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Bulletin of the

University of Minnesota Hospitals
and
Minnesota Medical Foundation

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Infant Methemoglobinemia in Minnesota

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I. INFANT METHEMOGLOBINEMIA IN MINNESOTA*

Due to Nitrates in Well Water

A. B. Rosenfield
Roberta Huston

Introduction

It should be emphasized at the outset that this is not primarily a clinical study. Comparatively few infants were examined and none were treated by the State Health Department. The data were furnished by the attending physicians but many physicians were visited to obtain more complete information. Most of the field work, however, was devoted to the engineering aspects of the water supplies. This was basically a study of a public health problem. The study was inaugurated to determine whether methemoglobinemia due to nitrates in well water had occurred in the past, whether it was still occurring, its frequency and its distribution. In addition, information was desired as to the characteristic signs and symptoms, the diagnosis and the treatment, particularly the preventive treatment. This information was made available to all physicians so that they might more readily recognize this disease and more adequately treat it. Toward this end the services of a pediatric consultant were made available as well as certain laboratory procedures not readily available in the rural areas. This study was a joint undertaking by the Division of Maternal and Child Health interested in the infants, and by the Section of Environmental Sanitation concerned with the toxic chemical in the water; its concentration, its variations, its distribution, and in methods of reducing or eliminating the chemical-(nitrate)-from the water. The subject will therefore be discussed from these two aspects.

It has been known for some time that the ingestion or absorption of various drugs such as sulfonamides, nitrobenzene compounds, acetanilid, bismuth subnitrate, sulphates, nitrites, and chlorates is capable of producing a cellular type of methemoglobinemia.[1] This is the acquired type, in contrast to congenital idiopathic methemoglobinemia of which 15 proved cases have been reported.[2] When no toxic agent could be detected in the acquired type, it was usually spoken of as idiopathic cyanosis.

In 1940, Schwartz and Rector[3] reported a case of methemoglobinemia of unknown origin in a 2 weeks old infant living in Montana, fed on diluted evaporated milk formula, which was successfully treated with methylene blue solution. The physical examination was negative except for abnormal color of skin. The blood contained 57 per cent methemoglobin but the water used in the formula was not examined for nitrates. This may have been, however, a case of nitrate poisoning from well water, as such cases have since been reported in Montana.

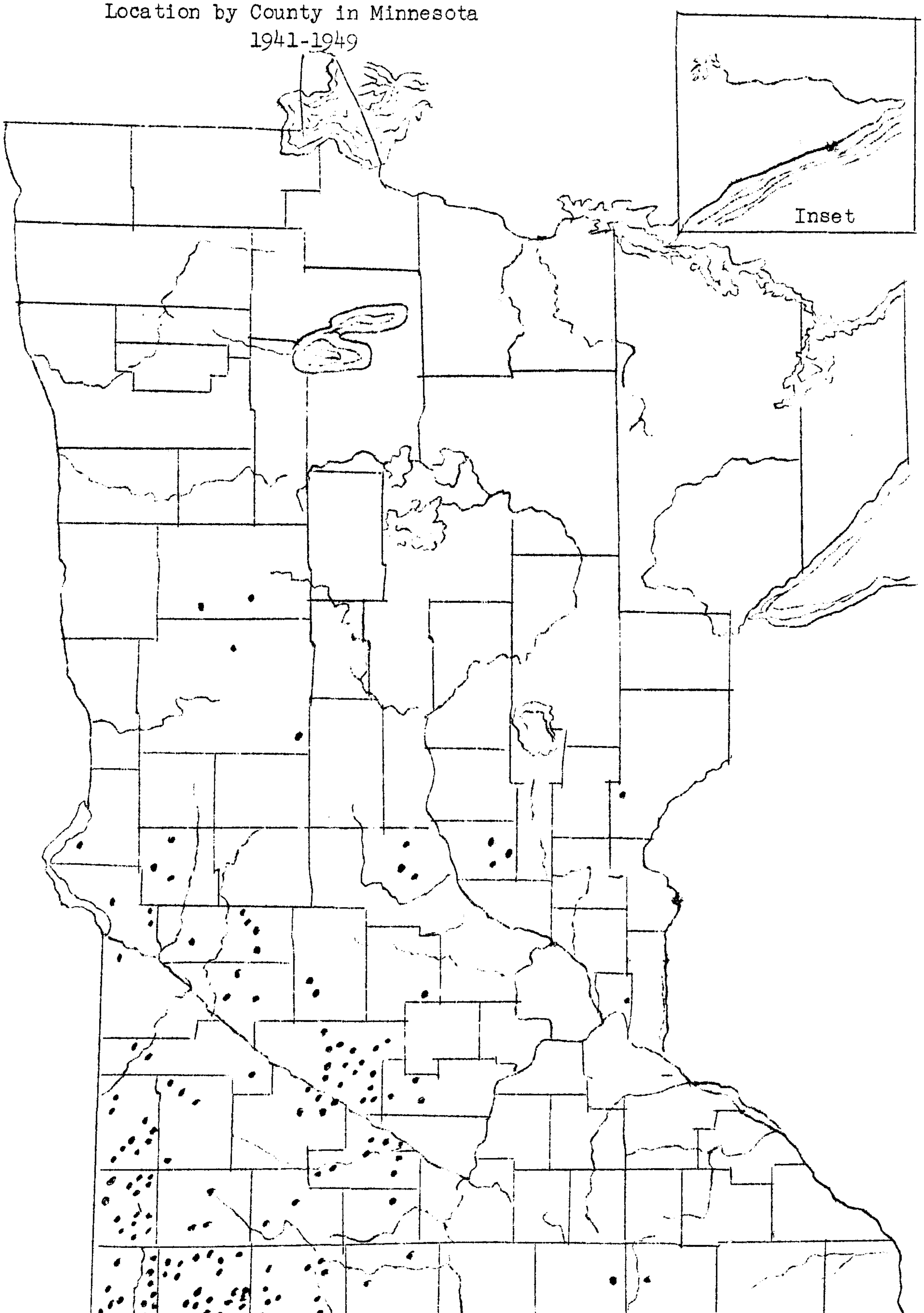
In 1945, Comly[4] discovered the etiologic factor in 2 Iowa infants about one month of age who probably would have been considered as cases of idiopathic cyanosis. Interestingly enough, the father of the first infant pointed out the answer by suggesting the possibility of a peculiar reaction between the well water and the soy bean preparation used in the formula, producing a poison which caused the infant's condition. An open-mindedness on the part of the admitting physician to what appeared to be a "cock and bull" theory led to analysis of the well water. This showed a high nitrate content and thus the etiologic factor was discovered.

Following Comly's report of 2 proved cases and 7 suspected cases from rural Iowa, Faucett and Miller[5] reported 3 cases in Kansas and Ferrant[6] reported 2 cases from Belgium. Since then, cases have been reported from rural Manitoba,[7,8] Ontario[8], and Saskatchewan,[9] Illinois,[10,11] Iowa,[12,13] Nebraska,[14,15] Michigan,[16,17] Kansas[18] and several other states. New York State reported its first 2 cases in July, 1949.[19] The condition, therefore, is apparently quite widespread in certain rural parts of the United States and

* Aided in Part by a Grant From the United States Children's Bureau.

