On the Evolution of Our Knowledge of Congenital Malformations of the Heart

The T. Duckett Jones Memorial Lecture

By HELEN B. TAUSSIG, M.D.

MY WARM association with T. Duckett Jones when he was in charge of the House of the Good Samaritan makes it a genuine pleasure to give the T. Duckett Jones Memorial Lecture. Although a year younger than I, Duckett was 4 years ahead of me in medical school and by the time I graduated he was established at the House of the Good Samaritan. Duckett offered me my first job—as a histologist to the Good Samaritan. Although I did not accept the position, we remained warm friends throughout his life.

His sister, Dr. Jean Jones Perdue has told me that when Duckett first expressed his desire to go into medicine their father, a dedicated general practitioner of the highest ideals, told Duckett that if he was going into medicine to make money he would give him no help, but if Duckett wanted to go into medicine to help the sick, he would support him to the hilt. Duckett dedicated his entire life to helping children with acute rheumatic fever and rheumatic heart disease. It was primarily through his influence that the Children’s Bureau recognized rheumatic fever as a crippling disease of childhood. He then translated thought into action by testifying in Congress for additional funds to be granted the Children’s Bureau for the support of this extension of their work. We all know how important this support has been to patients with rheumatic fever and also to the programs for the prevention of recurrences of rheumatic fever.

Another consequence of this forward-looking move was, after Dr. Robert Gross’ first ligation of a patent ductus, when the Children’s Bureau asked me whether congenital heart disease should be included in their cardiac program, all that was required was an affirmative answer. Everyone who has worked in the field of pediatric cardiology and cardiac surgery knows what a blessing the support given by the Children’s Bureau has been to children with congenital malformations of the heart, as well as to those with acute rheumatic fever. All this is thanks to Duckett Jones. It should never be forgotten that Duckett virtually gave his life in his work fighting for the prevention of acute rheumatic fever. Alas, Duckett died in 1954, at the age of 55.

Let us now turn to the subject of the day—the evolution of our knowledge of malformations of the heart.

The earliest knowledge of congenital malformations of the heart is buried in antiquity. Although Galen wrote about the “invisible pores” in the ventricular septum, he believed such pores must exist in order for the blood to pass from one side of the heart to the other. Whether he ever examined a malformed heart, we do not know.

The first period of which we have knowledge is that of isolated case reports. One such interesting report was written by Sandifort in 1777, and was translated by Dr. Lydia Bennett in 1946. This report, one of the earliest clinical and pathologic reports of a tetralogy of Fallot, is notable both because the family of the child requested the autopsy

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and because of Sandifort’s insight into the nature of the malformation. Sandifort emphasized that the boy “had been perfectly normal at birth” and therefore the physicians attributed the “unusually livid color which had been present since one year of age to some acquired disease.” Sandifort went on to say, “so imagine our surprise when we found the heart to be grossly malformed and that the aorta arose in part from the right ventricle, a condition which must have been present from birth.” Later in the report he went on to speculate that the ductus Botalli might have acted during early infancy to prevent the cyanosis! It was nearly 200 years before that idea was again seriously entertained.

By the middle of the nineteenth century many malformations had been described. Peacock published his book on congenital malformations in 1859. In his second edition in 1866, he showed several beautiful drawings of a tetralogy of Fallot. That same year Ebstein described the anomaly of the tricuspid valve which now bears his name; and H. St. John Brooks described two cases in which the right coronary artery arose from the pulmonary artery. H. St. John Brooks commented that the two coronary arteries received blood under different pressures and therefore when anastomosis developed between the two, the flow in the coronary artery which arose from the pulmonary artery would be in retrograde direction into the pulmonary artery! He was thinking in physiologic terms.

In 1875, Rokitansky published his work on the pathogenesis of cardiac septal defects. According to Maude Abbott he related malformations to “that new science of embryology” and dated the origin of malformations to the early weeks of embryonic life.

