subacute necrotizing myelitis, asymmetrical haemorrhagic encephalopathy, degenerative softening, and so on. We especially draw attention to reports of eosinophilic meningitis with focal malacia—with clinical acute paralytic signs (or those of transverse myelopathy) and a complete absence of evidence indicative of cause (virus, bacteria, or any other—but helminths never considered). It is even conceivable that some cases of reputed disseminated sclerosis, with predominant spinal signs, which do not progress after a primary paralytic attack could be of this nature. A study of the reported data in veterinary pathology might conceivably help to a better understanding. The observation of asymmetrical cerebral cavitation (caused by nematodes ?) in newborn and young calves by one of us (C. S.) might raise speculations in other directions; for multicystic degeneration in the brain of newborn and young children, of unestablished cause, is adequately dealt with in neuropathological literature.

Conclusion

Finally, some indirect support for our ideas arises from Wilder's (1950) work on human endophthalmitis. In 46 eyes of children and adolescents, received from many parts of the U.S.A., a variety of original diagnoses had been made; all showed some features of an eosinophilic or granulomatous lesion, but in none of the original sections were worms present. Serial sections (in one eye—2,300 slides) revealed the finding of a larva in 24 eyes, and the changes were so uniform in type that a diagnosis of nematode endophthalmitis was made for all 46. This disease has an exact analogy in an ocular disease of horses in India, known almost from antiquity, and is caused by *Setaria (digitata ?)*; peculiarly enough, it is sometimes associated with paraplegia (Kumri), which we think is cerebrospinal nematodiasis. Perhaps such human helminthic ocular lesions are no more than an extension in sequence and location of intracranio-vertebral nematodiasis—that is, helminthic parasites can enter the eye via the cranial cavity. In Japan, ocular filariasis in horses is also common, and is also caused by *Setaria digitata* (see Kume, 1951), but onset is about a month later in the year than that of the nervous disease, and both may occur together. This same probability might be remembered in human medicine.

REFERENCES

Beautyman, W., and Woolf, A. L. (1951). *J. Path. Bact.*, **63**, 635.
Evans, G. (1880). In H. H. Scott's *History of Tropical Medicine*, 2nd ed., 1942.
Innes, J. R. M. (1951). *Brit. vet. J.*, **107**, 187.
—— and Shoho, C. (1952). *Arch. Neurol. Psychiat.* (in press).
—— —— and Pillai, C. Perumal (1952). *Brit. vet. J.*, **108**, 71.
Kume, S. (1951). *Recent Advances in Veterinary Science*, p. 186. University, Tokyo. (In Japanese.)
Lumsden, C. E. (1949). *Brain*, **72**, 517.
McGaughey, C. A. (1951). *Brit. vet. J.*, **107**, 449.
Niimi, D., and Kimura, T. (1939-41). *Trans. Soc. path. jap.*, **29**, 466; **30**, 539; **31**, 609. (In Japanese.)
Olitsky, P. K., Casals, J., and Tal, C. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 276.
Sabin, A. B., Ginder, D. R., and Matumoto, M. (1947). *Amer. J. Hyg.*, **46**, 341.
Shoho, C. (1952). *Jap. J. exp. Med.* In press.
Shope, R. E. (1943). *J. exp. Med.*, **77**, 127.
Sugawa, Y., Mochizuki, H., and Yamamoto, S. (1949). First report on Japanese Equine Encephalitis. Government Experimental Station for Animal Hygiene, 9.
Syverton, J. T., McCoy, O. R., and Koomen, J. (1947). *J. exp. Med.*, **85**, 759.
Tanaka, T., Suu, S., Shoho, C., and Yamagiwa, S. (1945). *Jap. J. vet. Sci.*, **7**, 117.
Tiner, J. D. (1951). *J. Parasitol.*, **37**, Sect. 2, Suppl. 21.
von Brand, T., and Cullinan, R. P. (1943). *Proc. helminth. Soc. Wash.*, **10**, 29.
Wilder, Helenor C. (1950). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **54**, 99.
Yokagawa, S. (1923). Taiwan Igakkai Zasshi (*J. Formosan med. Ass.*), pp. 226, 241. (In Japanese.)

A note in the *Royal Army Medical Corps News* reports that Sir Almroth Wright's work at the Royal Victoria Hospital, Netley, has been commemorated by the erection of a plaque in the main hall of the hospital. Sir Almroth was at one time professor of pathology in the Army Medical School, and made the first trials of anti-typhoid inoculation on himself and the surgeons on probation in the laboratory of the hospital between 1895 and 1898.