METHEMOGLOBINEMIA CASES

Location by County in Minnesota
1941-1949



Map of Minnesota
State Dept. of Health

Figure 1

Canada.

PART I - MEDICAL ASPECTS

The first case of methemoglobinemia in Minnesota was reported in January 1947, by a physician at Tyler, in southern Minnesota. Since then, a total of 146 cases, including 14 deaths, have been voluntarily reported to the Minnesota Department of Health, since methemoglobinemia is not a reportable disease.

As physicians in Minnesota became more familiar with this condition, methemoglobinemia was considered more often in differential diagnosis as evidenced by requests for methemoglobin determinations in cyanotic infants as well as frequent requests for analysis of suspected farm wells. Doubtless, many mild cases which cleared up promptly were never reported. Familiarity with this condition by physicians as well as rural parents has apparently been responsible for a markedly decreasing incidence of reported cases in 1949, only 12 cases out of a 3 year total of 129 cases in 1947, 1948, and 1949. The last case was reported in July, 1949.

Distribution of Cases

Before discussing the findings, it might be well to point out the distribution of cases in this series. As can be seen from the spot map of Minnesota, Figure 1, practically all of the cases have occurred in the southern half of the state and most of them in southwestern Minnesota. There have been only 3 cases north of the midline of the state with Detroit Lakes, in Becker County, the most northerly reported case. No cases have been reported in the northern portion of the state.

Seasonal Incidence

The incidence of cases of methemoglobinemia varied from month to month. In 139 cases out of our 146 reported cases with reliable date of onset, the highest incidence occurred in June with 19 cases, October with 18 and April with 16 cases; the lowest number occurred in November with 6 cases. The 7 cases omitted above were seen by physicians between 1941 and 1946 before our study began which accounts for the lack of data. (Figure 2)

Table I

Occurrence of Methemoglobinemia in 129 Infants by Season of Year, Compared with Seasonal Occurrence of Births, Minnesota 1947, 1948 and 1949

Month of Occurrence	1947	1948	1949	Total	Per Cent	% of Births in Minnesota
Jan. - Mar.	13	8	9	30	23.2	25.0
Apr. - June	24	15	2	41	31.8	24.6
July - Sept.	13	15	1	29	22.5	26.3
Oct. - Dec.	14	15	0	29	22.5	24.1
TOTALS	64	53	12	129	100.0	100.0

Of the 129 cases that occurred in 1947, 1948, and 1949 (Table I) almost one-third occurred in the second quarter - April, May and June - (31.8%). The balance of the cases were more or less equally distributed in the other three quarters. The actual percentage of births in Minnesota during the same quarters were 25.0, 24.6, 26.3 and 24.1 respectively. There was a marked increase in the percentage of cases in the second quarter in comparison with the percentage of births in the same quarter. (Figure 3) Any significance is, however, questionable because of the small number of reported cases totaling 41, in comparison with the

OCCURRENCE OF METHEMOGLOBINEMIA
IN 146 INFANTS BY MONTHS
Minn. 1941-1949

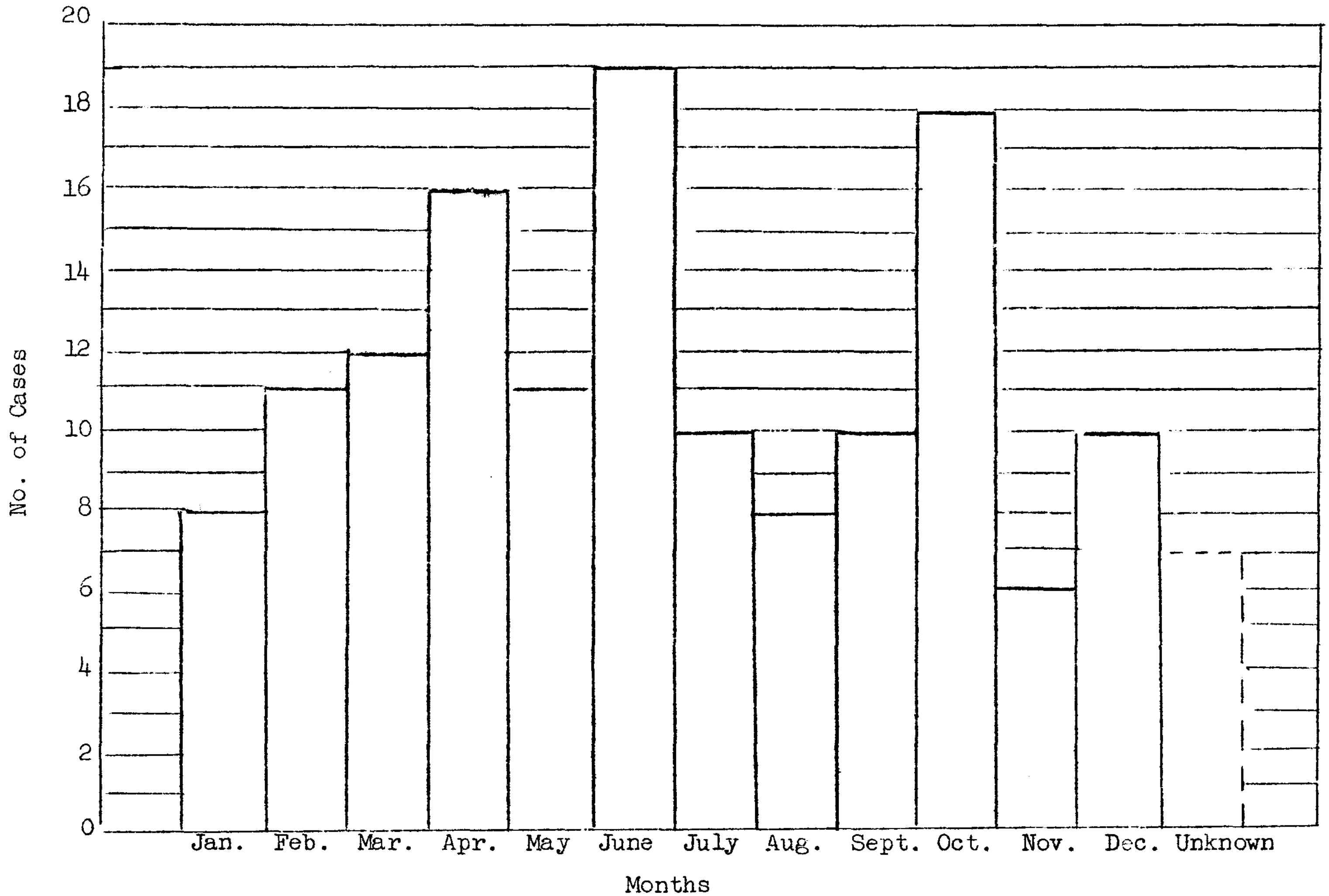


Figure 2

OCCURRENCE OF METHEMOGLOBINEMIA IN 129 INFANTS BY SEASON OF YEAR COMPARED WITH SEASONAL OCCURRENCE OF BIRTHS
Minn. 1947, 1948 & 1949

