started before irreversible acidotic damage has occurred.

SUMMARY

Two infants with cyanotic congenital heart disease are reported. Though both had arterial oxygen tensions of 20 mm. Hg, only one had a reduced oxygen uptake, developed a significant lactic acidosis and died. Attention is drawn to the importance of an assessment of acid-base balance as well as arterial oxygen tension in patients with cyanotic congenital heart disease in relation to the improvement in cardiorespiratory function and prognosis attendant on a normal acid-base balance.

We thank Dr. M. Braudo for permission to study Case 1 (Ku.), and Drs. I. Booth and R. S. Fowler for permission to study Case 2 (Sy.). Dr. B. S. L. Kidd carried out the cardiac catheterization in Case 2. We acknowledge also technical assistance by Mr. D. McIntosh and secretarial help from Miss C. MacLennan.

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CASE REPORT

Megaloblastic Anemia Occurring Simultaneously in White Female Monozygotic Twins

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A FAMILIAL tendency in pernicious anemia was suggested by Sinkler and Eschner[11] as early as 1896. Since that time, many additional families have been studied and an increased familial incidence of the disease has been reported.[2, 4, 6]

Although it appears that the predisposition to pernicious anemia is inherited, most probably as the effect of a single autosomal dominant factor,[7] pernicious anemia occurring simultaneously in monozygotic twins has only rarely been reported. Holly, Felts and Rheingold[5] reported such an instance in 1952. Unfortunately, the authors offered little statistical proof for the monozygosity of their 72-year-old Negro twins. In 1958 Arbo and Mohr[1] presented a well-authenticated report of the simultaneous development of pernicious anemia in white female monozygotic twins aged 79. These authors referred to an observation by Mosbech,[9] who in 1953 found but eight adequately substantiated cases in the literature. Five of these were in females. The age at onset of the pernicious anemia in these subjects varied from 35 to 85 years. In two instances the disease developed at the same time in each twin. In four others there was a difference in the age of onset, varying from one to nine years. McKusick[8] in 1961 failed to find a report of any new case since 1958, and a survey of the more recent literature has not been more successful.

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The purpose of this communication is to present a report of white female monozygotic twins who developed megaloblastic anemia almost simultaneously at the age of 63.

CASE 1.—The first twin, Mrs. M.MacD., developed symptoms of cholecystitis in 1956 and cholecystectomy was performed. The pathological report indicated the presence of cholecystitis and cholelithiasis. At the time of operation, her hemoglobin was found to be 12.8 g. %. In 1960, her blood was examined routinely during hospitalization for a minor gastric disorder, and her hemoglobin was found to be 9.7 g. %. In 1962, she was hospitalized for the investigation of this anemia, epigastric discomfort and paresthesias in the left foot. On physical examination, the papillae of her tongue were atrophic and vibration sense was absent in the left ankle.

The findings in the peripheral blood were as follows. The red blood cell count was 3.3 million per c.mm., the hemoglobin 8.9 g. %. The packed cell volume was 27%, the mean corpuscular volume 123 cu. microns and the mean corpuscular hemoglobin concentration 33%. The total white cell count was 6000 per c.mm., with 51% polymorphonuclear leukocytes, 45% lymphocytes, 1% monocytes, 2% eosinophils, and 1% basophils. The peripheral blood smear showed marked poikilocytosis, and anisocytosis with macrocytosis. The iliac-crest bone marrow revealed moderate hypercellularity of marrow particles. The morphology was that of a classical megaloblastic bone marrow compatible with pernicious anemia.

Canad. Med. Ass. J.
May 22, 1965, vol. 92

On a fractional test meal without histamine stimulation, no free hydrochloric acid was detected. The patient was treated with intramuscular injections of vitamin B_{12} without iron. An initial reticulocyte response of 6% was obtained. She made a complete recovery. Her hemoglobin a year later was 14.5 g. %, the paresthesias had disappeared, and the appearance of the tongue had become normal. She has been maintained on vitamin B_{12} therapy until the present writing, and has maintained good health.