The early twentieth century saw the true awakening of interest in congenital malformations of the heart. Spitzer developed his theory of the phylogenetic origin of malformations and physiologic interest in malformations was increasing. Lundsgaard and Van Slyke published their famous monograph on cyanosis. Maude Abbott, above all, truly aroused general interest in malformations of the heart. Her contribution was so great it is fitting briefly to review her life.

Maude Elizabeth Seymour Abbott was born in St. Andrews East, Quebec, on March 18, 1869. This was before the days that Canada thought women were worth educating. Fortunately for Dr. Abbott, Donalda College, the women’s branch of McGill University opened just before she finished high school. She was in the third class of women to be admitted to that branch of McGill and graduated with high honors. Then came the problem of studying medicine. The McGill School of Medicine was adamantly opposed to women. Again, fortune was with her: shortly after graduation, Maude Abbott received a message from the Medical Faculty of Bishop’s College (a rival of McGill) advising her that they had decided to admit women and she was invited to enroll.

Immediately after her graduation in 1894, Dr. Abbott went to Europe to study medicine. On her return to Montreal in 1898, Dr. Charles F. Martin invited her to work with him and Professor J. C. Adami at the Royal Victoria Hospital. Dr. Martin started her on a statistical study of functional heart murmurs and Dr. Adami made her assistant curator of the medical museum. The following year she was made curator. In 1900 she first met Sir William Osler. He was a great believer in pathology as a method of studying disease and he emphasized to Dr. Abbott the great opportunity she had in the McGill Medical Museum. As a result of that meeting she gave up practice and devoted her full energy, which was indeed great, to the museum. On the review of the pathologic material she came across a very unusual specimen which she thought was incorrectly labeled. She wrote Sir William Osler about it and he told her that Andrew Holmes, the founder of McGill Medical School had described that in 1824! The original report was published in the Transactions of the Medico-Chirurgical Society of Edinburgh, as at that time there was no Canadian Medical Journal. Dr. Abbott promptly looked up the original report and republished the case as the “Holmes Heart.”

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This case, Dr. Abbott repeatedly said, was the one that aroused her interest in congenital malformations.

Maude Abbott made the fullest possible use of her museum collection. Sir William Osler was the first to ask her to write a chapter on congenital malformations for his "System of Medicine."8 Thereafter she wrote numerous chapters for various Systems. In the third edition of Osler's and McCrae's System of Medicine,9 Maude Abbott wrote two paragraphs on "Surgical Treatment" in which she suggested that "surgery may be possible in pulmonary stenoses of the valvular type." She also stated "that operative interference in patent ductus arteriosus in the form of ligation of the ductus was suggested by Monroe but hesitated to resort to such a radical measure. Resection of the obliterated ligamentum arteriosus in case of a right aortic arch with symptoms of obstruction of the esophagus could readily be carried out if the diagnosis is made; Arkin had demonstrated that this is feasible."

My friendship with Dr. Abbott started in 1935 when we met in Boston and I told her of the two cases of nonfunctioning right ventricle. Quite characteristically she then and there arranged to take me to Dr. Paul D. White's home to dinner that night!

In 1935, I visited Dr. Abbott in Montreal and she taught me the diagnosis of a right aortic arch. "Maudie" as we called her, introduced me to everyone she knew in Montreal and while there she gave a dinner for me. How she loved parties! Perhaps because she had received so little attention in her early days. She was a delightful, friendly, warm-hearted person, who throughout most of her life was miserably treated by most of her medical colleagues. The great exceptions were Dr. Charles Martin, Dr. Adami, Dr. Harold Segall, and Dr. Paul Dudley White. Indeed, Paul Dudley White, more than anyone else, made Maude Abbott's work appreciated by her colleagues.

Maudie had a generous heart and was remarkably scientific in her work. She had a "statistical mind," at least so she told me, and she thought that malformations of the heart could be beautifully studied by statistical analysis. She was almost obsessed by her interest in congenital malformations of the heart and could talk all day, and with an occasional cat-nap, would continue all night on the subject. Indeed, we younger people had a hard time to keep up to her pace, especially as we could not take the cat-naps! She came from a conventional British family but in her personal life she threw both convention and science to the wind and was totally disorganized and delightfully helter-skelter. She loved poetry and knew a lot by heart. She frequently tried her own hand at it.

