lowest values in the groups here reported were probably indicative of anæmia. This certainly appeared to be true in the case of the university women. In the sub-group of 135 who were studied in the fall and in the subsequent spring there was a shift in the range of hæmoglobin levels and an increase of 0.8 gm. in the average. The principal change appeared to be a disappearance of low values, likely due to an increased supply of nutrients needed for hæmoglobin formation during the intervening six months. Those girls who took supplementary iron in the period between observations showed an average increase of 0.9 gm. %. The absence of change in those having values above 13 gm. % might indicate that this level is a normal one for young women. There is not sufficient evidence for this conclusion.

The similarity of the average value found for children in this study with averages previously reported would encourage us to conclude that the value was normal. The variation with age and sex should be recalled in interpreting average values for children and in the use of an average to assess survey results.

Measurement of hæmoglobin is generally regarded as so simple that little attention is paid to it. Results are frequently open to question. Determinations made with Dare or Sahli hæmoglobinometers are simple but not fool-proof. The procedure used in the present study is reasonably simple and rapid. Other recent methods are also available which provide the same advantages. It would seem that more attention should be given to hæmoglobin estimations and that attempts should be made, at least in hospital and in diagnostic laboratories, to provide accurate and dependable results.

Customary methods for the expression of hæmoglobin values are also open to question. The practice of giving values as percentages of some standard, particularly without stating the standard, serves no useful purpose and causes confusion. The plan of giving hæmoglobin values as grams % is simple, obviates current difficulties, and makes possible ready comparison with the results of others.

SUMMARY

Determinations of hæmoglobin were made in two groups of elementary school children, aged 5 to 16 years, and in a group of 1,080 university women students. For 718 children the range of values was 9.0 to 16.1 gm. % with an average of 12.5. The range for young women was 7.2 to 16.1 gm. % and the average was 12.0.

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REFERENCES

1. Medical Research Council Special Report Series, No. 252, H. M. Stationery Office, London, 1945.
2. MACY, I. G.: Nutrition and Chemical Growth in Childhood, Vol. II, Chas. C. Thomas, Springfield, Ill., p. 1404, 1946.
3. OHLSON, M. A., CEDERQUIST, D., DONELSON, E. G., LEVERTON, R. M., LEWIS, G. K., HIMWICH, W. A. AND REYNOLDS, M. S.: *Am. J. Physiol.*, 142: 727, 1944.
4. PEDLEY, F. G.: *Canad. M. A. J.*, 51: 351, 1944.
5. COLLIER, H. B.: *Canad. M. A. J.*, 50: 550, 1944.
6. MOLÉ, R. H.: *J. Physiol.*, 104: 1, 1945.
7. MCCARTHY, E. F. AND VAN SLYKE, D. D.: *J. Biol. Chem.*, 128: 567, 1939.
8. MACKAY, H. M. M., WILLS, L. AND BINGHAM, K.: *Brit. M. J.*, 1: 711, 1946.

CYANOSIS IN INFANTS IN RURAL AREAS

(Well-Water Methæmoglobinæmia)

Harry Medovy, B.A., M.D.,* W. C. Guest, M.D.† and Maurice Victor, M.D.‡

Winnipeg, Man.

INTERMITTENT or persistent cyanosis in an infant in the first few weeks of life is a cause for alarm to the parents and deep concern to the doctor. The physician naturally thinks of congenital heart disease, abnormalities of the respiratory tract, diaphragmatic hernia or enlargement of the thymus gland—all conditions which carry a serious prognosis. It is the purpose of this report to show that cyanosis in this age group may be due to methæmoglobinæmia brought about by the ingestion of contaminated well-water of high nitrate content. This condition is not necessarily serious and probably occurs much more frequently than has hitherto been suspected.

Since methæmoglobinæmia was first described in 1902,[1] sporadic cases have been reported from time to time. Usually the causative agent has been a drug such as acetanilide, phenacetin, potassium chlorate or one of the nitrates. With the introduction of sulfonamides, many more cases of methæmoglobinæmia were described. Enterogenous methæmoglobinæmia, a rare condition associated with diarrhœa in adults and probably due to absorption of nitrites from the

* Lecturer in Pædiatrics, University of Manitoba.
† Vita, Manitoba.
‡ Senior Intern in Medicine, Winnipeg General Hospital.

gut, has also been described. Even rarer is congenital methæmoglobinæmia, which is occasionally familial.[2]

The reported cases of methæmoglobinæmia in infancy have nearly all been in association with drugs, usually the nitrates. Bismuth subnitrate used for roentgenological diagnosis has produced, in several instances, severe, even fatal methæmoglobinæmia in infants.[3] Roe[4] in 1933 reported death from methæmoglobinæmia of a month-old baby who was treated for diarrhœa by two-hourly doses of 10 grams of bismuth subnitrate. Within 24 hours the infant became cyanosed. Oxygen therapy made no difference to the cyanosis. The nitrate was stopped after 44 hours, but the infant died 60 hours after the first dose of bismuth subnitrate was administered. Ever since this case report pædiatricians have rarely used this drug and have found the subcarbonate quite satisfactory.

