited number of ground-beef samples obtained from other states and from areas in Minnesota not involved in the outbreak suggested that gullet trimming was not widespread and that among the approximately 2.04 billion kg (4.5 billion lb) of hamburger produced annually in the United States,[11] only a small proportion contained bovine thyroid.

Because many of the beef neck trimmings produced by Plant A were distributed and consumed locally, the cases of thyrotoxicosis were clustered geographically and temporally, and repeated and prolonged exposure of the population to ground beef that contained thyroid tissue occurred. These factors made detection of this outbreak and its cause possible. Until then, the possibility that physiologically important quantities of bovine thyroid gland may be present in ground beef was unappreciated. Had products of this type been distributed more widely than in this outbreak, the dispersed cases would have appeared sporadic and not related to a common source. Even in this investigation, our reliance on physician-based and clinic-based surveillance methods resulted in an underestimate of the total number of persons affected by this outbreak. The clinical features of these cases, particularly the absence of goiter and the low radioactive-iodine uptake, would have suggested the diagnosis of silent thyroiditis. Indeed, after recognition of the cause of this outbreak, a case–control study in York County, Nebraska, revealed an association between the occurrence of thyrotoxicosis during the 1984 outbreak and ingestion of ground beef purchased from a single supermarket (Kinney JS, et al.: unpublished data). Initially, the illness identified in this outbreak was ascribed to silent thyroiditis. Thus, it is likely that sporadic cases or even outbreaks of thyrotoxicosis factitia of the present type may have occurred but were not recognized.

On August 29, 1985, because of this investigation, the USDA issued a nationwide advisory that temporarily prohibited gullet trimming in all USDA-inspected plants that slaughter beef and pork. Permanent prohibition of the use of livestock glands, as well as the muscle tissue surrounding the larynx, in the preparation of edible meat products has been proposed by the USDA.[12] As a result of our investigation, this outbreak of thyrotoxicosis caused by the consumption of bovine thyroid in ground beef was stopped. With the USDA prohibition on gullet trimming, it is likely that potential cases of thyrotoxicosis caused by a similar mechanism will be prevented throughout the United States.

We are indebted to Dr. James Felker, who referred the index case; to the physicians and staff of the Luverne (Minn.) Medical Center, especially Drs. Larry E. Lyon, Paul D. Rud, Richard J. Morgan, and Darrel W. Siebert; to the physicians and staff of Doctors Plaza, Marshall, Minn., especially Drs. O.M. Odland and V.D. LaPorte; to Drs. Roland Beckering and L.A. Laikola, the physicians and staff of the Central Plains Clinic, Sioux Falls, and other physicians throughout southwestern Minnesota, South Dakota, and Iowa who assisted us; to Dr. Mary Jo Jaqua-Stewart, University of South

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Dakota; to Leonard T. Kurland, M.D., Mayo Clinic; to the staffs of the Nobles–Rock Community Health Services Agency, especially Ms. Bonnie Frederickson, P.H.N., and Ms. Georgia Entenza, P.H.N.; to Kenneth Senger, Terrance Dosch, and Linda Johnson, South Dakota State Department of Health; to Laverne Wintermeyer, M.D., and Russell Currier, D.V.M., Iowa Department of Health; to Thomas W. Masso, Howard J. Anderson, and George D. Myrha, Minnesota Department of Agriculture; to W.S. Horne, and Drs. R. Voltberg and R. Stahnke, U.S. Department of Agriculture; to the state departments of health in California, Georgia, Michigan, and North Dakota; to Mr. Sam Pino and Dr. Gary Doern, University of Massachusetts Medical Center; and to the staff of the Divisions of Disease Prevention and Health Promotion and the Center of Health Statistics, Minnesota Department of Health, especially Larry Edmonson, Jan Forfang, Joseph Mariotti, John Clare, Jack Korlath, Juanita Heiser, Terry Ristinen, Lynne Pierson, Brenda Carlson, Kyle Stenstrom, and Eugene Senger.

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