

The First Stella Van Praagh Memorial Lecture: The History and Anatomy of Tetralogy of Fallot

Richard Van Praagh

Stella Van Praagh, MD (1927-2006) of Children's Hospital Boston was one of the greatest pediatric cardiologists and pediatric cardiac pathologists of the 20th and early 21st centuries. Née Stella Zacharioudaki from Crete, Greece, in addition to her stellar professional attainments, she was also an outstanding cuisinière, hostess, linguist, philosopher, and philanthropist. In 1962, she married Richard Van Praagh, MD, beginning a life-long collaboration that was in every sense an *affaire de cœur*. They had three children and seven grandchildren. Dr Stella was the author of more than 110 scientific publications which helped to clarify the pathologic anatomy, the clinical and laboratory diagnosis, and often the surgical management of many different forms of congenital heart disease, including dextrocardia, single ventricle, truncus arteriosus, tetralogy of Fallot (TOF), transposition of the great arteries, double-outlet right ventricle, sinus venosus defect, anomalous pulmonary venous drainage, the heterotaxy syndromes with asplenia or polysplenia, juxtaposition of the atrial appendages, and apical muscular ventricular septal defect. In 1999, Dr Stella Van Praagh received the Distinguished Achievement Award of the Society for Cardiovascular Pathology, and in 2004, she was honored with the Paul Dudley White Award of the American Heart Association. Dr. Stella Van Praagh was that vanishingly rare combination of brilliant clinician, internationally renowned medical scientist, and deeply cultivated humanist. The anomaly now known as the TOF was first described by Niels Stensen in 1671, with other early reports by Edouard Sandifort (1777), William Hunter (1784), and many others. In 1888, Etienne-Louis Arthur Fallot published five serialized contributions in *Marseille Médical* concerning what he called the "blue malady," in which he described the now classical tetralogy of pulmonary outflow tract obstruction, ventricular septal defect, aortic overriding, and right ventricular hypertrophy. The other outstanding feature of Fallot's report was its emphasis on clinicopathologic correlation. In 1924, Maude Abbott coined the term "tetralogy of Fallot." In 1970, Van Praagh and colleagues presented the concept that the TOF is basically just one anomaly, a failure of normal expansile growth of the subpulmonary infundibulum and its sequelae. The anatomy of TOF is presented angiocardio-graphically, diagrammatically, and anatomically. A morphometric study of typical neonatal TOF is presented, based on 16 autopsied heart specimens with age-matched normal controls. The morphometric study documents that TOF is characterized by a low-volume subpulmonary infundibulum. The diagnostic and surgical significance of these findings is highlighted. Two rare and recently discovered forms of TOF are presented: tetralogy {S,D,I}, and tetralogy {I,D,S}. Because tetralogy {I,D,S} has atrioventricular discordance, in addition to a standard TOF repair, such patients also need an inverted (mirror-image) atrial switch operation (inverted Senning or inverted Mustard procedure). Because associated malformations can be very important to the surgical outcome of patients with tetralogy, the associated anomalies found in 100 randomly selected autopsied cases are presented.

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It is a great honor for me to give the first Stella Van Praagh Memorial Lecture, focusing not only on her (Fig. 1), but also on the history and anatomy of tetralogy of Fallot (TOF). As most of you know, Dr. Stella Van Praagh was my wife and soul mate, who died of a stroke in 2006.

Born in Rethymnon on the north shore of Crete in 1927, Stella was the third child in a family of five children. She and her family fortunately all survived World War II. Stella was an eyewitness to the first airborne invasion of all time, watching from the basement of their family home as the German paratroopers descended on multicolored parachutes into their vineyard. As the dark of night descended, her father Constantine quietly told his family that they were leaving. Carrying whatever they could, they walked through terraced fields, high with unharvested grain, up into the mountains, to their ancestral village where they were greeted with open arms.

Growing up, Stella was a star student, essentially always the first in her class. In 1952, she graduated from the School of Medicine of the University of Athens, Greece. Following an externship at the Children's Hospital of Athens (1953-1954), she decided to emigrate to the United States, all by herself, knowing little English—except what she had learned from Mitchell Nelson's Textbook of Pediatrics. For Greek students of her time, French was the foreign language most studied.

Following a rotating internship in Christ Hospital, Jersey City, NJ (1954-1955), she became a fellow in Pediatric Cardiology at Buffalo Children's Hospital, Buffalo, NY, with the outstanding Dr. Edward C. Lambert, followed by a residency in Pediatrics (1955-1957). Stella then became a fellow in Pediatric Cardiology at Johns Hopkins Hospital in Baltimore, MD with Dr. Helen B. Taussig, the “mother” of Pediatric Cardiology (1957-1958). Later (1960-1961), Stella served as

a Senior Research Fellow in Pediatric Cardiology at the Hospital for Sick Children in Toronto, Canada with Dr. John D. Keith, who is widely regarded as the “father” of Canadian pediatric cardiology.

In 1961, Dr. Edward Lambert and Dr. Peter Vlad invited Dr. Stella Zacharioudaki to become a member of the permanent staff of the Department of Pediatric Cardiology of Buffalo Children's Hospital, an invitation which Stella happily accepted.

Stella and I were married in 1962. Early in that year, when I told Dr. Lambert that Stella and I were engaged to be married, he looked at me with a big smile and said, “Richard, congratulations! You snake! You snake!” Because I was working in Toronto as a fellow in pediatric cardiology, my announcement of our engagement meant that I would be depriving Dr. Lambert and the Buffalo Children's Hospital of their new cardiologist. Big Ed, as Dr. Lambert was fondly known, understood how good Stella was.

In 1965, Stella and I were invited by Dr. Alexander S. Nadas, Dr. Sidney Farber, and Dr. Robert E. Gross to join the staff of Children's Hospital Boston, where we have worked ever since. We had three children in 3 years—Andrew (1963), Helen (1964), and Alexander (1965). I thought this was a good beginning, but Stella said to me, “Dickie Dickie, that's the end.” And so I learned the meaning of the old saying: Man proposes, but woman disposes.

A superb cardiologist, Dr. Stella was adored by her patients, both American and Greek. At Children's Hospital Boston, Dr. Stella was our “Greek connection.” Patients and their parents coming from Greece were astonished to find that their Boston cardiologist knew not only what they were saying, but what they were thinking. A master teacher of congenital cardiac pathology and embryology, with emphasis on its diagnostic and surgical relevance, Stella's lectures for tired Cardiology fellows and Cardiac Surgical residents were legendary. She would often begin by serving hot homemade Greek Easter bread. A superb cuisinière, Stella made six different kinds of bread, never with a recipe. Her lectures were models of clarity and practicality. A cardiac surgical resident from South America spoke for many of our trainees when he said, “Dr. Stella, your explanation was so clear, I thought you were speaking Spanish.”

Dr. Stella was a linguist, a philosopher, and a philanthropist. Fluent in modern Greek, Byzantine Greek, and conversant with ancient Greek—the language of Aristotle, Plato, Aeschylus, Euripides, et al—Stella led an Ancient Greek studies group in Wellesley, MA, fondly known as the Mythology Club. They used the Loeb Classical Library bilingual editions, with English on one side and ancient Greek on the other. This way, Stella could check the accuracy of the English translation, and when necessary, improve on it. The participants, all grandmothers, not only read these books or plays, they *acted* them. And then they would discuss them—including the relevant ancient history.

Stella gave approximately \$100,000 to the renovation campaign of Harvard Medical School's Countway Library. These were her retirement savings and this magnificent library was her favorite charity.



Figure 1 Dr. Stella Van Praagh in her role as clinician in pediatric cardiology at Children's Hospital Boston.



Figure 2 Dr. Stella giving her farewell address at our retirement party in 2002.

Dr. Stella was a “mother” for all of our cardiology fellows and cardiac surgical residents who came to our lab, the Cardiac Registry. She was a teacher, counselor, and wise friend of matchless integrity and courage.