Maude Abbott had great loyalty for McGill. In 1910 they gave her an M. D. degree, Honoria Causa, and, happily for her, in 1936 they bestowed upon her their highest honor, Doctor of Law, Honoria Causa. Also happily for her, she lived to see the beginning of cardiac surgery in 1939. She died in 1940 at the age of 71.

Medicine for me was a much easier row to hoe. I have long been grateful to Harvard that on the opening of the School of Public Health, although women were permitted to study, they were not admitted as candidates for degrees. That was the deciding factor which led me to study medicine! Of course, at that time the Harvard Medical School refused admission to women. Consequently, I was forced to take anatomy at Boston University. There, in the fall of 1922, Dr. Alexander Begg, Professor of Anatomy and Dean of the Medical School, gave me a beef heart to study, saying it would do me "no harm to be interested in one of the larger organs of the body as you go through medical school." Two years later he urged me to transfer to Hopkins to complete my medical training. While a medical student I worked in the Heart Station under Dr. Edward P. Carter. Upon graduation, when the Department of Medicine refused me an internship in medicine, Dr. Carter offered me a fellowship in his laboratory.

Dr. Edwards A. Park, that great pediatri-
Cian who has trained so many of us, came to Baltimore in the fall of 1927. He was a great believer in special clinics to study special diseases. He started the tuberculosis clinic, the cardiac clinic, the psychiatric clinic, and the endocrine clinic. He sought help for the cardiac clinic from Dr. Carter. Consequently, as I was working in Dr. Carter’s laboratory, I was allowed to work in the cardiac clinic with Dr. Benjamin Harris, who was senior to me and also working in the Heart Station that year. For the following 2 years Dr. Clifford Leach was in charge of the children’s cardiac clinic.

In 1930, Dr. Park put me in charge of the clinic. He gave me a social worker, a technician, and an electrocardiograph machine. Dr. Leach left me a list of 200 names. When the fluoroscope was installed in the Harriet Lane Home in 1930, Dr. Park said to me, “Now Dr. Taussig, you are going to learn congenital malformations of the heart,” and then he added, “and when you do, it will be a great day.”

Dr. Park urged, almost ordered, me to take an electrocardiogram on every patient and to fluoroscope every patient. He sent me to New York City to learn fluoroscopy from May Wilson. He forced the Harriet Lane house staff to refer cardiac patients to me. Thus, I began my studies on rheumatic fever and also with no great enthusiasm, my studies on congenital malformations of the heart.

The dawn of my interest in congenital malformations came in the fall of 1935, when I fluoroscoped a little cyanotic baby and could see no enlargement of the right ventricle. To my delight, when the electrocardiogram was developed and printed (as was necessary in those days), the electrocardiogram showed left axis deviation! I made the clinical diagnosis of an absent right ventricle. As luck would have it, a month later another cyanotic baby was presented on ward rounds. When Dr. John Washington, then resident in pediatrics, put up the x-rays he said, “Oh, excuse me, those are the wrong x-rays; they belong to another baby.” I replied, “No, these x-rays belong to this baby. It is another baby with the same malformation!” Then and there I realized that malformations of the heart repeated themselves and that similar malformations caused similar changes in the size and shape of the heart. The key to clinical diagnosis of malformations of the heart had been turned.

My approach differed from Maudie’s in that she applied statistical analysis to the malformations whereas my interest lay in the rationale of specific findings in relation to particular patients. For example, the only difference between the two babies with a nonfunctioning right ventricle was that in the first baby, the liver pulsed even though it was not engorged, whereas the second showed no such pulsations. Why this difference? In those days autopsies were eagerly sought by the house staff to determine whether my “crazy” diagnoses were right. The autopsies on these two infants confirmed the diagnosis of a “nonfunctioning right ventricle” and showed that the second had a gross defect in the atrial septum, whereas the first had only a small opening in the foramen ovale which explained the pulsations in the liver of normal size. Thus, the door was opened for clinical diagnosis of malformations of the heart on a broad functional basis.