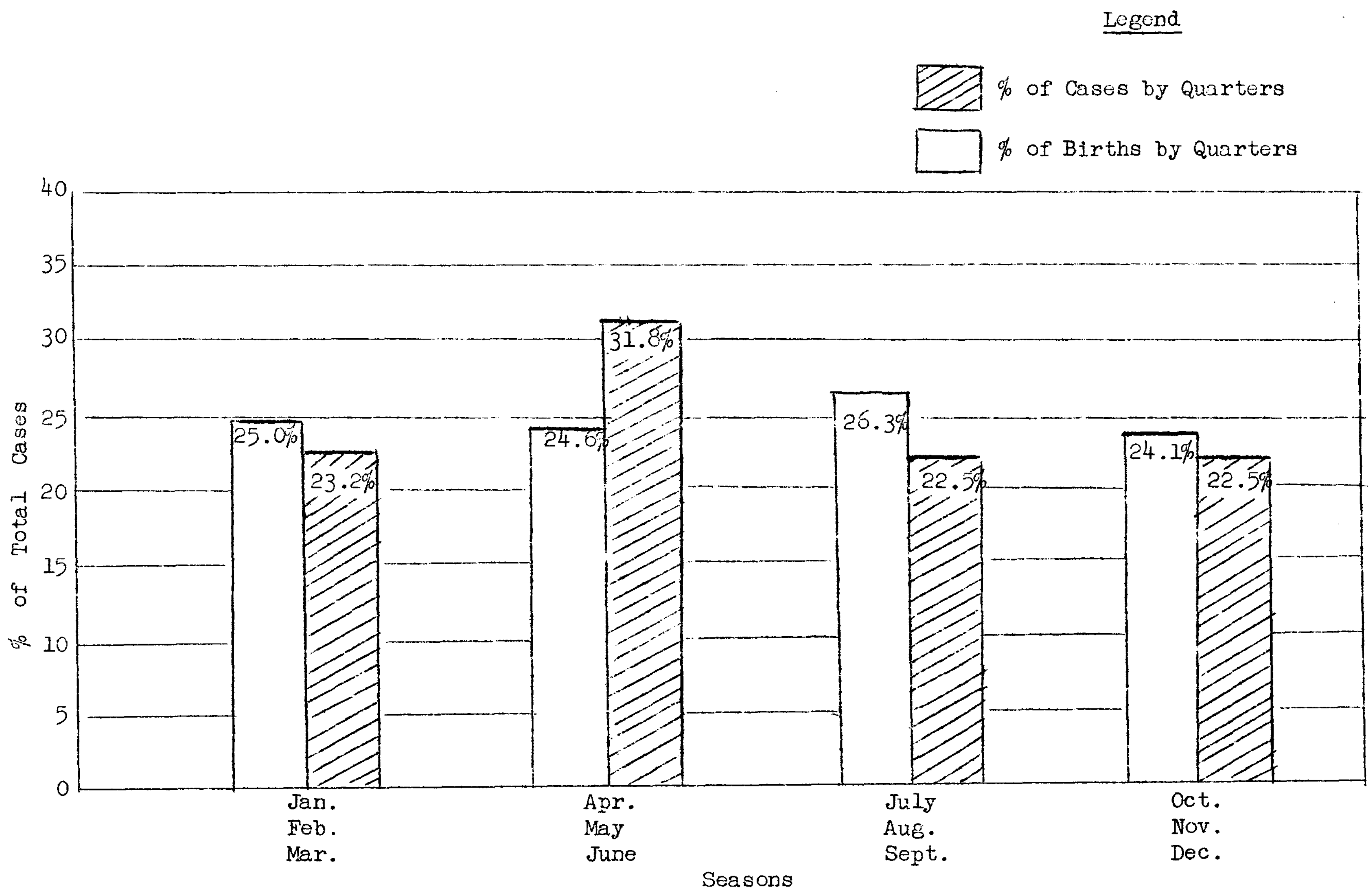


Figure 3

births which total 54.415. Incidentally, it should be stated that it has not been possible to demonstrate any significant seasonal variations in the concentration of nitrate nitrogen in farm or municipal wells by periodic samplings carried out on a number of water supplies. This will be discussed in more detail under water supply aspects.

Table II

Age at Onset of Symptoms

Age at Onset of Symptoms in 133 Cases of Methemoglobinemia*

Age	Under 14 days	14 days-1 mo.	1-1½ mo.	1½-2 mo.	2-5 mo.
No. of Cases	16	69	29	8	11
% of Cases	12.0	51.8	21.8	6.1	8.3

* Out of total of 146 cases, 13 lacked this information

As to age at onset of symptoms, over half occurred between 2 and 4 weeks of age; almost three fourths occurred between 2 and 6 weeks of age; over 90 per cent occurred under 2 months; and only 8.3 per cent were between 2 and 5 months of age. The youngest case was 7 days old and the oldest was 5 months old.

There were 21 infants who were breast fed for a variable period of from 1 to 4 weeks before being changed to a formula containing well water. These infants, therefore, developed symptoms at an age from 1 to 4 weeks later than the non-breast fed infants.

Length of Exposure to Suspected Well Water

Table III

Number of Days on Well Water Before Symptoms in 114 Cases of Methemoglobinemia*

No. of Days	1 day	2-6	7-14	15-21	22-30	Over 30
No. of cases	1	17	33	28	14	21
% of Cases	0.9	14.9	28.9	24.6	12.3	18.4

* In 32 cases this information was not available.

The number of days the infant was on well water before symptoms developed was dependent on a number of factors, such as the nitrate nitrogen content of water, the amount of water in formula, amount and frequency of feeding, supplemental water feeding, length of time water was boiled, various physiologic considerations, and probably other unknown factors.

More than half of the 114 infants on whom this information is available (61 cases) developed symptoms in 1 to 3 weeks after being on a formula requiring considerable water as a diluent. Eighteen per cent of these infants were on well water more than 30 days, the longest period being 60 days; about 15% developed symptoms in less than 7 days. The shortest period before symptoms developed was 1 day, in a two month old infant, on an evaporated milk formula diluted with water containing 140 parts per million of nitrate nitrogen. In this case the water was boiled for over 30 minutes to make sure all the "bugs" were killed. As a result, the nitrates were concentrated almost three-fold by evaporation of water. This was demonstrated in the laboratory by boiling a sample of water from this particular well for 30 minutes. Before boiling the nitrate nitrogen content was 140 parts per million; after 30 minutes boiling it was 410 parts per million as a result of evaporation.

Symptoms

The characteristic symptom is a grayish blue or brownish blue cyanosis which begins around the lips, spreads to the fingers and toes, the face, and eventually covers the entire body. This occurred in all cases. When well developed, it is quite obvious. In early or mild cases the mother may not notice the cyanosis until her attention is called to it by a relative or neighbor. Incidentally, farmers who have become familiar with this condition call these infants "blue water babies". In several cases a physician making a routine periodic physical examination first noted the cyanosis.

Formulas

Table IV

Infant Formulas in 116 Cases of Methemoglobinemia*

Type of milk in Formula	Cases No.	Cases Per Cent
Evaporated	46	39.7
Powdered	41	35.3
Cow's	29	25.0
Breast fed	0	0

*Balance of 146 cases did not report formula used.