She was also a role model for young female cardiology fellows and cardiac surgical residents. Stella’s human qualities were as important as her professional attainments. Stella was proof that a young woman cardiologist or cardiac surgeon could be a complete, well-rounded human being: an excellent clinician, a first-class research person, a great teacher, and also a wonderful mother, wife, and amazing cuisinière. As Stella once said to me, “Dickie, you and I have proved that a husband and a wife really *can* work together.”

Now permit me to share a few more photos of Stella with you.

Figure 2 is a picture of Stella giving her talk at our retirement party in 2002. Her enthusiasm was magnetic, and her message was both accurate and charming.

Figure 3 shows a picture—just after dinner—at Blueberry, our summer cottage in New Hampshire, with some of our fellows from the Cardiac Registry. Stella called them our

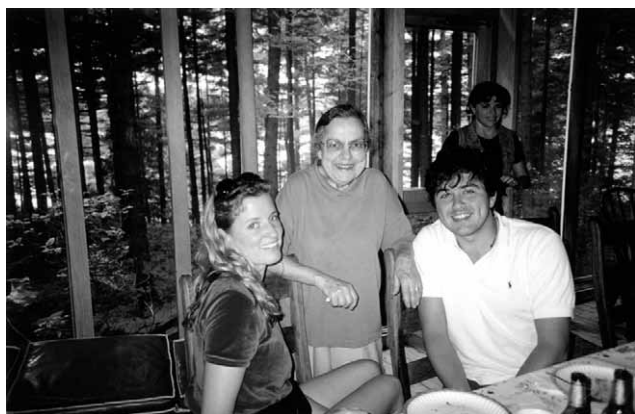


Figure 3 At Blueberry, our summer cottage near Washington, New Hampshire, with some of our fellows whom Stella fondly called our Cardiac Registry family. Dinner had just ended with blueberry pie.



Figure 4 Dr. Stella as hostess, entertaining at home in Wellesley, Massachusetts.

“Cardiac Registry family.” To Stella’s right is Julia de Vivie, now a pediatric cardiologist in Hamburg, Germany and the daughter of Prof. Rainer de Vivie, who has only recently retired as the Chief of Pediatric Cardiac Surgery in Köln (Cologne), Germany. To Stella’s left is Christian Kreutzer, now a pediatric cardiac surgeon in Buenos Aires, Argentina, the son of Prof. “Billy” Kreutzer, who retired a short time ago as the Chief of Pediatric Cardiac Surgery in Buenos Aires. In the background, just coming in from outside, is Maria Concepcion (“Connie”), now a pediatric cardiologist in Mexico.

Figure 4 is a picture of Stella entertaining at home in Wellesley, MA. Conversation with Stella was both fun and fascinating—often a real education. This was how the Mythology Club began—at the insistence of her devoted friends. “You must teach us. We want to learn,” they kept saying.

Figure 5 shows Stella as a mother and grandmother. This photo was taken in the back garden of Helen, our dear daughter who died of malignant melanoma in 2001 at the age of 37 years. Helen is survived by her husband Jean-Pierre Parnas, universally known as “J-P,” and by her two sons Benjamin and David, now 14 and 12 years of age. Thus, Stella was no stranger to sorrow. But she carried on as bravely as



Figure 5 Stella in her role as loving mother and grandmother.



Figure 6 Here Dr. Stella Van Praagh is teaching in the Cardiac Registry by demonstrating and discussing congenitally malformed heart specimens. The participants included pediatric cardiology fellows, cardiac surgery residents, radiology residents, pathology residents, echocardiography technicians, operating room nurses, and visitors from other institutions. To Dr. Stella's right is Dr. Juan Campbell from Caracas, Venezuela, who is now practicing pediatric cardiology in Chicago.

possible and took joy in her sons, son-in-law, daughters-in-law, and grandchildren (now seven in number).

Figure 6 depicts Dr. Stella Van Praagh as teacher. Here she is in the Cardiac Registry (the Cardiac Pathology Laboratory), showing fresh or formalin-fixed and water-washed congenital heart specimens at her regularly weekly teaching sessions for Cardiology fellows, Cardiac Surgery residents, and often for visiting cardiologists and cardiac surgeons. I would do the same thing. So there were two conferences every week in the Cardiac Registry where we would demonstrate and discuss virtually any kind of congenital heart disease. Topics might include the kinds of congenital heart disease our surgeons were going to operate on in a day or two. After the heart specimen demonstration, the participants would often put on latex gloves and examine the heart specimens for themselves.

Learning based on heart specimens, with a very knowledgeable guide such as Dr. Stella, is vastly superior to trying to learn from books, journals, or slide presentations. Heart specimens are “real,” palpable, and 3-dimensional. These features are very important, particularly for interventional cardiologists and cardiac surgeons.

Dr. Stella Van Praagh was one of the most outstanding pediatric cardiologists and pediatric cardiac pathologists of the 20th and early 21st centuries. The author of more than 110 scientific publications, she and her colleagues helped to clarify the pathology, embryology, and clinical diagnosis of dextrocardia,^{1,2} single ventricle,^{3,4} and truncus arteriosus.^{5,6} She and her colleagues presented the insight that the TOF is really just one anomaly—underdevelopment of the subpulmonary infundibulum and its sequelae, not four different and unrelated malformations. This anomaly is a nonrandom tetrad. We jokingly referred to the TOF as the “monology of Stensen” because, as will be seen, tetralogy was originally

described by Bishop Stensen in 1671—217 years before Fallot's beautiful description in 1888.⁹

Dr. Stella was one of those who documented the fact that transposition of the great arteries (TGA) can have a posterior aorta and an anterior pulmonary artery,¹⁰ instead of vice versa, indicating in 1971 that TGA could no longer be defined as an anterior aorta and a posterior pulmonary artery. Instead, TGA had to be defined in a literally accurate way: *trans* = across and *positio* = placement (Latin). If the great arteries were *placed across*—the ventricular septum being the tacit frame of reference—then transposition was present, no matter what the antero-posterior relationship of the great arteries was. Thus, TGA was what Dr. John Kirklin would later call “ventriculo-arterial discordance.”

This literally accurate definition of TGA in terms of ventriculo-arterial alignments would cast a long shadow. Double-outlet right ventricle (DORV), double-outlet left ventricle (DOLV), and anatomically correct malposition of the great arteries (ACM) were all soon redefined in terms of their accurate ventriculo-arterial alignments. Previously, they had all been lumped together as forms of TGA. It was no longer DORV *with or without* TGA. Instead, it was DORV *or* TGA.¹⁴ Ditto for DOLV. It was no longer anatomically corrected *transposition* of the great arteries.¹¹ Instead, it became anatomically corrected *malposition* of the great arteries¹³; because ventriculo-arterial concordance is present, by definition in ACM, everyone realized that—accurately speaking—*transposition* of the great arteries is not present. Hence, *malposition* was substituted for accuracy.^{12,13}

After 10 years of work, Dr. Stella Van Praagh and her colleagues published a very comprehensive study of DORV,¹⁴ revealing how superficial and incomplete the earlier concepts of DORV had been.

Her understanding of ancient Greek helped make it possible to understand what Aristotle, the discoverer of the cardiovascular system, had meant by saying that normally, the human heart has three ventricles.¹⁵ By retranslating Aristotle's text from ancient Greek, Dr. Stella played an important role in deciphering this mystery that had gone unsolved for more than 2,300 years.

As she grew older, her papers just kept getting better and better. In 1994, she and her colleagues published a new understanding of sinus venosus defect,¹⁶ namely, that it is unroofing of the right pulmonary veins; this defect is what the surgeon patches. The so-called sinus venosus atrial septal defect (ASD) is not an ASD. Instead, it is the normal opening of the right pulmonary vein(s) passing through the atrial septum to drain into the left atrium. In sinus venosus defect, one can see this opening because of the unroofing defect: focal absence of the posterior wall of the right atrium and of the adherent anterior wall of the right pulmonary vein(s).¹⁶

In 1995, Dr. Stella Van Praagh and her associates presented a new understanding of anomalous pulmonary venous drainage.¹⁷ She showed that partially or totally anomalous pulmonary venous drainage into the right atrium can be due to malposition of septum primum, with normally connected pulmonary veins,¹⁷ *not* due to abnormal connection of the pulmonary vein(s) as had previously been thought.