HEREDITARY METHAEMOGLOBINAEMIC CYANOSIS

BY

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The increased interest in heart surgery, as introduced by Tousin, Gross, Blalock, d'Allaines, Bonzelot, Lenègre, Soulie, Karayannopoulos, Tountas, Karageorges, and Papanicolis, has drawn attention to the problem of cyanosis as a whole, and not merely as a symptom of congenital malformation of the heart. In a series of investigations of the various cyanotic conditions which I have been carrying on with my associates, Drs. Loucatos and Loutsides, since 1946 (Codounis, Loucatos, and Loutsides, 1947, 1948; Codounis, 1948, 1949), a morbid autonomous entity of the red corpuscle has been defined which we have called "hereditary methaemoglobinaemic cyanosis" (H.M.C.) and which has been increasingly attracting medical attention.

Since 1844, when François described the first Belgian cases of cyanosis without cardiopathy, only 19 similar cases had been noted in the literature up to 1945 by Sievers and Ryon, including their one case and the two of Lian and his co-workers. With the addition of single cases by Graybiel *et al.* and Barcroft and his associates, the total recorded cases of this kind of cyanosis was raised to 21 by the end of 1945.

In 1946 we added our 14 cases of the Vaftochilary family (Chart 1), demonstrating definitely for the first time the hereditary mode of transmission of congenital and familial methaemoglobinaemic cyanosis. At the same time we completed the study of its clinical, biological, and therapeutic aspects. Confirmation of our conclusions has come from Bensis, Gouttas, Pyrros, and Vacrinos (Athens Medical Society, 1947); King, White, and Gilchrist (1947); Gibson and Harrison (1947), who published five cases in a family of nine; and Lutembacher (1949), who found six similar cyanotic cases in four generations of one family. A case has also been reported by Fisher and Wide Price (1949).

Having had occasion during the last two years to study a new genealogical tree comprising 85 members who lived throughout Southern Greece, including 10 born cyanotics, I thought it might be of interest to present this study with a summary of our investigations as a whole. I hope that this research will adequately elucidate this genotypic disease of the blood and differentiate it from other cyanotic conditions.

A New Family Tree

In the study of our second family tree (Chart 2), the Melaniarides (a nickname given the family by people of the district who were impressed by their unusual colouring: *melani*, ink; *vafo*, colouring; *helos*, lips) we followed the system used in that of the Vaftochilary family. Convinced after a series of clinico-biological tests that the two cyanotic sisters—Nos. 7 and 8 of this tree—who came to see us in October, 1949, with a diagnosis of congenital heart disease were actually H.M.C. cases, we thought it wise to undertake a special investigation in order to reach 85 members of the different families of this tree spread over a number of

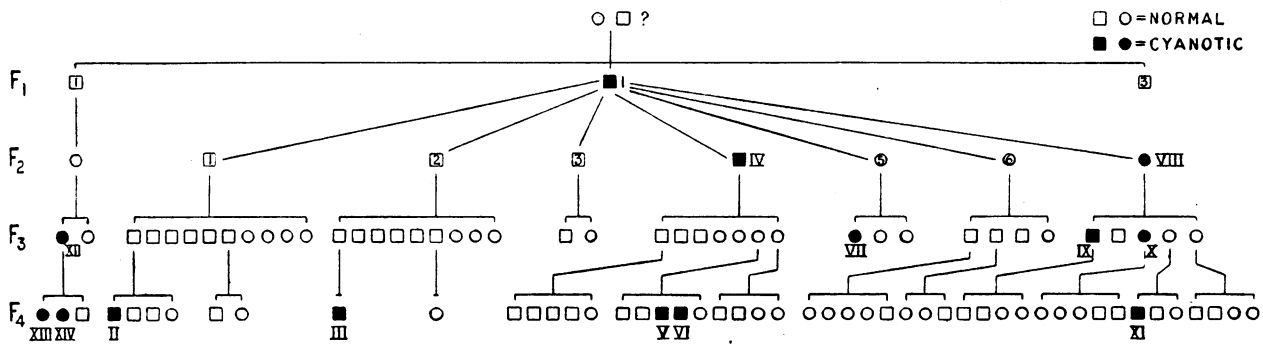

CHART 1.—Genealogical tree of the Vaftochilary family.

villages in the Peloponnese. This investigation had two objectives: to complete our information, and to examine and confirm facts concerning those living subjects suffering from cyanosis—their husbands and wives, their ancestors and descendants—and inquire about the dead. We had to travel long distances by foot or on mule-back over rough terrain. It was thus possible for us to study points of clinical and laboratory interest and to examine spectroscopically the living cases Nos. 2–10 of the third, fourth, and fifth generations.