The formulas used are of special interest. Evaporated and powdered milk, which require large amounts of water as diluent, were used in 75 per cent of 116 cases with this information available. Diluted cow's milk was used in 25 per cent. No cases occurred among infants in this group who were breast fed, with only one possible exception. This was a 3-week's old infant who was breast fed, but during the four days preceding the onset of cyanosis was given, in addition, a formula of liquid SMA diluted with 1 to 1½ ounces of well water on only 3 occasions, plus 1½ ounces of water daily. On examination, in addition to the cyanosis there was a loud systolic murmur over the entire chest, diagnosed as congenital heart disease, from which he died some time later. Methemoglobin totaled 1.57 grams per 100 ml. of blood which constituted 8.4 per cent of the hemoglobin, and the well water contained 196 parts per million of nitrate nitrogen. It is difficult to understand how methemoglobinemia could be present with such a small quantity of formula and water and in view of the pathology present. In spite of this one possible exception, this would appear to be another reason for urging breast feeding during the first 2 months of life, especially in rural areas, as Medovy has suggested.[8]

Differential Diagnosis

In the differential diagnosis certain serious conditions must be ruled out. Among them are congenital heart disease, abnormalities of the respiratory tract such as pneumonia, atelectasis, pneumothorax, diaphragmatic hernia and congenital pulmonary and tracheal malformations, as well as "thymic syndrome." It should be remembered, as Ferrant[6] has pointed out, that there is a striking difference between the cyanosis and the alarming condition of the patient on the one hand and the normal pulse and respiration and lack of physical findings on the other. If the cyanosis is severe and persistent, systemic effects are produced due to anoxemia, and death may occur.[1,20]

Diagnosis of Methemoglobinemia

The diagnosis of methemoglobinemia may

be presumptive or absolute. In either case, however, it must first be suspected. A presumptive diagnosis may be made, if on removal of venous blood for a hemoglobin determination the blood is chocolate colored, and if there are more than 10 to 20 parts per million of nitrate nitrogen in the water used in the formula. If the blood is not examined, a presumptive diagnosis is justified if there is a spontaneous disappearance of cyanosis in 24 to 48 hours on changing the water in the formula, and the nitrate nitrogen content of the water used exceeds the suggested maximum of 10 to 20 parts per million. In either case the history and physical finding should be typical. An absolute diagnosis is made by demonstrating a definite methemoglobin line on spectroscopic examination[1] or by the chemical analytic method of Evelyn and Malloy.[21]

Methemoglobin Levels

Table V

Methemoglobin Determinations*

Mhb. Gm/100 ml. of blood	NO_3N ppm. in well water	Days on formula	Formula and well water	Age at onset in days
0.355	66	19	SMA	24
0.65	40	11	Evap.	25
0.97	100	49	Biolac	56
0.985	140	1#	Evap.	64
2.5	73	18	SMA	24
3.00	110	47	SMA plus Biolac	58
3.05	110	20	2/3 dil. cow's milk	36
4.95	500	9	1/2 dil. cow's milk	45

* By method of Evelyn and Malloy
\# Water was boiled for over 30 minutes

In the above 8 cases the diagnosis was confirmed by methemoglobin determinations by the method of Evelyn and Malloy,[21] using an electric colorimeter which was transported to the bedside of the patient on long distance telephone request to the State Health Department from the attending physician. Facilities for methemoglobin determination were not available in the rural areas where cases occurred. The readings varied from a low of 0.35 grams per 100 ml. of blood two days after hospitalization, to a high of 4.95 grams per 100 ml. of blood.

Treatment

Treatment in most cases consisted of changing the water used in the formula to an approved municipal supply, with prompt recovery. In 46 infants oxygen was used, but most of the physicians did not think it was of any benefit. Furthermore, removal of the infant to a hospital automatically changes the water supply and is probably responsible for the recovery in 24 to 48 hours. In severe cases more active treatment becomes necessary. One per cent methylene blue solution, 1 to 2 mg. per kg. intravenously, may be life saving.[22] It was used in 9 cases with prompt recovery, the cyanosis clearing up in less than half an hour.

Mortality

There were 14 deaths, a mortality rate of 9.6 per cent. No specific treatment was used in these cases since the condition was either not recognized or methylene blue solution was not readily available. It is of interest to note that 4 deaths were ascribed to thymic hypertrophy or syndrome, notwithstanding the fact that the symptoms were characteristic of methemoglobinemia, and the well water used in the infant's formula contained 70, 120, 150, and 200 parts per million of nitrate nitrogen, respectively. There were no autopsies done on these 4 infants. In Minnesota during 1947 and 1948, 15 infant deaths were reported as due to hypertrophy of the thymus, of which the 4 mentioned above were actually deaths from methemoglobinemia. Many cases of cyanosis in early infancy in rural areas have probably been incorrectly treated for hypertrophy of the thymus in the past. Donahoe[23] reported 5 cases of cyanosis in babies on farm well water who had been given from 2 to 8 x-ray treatments for suspected thymus enlargement, but which were cases of nitrate cyanosis. Two of the thymic deaths in this series received x-ray treatment. Several infants who recovered also received x-ray treatments. Dr. G. B. Logan, Section of Pediatrics at the Mayo Clinic, states[24], "I do not believe that an enlarged thymus is a cause of death unless it can be shown by autopsy examination."

Typical Case Histories

Case 1. Female infant, born October 1, 1948, and discharged from hospital October 6, 1948. The formula consisted of SMA and well water, equal parts, a total of 24 ounces daily and 4-5 ounces of supplemental water between feedings. At age of 24 days, vomiting occurred; on 25th day of life, cyanosis developed. The following day a physician made a diagnosis of congenital heart disease. Five days later the infant was hospitalized at a nearby clinic where a diagnosis of methemoglobinemia due to nitrates was made. Changing the water in the formula to an approved municipal supply resulted in recovery in 2 days. Blood examination showed the presence of methemoglobin to the extent of 2.5 grams/100 ml. of blood. Analysis of the well water showed nitrate nitrogen 73 ppm., sulphates 70 ppm. and chlorides 28 ppm. The formula was changed to 24 ounces pasteurized milk, 8 ounces water from municipal supply and Karo. There was no recurrence.

Case 2. A female infant was discharged from the hospital to the farm home on an evaporated milk mixture. At the age of 10 days vomiting developed and persisted for several days. At the age of 20 days a generalized grayish-blue cyanosis developed. On the 22nd day of life the infant was hospitalized when fluoroscopic examination of the chest resulted in a diagnosis of hypertrophic thymus. Oxygen was given as well as x-ray treatments daily for 3 days. Symptoms cleared up and the infant was discharged. Three days later while on the same formula containing well water, cyanosis became marked and the infant was hospitalized again. The physical examination of the heart, lungs, and thymus was negative and the cyanosis cleared up in 3 days without any treatment, other than the change of the water. Analysis of the water from a shallow farm well showed nitrate nitrogen 90 ppm., nitrite nitrogen 4 ppm., sulphates 100 ppm. and chlorides 140 ppm. The water used in the formula was changed and there was no recurrence.

Case 3. Female infant, born August 10, 1947, weight 7 pounds, discharged from hospital August 16, 1947, on a Lactogen formula, 16 ounces daily. On 22nd day of life, infant developed diarrhea. On the 29th day the infant was seen by a physician who found cyanosis of the face and chest, made worse on crying. Admitted to hospital with diagnosis of "infection of the stomach." Infant was discharged on 5th day when symptoms had cleared up. On return to the farm home the same well water was used and 4 days later diarrhea and cyanosis returned. The physician changed the water to a municipal supply with recovery and no further recurrence. The farm well water contained nitrate nitrogen 37 ppm., sulphates 14 ppm., and chlorides 33 ppm.