Also in 1995, Dr. Stella and her surgical colleagues published a detailed study of the systemic and pulmonary venous connections in a large series of autopsied patients with visceral heterotaxy and asplenia.¹⁸ The morphologic anatomic data did not support the notion of atrial level isomerism. Even in asplenic patients, it was often possible to diagnose the basic type of atrial situs.¹⁸ But when this was not possible with confidence, the diagnosis of atrial situs ambiguus was made, indicating that we were not sure what the basic type of atrial situs was, but without stating that atrial mirror-imagery (isomerism) was present. In the heterotaxy syndrome, particularly with asplenia, the pattern of atrial anatomic organization was found, in a minority of cases, to be *scrambled*, and hence undiagnosable. But often with asplenia, and almost always with polysplenia, it was possible to diagnose the type of atrial situs (solitus or inversus) that was present.¹⁸ This is important because until one understands the pattern of anatomic organization (the situs) of the three main cardiac segments—atria, ventricles, great arteries—one cannot understand the heart. For example, is there atrioventricular concordance or discordance? If TGA coexists, is it complete (noninverted) or corrected (inverted)? The problems with the concept of atrial level isomerism are two: (1) it is anatomically erroneous; and (2) it blocks accurate anatomic understanding. This problem has nothing to do with terminology. Instead, it has to do with accurate anatomic diagnosis. Dr. Stella and her colleagues did their best to present these data in an accurate and noncontentious way.¹⁸ Interested only in accurate understanding, she was never a polemicist. Quite the contrary, as a survivor of war and occupation, Dr. Stella was an ardent peacemaker and an apostle of the truth, with a small “t.”

In 1996, Dr. Stella Van Praagh and her colleagues published two anatomic studies indicating that there are two mirror-image syndromes in patients with juxtaposition of the atrial appendages: (1) juxtaposition involving malposition of the *morphologically right atrial appendage*¹⁹ is a syndrome of morphologically right heart hypoplasia; and (2) juxtaposition involving *malposition of the morphologically left atrial appendage*²⁰ is a syndrome of morphologically left heart hypoplasia. Each syndrome occurs both in viscerotransposition and in viscerotransposition inversus.^{19,20} Thus, the key to understanding these two opposite syndromes of juxtaposition of the atrial appendages is to diagnose which atrial appendage is malpositioned—the *morphologically right*¹⁹ atrial appendage or the *morphologically left*²⁰ atrial appendage.

In 2000 and 2002, Dr. Stella Van Praagh and colleagues published a new operation for the closure of apical muscular ventricular septal defects (VSD).^{21,22} Designed by Dr. Stella and first performed by Dr. Giovanni Stellin and colleagues,²¹ this new procedure involves a *right* ventricular apical infundibulotomy, instead of the conventional *left* ventricular apical incision. Using a right ventricular apical incision, one opens into the infundibular apical recess which lies in front of the septal and moderator bands, giving excellent exposure and avoiding a systemic left ventricular apical incision (with its risk of subsequent left ventricular apical aneurysm). Apical muscular VSDs typically open into the infundibular apical

recess in front of the moderator band, rather than into the right ventricular sinus apex, which lies behind the moderator band. This is why apical muscular VSDs are often so hard to see or reach via the tricuspid valve, either interventionally with a catheter-mounted occlusion device, or surgically.

Dr. Stella Van Praagh was the recipient with her husband of the Distinguished Achievement Award for 1999 of the Society for Cardiovascular Pathology. In 2001, the Cardiac Registry of Children's Hospital Boston was renamed the Drs. Stella and Richard Van Praagh Cardiac Registry. In 2004, Dr. Stella was honored with her husband as a visiting professor for the Sylvia P. Griffiths Teaching Day of the Division of Pediatric Cardiology, at the Morgan Stanley Children's Hospital of New York-Presbyterian. Also in 2004, Dr. Stella was the recipient with her husband of the Paul Dudley White Award of the American Heart Association.

As her achievements and honors indicate, Dr. Stella Van Praagh was a pre-eminent pediatric cardiologist and pediatric cardiac pathologist. The breadth and depth of her expertise in these two different but closely interrelated fields were unmatched. Being the soul of modesty and self-effacement, she would strongly disagree with this assessment. But for many of those who knew her, Dr. Stella Van Praagh was, quite simply, incomparable.

The History and Anatomy of Tetralogy of Fallot

The anomaly now known as the TOF^{8,23} was first described, insofar as is known, by Niels Stensen in 1671. His name was also rendered as Nicolaus Steno (in Latin). Stensen (1638–1686) was a Danish anatomist and naturalist from Copenhagen. He is said to have given up his medical career for the church, becoming the Bishop of Titiopolis in 1667. However, 4 years later he published the first known case of tetralogy in 1671. He did not publish his discovery of the anatomy and function of the excretory duct of the parotid gland—Stensen's duct—until 1682. He described the principles leading to the formation of the Earth's crust and fossils in 1669.²⁴ Thus, Stensen was a professor of anatomy with the wide-ranging interests and expertise of a 17th century naturalist.

Erik Warburg's translation into English of Stensen's²⁵ Latin paper reveals the following. Stensen's patient was a malformed fetus (age not stated or estimated). The salient findings were as follows: cleft palate; right-sided hare lip; all fingers of the left hand were united by a common skin fold; the third finger was the shortest; the left thumb was free (not united with the fingers); the sternum was split; the heart, liver, spleen, right kidney, and most of the intestines were outside of the thorax and abdomen; these organs were uncovered; lungs were in the thorax; the kidneys were lobulated; the adrenals were large and triangular. Thus, this fetus had ectopia cordis, thoracic and abdominal, with ectopy of much more than just the heart. The diaphragm, with the expected diaphragmatic defect, was not described.

Turning to the heart, Stensen said that the pulmonary artery was much narrower than the aorta. The ductus arteri-

osus was absent. There was a subaortic VSD with an overriding aorta. Consequently, I think that this fetus with multiple congenital anomalies including ectopia cordis probably did have what we now call “TOF with pulmonary outflow tract atresia.”

Edouard Sandifort (1742-1814), a Dutch physician, described tetralogy in 1777.²⁶ His patient, called “the blue boy,” died at 12 4/12 years of age. He had been thought clinically to have asthma. However, an autopsy, suggested by the parents, revealed a congenitally malformed heart, the description of which sounds like tetralogy. Again, there was no sign of a ductus arteriosus or a ligamentum arteriosum. Sandifort mentioned the case report of Stensen.

William Hunter (1718-1783), the elder brother of his more famous younger brother John,²⁷ was a Scottish physician (University of Glasgow) who moved to London where he became a leading obstetrician and obstetrical anatomist. In 1770, Hunter built a private lecture theatre, dissecting room, and a museum at his residence in Great Windmill Street. In 1774, three cases of congenital heart disease were published posthumously, attributed to Dr. William Hunter.²⁸ He had read this presentation before the Society of Physicians in London 1 year previously (July 28, 1783). Hunter’s case 2 was a 13-year-old boy with tetralogy and blue spells.

Numerous other case presentations followed, by Pulteney (1785),²⁹ Abernethy (1793),³⁰ Bell (1797),³¹ Dorsey (1812),³² the first American case report from the University of Pennsylvania, Farre (1814),³³ Thaxter (1816),³⁴ Peacock (1858 and 1869),^{35,36} Widman (1881)³⁷ a very early Polish case report of tetralogy, and finally, Fallot (1888)^{9,23} (Fig. 7).