Case 1 of the first generation died of old age at 80, and we collected data from the country doctor and older persons who had known him. Our investigations also included the husbands or wives unaffected by the disease and other unaffected relatives, not only clinically but spectroscopically, in order to detect methaemoglobin in the blood. This test was negative for all non-cyanotic cases.

1. Branch A

From the first couple of the Melaniarides family two daughters and one son were born, who constitute the first generation (F_1). We do not know which of the two parents transmitted the morbid trait to the later generations of this tree.

The two daughters of this first generation present no apparent cyanosis. The son, however, cyanotic No. 1, ancestor of five successive generations of Branch A, had suffered, according to information given by the country doctor and others, from a very marked cyanosis ever since his birth. Despite the disease he had attained the age of 80 when he died. He was the father of two sons and one daughter, none of whom showed any signs of cyanosis. The disease, however, skipping a generation, was transmitted through his two sons to his grandchildren (F_3). One of his sons, although not cyanotic, transmitted the morbid trait to his only son in a very noticeable degree (No. 2—F_3). The other, although having inherited the morbid trait in a latent manner, did not transmit it directly to any of his children—two sons and one daughter—but through one of his carrier sons to his granddaughter (No. 3—F_4). She in turn married a healthy individual of Branch C of this tree (we shall see further that this branch gave rise to no cyanotics whatsoever), and transmitted the disease directly and to a morbid degree to one of her sons and one of her daughters out of a family of five (Nos. 4 and 5—F_5). This branch has thus produced five cyanotics out of 21 members.

2. Branch B

This branch comprises 47 members spread through four generations. They are the descendants of sister B of cyanotic No. 1, whose descendants we have just studied up to the fifth generation. This branch is of particular interest. It has, like Branch A, produced five cyanotics—No. 6 in the F_3 and Nos. 7, 8, 9, and 10 in the F_4. Considering all that has preceded, we must conclude that the morbid trait was transmitted by sister B, and that she must have been a carrier in the latent stage.

This carrier B of the first generation married an unaffected individual, gave birth to three sons and two daughters, and transmitted the disease in a latent stage to only one of the three sons. The latter, father of five sons and two daughters, transmitted the cyanosis to a marked degree to one of his daughters (No. 6—F_3) and in a latent form to one of his sons. This son married a normal individual, had four daughters, of whom three were complete cyanotics from birth (Nos. 7, 8, and 9—F_4), and two sons, of whom one was also a cyanotic from birth (No. 10—F_4).

It is noteworthy that in this family we find not only the congenital and hereditary character of the disease, but also the familial character, as in the F_5 generation of Branch A. We also met this familial character of the cyanosis in the family tree of the Vaftochilarys.

3. Branch C

Among the 16 members of this branch in four generations, all descendants of sister C of cyanotic No. 1, we have not encountered one single cyanotic. It will be of interest to study later generations in order to see whether they are devoid of cyanosis or will eventually produce some cyanotic condition.

Discussion of the Cases

The members of the Melaniarides family did not intermarry. The disease affects and is transmitted by men as well as women, as is seen in other hereditary diseases such as haemolytic congenital jaundice (Lemy), some kinds of thrombocytopenia, various anaemias such as sickle-cell anaemia, etc. There seems, however, to be a predominance in the male sex in the inheritance of the disease as well as in its transmission.

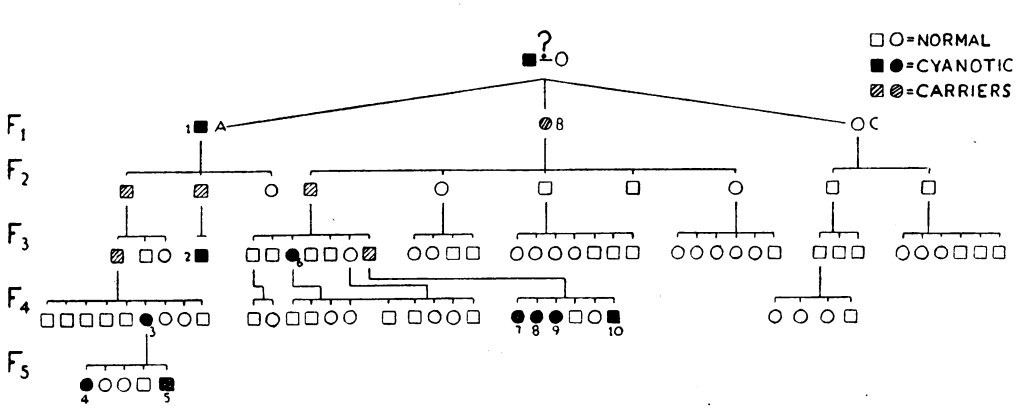

CHART 2.—Genealogical tree of the Melaniarides family.