In 1940 Schwartz and Rector[5] reported a case of "Idiopathic Methæmoglobinæmia" in a two weeks' old infant in a small Montana town. The birth was normal. The infant had received no drugs. It was fed an evaporated milk mixture. There was no mention of the water used in the formula, but it was probably well-water. On admission to hospital the history was that of an intermittent cyanosis, which had suddenly become more intense. There was no evidence of disease of the heart or lungs. The cyanosis did not respond to oxygen or coramine. Spectroscopic examination proved the presence of methæmoglobinæmia. One c.c. of 1% methylene blue (3 mgm. per kilo body weight) was injected intravenously. The cyanosis disappeared within half an hour. At 8 months of age the baby was in good health and of normal colour. There seems little doubt that this is the first reported case of methæmoglobinæmia due to well-water.

In 1945 Comly[6] reported from rural Iowa two cases of methæmoglobinæmia in infants, caused by the use of milk formulæ containing well-water of high nitrate content. Two later articles[7, 8] have described similar cases occurring in Belgium and in rural Kansas.

The following are descriptions of one definite and one probable case occurring in rural Manitoba and rural Ontario.

CASE 1

Baby girl A.H., was born April 24, 1946. The delivery was normal; birth weight 7 lb. 11 oz. She appeared normal at birth except for minor bilateral malformations of the pinnæ of the ears. The mother, older brother and sister all have the same malformation. The baby's course in hospital was normal.

On the tenth day the baby was discharged to its home at Greenridge, Man. Coincidentally the mother's breast milk became scanty and the baby was given a formula of milk 16 oz., water 14 oz. and syrup 1 oz.

On May 27, at the age of 5 weeks, the baby was brought to the hospital at Vita, Man., because of cyanosis dating back to the age of 3 weeks. Except for the marked cyanosis no other findings were evident. The baby was immediately sent to Winnipeg for consultation, where she was promptly seen on arrival. She had now a peculiar slate-grey cyanosis, breathed somewhat rapidly and appeared rather listless, although not alarmingly so. There were no signs of disease of the heart or lungs. There was no diarrhœa. With the Iowa cases in mind, the parents were questioned about the water supply. It then developed that the mother had made the formula out of rain-water for the first two weeks and then had switched to well-water. The cyanosis had developed within a few days of this change. No drugs had been given.

Venous blood was drawn and sent to Professor F. W. White of the Department of Biochemistry of the University of Manitoba. It was chocolate brown in colour. A methæmoglobin band was seen on spectroscopic examination. (Colour photographs were taken of the baby for purposes of record.)

The parents were anxious to get home, and, since the baby's general condition was satisfactory, they were allowed to go, with instructions not to use the well until the water had been analyzed, and to give the baby ascorbic acid 25 mgm. every four hours.

Two days later the parents reported, by phone, that the cyanosis was almost gone by the time the baby reached home and was completely gone the next day. No ascorbic acid had been given by the parents, because of the evident, spontaneous improvement.

In January, 1947, the family doctor reported the baby to be in good health and of normal colour and appearance.

The well in question was examined by an inspector from the Manitoba Department of Health and Public Welfare and the following observations made. "The well is on down grade, 150 feet from the barn, 250 feet from the house. It was not well protected, had a wooden platform and the animals were watered close by. The well itself was 20 feet deep with a bucket conveyance and a manual lift pump. The yard around the house was found in a satisfactory condition. The barn yards were generally in an unsanitary condition with manure, water and pig-pen wastes, etc."

Mr. W. M. Ward of the Bureau of Industrial Hygiene analyzed the well-water and found 150 parts of nitrate and 0.92 of nitrite per million. A later specimen contained 250 parts of nitrate per million, indicating even greater contamination. The upper limit of safe nitrate content is regarded as 10 parts per million.

This then is a case of an infant developing methæmoglobinæmia originating in contaminated well-water of high nitrate content, and spontaneously cured by discontinuing the use of this water. Spontaneous recovery under these circumstances probably occurs frequently, and is

in accord with the observations of Halpern and Roche, quoted by Ferrant,[7] that if the toxic agent is withdrawn, sponataneous transformation of the methæmoglobin into normal hæmoglobin occurs and is almost complete after thirty-six hours.