Before continuing, I hasten to add that I have not mentioned all of the early “pre-Fallot” reports. But those that I have cited^{25,26,28-37} indicate that such publications were quite frequent, a fact that Fallot unhesitatingly acknowledged.^{9,23}

What then, was so special about Etienne-Louis Arthur Fallot’s serialized reports in *Marseille Médical* of 1888?⁹ Parenthetically, his friends called him Arthur, which is how he signed his published work.⁹ These five serialized contributions that make up his report⁹ were written with flair and charm, typical of the best of 19th century serialization. Just listen to a literal translation of his first sentence:

One of the happy hazards which comes sometimes to procure for the clinician precious occasions to instruct himself, has in the space of several years, made to pass beneath our eyes three cases of a rare and curious malady, on the pathologic anatomy of which reigns, even in the informed medical public, grave errors and singular incertitudes: we have had the occasion to observe during their life and at autopsy following their death, three subjects afflicted with the malady called cardiac cyanosis, and it would be according to us, much more correct to designate exclusively under the name of blue malady.

I hear similarities with Charles Dickens and Arthur Conan Doyle.

But there was much more to Fallot than elegant style; there was also substance and clinical relevance. He described the *tetralogy* (the four cardinal anatomic features that so often oc-



Figure 7 Etienne-Louis Arthur Fallot was born at Sète on the Gulf of Lyons of the Mediterranean Sea on September 20, 1850. He studied medicine at the École de Médecine of Marseille. Following graduation, he became an intern of the Hospital of Marseille and passed a competitive examination known as the Concours de Médecine des Hôpitaux in 1883. In 1886, Fallot taught pathologic anatomy—just 2 years prior to his famous publication. In 1888, Fallot was appointed Professor of Hygiene and Legal Medicine, a post he held until his death in 1911 at 61 years of age. A respected and experienced clinician, Fallot was Chef de Clinique (Chief of the Clinic) at the Hôtel-Dieu Hospital in Marseille and Chef de Service (Chief of Service) of l’Hôpital de la Conception, Marseille. In 1888, Fallot⁹ famously coined the term *tetralogy* for the four anomalies that occur together and characterize this malformation: (1) pulmonary outflow tract obstruction (stenosis or atresia); (2) VSD; (3) aortic overriding; and (4) right ventricular hypertrophy. Fallot also presented this tetralogy of anomalies as a clinical entity—a cause of *la maladie bleue*. (Reprinted with permission from Van Praagh.²³)

curred together in cyanotic patients). He emphasized that cyanosis was not caused by a patent foramen ovale, as many had proposed. Fallot attributed the morphogenesis of the tetralogy to an intrauterine pathologic process involving the pulmonary valve and the subpulmonary infundibulum. In other words, he understood that one pathologic process accounted for the nonrandom association of the tetrad: (1) pulmonary outflow tract obstruction (stenosis or atresia); (2) VSD; (3) aortic overriding; and (4) right ventricular hypertrophy. Fallot was also aware of and acknowledged the prior contributions of Stensen,⁸ Sandifort,²⁶ and many others.

Nor did Fallot call this anomaly the TOF. Instead, he called it *la maladie bleue* (the blue malady) or *cyanose cardiaque* (cardiac cyanosis).⁹ Instead, it was Maude Abbott³⁸ (Fig. 8) of Montreal, Canada who coined the now familiar diagnosis of “tetralogy of Fallot” in 1924; she thought this designation was briefer and more convenient than having to list all four anomalies making up the tetralogy.

Thus, in 1888 Fallot understood that this tetralogy was basically just one anomaly involving the pulmonary valve



Figure 8 Maude Elizabeth Seymour Abbott (1869-1940) was a Canadian pioneer in pediatric cardiology and in pediatric cardiac pathology. Working at McGill University in Montreal, Abbott and Dawson³⁸ in 1924 coined the term “tetralogy of Fallot.” Abbot thought the tetralogy of Fallot was more convenient than the longer designation “pulmonary stenosis and atresia with defect of the ventricular septum,” which was the pre-1924 equivalent. (This rare photograph of Dr. Maude Abbot, to our knowledge previously unpublished, was discovered in the Archives of the Rare Books Department of the Countway Library of Medicine, Harvard Medical School, Boston.)

and the subpulmonary infundibulum, not four different unrelated malformations that occurred together by chance.

We reached a very similar conclusion in 1970⁷; namely, that the TOF results from underdevelopment of the subpulmonary infundibulum in 3 dimensions (Figs. 9-16), and that the classical tetralogy consists of the sequelae of an underdeveloped, low-volume and hence obstructive infundibulum. The pulmonary valve is the “back door” of the subpulmonary conus, which helps to explain the frequent but not universal involvement of the pulmonary valve in the right ventricular outflow tract obstruction of TOF. By contrast, the subpulmonary infundibulum is *always* abnormal in tetralogy. Basically, tetralogy is an infundibular malformation.

The understanding that the TOF is basically one abnormality⁷ (the “monology of Stensen”) had important diagnostic and surgical consequences.^{23,40} Once the central role of smallness of the subpulmonary infundibulum in tetralogy was appreciated, then we came to understand how tragically misguided the old-fashioned repair of tetralogy really was. This old-style repair of tetralogy often began with a long, low, J-shaped or hockey-stick-shaped right ventriculotomy, to provide good visualization of the VSD. This was followed by extensive myocardial resection of the parietal band (conal

septum), of the septal band, and with thinning of the right ventricular free wall. Much of this myocardial resection was proximal or upstream relative to the infundibular and pulmonary valvar obstruction. The result of this surgical technique included significant wounds of the right ventricle proximal to the outflow tract obstruction, predisposing to low cardiac output and death postoperatively. The thinned right ventricular free wall often became a paradoxing right ventricular outflow tract aneurysm. No wonder so many patients with typical TOF used to die postoperatively in low cardiac output. If the problem was not right ventricular “infarction” secondary to extensive and unnecessary myocardial resection, it was unrelieved right ventricular outflow tract obstruction because of fear of transannular patches, or both.

Once the foregoing was understood, our surgical approach was transformed and our results improved dramatically.⁴⁰ The infundibulotomy became as short as possible. Right ventricular myocardial resection was abandoned virtually altogether. Castaneda and his colleagues⁴⁰ found that in the young infant with TOF, there really is very little muscle to excise. If one operates early enough, postnatal secondary right ventricular myocardial hypertrophy has not yet occurred. The use of transannular patches without myocardial resection achieved the dual objectives of minimal right ventricular trauma and absence of right ventricular outflow tract obstruction.

Then we realized that TOF could be successfully repaired at any age—in the newborn period (the first 30 days), or in infancy (the first year of life). This in turn led to what came to be known as the Castañeda doctrine.⁴⁰

Its main tenets were:

1. Repair TOF whenever the patient needs it, at any age—in the newborn period, if necessary.

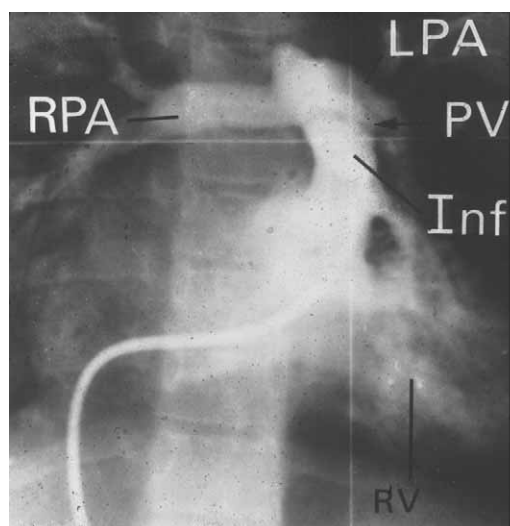


Figure 9 Typical TOF, selective right ventricular angiogram, postanterior projection. The subpulmonary infundibulum is smaller than normal (ie, smaller in volume than normal). The pulmonary artery branches are also smaller than normal. Inf, infundibulum; LPA, left pulmonary artery; PV, pulmonary valve; RPA, right pulmonary artery; RV, morphologically right ventricle. (Reprinted with permission from Van Praagh et al.⁷)