It is still not known whether in this tree of the Melaniarides family the transmission of the morbid trait follows Mendelian laws, as it does in the Vaftochilary family tree. It appears to be a recessive, as noted by Gibson and Harrison in their case. Lutembacher, Zacopoulos, and we ourselves found cases with inheritance apparently as a dominant character. Thus in four out of five complete genealogical trees of H.M.C. in the literature, the transmission of the morbid trait seems to occur as a dominant, whereas in one (that of the Melaniarides) it seems to be recessive.

In a paper (Codounis, Loucatos, and Loutsides, 1948) we stressed the difficulties encountered by the student of human heredity. In the transmission of morbid hereditary traits several factors and mechanisms are involved, as Butterworth, Kracke, and Riser (1950) also point out in their study on the heredity of spherocytic anaemia in the negro. Therefore, in the hope that fresh studies will further illuminate this field of heredity, we prefer to leave the discussion open concerning the dominant or the recessive mode of transmission of the cyanotic trait.

Since this study 18 cases in two further trees have been discovered by Zacopoulos, a director of the Cardiological Clinic of Military Hospital 423. He suspected that two unrelated soldiers who were patients in his clinic were suffering from cyanosis without cardiac anomaly. He brought them to me, and clinical and spectroscopic blood examination proved that they were actually suffering from H.M.C. One soldier came from Tripolis, in the Peloponnese, and the family consisted of 26 members in four generations, with seven born cyanotics. The other soldier's family tree, in Ptolemais, in Macedonia, consisted of 26 members in three generations, with 11 born cyanotics.

Baltzan and Sugarman (1950) also made a study of a new family tree of four generations which contained 15 cyanotics with inheritance as dominant. This brings the grand total of reported cases up to 92 (see Table). Incidentally, these authors claim to be the first to describe and prove the hereditary basis of this disease, having apparently overlooked all the previous work cited above.

Table Showing the Family Trees of H.M.C. Published from 1946 to 1951

Authors	Nationality	Age	Generations	Members	Cyanotics	Males	Females	Mode of Transmission of the Morbid Trait	Met-Hb		Total Met-Hb (g.%)
									Method of Determining	Amount (g.%)	
Codounis, Loucatos, Loutsides (1946) "Vaftochilary" tree	Greek	6–80	IV	103	14	8	6	Dominant	Spectroscopic		25–30
Codounis, Loucatos, Loutsides (1949) "Melaniarides" tree	,,	6–80	V	85	10	4	6	Recessive	,,		18–40
Lutembacher's tree (1949) ..	French	8–85	V	21	7	2	5	Dominant	,,		—
Zakopoulos's "Tree of Tripolis" (1950)	Greek	18–75	IV	26	7	5	2	,,	,,		10–52
Zakopoulos's "Tree of Ptolemais" (1950)	,,	23–70	III	26	11	5	6	,,	,,		10–52
Baltzan and Sugarman (1950)	Canadian	16–35	IV	33	15	9	6	,,	,,	18–32	15–24

Clinico-biological Aspects of Hereditary Methaemoglobinaemia

On the basis of our experience it is proposed to give a clinico-biological description of this new hereditary disease of the blood, which is an autonomous morbid entity of the red corpuscle.

A. Symptomatology

The dominant clinical symptom which impresses the physician as well as the patient and others is the cyanotic hue, which is violet and sometimes even brownish. The word cyanosis does not always convey a precise idea of the colour of these patients. The hue is usually dichromatic between the blue and the red, or the violet blue and the brown.

The degree of cyanosis is relative to the amount of methaemoglobin present in the blood, varies with each patient, and can be described as light, medium, and marked. Although the cyanosis is ordinarily generalized over the whole body, it is particularly noticeable in the lips, the mucous membrane of the mouth, the tongue, the palate, and the nose, in the cheek-bones and ears, and at the extremities of the fingers and toes, especially under the nails. It may occasionally vary slightly after a muscular effort in some cases, and is a constant characteristic in all patients, being present from birth. Despite the chronic nature of the condition we have never encountered clubbing of fingers, a clinical feature which differentiates it at once from other cyanoses (pulmonary, cardiac, etc.).