The next step came when Dr. T. McNair Scott, during his residency in Harriet Lane Home, asked me why a 4-year-old child with a tetralogy of Fallot had died. He commented that the child did not go into heart failure but just became bluer and bluer and finally died. I replied, “he died from anoxemia and not from cardiac failure. He simply could not get enough blood to his lungs to live.”

Thus, on the basis of the first two children with a nonfunctioning right ventricle and pulmonary atresia who had died as the ductus closed and the baby who died of anoxemia, I came to realize that circulation to the lungs was essential for extrauterine life. The more I studied and observed, the more I realized that many cyanotic babies died as the ductus closed and that babies who were not cyanotic frequently became so with the closure of the ductus. Thus, I appreciated two things,
(1) that malformations were not static and (2) that closure of the ductus arteriosus was usually fatal to an infant with a pulmonary atresia and made a patient with a tetralogy of Fallot and pulmonary stenosis worse. Once at a staff Clinical Pathological Conference, Dr. William McCallum, that eminent pathologist, when he was trying to trace the circulation of the blood in an infant with a malformed heart said, “One can hardly see how the infant lived.” I remember his great astonishment when I replied, “Dr. McCallum, it is because the circulation became incompatible with life that we are discussing this infant in your department and not in Dr. Park’s.” Thus, my thoughts were not how these babies managed to live, but why they died.

Consequently, I turned my thoughts to the mechanism of the closure of the ductus with the idea that prevention of the closure of the ductus would be of benefit to cyanotic infants with pulmonary stenosis. As you all know, I never got very far with that idea. Nevertheless when Dr. Robert Gross published his first report on the successful closure of a patent ductus, I immediately realized it should be possible to build a ductus for the cyanotic child. Some of you will recall the days in Harriet Lane when I used to say, “This child would be helped if we could only build a ductus.”

Again, I am grateful to Harvard and to Dr. Robert Gross that while in his first flush of success of closure of a patent ductus, when in answer to my inquiry, he told me he had built many a ductus but was not in the least interested in my suggestion of creating a ductus for a cyanotic child. So I returned to Baltimore to bide my time until Dr. Alfred Blalock became surgeon-in-chief. He was known for his work on thymoma and on shock and he was considered a vascular surgeon as he had operated successfully on three children with patenty of the ductus arteriosus!

When Dr. Blalock came to Baltimore, Dr. Park immediately interested him in the problem of coarctation of the aorta. I finally took courage and had Dr. Blalock operate on a defective child with a patent ductus. At the end of the operation I said to him, “Dr. Blalock, I stand in awe and admiration of your surgical skill but the truly great day will be when you build a ductus for the child dying of anoxemia and not when you tie off a ductus for a child with a little too much blood going to his lungs.” Dr. Blalock gave a sigh and replied, “When that day comes, this will seem like child’s play.” Two years to the day he did his first anastomosis!

The intervening 2 years were years of hard work. Dr. Blalock accepted the challenge and carried the problem to the laboratory. First he tried to create pulmonary stenosis. That was hard, and, furthermore, the creation of pulmonary stenosis would not produce cyanosis. So at my suggestion, his remarkable technician, Vivian Thomas, put the right pulmonary artery into the left atrium in an attempt to cause cyanosis and polycythemia with the idea of subsequently putting the left subclavian artery into the pulmonary artery to relieve the cyanosis. The direction of half the blood from the lungs to the left atrium did not lead to polycythemia. It proved necessary in addition to do a partial lobectomy. These experiments took time.