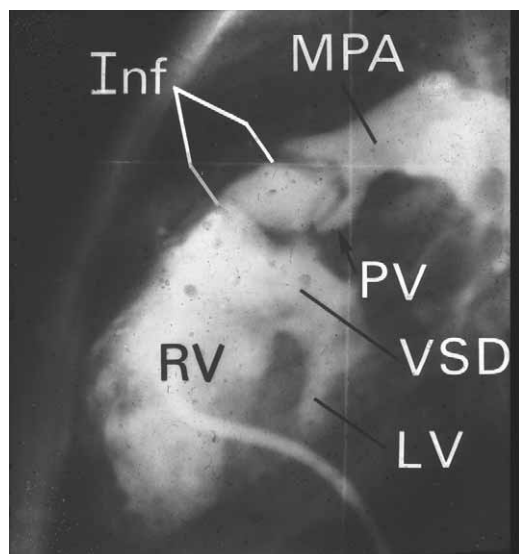


Figure 10 Typical TOF, selective right ventricular angiogram, left lateral projection simultaneous with Fig. 9. The subpulmonary infundibulum has smaller volume than normal. The infundibular (conal) septum (unlabelled) is hypoplastic and malaligned anterosuperiorly, narrowing the inlet into the subpulmonary infundibulum and resulting in pulmonary infundibular stenosis. Malalignment of the infundibular septum anterosuperiorly also opens up the space above the ventricular septum (unlabelled), resulting in a large VSD between the hypoplastic and anterosuperiorly malaligned infundibular septum above and the normally located ventricular septum below. The pulmonary valve is thickened and obstructive, resulting in pulmonary valvar stenosis. The main pulmonary artery is smaller than normal. The presence of infundibular and valvar pulmonary outflow tract stenosis resulted in right-to-left shunting of unoxygenated blood from the right into the left ventricle through the conoventricular malalignment VSD. Inf, subpulmonary infundibulum; LV, morphologically left ventricle; MPA, main pulmonary artery; PV, pulmonary valve; RV, morphologically right ventricle; VSD, ventricular septal defect. (Reprinted with permission from Van Praagh et al.⁷)

2. One operation is better than two; whenever possible, avoid palliative surgery such as Blalock-Taussig shunts.

Thus, an accurate understanding of the “monology of Stensen”⁷ cast a long and important management shadow.

Now let us return to the pathologic anatomy of TOF in somewhat greater detail. Angiocardiology and other more modern imaging modalities often give an even clearer, less distorted picture of the anatomy than photos of heart specimens do.

Figure 9 shows the abnormally small subpulmonary infundibulum of typical TOF in posteroanterior projection. The main pulmonary artery and branches are also smaller than normal.

Figure 10 is a simultaneous left lateral projection of this selective right ventricular injection. Note that the conal septum is displaced anterosuperiorly, narrowing the inlet into the small subpulmonary infundibulum, contributing to the right ventricular outflow tract stenosis. The pulmonary valve is thickened and stenotic, also contributing to the right ven-

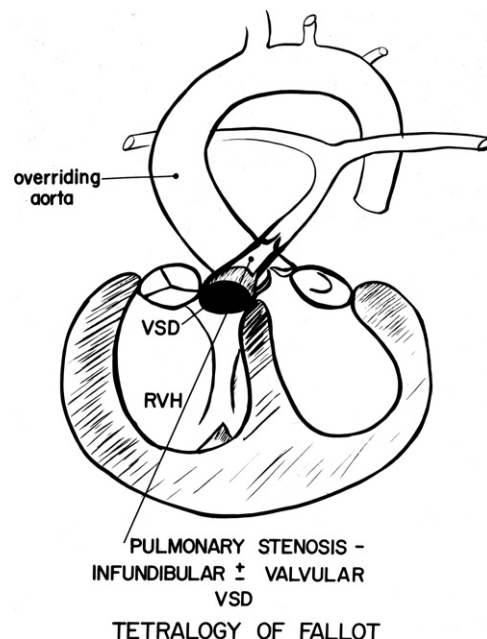


Figure 11 Diagram of typical TOF, which is characterized by: (1) pulmonary outflow tract stenosis that is always infundibular, and may or may not be valvar; (2) ventricular septal defect (VSD); (3) aortic overriding; and (4) right ventricular hypertrophy (RVH). This is *typical* TOF in the sense that in its most severe form, there is pulmonary outflow tract atresia (the “pseudotruncus” of the older literature). We think that the reason these four abnormalities occur so frequently together, in a nonrandom way, is that they are all interrelated.⁷ The concept is that a small-volume subpulmonary infundibulum is the basic anomaly, resulting in pulmonary outflow tract obstruction (stenosis or atresia). There is a VSD because the small-volume infundibulum cannot begin to fill the space above the septal band and the ventricular septum. The infundibular septum is malaligned anterosuperiorly above the right ventricle (compared with normal) because of failure of normal expansile growth of the infundibulum. Failure of normal morphogenetic growth of the infundibulum means that the infundibular outflow tract floor—the conal (infundibular) septum—fails to expand in a rightward, posterior, and inferior direction, thereby helping to close the interventricular foramen. Failure of this normal morphogenetic movement of the infundibular septum to occur results in aortic overriding. Because the infundibular septum is abnormally malaligned above the right ventricle, aortic overriding occurs because the aortic valve is attached to what should be the left ventricular outflow tract surface of the infundibular septum. Because the infundibular septum is anterosuperiorly malaligned above the right ventricle, so too is the attached aortic valve. Right ventricular hypertrophy is a postnatally acquired sequela, not present at birth in TOF. The hypoplastic (low-volume) subpulmonary infundibulum also explains the abnormal spatial locations of both semilunar valves in tetralogy: why the pulmonary valve is abnormally leftward, posterior, and inferior; and why the aortic valve is reciprocally abnormally rightward, anterior, and superior—and hence overriding (see text). Thus, the TOF may be understood as the *monology of Stensen*: basically just one malformation (a low-volume subpulmonary infundibulum and its sequelae), not four unrelated anomalies, first described by Stensen in 1671,⁸ not by Fallot in 1888.⁹ We are not trying to change conventional terminology. Instead, the point is that this understanding is important diagnostically and surgically (see text).

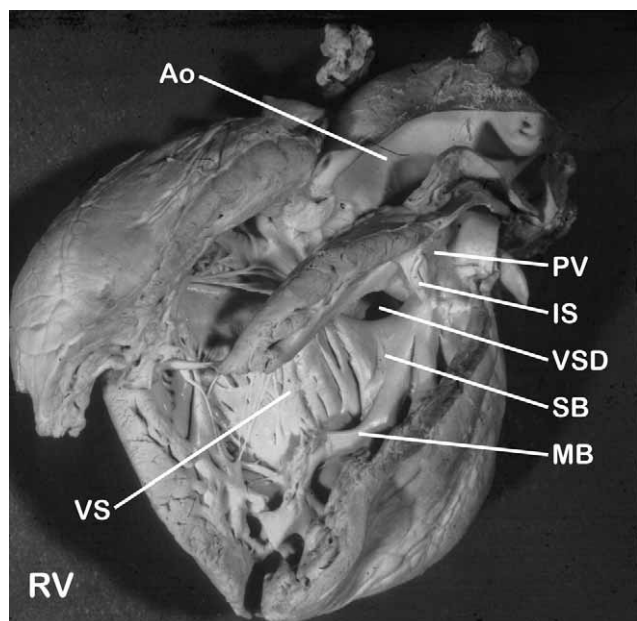


Figure 12 The anatomy of typical TOF: the pulmonary outflow tract. The opened right ventricle shows that the hypoplastic infundibular septum (IS) intersects the left anterior division of the top of the septal band (SB). This anterosuperior malalignment of the infundibular septum leaves the space above the “Y” of the septal band wide open, resulting in a ventricular septal defect (VSD). The pulmonary valve (PV) is stenotic and bicuspid. The ascending aorta (Ao) is large. MB, moderator band; VS, right ventricular septal surface. (Reprinted with permission from Van Praagh et al.⁷)

tricular outflow tract stenosis. There is a large VSD located beneath the anterosuperiorly displaced infundibular (conal) septum and above the normally located ventricular septum. This is a malalignment conoventricular type of VSD (ie, it lies between the conal and the ventricular septa), and the defect is present because the hypoplastic conal septum is malaligned anterosuperiorly.