As additional symptoms, we note a tendency to dizziness, headaches, dyspnoea (after physical effort), tachycardia, occasional nervous irritability, and, in some cases, general physical weakness. The intensity of these subjective troubles is directly related to the intensity of the cyanosis.

The light form of cyanosis usually presents no serious subjective troubles except an occasional increase during the winter season, or menstruation and other intercurrent conditions.

Cases of moderate and marked cyanosis often present symptoms of anoxaemia. Headaches are the most common manifestation. These disappear as a rule after an injection of 300 to 500 mg. of ascorbic acid or 50 ml. of a 1% solution of methylene blue in isotonic glucose.

Beside these positive signs, an absence of other signs differentiates H.M.C. from all other cyanotic conditions. Thus physical examination never reveals cardiovascular or pulmonary lesions; arterial blood pressure and venous pressure are usually normal; and radiography and electrocardiography are normal.

Dr. Korylos, Director of the Ophthalmological Clinic of the Red Cross Hospital in Athens, reports: "The cases of H.M.C. which we have examined showed no important ophthalmological signs except a light change in the colour of the retina and the diameter of the capillaries. The retina is of a reddish-blue colour. The capillaries, especially the veins, are enlarged and varicose-like. In one case only, the following noteworthy signs were observed: in the right eye, divergent strabismus due to amblyopia, the lens showing a posteriorly cupped cataract; in the left eye, except for a light congestion of the pupil, nothing abnormal was found."

B. Biochemical Remarks

The characteristic sign of this congenital, familial, and hereditary disease is the constant presence in the blood of intracellular methaemoglobin (Met-Hb), which may be discovered spectroscopically. The Met-Hb is the cause of the cyanosis in this disease in our own cases as well as in those described in the medical literature, with the exception of Lutembacher's, in which, despite the intense cyanosis and other features, the band of Met-Hb was missing from the spectrum.

This absence of Met-Hb, if it be later confirmed by other authors, must lead us to suppose that there can be asymptomatic cases of H.M.C. from which one of the clinical or haematological symptoms may be lacking. A similar case was reported in the case of spherocytic anaemia of the negro by Butterworth and his co-workers. But we wonder

whether Met-Hb was actually absent, because we ourselves would more than once have failed to find it if we had not made special efforts. In such cases one must use for the spectroscopic test: (1) a solution of blood in distilled water in the proportion of 1:20, 1:10, or even 1:5; (2) a strong light to develop the spectrum. It often happens, in fact, that Met-Hb, when present in small quantities, does not give the characteristic band in the red if the solution of the blood for spectroscopic examination is too diluted.

The quantitative measurement of Met-Hb by the Dubost method has given us yields from 25–50% of the total haemoglobin (Vaftochilary family), 18–40% for the Melaniarides, and 10–52.5% for the cases of Zacopoulos. It was always intracellular and never extracellular, and discoverable *in vivo* in the ear lobe.

As regards other blood examinations, occasionally we find a slight increase in red and white blood cells, the haemoglobin is either normal or slightly subnormal, the cells normal, and other blood constituents all normal, like the W.R. Urine analysis has also usually been normal.

We have failed to find any correlation whatsoever between this methaemoglobinaemia and blood groups, including the Rh factor. In a certain number of our patients we found a decrease below 0.40 mg. ascorbic acid per 100 ml. of blood. This C-hypoavitaminosis was confirmed by the saturation method.

C. Prognosis

The prognosis of H.M.C. is good, since most of the patients reach an advanced age.

D. Treatment

Although convinced of the hereditary nature of the disease, we have also, however, tried the therapeutic means employed in other cyanoses—ascorbic acid and methylene blue—by intravenous injections or orally. The favourable influence of these drugs on the cyanosis as well as on the subjective troubles of the patients and the sometimes spectacular reduction of methaemoglobin to haemoglobin are only temporary, and continuous oral administration of ascorbic acid is necessary. It is interesting, by the way, to note that the patients themselves felt the favourable effect of lemon and orange juice and other foods rich in ascorbic acid.