CASE 2

Baby boy McG. was born in rural Ontario November 1, 1946. Birth story was uneventful. On December 14 he was given a formula consisting of evaporated milk, water and corn syrup. The mother's description of the course of events is quoted verbatim. "During the next week we noticed blueness and the following Saturday he was definitely ill but not continuously blue. Some days he would be positively deathlike in appearance and later in that same day would show improvement."

The infant became worse during Christmas week, did very little crying and appeared to be quite listless. On the advice of Dr. Colbert of Dryden, Ontario the baby was brought in to Winnipeg for consultation. He arrived on December 30 but was not seen by us until the following day. During this interval Winnipeg water was used in the formula. On examination in the office some thirty-six hours after his arrival in the city, his colour seemed normal and no evidence was found of any abnormality of heart or lungs. The mother expressed embarrassment at bringing an apparently normal baby several hundred miles to a doctor's office but was obviously pleased at the evident recovery of her baby. An x-ray film of the infant's chest was normal. In view of our experience with the previous case the mother was advised to have the well-water used in preparation of the formula analyzed and was warned not to use this water until the report was received.

Dr. A. R. Bonham, chief provincial analyst of the Ontario Department of Health reported that the well-water contained 110 parts of nitrate per million.

On February 4 the mother wrote as follows: "The baby is now in splendid health and there has been no recurrence of blueness. . . . I now use water from a well 100 yards from the house. The well containing the nitrate is inside the house—the well from which I am using water now is outside."

MECHANISM OF PRODUCTION

Methæmoglobin is normally present in blood to the extent of 1%.[11] It is not toxic in itself, but is unable to carry oxygen. When two-thirds of the hæmoglobin of a dog has been transformed into methæmoglobin, death results.[10]

The mechanism by which methæmoglobinæmia is produced in infants has been explained as follows: it is established that the nitrite ions, by uniting with hæmoglobin, produce methæmoglobin. Normally neither nitrites nor nitrates are ingested. When nitrates are ingested or produced in the intestinal tract these are not absorbed but are reduced to nitrites, and then to ammonia and excreted as such. In the presence of greatly increased quantities of nitrates, due either to ingestion of nitrate drugs or of well-water with a high nitrate content, it is possible that the nitrites have no time to be completely reduced, and reach the circulating blood. This is particularly apt to occur if diarrhœa is present. Perhaps the mucosa of the infant allows more rapid absorption of nitrites. The nitrite ion is the effective agent in the production of methæmoglobinæmia. This has been well established by several investigators. A molecule of nitrite ion reacts with two molecules of hæmoglobin to form methæmoglobin.

Normally methæmoglobin is reduced by an enzyme system within the blood corpuscles. However if methæmoglobin accumulates in great excess this mechanism may break down and the amount of methæmoglobin in the blood may rise to dangerous levels. Simple withdrawal of the source of excess nitrite results in the almost complete disappearance of excess methæmoglobin in 36 hours.

For the infants reported herewith, and from Iowa, Kansas and Belgium, water with a high nitrate content due to contamination of improperly constructed wells by animal and vegetable waste, was used in making up evaporated or powdered milk feedings. The ingestion of excess nitrate resulted in cyanosis, which, in our cases and in some of the previously reported cases, cleared up spontaneously within 36 to 49 hours after discontinuing the use of the contaminated well-water.

Frequency.—Clinical methæmoglobinæmia in infancy due to the ingestion of well-water is probably more common than realized. Cases have so far been reported from rural areas of Iowa, Kansas, Belgium, Manitoba and Ontario. The publication of these cases has brought to light many other cases of transient cyanosis by physicians who were previously unaware of the cause of the methæmoglobinæmia.

When one considers how many thousands of poorly constructed, contaminated wells there must be in rural areas in Canada, one wonders why more cases of well-water methæmoglobinæmia have not been reported. There are probably many cases of minimal transient cyanosis that are never seen by the doctor. The more severe cases which find their way to a consultant usually arrive too late to show the characteristic cyanosis since there is a natural tendency to rapid disappearance of the

methæmoglobin if the infants are fed milk mixtures which are free of nitrates.

All the reported cases have occurred in infants in the first two months. No cases have occurred among older children even though the same well-water of high nitrate content was used for drinking. This suggests that the two factors most concerned in the production of methæmoglobinæmia are the nitrate content of the well-water and the body weight of the infant. Infants fed on breast milk or undiluted acidified milk mixtures would not be likely to develop the disease. The risk of methæmoglobinæmia rises proportionately with the amount of water used in the infant's feedings. The incidence of cases of well-water methæmoglobinæmia would therefore be greatest in areas where farm sanitation was poor, wells poorly constructed and dried milk mixtures extensively in use.