Because there is infundibular and valvar right ventricular outflow tract stenosis, the contrast shunts from right to left—from the anterior and right-sided right ventricle into the posterior and left-sided left ventricle. This right-to-left shunting of systemic venous (unoxygenated) blood in the right ventricle into the arterial (oxygenated) blood in the left ventricle results in cyanosis, typically when the systemic arterial oxygen saturation is less than 85%. The VSD usually is large and nonrestrictive. The systolic right ventricular pressure typically is systemic.

The main pulmonary artery and its branches are smaller than normal because they carry less than the normal volume of venous blood per unit time, in turn because of the coexistence of pulmonary infundibular and valvar stenosis that results in right-to-left shunting through the VSD, away from the main pulmonary artery and its branches.

The pulmonary valve is abnormally left-sided, inferior, and posterior because the subpulmonary conus is underdeveloped (hypoplastic in 3 dimensions). The aortic valve in TOF is *reciprocally* too right-sided, superior, and anterior. The abnormal location of the aortic valve is widely recog-

nized and is called aortic overriding—because the aortic valve overrides the ventricular septum above the VSD.

The *reciprocally* abnormal location of the pulmonary valve is not as widely understood—because the pulmonary valve still communicates with the right ventricle, albeit too narrowly.

The development of the subpulmonary infundibulum (subnormal in tetralogy) and the resorption of the subaortic infundibular free wall (essentially normal in tetralogy) are the two drivers of the semilunar valvar locations. Underdevelopment of the subpulmonary infundibulum means that the pulmonary valve is not elevated as superiorly, and is not protruded as anteriorly as it normally is (Fig. 10.). The reciprocal

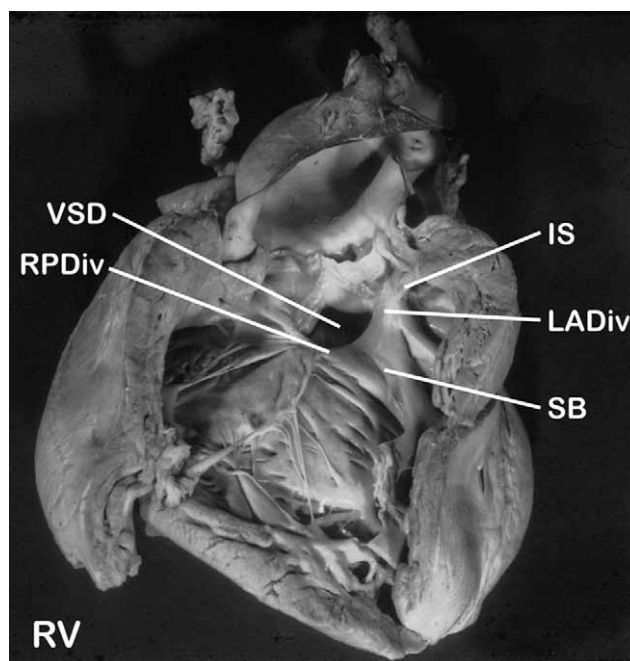


Figure 13 The anatomy of typical TOF: the aortic outflow tract from the same opened right ventricle shown in Fig. 12. Again, note how hypoplastic the infundibular septum (IS) is. The IS intersects with the left anterior division (LA Div) of the “Y” of the septal band (SB). The thin right posterior division (RP Div) of the “Y” of the septal band is also well seen. The “Y” of the septal band—between the LA Div and the RPDiv—forms the inferior rim of the ventricular septal defect (VSD) as seen from the right ventricle. Because the RPDiv of the septal band is slender (gracile), the VSD is confluent with the anterior leaflet (AL) and the septal leaflet (SL) of the tricuspid valve; hence, the VSD is said to be paramembranous (or juxtamembranous). The RPDiv of the septal band forms the muscle of Lancisi, also known as the muscle of Lushka, or the medial papillary muscle. The right bundle branch of the atrioventricular conduction system enters the right ventricle beneath the RPDiv and then runs down the septal band (SB) and on to the moderator band to reach the anterior papillary muscle and the right ventricular free wall. When the muscle of Lancisi is thin and delicate, as in this heart, it offers very little protection to the entering right bundle branch during surgical patch closure of the “lower angle” of the VSD. This is why many surgeons place their sutures into the membranous tricuspid tissue at this point, rather than into the myocardium, in order to avoid surgically induced heart block. (Reprinted with permission from Van Praagh et al.⁷)

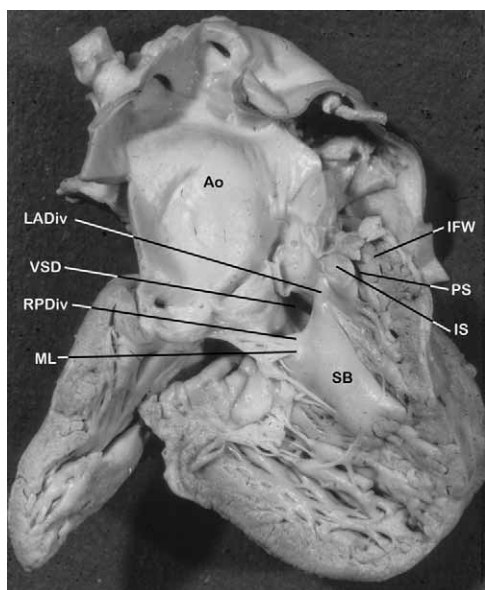


Figure 14 The anatomy of TOF with severe right ventricular outflow tract stenosis. The opened right ventricle reveals that the transected infundibular septum (IS), the “floor” of the subpulmonary infundibular outflow tract, and the infundibular free wall (IFW), the “roof” of the subpulmonary infundibular outflow tract, are very close together, resulting in severe infundibular subpulmonary stenosis (PS). These findings suggest that there has been a major failure of expansile growth and development of the subpulmonary infundibulum. The “floor” of the infundibulum (IS) is very close to the “roof” of the infundibulum (IFW); hence, the infundibular outflow tract has a very shallow cavity, because the “floor” is so close to the “roof.” Note that the infundibular septum intersects the ventricular septum anterior to the left anterior division (LADiv) of the septal band (SB). The space above the septal band is wide open; this malalignment conoventricular ventricular septal defect (VSD) is as big as it can be. The right posterior division (RP Div) of the septal band (SB) is very slender; hence, this VSD is paramembranous. The muscle of Lancisi (ML) is where the anterior leaflet of the tricuspid valve inserts into the septal band. Just as the pulmonary artery and its branches are small, the ascending aorta (Ao) is reciprocally huge, both for hemodynamic reasons (not because of truncal malseptation). Per unit time, the pulmonary arteries carry only a small proportion of the right ventricular output because of the severity of the right ventricular outflow tract stenosis; by contrast, per unit time, the ascending aorta conveys most of the output of both ventricles. (Reprinted with permission from Van Praagh et al.⁷)

consequence is that the aortic valve is not carried as posteriorly, inferiorly, and leftward as it normally is, resulting in aortic overriding.

The abnormal location of the aortic valve in tetralogy (overriding) is widely recognized and is part of the classic tetrad. The reciprocally abnormal location of the pulmonary valve in tetralogy is not as widely recognized or understood, even though it is clearly apparent, for example, angiocardio-graphically (Figs. 9-10). Comparison of tetralogy angios with those of a normal heart will clearly reveal these differences. Despite the presence of aortic-mitral fibrous continuity in tetralogy—often more tenuous and less tight than normal—

both semilunar valves are somewhat abnormally located in tetralogy.