Meanwhile, Dr. Park continued to urge Dr. Blalock to devise an operation for the correction of a coarctation of the aorta. The major problem was whether clamping the aorta would cause paralysis of the lower extremities. Dr. Blalock felt certain that if a normal aorta could be clamped with impunity, then the coarctated aorta, in which collateral circulation had developed, could safely be clamped. Again he took the problem to the laboratory. Experience has shown the chances are fifty-fifty that clamping of the aorta will cause paralysis of the lower extremities. Dr. Gross was working on the problem in Boston, while Dr. Blalock was working on it in Baltimore. It so happened that Dr. Gross’ dogs did not develop paralysis of the lower extremities and Dr. Blalock’s did. Thus, Gross developed the end-to-end
anastomosis for coarctation of the aorta at the same time that Dr. Crafoord developed the operation in Stockholm and Dr. Blalock developed a bypass operation by anastomosing the carotid artery to the descending aorta. When Dr. Blalock reported his technic to Dr. Park, I immediately said, “If that is possible, why not put the subclavian artery into the pulmonary artery. That is all that is necessary for the cyanotic child.”

After further experimental work on dogs, creating polycythemia and anastomosing the subclavian artery to the pulmonary artery, Dr. Blalock said he was ready to perform the operation provided I was convinced it was sound.

The fact that the first three operations were successful attests to the brilliancy of Dr. Blalock’s surgical skill. It was, however, only at the end of the third operation that we saw the value of the operation. That operation was on an utterly miserable, small, 6-year-old boy who had a red-blood-cell count of 10 million and was no longer able to walk. When Dr. Blalock first removed the clamps, the blood welled up in the child’s chest. Dr. Blalock quickly controlled the hemorrhage and poured in plasma. Suddenly, Dr. Merrill Harmel cried, “He’s a lovely color now” and I walked around to the head of the table and saw his lovely normal pink lips! The child woke up in the operating room and asked, “Is the operation over?” When Dr. Blalock said “Yes,” the child said “May I get up now?” From that moment on he was a happy and active child.

So let us pause for a moment and pay tribute to my colleague of 20 years, the late Dr. Alfred Blalock. His operation on blue babies opened up the field of cardiac surgery because many people felt that if a deeply cyanotic child could tolerate an operation, almost any other child could. Dr. Blalock’s work fired the imagination of young surgeons and they flocked to Baltimore for training. Having seen Dr. Blalock in action many times, I think that he showed his greatness as a teacher of surgery quite as much as he did in his actual surgery. He was a remarkable teacher, knowing how to leave the young surgeon to operate alone and yet to be on hand to help when necessary.

In the last 20 years the advances in surgery have been many and rapid. An anastomosis now seems like a simple operation. Nevertheless, a good anastomosis does require skill and to be effective it must be done on the side opposite to the aortic arch. A subclavian-pulmonary anastomosis performed on the side opposite to the aortic arch offers a child between 6 and 10 years of age 10 to 18 years of good life and possibly more.

Cardiac catheterization and angiography have had a remarkable history. When one considers how widely cardiac catheterization is done throughout the world and the steady advances made in the technics and the instrumentation used in this procedure, the criticism that was leveled against Dr. Werner Forssman in 1929, when he first passed a catheter into his own heart, seems almost incredible. He repeated the procedure to show that it was safe. Nevertheless, when he applied for a grant to study the circulation he was summarily dismissed from the hospital for making such a radical proposal! Nearly 12 years elapsed before Dr. André Cournand heard of it. He immediately envisioned its potentiality in the study of cardiopulmonary physiology and Dr. Cournand together with Dickinson Richards perfected the technic of cardiac catheterization. Forssman’s pioneer work was not truly appreciated until 1956, when he, André Cournand, and Dickinson Richards received the Nobel Prize for Medicine and Physiology.

Similarly, little attention was paid to Dr. Castellano’s' pioneer work on angiography. In 1937, he demonstrated that the diagnosis of a complete transposition of the great vessels could be established by the injection of radiopaque material into the right ventricle. Nevertheless, angiography did not come into its own until after Dr. Blalock had perfected the anastomotic procedure for a tetralogy of Fallot. Indeed, it is worthy of note that Dr. Blalock had done 150 operations on children with decreased pulmonary
blood flow before cardiac catheterization or angiocardiography were available at the Johns Hopkins Hospital.