Case 4. Male infant born August 29,

1948, discharged September 3, 1948. The infant was breast-fed but on September 10, 3 days before symptoms appeared, the mother added a formula consisting of cow's milk 12 ounces and water 4 ounces. In addition, 8 ounces of supplemental water were given daily. On September 13 at the age of two weeks the infant developed fussiness, excessive crying, and cyanosis of lips during crying spells. Heart, lungs and thymus negative, temperature 96°. Diagnosis was methemoglobinemia. Treatment consisted of oxygen, with recovery in 24 hours. Hemoglobin 69%, wbc. 11,000, methemoglobin 4.95 grams/100 ml. Well water contained nitrate nitrogen 500 ppm., sulphates 980 ppm., chlorides 480 ppm.

Case 5. Female infant, born November 1, 1948, birth weight 7 pounds 1½ ounces, discharged on 7th day. The formula consisted of Biolac 1 ounce and 1½ ounces of water, 4 ounces per feeding, 5 times daily, plus 10 ounces of supplemental water. The water was boiled 5 minutes. At the age of 7 weeks diarrhea and fussiness developed. The mother then diluted the formula with additional well water. Three days later a grayish-blue cyanosis began around the lips and hands and became generalized, accompanied by listlessness. The following day the infant was sent to the hospital. The physical examination was negative except for a duskiness of the skin. A diagnosis was made of methemoglobinemia. On the physician's request a methemoglobin determination was made at the bedside that evening which showed 0.97 grams'100 ml. of blood and 10 grams of hemoglobin per 100 ml. of blood. Twelve hours later (the following morning) the methemoglobin had dropped to 0.49 grams'100 ml. with clearing of the cyanosis. The mother was advised to use water from a neighboring municipal supply. The well water previously used contained nitrate nitrogen 100 ppm., sulphates 1200 ppm. and chlorides 210 ppm. Five minutes of boiling increased the nitrate nitrogen content to 166.25 ppm. No recurrence of symptoms.

Case 6. Female infant born June 3, 1947, weight 7 pounds, 15 ounces, discharged from hospital June 12, 1947, on formula of Carnation milk 14 ounces, water 21 ounces, and dextromaltose 7 tablespoons, with 5 ounces of supplemental water, boiled for 10 minutes. At routine physical check-up at age of 3 weeks a physician noted cyanosis. City water was substituted with recovery in 24 hours and no recurrence. Analysis of farm well water showed nitrate nitrogen 62 ppm., sulphates 360 ppm., and chlorides 84 ppm.

Discussion

The question as to why only young infants, usually under 2 months of age, and not older members of the family, develop cyanosis is difficult to answer. Incidentally, not all young infants develop this condition. There have been a number of instances in this series where 1 infant developed cyanosis, whereas a sibling, born 1 or 2 years previously, fed on a similar formula and using water from the same well, failed to develop cyanosis. Older children and adults, drinking the same water, did not develop this condition.

According to Comly,[4] there are a number of factors which make an infant more susceptible to nitrate cyanosis than older persons. The most important single factor, in his opinion, is that the infant has less oxidizable hemoglobin than an adult. Other factors suggested are: that there is a high fluid intake with greater turnover of water in proportion to body weight; that the intestinal flora may contain more nitrite converters; that the infant's intestinal mucosa is more easily damaged and favors absorption of nitrites; that the limited excretory power of the young infant's kidney may favor nitrogen retention; and that nitrate ions may be more firmly bound by infantile hemoglobin because of immaturity of certain enzymes.

According to Ferrant,[6] nitrates in well water are probably more toxic for newborn infants than for adults, especially if the infants have digestive disorders. This may be a factor as 14 per cent in this series had diarrhea.

Cornblath and Hartmann,[25] however, claim that only younger infants develop methemoglobinemia upon ingestion of water containing nitrates, because of the low gastric acidity characteristic of the neonatal period.[26] As a result of experimental work, they postulate that if there is no free acid in the stomach and the pH of the gastric juice is over 4.0, nitrite-producing organisms can exist high in the gastro-intestinal tract in sufficient number to reduce nitrates to nitrites before the former can be completely absorbed. In their control group of infants, the gastric acidity was increased by lactic acid milk feeding. In these cases they were unable to produce methemoglobinemia with mixtures containing high nitrate content. This appears to be a reasonable explanation. In 3 cases of methemoglobinemia in this reported series the pH was 4.5, 5.0 and 5.5, respectively.

One final factor must be mentioned. Apparently, the cyanosis may clear up spontaneously when the infant becomes older. This may be due to the fact, as pointed out by Cornblath and Hartman[25] and others,[26,27] that the gastric acidity increases in older infants. This was illustrated in this series where three cases occurred in one family, one case in 1941, one in 1942 and one in 1944. All three infants developed cyanosis, vomiting, diarrhea and excessive crying at the age of one week while on a SMA formula. In the first two cases the symptoms cleared up at the age of 3 months with no treatment and with no change in the farm well water used in the formula. The infant born in 1944 was hospitalized when cyanosis developed and cleared up in a few days. On returning to the farm home the cyanosis recurred. Notwithstanding the skepticism of the family physician, the parents changed the water with prompt clearing up of all symptoms.

There are undoubtedly, however, other factors, and these are all debatable theories.

In passing, it might be of interest to mention a veterinary disease of similar nature as an interesting side-light. In the spring of 1949 a herd of cattle in rural Manitoba became ill after eating sugar beet tops.[28] Cyanosis was a prominent symptom, giving the appearance of "purple cows." The blood was chocolate-brown in color and methemoglobin was demonstrated. Methylene blue solution was successfully used in treatment but a number of cows died. Analysis of the sugar beet tops showed a high nitrate content but the water contained no nitrates.

While no such cases in farm animals have been reported in Minnesota this condition is not new. In 1937 a review[29] was made of similar outbreaks of "purple cows" which had occurred in Colorado and Wyoming due to eating oat hay or straw. This condition has occurred since 1923 and has been called "oathay disease." Methemoglobin was demonstrated in the blood and the oathay and oats contained large amounts of potassium nitrate. Unfortunately, the water used was not analyzed for nitrate. Apparently horses and sheep may also suffer from this type of poisoning. In certain areas in these two states other plants such as certain weeds, wheat, barley, and cane sorghum sometimes contain sufficient nitrates to cause methemoglobinemia. It has also been reported in sheep in South Africa.

RESUMÉ OF WATER SUPPLY ASPECTS

Nitrate determinations on samples from water supplies were made in the earlier days of the Minnesota Department of Health but were gradually discontinued as a part of the sanitary analysis with the advent of modern bacteriological methods. The health department's interest in the nitrate concentrations of water supplies in the state has been renewed since the first suspected case of methemoglobinemia was reported at Tyler, Minnesota, in January 1947. From January 1947 to January 1950, investigations were made of all water supplies which were reported to be, or suspected of being, involved in cases of methemoglobinemia. In many instances physicians were interviewed in an attempt to determine whether the problem was more widespread than existing information would indicate. The results of these interviews showed that there were, undoubtedly, many cases of methemoglobinemia which were either not being properly diagnosed or were not reported.