These anatomic details are relevant to surgical repair: to VSD patch placement because of aortic overriding; and to right ventricular outflow tract reconstruction because of the abnormally leftward, posterior, and inferior location of the pulmonary valve in TOF.

Figure 11 is a diagram of typical TOF showing the essence of this malformation: pulmonary outflow tract obstruction (stenosis or atresia), which always involves the subpulmonary infundibulum, and may or may not involve the pulmonary valve.

Why is There Always a VSD?

Because the subpulmonary infundibulum is too small in 3 dimensions (Fig. 11). Normally, the subpulmonary infundibulum largely fills the space above the ventricular septum and septal band; but not in tetralogy. Because the subpulmonary infundibulum is too small, it cannot fill the space above the ventricular septum and septal band, resulting in a VSD. Consequently, as seen from the right ventricle (Fig. 11), the VSD is limited inferiorly by the top of the septal band, which

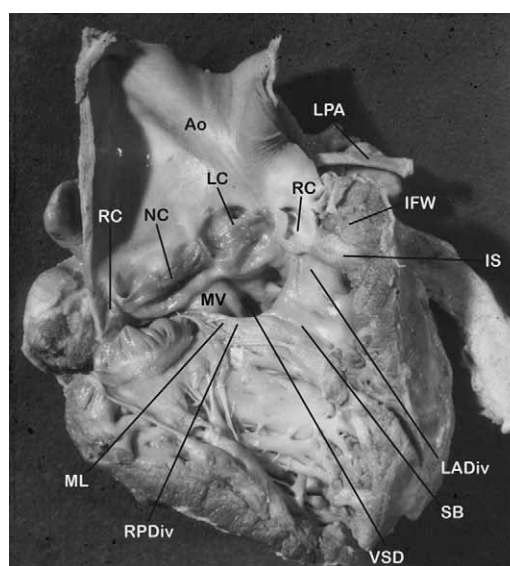


Figure 15 TOF with right ventricular outflow tract atresia. The opened right ventricle shows that the infundibular septum (IS) and the infundibular free wall (IFW) are touching (ie, fused). Consequently, there is no infundibular outflow tract lumen. Note how small the left pulmonary artery (LPA) is, and how reciprocally large the ascending aorta (Ao) is. The space above the septal band (SB) is wide open, resulting in a large subaortic conoventricular paramembranous type of ventricular septal defect (VSD). Through the VSD, one can see that there is aortic-mitral direct fibrous continuity, which is characteristic of tetralogy. Note that it is the left coronary (LC) leaflet of the aortic valve that is in direct fibrous continuity with the anterior leaflet of the mitral valve (MV). The noncoronary (NC) leaflet of the overriding aortic valve is only in tenuous fibrous continuity with the mitral valve, reflecting mildly subnormal aortic-mitral approximation in some cases of tetralogy, particular in those with severe infundibular underdevelopment. (Reprinted with permission from Van Praagh et al.⁷)

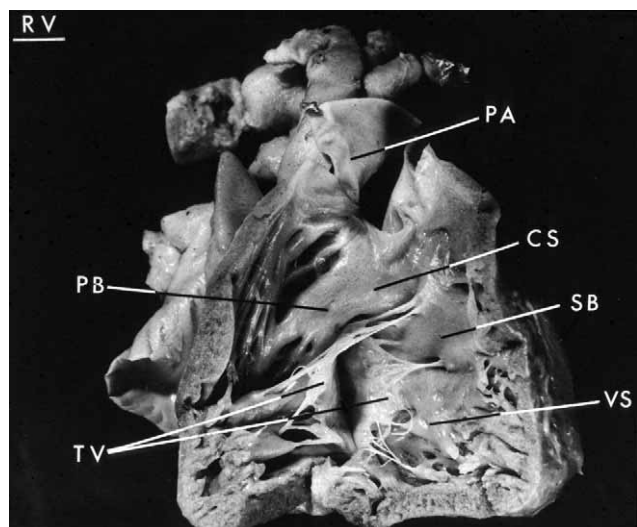


Figure 16 The structurally normal right ventricle and subpulmonary infundibular outflow tract reveal several major differences on comparison with TOF (Figs. 12-15). In the normal right ventricle, the area above the septal band (SB) is filled by a well-developed conal septum (CS) or infundibular septum, and the normally developed infundibular septum extends out onto the right ventricular free wall as the parietal band (PB). The pulmonary valve normally is well developed, tricuspid, and nonobstructive. The subpulmonary infundibular chamber is also well expanded and nonobstructive. (Reprinted with permission from Van Praagh et al.⁷)

forms a Y-shaped structure known as the “Y” of the septal band. The two limbs of the Y of the septal band are formed by the left anterior and the right posterior divisions. These two divisions forming the top of the “Y” of the septal band constitute the inferior margin of the VSD in tetralogy.

The superior margin of the VSD, as seen from the right ventricle (Fig. 11), is formed by the inferior rim of the conal septum that is malaligned anteriorly, superiorly, and to the left relative to the septal band.

It is widely thought that the subpulmonary infundibular stenosis of typical tetralogy is caused by the malalignment of the conal (infundibular) septum. In a sense, this is true. However, the reason that the conal septum is where it is appears to be related to conal hypoplasia in 3 dimensions (ie, a failure of normal expansile growth of the subpulmonary infundibulum as a whole) involving both the infundibular free wall and the infundibular septum, not just malseptation involving malposition the infundibular (conal)* septum only.*

We often describe TOF as being characterized by anterior, superior, and leftward malalignment of the infundibular septum compared with normal because superficially, that is how it looks. But we think that this is exactly the opposite of what has really happened—or of what has failed to happen—in tetralogy. Instead, we think that the malaligned conal septum

in tetralogy is where it is because of a failure of conal expansile growth as a whole. In tetralogy, because of conal hypoplasia, there has been failure of the conal septum to expand posteriorly, inferiorly, and to the right. Thus, infundibular underdevelopment in tetralogy results in pulmonary outflow tract obstruction (stenosis or atresia), and in a typically large malalignment type of conoventricular VSD (Fig. 11).

The VSD in tetralogy may or may not be confluent with the fibrous tissue of the tricuspid valve (Fig. 11), depending on whether the right posterior division of the septal band permits, or prevents confluence between the VSD and the membranous tissue of the tricuspid valve.

When the VSD is confluent with the membranous tissue of the tricuspid valve, ie, when the right posterior division of the septal band is thin and delicate and does not preclude confluence of the defect with the tricuspid valve, then the VSD is said to be *paramembranous*. But when the right posterior division of the septal band is thick and prominent, it may well prevent confluence of the VSD with the tricuspid valve; in this case, the VSD is said not to be *paramembranous*. The right bundle branch of the atrioventricular conduction system enters the right ventricle just beneath the right posterior division of the septal band. Thus, a thick and prominent right posterior division of the septal band, resulting in a *non-paramembranous* VSD, affords some degree of protection of the right bundle branch during surgical VSD closure. To avoid right bundle branch block during patch closure of the VSD, many surgeons place sutures into the adjacent tricuspid leaflet tissue, where the conduction system—being specialized muscle—never runs.

Paramembranous or *juxtamembranous* means beside the membranous tricuspid tissue: *para* = beside (Greek), and *juxta* = beside (Latin).

In the interests of accuracy, we avoid the term *perimembranous* that has been used in this context because *peri* (in Greek) means around (not beside). The VSD in tetralogy does not extend around the membranous septum. There is a huge difference in meaning between *para*- and *peri*. Following tricuspid valve replacement, for example, one way may have a paravalvar leak—readily fixable surgically. If one has perivalvar leak, one is facing a much more serious problem.

Thus, underdevelopment in 3 dimensions of the subpulmonary infundibulum explains two of the most important features of the classical tetrad: (1) pulmonary outflow tract obstruction (stenosis or atresia); and (2) the malalignment conoventricular VSD, that may or may not be *paramembranous*.

What about the third and fourth features of Fallot’s classical tetralogy?