Although it is true that the light and medium cases of methaemoglobinaemia are symptomless, the cyanosis in itself is nevertheless not very pleasant, especially for young girls. Thus one sees them submitting to an intravenous injection of methylene blue or ascorbic acid (300 to 500 mg.) in order to obtain, usually at the end of 10 minutes, a decoloration which may last 10 to 15 days, and which is made to last by absorbing 10 to 30 mg. ascorbic acid daily if they do not prefer an injection every 10 or 15 days.

Summary

A new genealogical tree of hereditary methaemoglobinaemic cyanosis (H.M.C.) of five generations, comprising 85 members and including 10 born cyanotics, is described.

H.M.C., also known as congenital or familial cyanosis, or methaemoglobinaemic idiopathic cyanosis, is a distinct clinical entity characterized by the presence of methaemoglobin in the blood, and the absence of clubbing of the fingers. It exists from birth and is inherited by both sexes, with a preponderance in men.

It is thus quite distinct from cyanosis due to congenital heart disease or arteriovenous shunt, to polycythaemia, or to drug intoxication.

Although 42 out of the 92 described cases are in Greeks, the condition has been reported from all continents, so far only in white men.

It is a pleasant duty to express our gratitude and thanks to Mr. Constantine Georgopoulos, president of the Hellenic Red Cross, for the encouragement and support which he gave us in the pursuit of our investigations; and also to Professor D. Chondros for his learned advice and for the loan of the precious spectroscope, of which he deprived himself in order that we might make our measurements of methaemoglobin.

REFERENCES

Baltzan, D. M., and Sugarman, H. (1950). *Canad. med. Ass. J.*, **62**, 348.
Barcroft, H., *et al.* (1945). *Clin. Sci.*, **5**, 145.
Butterworth, C. E., Kracke, R. R., and Riser, W. H. (1950). *Blood*, **5**, 793.
Codounis, A. (1948). First International Conference of Hematology Buffalo, N.Y.
—— (1949). *Sang*, **20**, 195.
—— Loucatos, G., and Loutsides, E. (1947). *Bull. Acad. Méd. Paris*, **32**, 597.
—— —— —— (1948). *Sang*, **19**, 65.
Fisher, B., and Price, J. W. (1949). *J. Lab. clin. Med.*, **34**, 1677.
Gibson, Q. H., and Harrison, D. C. (1947). *Lancet*, **2**, 941.
Graybiel, A., *et al.* (1945). *Bull. Johns Hopk. Hosp.*, **76**, 155.
King, E. J., White, J. C., and Gilchrist, M. (1947). *J. Path. Bact.*, **59**, 181.
Lutembacher, R. (1949). *Presse méd.*, **57**, 276.

METHAEMOGLOBINAEMIA DUE TO NITRATES IN WELL-WATER

BY

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Since Comly (1945) reported two cases of cyanosis due to methaemoglobinaemia in young infants caused by the ingestion of nitrates in well-water, numerous cases have been reported from Canada and the U.S.A., a few from Belgium, and some from other countries. Ewing and Mayon-White (1951) reported cases found in a rural area of Suffolk, which were the first recorded in the United Kingdom. It is believed that the present case is the first to be detected in Northern Ireland, although the circumstances necessary for the production of the condition must be relatively common in a predominantly rural community such as this.

Case Report

This infant, a female, was born by normal spontaneous delivery at full term; she cried quickly and gave no trouble in the immediate post-natal period. She was breast-fed for three weeks only, and then weaned on account of "insufficient milk." She was put on to feeds of full-cream dried milk, on which she gained weight. One week after receiving the artificial feeds she began to vomit two or three times a day, generally one to two hours after a feed, quite copiously but not very forcefully. She appeared to be in pain before the vomit. Citrate tablets given in the feeds seemed to reduce the vomiting for a week, but it then recurred, and for five days before her attendance at the outpatient department it had been severe. The bowels were opened once or twice a day, the stools being greenish. On the day before attending hospital she was noticed to be blue, almost black, about the lips and finger-tips.

On examination (June 29, 1951) the infant was seen to be well nourished and energetic. There was generalized slate-blue cyanosis, especially over the lips and fingers. The mouth and throat were healthy. No abnormal signs could be detected in the heart or lungs. The abdomen was normal, the spleen could not be palpated, and no pyloric tumour was felt. The association of marked cyanosis with the generally well-nourished appearance of the infant and the absence of signs in the heart or lungs led to a tentative diagnosis of enterogenous cyanosis. Inquiry revealed that the family drew their water from a well on their own farm. The child was accordingly admitted for confirmation of the diagnosis and for treatment.

Investigations.—Unfortunately it was not possible to carry out a blood examination until the following morning, by