Had the laboratory technic preceded the clinical studies, the clinical diagnosis of malformations of the heart would have been greatly delayed. At the present time the responsibility is ours to teach the young cardiologist basic clinical diagnosis so that needless catheterizations are not done. This is not a theoretical problem, for we all know that most children who are referred to a cardiac center for operation are restudied in detail and frequently cardiac catheterization or angiocardiography or both are repeated before surgery. Truly, a well-trained pediatric cardiologist should be able to make a reasonably accurate clinical diagnosis and know whether or not a child needs operation and approximately at what age the operation should be performed. A good clinical diagnosis can usually be made by careful history, physical examination, electrocardiogram, x-ray and fluoroscopy, and simple laboratory tests such as hematocrit and hemoglobin determinations. Cardiac catheterization and detailed studies should be performed at the center where the operation is contemplated. A preliminary catheterization is an added expense and though the risk may be small, it is an unnecessary risk. Moreover, the preliminary catheterization often destroys a vein that might be used to good advantage at a future date when detailed pinpointing of the exact structure of the heart is desired.

All problems in the diagnosis and correction of congenital malformations of the heart are not yet solved but the impetus to the solution of these problems is so great that progress is certain to continue.

Our next great step forward will come in the field of etiology and the prevention of malformations.

This era has already dawned. The first rays of light crossed our horizon when Gregg\textsuperscript{11} showed the extremely high incidence of congenital cataract, microcephaly and congenital malformations of the heart in infants born to women who had suffered from rubella during early pregnancy. Initially, many persons were startled to find that a mild infection could seriously injure the fetus. Then physicians appreciated that the production of malformations resulted from a noxious agent which could pass through the placenta and which was severe enough to injure but not so severe as to kill the fetus. Furthermore, malformations clearly occur during early pregnancy, i.e., at the time the embryo is developing. The observations of Gregg\textsuperscript{11} and of Swan et al.\textsuperscript{12} have led to the consideration of the possibility that other virus infections might injure the embryo or the fetus. Evidence is now accumulating that such may be the case.

The thalidomide tragedy demonstrated that drugs could be severely teratogenic. It also showed that drugs might have an entirely different action on embryonic tissues than on adult tissue. It is important to remember that although viruses and drugs have been shown to have a teratogenic action during early pregnancy, i.e., while the embryo is developing, this does not preclude the possibility that drugs and other agents may injure the fetus at a later time during pregnancy.

Our evolution of knowledge concerning supravalvular aortic stenosis opens up another possible type of injury to the fetus and the child and also another perimeter in the study of malformations. We are all familiar with the great variation in the severity of any one malformation. Thalidomide showed that the type of malformation varies with the time at which the toxic agent acts. Evidence is now accumulating to show that a relationship exists between two totally different conditions. A clinical syndrome appears to extend from severe idiopathic hypercalcemia to supravalvular aortic stenosis; both conditions are associated with widespread injury to the vascular tree and both are or may be associated with mental retardation.

Let me review the basis of this statement. Supravalvular aortic stenosis was first described by Denie and Verheugt\textsuperscript{13} in 1958. In 1961, Williams, Barratt-Boyes, and Lowe\textsuperscript{14} drew attention to the similarity of facies in
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these patients, each to each, and delineated the clinical syndrome of supravalvular aortic stenosis associated with mental retardation and a characteristic facies. Subsequently, Beuren et al.,15 showed that peripheral pulmonary stenosis was part of the clinical syndrome, and, in addition, that these patients showed abnormalities of the dentures. In 1963, Black and Bonham-Carter16 pointed out the similarity of facies of patients with supravalvular aortic stenosis to those in infants with idiopathic hypercalcemia. Since then evidence has rapidly accumulated which indicates that some relation exists between the two conditions. Garcia, Friedman, Kaback, and Rowe17 reported a baby with supravalvular aortic stenosis who had a high blood calcium and was found to be hyperreactive to vitamin D. In the spring of 1964, Bonham-Carter and Sutcliffe18 reviewed the autopsies of six cases of idiopathic hypercalcemia and reported the occurrence of multiple arterial stenoses associated with this disease. Among the six cases were two with supravalvular aortic stenosis, and one with a mild valvular aortic stenosis, three with renal artery stenosis and three with peripheral pulmonary stenosis, and one had a mild coarctation of the aorta. They put forth the hypothesis that mild arterial stenoses noted in these children might be the effect of the hypercholesteremia and the hypercalcemia of this disease upon the growth of "stress points" in the arterial tree; furthermore, they pointed out that possibly the most severe form of this disease might occur during intrauterine life, and the mothers of such children might, at least during pregnancy, be found to be sensitive to vitamin D.