Prognosis.—The only reported death is in a case of Ferrant's.[7] If the condition is promptly recognized and the contaminated well abandoned spontaneous recovery may be expected within a matter of two or three days. Treatment with methylene blue appears to be very successful in the more severe cases.

Treatment.—(1) Spontaneous recovery. In both of the reported cases no treatment was given other than discontinuing the use of the suspected well-water. The most important factor in treatment is therefore the recognition of the disease. Complete recovery occurs within one or two days.

(2) Methylene blue. In 1933 Williams and Challis[12] reported the use of methylene blue in the treatment of methæmoglobinæmia due to aniline dye poisoning. Experimentally methylene blue will reconvert methæmoglobin to hæmoglobin in 10 minutes, if the methæmoglobin content has not risen to more than 40 to 50% of the total pigment. One mgm. per kilo body weight is given intravenously. (0.5 c.c. of 1% methylene blue to an infant weighing 8 lb. would be a suitable dose.) This is the method of choice for severely cyanosed cases.

(3) Ascorbic acid. This has been successfully used by Barcroft in the treatment of familial methæmoglobinæmia where the normal enzyme system is at fault. Barcroft is not optimistic about its value in methæmoglobinæmia due to drugs, and no reported cases of its use in these cases have been noted.

CONCLUSION

1. Two cases of cyanosis in young infants due to excessive nitrate in contaminated well-water are reported.

2. Spontaneous recovery occurred in both cases.

3. Well-water methæmoglobinæmia should be considered as a possible cause of cyanosis in an artificially fed infant.

4. The ideal feeding for an infant is breast milk. Where the water supply is suspected the safest artificial feedings are those that require the least water in their preparation. In order of safety these would be: (*a*) undiluted acidified milk mixtures; (*b*) cows' milk mixtures; (*c*) evaporated milk mixtures; (*d*) dried milks.

Since this article was submitted, one baby has been seen personally, and three others heard about by personal communication. All of these babies had marked cyanosis in the first two months of life, and all recovered within a few days of changing the source of water in the formula. All were artificially-fed babies living in rural areas. The water in each case is being tested for nitrate content.

Dr. Bruce Chown, Pathologist, Children's Hospital, Winnipeg, gave valuable suggestions in the preparation of this paper. Dr. Frank W. White of the Department of Biochemistry of the University of Manitoba, did the blood analyses. Mr. M. W. Ward did the water analyses. Dr. Max Bowman of the Department of Health and Public Welfare, gave valuable assistance in investigating the well in the Manitoba case.

REFERENCES

1. STOKUIS AND TALMA: Cited by Ferrant, M., *J. Pædiat.*, **29**: 585, 1946.
2. BARCROFT, *et al.*: *Clinical Science*, **5**: 145, 1945.
3. ROE, H. E.: *J. Am. M. Ass.*, **101**: 352, 1933.
4. *Ibid*: *J. Am. M. Ass.*, **101**: 352, 1933.
5. SCHWARTZ, A. S. AND RECTOR, E. J.: *Am. J. Dis. Child.*, **60**: 652, 1940.
6. COMLY, H. H.: *J. Am. M. Ass.*, **129**: 112, 1945.
7. FERRANT, M.: *J. Pædiat.*, **29**: 585, 1946.
8. FAUCETT, R. L. AND MILLER, H. C.: *J. Pædiat.*, **29**: 593, 1946.
9. HALPERN AND DUBOST: Cited by Ferrant, M., *J. Pædiat.*, **29**: 585, 1946.
10. ROCHE, J.: Cited by Ferrant, M., *J. Pædiat.*, **29**: 585, 1946.
11. PAUL, W. D. AND KEMP, C. R.: *Proc. Soc. Exper. Biol. & Med.*, **56**: 55, 1944.
12. WILLIAMS, J. R. AND CHALLIS, F. E.: *J. Lab. & Clin. Med.*, **19**: 166, 1933.

The office of apothecary is of very ancient date. The Greek and Roman physicians were their own apothecaries, and when they ceased to act in that capacity is not exactly known. Conring asserts (*De Antiquitatibus academicis*) that the physicians in Africa first began to give up the preparation of medicines as early as the time of Avenzoar, in the eleventh century. This accounts for many Arabic terms of art being introduced into pharmacy and chemistry, and explains why the first known apothecaries were in the lower part of Italy and their legal establishment in the kingdom of Naples.