In January 1949, a communication was sent to all physicians in the state asking them to report any suspected case of methemoglobinemia that had come to their attention in the past several years. The physicians were also asked to notify the Department immediately of any new cases.

A study was made of the 146 old and new cases reported as a result of this communication. Each study consisted of accumulating all epidemiological data and obtaining all pertinent information on the water supply involved. Dug wells were found to be the source of water in 129 cases, and drilled wells in 4 cases. Eleven of the wells were involved in more than one case and two wells caved in before samples were obtained. None of the wells contained less than 10 ppm. nitrate nitrogen (NO_3N) as shown in Table VI. (A concentration of 10 ppm. is the maximum recommended by most workers.)[4,10,15]

Table VI

Nitrate Nitrogen Concentration in Wells Concerned in Methemoglobinemia Cases*

NO_3N ppm.	Type of Well	
	Dug	Drilled
Less than 10	0	0
10 - 20	2	0
21 - 50	25	1
51 - 100	52	2
Over 100	50	1

Only two wells contained between 10 - 20 ppm. NO_3N. Insufficient clinical data were available on both of these cases, and they are considered questionable. The samples from many of the 26 wells which contained 21 to 50 ppm. were collected a year or more after a methemoglobinemia case had occurred, and in some instances the well had been abandoned subsequent to the case of methemoglobinemia. The lowest nitrate nitrogen on a sample collected at the time of the infant's illness was 36 ppm.; the highest was 500 ppm.

From the information obtained on the cases reported early in the study and from data published by other workers[12, 13,14,15,18,30] it was considered desirable to determine what factors might influence the nitrate concentration of water from wells. Among the questions which occurred in this connection were the effects on nitrate concentration of pumping, seasonal variations, location and construction, depth and type of wells, and the geology of the area.

<u>Effects of Pumping on Nitrate Concentration</u>

In order that sampling errors might be eliminated insofar as possible, it was considered necessary that the effect of pumping and the time of sample collection on the nitrate concentration be determined.

Four test runs were made on three different wells. Three of the runs were made over periods of one hour each, with samples being collected every minute for the first five minutes, and every five minutes thereafter. The fourth run was made with samples being collected every hour for a period of 6 hours. It was concluded from these pumping tests that no significant change in the nitrate concentration is noted with length of pumping, and that the time of collection of the sample after pumping begins is not critical.

*The phenoldisulfonic method described in the ninth edition of "Standard Methods of the Examination of Water and Sewage" was used for determining the NO_3N concentration for these tests and all others reported in this paper.

Effects of Seasonal Variation on Nitrate Concentration

To determine the effects of seasonal variation on nitrate concentration, arrangements were made to have samples submitted from certain specified municipal and private wells at routine intervals.

Municipal Supplies:

During this study, 28 (5.4%) of the 514 municipal supplies in the state were found to contain over 5 ppm. NO_3N; 16 (3.1%) of these contained 10 ppm. or more. The highest concentration was 27 ppm. in a dug well used as the source for a municipal supply in the section of the state from which most of the methemoglobinemia cases have been reported. The health officer of this community advised all residents not to use this water for infant formulas. No cases of methemoglobinemia have been reported from this supply. Eight supplies, ranging in nitrate nitrogen from 5 to 27 ppm., were selected for bi-weekly sampling which was begun in February 1949. Samples were collected from the sources of supply and from the distribution system in each instance.

Private Supplies:

Four of the wells involved in cases of methemoglobinemia were sampled bi-weekly beginning in February 1949. These included two wells which were later reconstructed. The remaining two were dug wells, one at Tyler (Lincoln County), and the other at Woodstock (Pipestone County), both of which were located satisfactorily. A fifth supply, a drilled well located one-half mile west of the reconstructed well at Luverne, was also sampled, although this well was not involved in a case.

These periodic samplings were continued for a period of one year. From the data obtained, it is concluded, within the limits of this study, that the nitrate concentration of a well water remains fairly constant and that seasonal variations do not occur.

Effects of Location and Construction on Nitrate Concentration

An analysis of the data obtained on the location and construction of the 133 wells investigated in connection with cases of methemoglobinemia showed that none was both located and constructed satisfactorily as judged by the standards of the Minnesota Department of Health. (These standards for safe water supplies specify that a well should be located at least 50 feet from all sources of contamination such as barnyards, privies, etc. The well should be provided with a water-tight casing which extends at least 10 feet below and 1 foot above the grade. Vitreous and concrete tile, wood, and galvanized sheet metal curbings are not acceptable. A reinforced concrete platform which extends at least 2 feet from the well casing in all directions should cover the wall. A tight seal at the pump base and a stuffing box head on the pump are also specified. Pit construction is not approved.)

None of the drilled wells and only 36 of the dug wells were located satisfactorily as shown in Table VII. Seventy-three wells were located within 50 feet of a source of animal contamination (barnyard, hog pen, etc.,) and 13 within 50 feet of a source of human contamination (privy or cesspool). No data were obtained on 11 supplies.

Wood curbing was used in 34 wells, concrete tile in 70. All but 13 of the 121 wells on which data were obtained had wooden platforms.

Since no conclusions could be reached from the preceding data on the significance of location and construction on nitrate concentration, a survey was undertaken of all school wells in Nobles and Kandiyohi Counties. Wells at farms adjacent to the schools were also surveyed and used as a basis of comparison, since it was believed that the school environment afforded well locations which

Table VII

Physical Features and Nitrate Concentrations of Wells Involved in Cases

Number surveyed: 133

PHYSICAL FEATURES	NO_3N CONCENTRATIONS - p.p.m.							
	10 - 20*		21 - 50		51 - 100		Over 100	
	Dug	Drilled	Dug	Drilled	Dug	Drilled	Dug	Drilled
LOCATION:								
Satisfactory	1		5		16		13	
Unsatisfactory			19	1	30	2	34	1
No Data	1		1		6		3	
CONSTRUCTION:								
Curbing:								
Wood			6		15		13	
Concrete tile	1		12		29		28	
Rock or Brick			3				3	
Metal				1		2		1
No Data	1		4		8		6	
PLATFORM:								
Wood	1		23		39	2	42	1
Concrete					6		5	
Metal					1			
None				1				
No Data	1		2		6		3	
DEPTH - in feet:								
Less than 20			3		3		5	
20 - 40	1		7	1	20		17	
41 - 60			5		3		6	
61 - 75			1		5		3	1
76 - 100					4	1	3	
101 - 150			1		1		1	
Over 150					1	1		
No Data	1		8		15		15	

* No wells contained less than 10 p.p.m.

are normally free of gross organic pollution as contrasted with sites generally found in farmyards.

In the Nobles County Survey, 30 rural school and 64 farm wells were studied. The nitrate concentration in the school wells was lower than in the nearby farm wells in all but three instances.

Sixty-eight school and 15 farm supplies were studied in the Kandiyohi County Survey. Only one of the school wells and six of the farm supplies contained over 10 ppm. NO_3N.

From the data obtained on these two surveys, it appeared that school wells containing over 10 ppm. NO_3N occur less frequently than do comparable farm wells. It also appears that in the case of dug and of drilled wells, the location factor did not have too much bearing on whether the water would yield a high nitrate content or not.