What is the relation between these two conditions? The first report of idiopathic hypercalcemia with failure to thrive, was by Lightwood in 1952.19 That same year, Fanconi, Gerardet, Schlesinger, Butler, and Black20 published an extensive study of the severe forms of idiopathic hypercalcemia. Since then, numerous cases have been reported. Although the exact relation of idiopathic hypercalcemia to vitamin D is not clear, the evidence is extremely strong that idiopathic hypercalcemia is related to the metabolism of vitamin D. In 1957, Bongiovanni et al.21 showed that infants with idiopathic hypercalcemia are sensitive to vitamin D and that a given dose of vitamin D remained in the blood of such infants for a longer period at a higher level than the same dose in a "normal" individual. The following year, Fellers and Schwartz22 presented evidence to show that idiopathic hypercalcemia represented an "inborn error" of metabolism of vitamin D. The recent report by Kenny et al.,23 substantiated this conception.

Let us consider for a moment what such an inborn "error" of metabolism means. Actually this metabolic variant appears to enable the individual to react with a greater rise and a longer duration to small doses of vitamin D than does the so-called "normal" individual. Fifty years ago infants received their vitamin D from breast milk: man received his vitamin D from sunlight and from food. In those days this "inborn error" of metabolism would have been a beneficial gene, as it would have enabled the individual better to utilize exogenous vitamin D and sunlight and it would thereby help to produce strong and healthy individuals. Then came the days of formulas, boiling milk and destroying vitamin D. This led to florid rickets. Next came the discovery of the role of cod liver oil and the isolation and the production of vitamin D. As is so common, the popular belief was that if "some is good, more is better." The result was the overdosing with vitamin D and adding it to various foods. Then came the recognition of vitamin D intoxication and idiopathic hypercalcemia.

Now we are coming to appreciate that there exists an inborn variation in man's ability to metabolize vitamin D and that some individuals may be injured by doses of vitamin D which are safe for others. Indeed, such persons may prove to be injured by excessive sunlight. If this is true, the effect of vitamin D and sunlight may vary with the genetic make-up of the mother and the offspring. The amount of vitamin D which the mother receives during pregnancy, the time at which...
it is given, and the length of time over which it is given, might determine its effect upon the fetus. Needless to say the effect would also vary with the genetic make-up of the fetus. Furthermore, these various factors might affect a susceptible individual any time during his life.

Dr. Hogart Wiltse is now working on this problem in our laboratory. The problem may well be, and, probably is, far more complicated than has just been suggested. The experimental work of Hans Selye24 in the production of calciphylaxis may be of fundamental importance and a “challenger” may be necessary. In this connection it is worth bearing in mind that iron is given almost as freely as are vitamins and in the experimental animal, iron is known to be a challenger to vitamin D.

The fact that abnormalities of the aortic valve and mild degrees of valvular aortic stenosis have been reported in infants dying of hypercalcemia makes one wonder whether a congenital valvular aortic stenosis as well as supravalvular aortic stenosis may prove to be related to the patient’s intake and metabolism of vitamin D, or to his exposure to sunlight. Indeed, will the calcific aortic stenosis of advancing years, the nature of which has so long defied pathologists, prove to be of some similar etiology? Inasmuch as the underlying injury to the vascular tree appears to be widespread both in infants dying of hypercalcemia and those with supravalvular aortic stenosis, and that these conditions may be associated with hypercholesteremia, one cannot help wondering whether these factors may ultimately have some bearing on the problem of cholesterol metabolism.

When these problems are solved the gap between congenital malformations and acquired heart disease may greatly diminish. In many instances both may prove to be the reaction of the individual’s genetic make-up to his changing environment.

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The Teacher

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