CASE 2.—The second twin, Mrs. M.J.G., was investigated when her twin sister was discovered to have pernicious anemia. She also suffered from symptoms of cholecystitis, and had had her gallbladder removed in 1960. The pathologist's diagnosis was cholecystitis and cholelithiasis. At that time her hemoglobin was 11.9 g. %. At no time did she develop atrophy of the papillae of the tongue or evidence of involvement of the nervous system. Her peripheral blood and her bone marrow were examined in 1962. The red blood cell count was 3.2 million per c.mm. and the hemoglobin 10.8 g. %. The packed cell volume was 35%, the mean corpuscular volume 123 cu. microns, and the mean corpuscular hemoglobin concentration 31%. The total white cell count was 6900 per c.mm. with 64% polymorphonuclear leukocytes, 30% lymphocytes, and 6% eosinophils. The peripheral blood smear showed marked poikilocytosis and anisocytosis with macrocytosis. The red blood cell morphology suggested pernicious anemia. The iliac-crest bone marrow revealed moderate hypercellularity of marrow particles with slight generalized hyperplasia, the latter typically megaloblastic in type.

A fractional test meal without histamine stimulation revealed complete absence of free hydrochloric acid. The patient was treated with intramuscular injections of vitamin B_{12} without iron. Within six months her hemoglobin level had increased to 12.6 g. %. She has been maintained on injections of vitamin B_{12} until the present writing, and has remained in good health.

It was realized that a Schilling test would have been very useful. However, one of the twins now lives in Denver, Colorado, only coming to Antigonish on vacation. The other lives some miles away.

GENETIC AND STATISTICAL DISCUSSION

The blood groups of each of these apparently identical twins were examined. Both patients belonged to group O, MMS, P_1, cDE/cde (probably), K-k+, Fy(a+), Le(a-b+), Jk(a-b+). In addition their sera were tested to determine the transferrin, haptoglobin, Gm, and Inv plasma protein groups. Both patients were Inv(a-), Hp2-2, Tf CC, and Gm (a-b+x-c-).

It is easier to prove monozygosity when the blood groups of the parents of twins are known. Unfortunately the parents of the twins described in this report are dead. It is still possible[13] to compute the possibility of the twins being monozygotic. For most of the blood groups, tables are available giving the relative chances in favour of dizygosity for each individual group.[10] These probabilities are listed in Table I. The figures quoted for the Kidd blood groups[10] can be improved upon as the reaction of the cells to both Jk(a) and Jk(b) antiserum was known in our cases. To do this, the possible matings that can give rise to Jk(a+b+) offspring, their frequency, the probability of dizygotic twins being alike with respect to the Kidd groups, and the probability of occurrence of such dizygotic twins were worked out (Table II). The probability that dizygotic twins will be alike with respect to the Kidd blood groups is therefore:

TABLE I.—PROBABILITY OF DIZYGOTIC TWINS HAVING THE SAME CHARACTER WITH RESPECT TO ZYGOSITY, SEX, AND VARIOUS BLOOD GROUPS

Character	*Monozygotic*	*Dizygotic*	*Dizygotic-monozygotic*
Zygosity	0.3	0.7	2.3333
Sex	1.0	0.5	0.5
O	1.0	0.6890	0.6890
MMS	1.0	0.5161	0.5161
P_1	1.0	0.8489	0.8489
cDE/cde	1.0	0.4179	0.4179
Fy(a+)	1.0	0.6319	0.6319
K-k+	1.0	0.9485	0.9485
Le(a-b+)	1.0	0.8681	0.8681

$$P(DZ) = \frac{2p^3q + 4p^2q^2 + 2pq^3}{4p^3q + 6p^2q^2 + 4pq^3},$$

$$= \frac{2pq(p^2 + 2pq + q^2)}{2pq(2p^2 + 4pq + 2q^2 - pq)}$$

$$= \frac{1}{2 - pq}$$

$$= \frac{1}{2 - 0.2498}$$

$$= \underline{\underline{0.5714}}$$

The allele frequencies[10] are $p = Jk(a+) = 0.5142$
$q = Jk(b+) = 0.4858$

The same calculations can be made with respect to the Inv, Gm and haptoglobin plasma-protein groups. The allele frequencies for the first two were obtained from Steinberg[12] and for the last from McKusick.[8] The results of these calculations are shown in Table III. The transferrins are not relevant in this instance because the chance of dizygotic twins both being Tf CC approaches 1.[3] As the genotypes at each locus are independent of those at other loci, all the probabilities may be combined to derive an estimate of the probability

TABLE II.—THE POSSIBLE MATINGS THAT CAN GIVE RISE TO Jk(a+b+) OFFSPRING, THEIR FREQUENCY, THE PROBABILITY (P) OF DIZYGOTIC TWINS (DZ) BEING ALIKE, AND THE PROBABILITY OF OCCURRENCE OF SUCH DIZYGOTIC TWINS WITH RESPECT TO THE KIDD BLOOD GROUPS