In an attempt to further determine the effects of construction on the nitrate content of a well, two wells which were high in nitrate and which had been sampled over a period of at least six months, were reconstructed. The wells chosen were a satisfactorily-located dug well of 30 foot depth located outside the city limits of New Ulm in Brown County, and a poorly-located drilled well, 71 feet deep, located three miles southwest of Luverne in Rock County.

The upper ten feet of each well were reconstructed so as to eliminate the possibility of contamination entering the well from surface drainage. Sampling of the wells after reconstruction did not show a significant reduction in the nitrate concentration. Therefore, contrary to work done by Sanger,[14] good construction for a depth of ten feet failed to exclude nitrate.

Effect of Depth and Type on Nitrate Concentration

From a tabulation of the data obtained from all the well studies, it was apparent that there is a greater probability of high nitrate concentration occurring in shallow wells than in deep wells. Dug wells are more frequently the source of water high in nitrate than are drilled wells. It is significant that in the dug wells, a very large percentage (62%) of the wells showing nitrates in excess of 10 parts per million were less than 75 feet in depth. In general, it can be said that, within the limits of this study, nitrate can be expected to occur more frequently in the shallow wells, (75 feet or less), than in the deep wells.

Effect of Geology on Nitrate Concentration

During the period January 1, 1947 to August 1, 1949, the laboratory made nitrate determinations on 2,912 water samples. Approximately 800 were submitted specifically for nitrate determination; the remainder were collected primarily for some other reason. Of these samples, 441 (15%) collected from wells in 55 counties contained over 10 ppm. NO_3N. The highest concentration found in each county is charted in Figure 4. The white areas indicate counties in which the highest NO_3N concentration of samples included in this study is less than 10 ppm. The vertical-lined area, predominating in the southwest corner, indicates the occurrence of NO_3N concentrations of over 100 ppm. The southwestern section is the area from which most of the methemoglobinemia cases have been reported.

A review of the geology of the State of Minnesota shows that it is, for the most part, a heavily glaciated area, and that in most instances where high nitrates have been encountered, they have been found in wells drawing water from the drift. One characteristic common to the western portion of the state where high nitrates have been encountered is the heavy soil. Those counties which show less than 10 parts per million nitrate nitrogen in the northern portion of the state very frequently have lighter soils containing considerable quantities of sand. At the present time, there are approximately 10 counties in southern half of the state which show no wells with concentrations of NO_3N over 10 parts per million. It is not known whether more extensive studies would show similar results. Because of the peculiar distribution of water high in nitrates in Minnesota, it would appear that there are certain geological factors which are involved. What these factors are, and the nature of their operation, has not been established by this study.

SUMMARY

1. One hundred forty-six cases of methemoglobinemia, including 14 deaths, due to nitrates in farm well water supplies in Minnesota are reported.

NITRATE NITROGEN CONCENTRATION IN WELL WATER
Highest Concentration Found in County
1947-1949

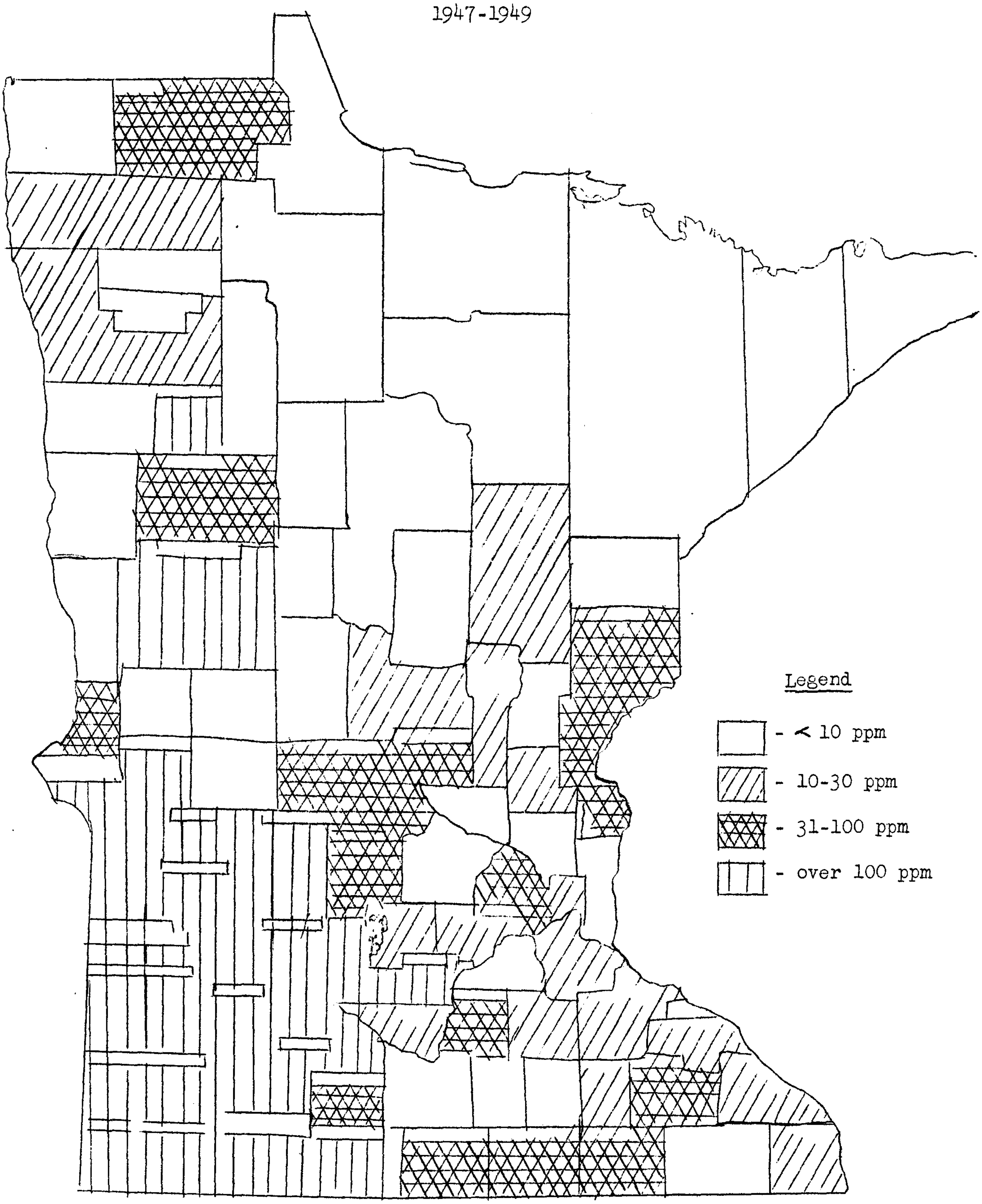


Figure 4

2. Dry and evaporated milk formulas as well as diluted cow's milk formulas which require large amounts of water as diluent are most dangerous.

3. Since no infants who were breast-fed, with one possible exception, developed methemoglobinemia, this would appear to be another argument in favor of breast feeding during the first two months of life, especially in rural areas.

4. Data are presented on water supplies suspected of being implicated in cases of infant methemoglobinemia in Minnesota. In all but two of these cases, the nitrate nitrogen content of the water was in excess of 20 ppm. In the two exceptions mentioned, the clinical histories of the suspected cases were inconclusive.

5. Test runs on several wells did not show a significant change in the nitrate concentration with length of pumping.

6. Periodic sampling of municipal and private supplies over a one year period indicate that the nitrate concentration of a well remains fairly constant and that significant seasonal variations do not occur.

7. Studies of rural school wells and similarly constructed nearby farm wells indicate that the nitrate content of the school well water was less than that of water from the farm wells.

8. Reconstruction of two wells failed to show, as some workers thought, that good well construction for a depth of ten feet could be expected to exclude nitrates.

9. Nitrates seem to occur more frequently in the shallow wells, (75 feet or less), than in deep wells.

10. No method was found by which nitrates could be removed from water. Since this paper was published, Krueger[31] reported using the resin IRA - 400 to remove nitrates from water. This resin works on the anion exchange principle which is similar to the cation exchange that takes place in zeolite softeners.

11. None of the cases of methemoglobinemia in Minnesota on which sufficient data was obtained occurred from using water containing less than 30 ppm. NO_3N in feeding an infant. However, 10 ppm. has been generally accepted as the point above which the water should be viewed with suspicion because of the possibility of a dangerous level being reached through other factors such as boiling.

ADDENDUM

Since this paper was written, 2 additional cases of methemoglobinemia have been reported to the Minnesota Department of Health.

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II. MEDICAL SCHOOL NEWS

Coming Events

March 27-29 - Continuation Course in Dermatology for General Physicians..

April 10-12 - Continuation Course in Pediatrics for Specialists.

April 17-19 - Continuation Course in Gynecology for General Physicians.

April 20-22 - Continuation Course in Cardiovascular Diseases for General Physicians.

* * *

Surgical Societies' Gifts Support Radio Research Report

Gifts to the Minnesota Medical Foundation from the Minneapolis Surgical Society and the St. Paul Surgical Society will make it possible to present a monthly radio program "Medical Research Report" over KUOM and other radio stations serving Minnesota. The broadcasts, which will be produced through the combined efforts of Dr. Ruth Grout, of the School of Public Health, and the staff of KUOM, will feature brief reports on various research activities being conducted at the University of Minnesota Medical School and elsewhere.

These programs are an outgrowth of KUOM's regular weekly feature, "Medical Research Report", a program sponsored by the National Society for Medical Research. This society provides weekly radio scripts on current developments in the basic medical science fields and in pre-clinical and clinical fields of medicine.

One of the purposes of these programs has been to emphasize for the lay listener the importance of medical research. Emphasis has also been placed on the importance of animal experimentation to the continued progress of medical science.

The gifts from the Minneapolis and St. Paul Surgical Societies will make it possible to create a Medical Research Report program of particular interest to Minnesota listeners. The thanks of all members of the Foundation and all faculty members are due to the Surgical Societies for their support in this important activity in lay education.

* * *

Progress Note -- Heart Hospital

Construction of the Variety Club Heart Hospital continues to show steady progress. The building is now closed in, heating lines have been connected to the main university channels, and the general plan of the various floors is now apparent on inspection. Corridors are taking form, and partitions are defining patient rooms, class rooms, headquarters for nurses, and other rooms vital to a teaching hospital. Present plans call for official dedication of the building in early fall of 1950.

III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

March 12 - March 18, 1950

No. 280

Sunday, March 12

9:00 - 10:00 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Surgical Conference; Rm. M-109, U. H.

Monday, March 13

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U, H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 11:50 Roentgenology-Medicine Conference; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Classroom, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Public Health Seminar; Subject to be announced; 113 Medical Sciences.

4:00 - Pediatric Seminar; To be announced; Albert Miller; 6th Floor West, Child Psychiatry, U. H.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy, O. J. Baggenstoss and Staffs; M-109, U. H.

8:00 - Clinical Research Club Meeting; 1-Hyaluronidase Inhibitors and Nucoproteins in Nephritis and Nephrosis; Vincent C. Kelley: 2-Syncope in Vincent Aortic Stenosis; James F. Hammarsten: 3-The Prophylaxis and Treatment of Respiratory Disease in Children with Antihistaminics; Spencer F. Brown: Eustis Amphitheater, U. H.

Tuesday, March 14

8:15 - 9:00 Roentgenology-Surgical-Pathological Conference; Craig Freeman and L. G. Rigler; M-109, U. H.

8:30 - 10:20 Surgery Conference; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell; Veterans Hospital.

11:00 - Contagion Rounds; Forrest Adams; Sta. L, General Hospital.

12:30 - Pediatric-Surgery Rounds; Drs. Stoesser, Wyatt, Chisholm, McNelson and Dennis; Sta. I, Minneapolis General Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:30 - 2:30 Pediatric Psychiatry Conference; R. A. Jensen and Staff; 6th Floor, West Wing, U. H.

1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Physiology-Surgery Conference; Studies on Ext. Pancreatic Secretion; R. Ferguson; Eustis Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 Porphyrin Seminar; C. J. Watson, Samuel Schwartz, et al; Powell Hall Amphitheater.

5:00 - 6:00 X-ray Conference; Presentation of Cases by General Hospital Staff; Drs. Lipschultz and Mosser; Todd Amphitheater, U. H.

Wednesday, March 15

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker; Veterans Hospital.

Wednesday, March 15 (Cont.)

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:00 - 1:00 Radio-Isotope Seminar; Distribution of Sulfer^{35} in Animal Tissues Following Its Administration as DL-Methionine-S35; Henry S. Block; 113 Medical Sciences.

12:15 - Staff Meeting; Main Classroom, General Hospital.

3:00 - Pediatric Rounds; C. J. Huenekens; Sta. I, General Hospital.

3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.

4:00 - 5:00 Infectious Disease Rounds; Todd Amphitheater, University Hospitals.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; E-101, U. H.

Thursday, March 16

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - Pathology Conference Clinic; Main Classroom; General Hospital.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Classroom, Minneapolis General Hosp.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hosp.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Classroom, Minneapolis General Hospital.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Presentation of Miller Hospital Cases; Drs. Peterson and Paulson; Todd Amphitheater, U. H.

7:30 - 9:30 Pediatrics Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Friday, March 17

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

Friday, March 17 (Cont.)

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser, and Staffs; Minneapolis General Hospital.

11:45 - 12:50 University of Minnesota Hospitals General Staff Meeting; Psychological Medicine in a General Medical Setting; Richard McGraw; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.

1:00 - 1:50 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

3:00 - 6:00 Demonstrations in Cardiovascular Physiology; M. B. Visscher et al; 301 M. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater,U. H.

4:15 - 5:15 Electrocardiographic Conference; Demonstration (lectures VII & VIII); George N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

5:00 - 6:00 Otolaryngology Seminar; Review of Current Literature; Dr. Karandjeff: Discussor; Dr. Hoshfilzer; Todd Memorial Room, U. H.

Saturday, March 18

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; M-109, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Small Classroom, Minneapolis General Hospital.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

9:00 - 11:30 Psychiatry Conference; Psychosomatic Medicine; Clarence K. Aldrich; Powell Hall Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

Saturday, March 18 (Cont.)

9:00 - 11:30	Surgery-Roentgenology Conference; Todd Amphitheater, U. H.
10:00 - 11:50	Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
10:00 - 12:50	Obstetrics and Gynocology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.
11:00 -	Contagion Rounds; Forrest Adams; Sta. L, General Hospital.