Matings	*Frequency (A)*	*P (DZ) (B)*	*P (occurrence) (A X B)*
JkaJka x JkbJkb	$2p^2q^2$	1	$2p^2q^2$
JkaJka x JkaJkb	$4p^3q$	½	$2p^3q$
JkaJkb x JkaJkb	$4p^2q^2$	½	$2p^2q^2$
JkaJkb x JkbJkb	$4pq^3$	½	$2pq^3$

TABLE III.—PROBABILITY OF DIZYGOTIC TWINS BEING IDENTICAL WITH RESPECT TO THE Gm, Inv, AND HAPTOGLOBIN PLASMA GROUPS

Character	*P(DZ)*
Inv (a-)	0.8333
Hp 2-2	0.5162
Gm (a-b+)	0.6

that the twins are dizygotic. This figure will be arrived at by multiplying the individual probabilities as follows:

2.333 x .5 x .689 x .5161 x .8489 x .4179 x .6319 x .9485 x .8681 x .5714 x .8333 x .5162 x .6 = .0113

The probability that the twins are monozygotic is therefore 1–.0113 = .9887. This figure is highly significant, and we conclude that the twins described in this report are truly monozygotic.

DISCUSSION

Two physically identical 63-year-old female twins developed anemia almost simultaneously. In neither case was free hydrochloric acid demonstrated in the gastric contents, although histamine stimulation was not used. In one twin, paresthesias of one foot developed, and vibration sense was absent in one extremity on physical examination. In both twins, peripheral blood and bone marrow studies showed evidence of a megaloblastic anemia. A reticulocyte response was obtained following the administration of intramuscular vitamin B_{12} without iron in one of the twins, with total remission of her signs and symptoms. In both cases the hemoglobin returned to normal. The patients are both receiving intramuscular vitamin B_{12} therapy, and remain in good health. The probability that the twins are monozygotic is .9887; this figure may be considered conclusive evidence of monozygosity.

The clinical and laboratory findings and the subsequent course of the disease leads us to believe that both twins are suffering from a megaloblastic anemia of the pernicious type. The nearly simultaneous onset of the anemia in identical twins is of interest, because probably not more than 12 cases of this nature have been reported in the medical literature.

SUMMARY

Female white monozygotic twins had attacks of cholelithiasis within a four-year period. Subsequently both developed megaloblastic anemia within a few months of each other, at the age of 63. A short review of the literature and a genetic and statistical analysis are included.

We wish to thank Professor A. G. Steinberg, Western Reserve University, Cleveland, Ohio, for the determination of the serum protein groups, and Professor H. C. Read, Dalhousie University, Halifax, Nova Scotia, for the determination of the blood groups, and for reviewing the slides of the bone marrow.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

IT IS VERY HUMILIATING

The fact that tonsils and adenoids are present is of course no reason that they should be removed, and I think it has been this indiscriminate removal that has caused odium to be cast upon the operation. But if operation is indicated, then enucleation is certainly required. The tonsil is a gland and should be treated as any other gland elsewhere in the body. Because it is situated in the fauces is no reason why it should not be treated according to ordinary surgical principles. Tonsillotomy has not given us the results we expected. It is very humiliating to the laryngologist and discouraging to his patients, to have them return, or what is more likely, to go to someone else, and complain that since their tonsil operation they are just as bad or even worse than they were before. What is done in a tonsillotomy is to shave off more or less of the tonsil and to open up the lacunæ widely and freely, leaving behind an equally or more diseased part of the tonsil. As healing occurs the surface becomes cicatrized over, thus sealing up the lacunæ and in that way forming a perfect incubator for the growth of micro-organisms. The question of the removal of the tonsils is very often determined more by their septic condition than their size. When a tonsil has lost most of its lymphoid tissue and is riddled with pus it is no longer a defence but a distinct source of danger to the organism. The protective function of the tonsil is then certainly nil.

One question I think must be asked in forming an opinion as to whether a case should be referred to a specialist or not in regard to the tonsils is, does the enlargement form an obstruction to respiration? I have noticed defects in the chests of children with enlarged tonsils and I have thought that a great deal of benefit has been derived from the removal of this obstruction; there has been increased capacity of the chest, increase in circulation and the constitutional benefit derived thereby has been marked.—J. T. Rogers and W. F. Hamilton, Discussion before the Montreal Medico-Surgical Society, *Canad. Med. Ass. J.*, 5: 562, 1915.