(3) Why aortic overriding? Because of the *anterior* malalignment of the infundibular septum—above the anterior morphologically right ventricle. As will be seen, the aortic valve is often in somewhat subnormal fibrous continuity with the mitral valve posteriorly; and the aortic valve also extends abnormally anteriorly because of the anterior malalignment of the conal septum (Fig. 11).

(4) What about right ventricular hypertrophy (Fig. 11)? This feature is present in tetralogy only postnatally. Prenatally, right ventricular pressure normally is systemic because

*The infundibulum and the conus are the same structure. *Infundibulum* means funnel (Latin). *Conus* means cone (Latin). Infundibulum is an inside look at this structure, whereas conus is the outside appearance of the same structure, as in an embryologic reconstruction. We and most others use the terms “infundibulum” and “conus” interchangeably.

the right ventricle is the systemic ventricle for the lower systemic circulation via right-to-left shunting through the ductus arteriosus. Only postnatally does the right ventricle become abnormally hypertrophied in tetralogy because of persistence of systemic pressure in the right ventricle due to the coexistence of pulmonary outflow tract obstruction and a large nonrestrictive subaortic VSD (Fig. 11). Hence, in tetralogy, right ventricular hypertrophy is a postnatally acquired sequela, not part of the congenital malformation.

Thus, from a developmental standpoint, TOF is not really a tetralogy. Developmentally, it is at most a trilogy (the classic tetralogy minus right ventricular hypertrophy). Basically, as indicated previously we think that the TOF is really only one anomaly (underdevelopment of the subpulmonary infundibulum in 3 dimensions) and the sequelae thereof (the “monology of Stensen”).⁷ These insights are recorded here in the interests of deeper understanding; we are not trying to change diagnostic terminology. We still make the diagnosis of TOF,^{7,23} and we have every desire to honor Etienne-Louis Arthur Fallot of Marseille (Fig. 7) and his excellent contribution.⁹

Figure 12 shows the opened right ventricle and the pulmonary outflow tract of typical TOF {S,D,S} with moderate pulmonary outflow tract stenosis and a bicuspid pulmonary valve. The hypoplastic infundibular septum is displaced anteriorly. The infundibular septum intersects the left anterior division of the Y of the septal band. Normally, the infundibular septum is larger and it “should” be displaced posteroinferiorly, filling the space above the ventricular septum which is wide open, resulting in a large malalignment VSD. The subpulmonary infundibulum forms a stenotic cone, resulting in right ventricular infundibular and valvar stenosis. The small main pulmonary artery, the large ascending aorta, and the right ventricular hypertrophy are also noteworthy.

Figure 13 shows the same opened right ventricle and the aortic outflow tract. The septal band is better seen. The small infundibular septum can be seen intersecting the left anterior division of the septal band. The small subpulmonary cone can be seen to the left of the infundibular septum. The whole space above the Y of the septal band is wide open, resulting in a large subaortic VSD. Normally, this space is filled by the conal septum. This subaortic malalignment VSD is paramembranous (ie, confluent with the tricuspid valve). The large aortic valve is dextroposed (ie, aortic overriding is present).

Figure 14 shows the opened right ventricle of another patient with TOF in whom the right ventricular outflow tract obstruction is more severe than in the previous patient (Figs. 12-13). The infundibular outflow tract—anterior to the malaligned and transected conal septum (to the viewer’s right relative to the conal septum)—is very tight. The conal septum intersects the ventricular septum anterior to the left anterior division of the Y of the septal band. Hence, the entire space within the limbs of the septal band is wide open, completely unfilled by the conal septum. The subaortic VSD is as large as it can be. Again, this is a large subaortic conoventricular paramembranous VSD. The large overriding aorta and the right ventricular hypertrophy are well seen.

Figure 15 shows the opened right ventricle of another patient with TOF who has pulmonary outflow tract atresia. (In the older literature, this was often called “pseudotruncus.”) The infundibular septum is fused with the infundibular free wall; consequently, there is no infundibular outflow tract lumen. Note how very small the left pulmonary artery is. The ascending aorta is reciprocally huge. The space above the septal band and ventricular septum is as large as it can be, because of the anterior malalignment of the hypoplastic infundibular septum. The subaortic VSD is conoventricular and paramembranous. Through the large VSD, one can see that there is aortic-mitral fibrous continuity, typical of TOF. Right ventricular hypertrophy is marked.

Figure 17 shows the opened left ventricle of a patient with TOF. Although there is direct fibrous continuity between the large aortic valve above and the unremarkable mitral valve below, the aortic-mitral approximation is not quite normal. In the normal heart, the noncoronary-left coronary commissure of the aortic valve is above the middle of the deep anterior or aortic leaflet of the mitral valve. In this tetralogy patient, the noncoronary-left coronary commissure sits above the right-most and posterior portion of the anterior mitral leaflet (not above the middle of the anterior mitral leaflet). In other words, in the normal heart both the left coronary and the noncoronary leaflets of the aortic valve are in direct fibrous continuity with the anterior (or aortic) leaflet of the mitral valve. But, in tetralogy, often only the left coronary leaflet is in direct fibrous continuity with the mitral valve (ie, the noncoronary aortic leaflet often has little or no direct fibrous contact with the anterior mitral leaflet).

This means that in TOF, dextropositioning (overriding) of the aortic valve is “real”; ie, aortic dextropositioning is related to mildly subnormal aortic-mitral approximation posteriorly, as well as to aortic annular dilatation and to abnormally right-sided attachment to the malaligned conal septum anteriorly. Thus, both semilunar valves in tetralogy are reciprocally mildly abnormally located. The aortic valve is somewhat too right-sided, anterior, and superior, while the pulmonary valve is somewhat too left-sided, posterior, and inferior. What we call “aortic overriding” is really a *failure to achieve completely normal levopositioning of the aortic valve*. In normal cardiogenesis, the morphogenetic movements of the semilunar valves are very real; in TOF, the morphogenetic movements of both the pulmonary valve and the main pulmonary artery and of the aortic valve and the ascending aorta are both reciprocally subnormal.

Only the abnormally located aortic valve is recognized by the classical tetrad (aortic overriding), probably because of its obvious hemodynamic importance: blue systemic venous blood being ejected directly into the aorta, resulting in cyanosis.

However, the abnormal location of the pulmonary valve is also of considerable, if more subtle, hemodynamic dynamic importance. One needs to understand right ventricular outflow tract stenosis or atresia. The following attempted explanation may help. The right ventricular infundibular free wall cannot get out of the way. It is the fixed, unmoving, right ventricular outflow tract “roof.” The conal septum, by contrast, is the moveable right ventricular outflow tract “floor.” The location of the right ventricular outflow tract floor (the

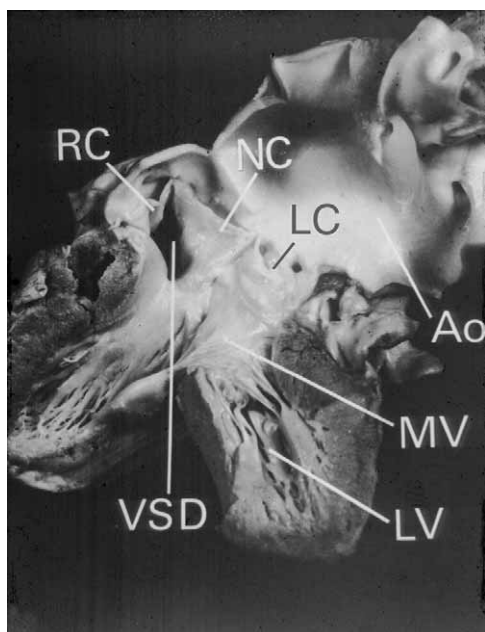


Figure 17 The morphologically left ventricle (LV) and the aortic outflow tract in TOF. The aortic-mitral fibrous continuity in tetralogy typically is mildly subnormal: between the left coronary (LC) leaflet of the aortic valve and the anterior or aortic leaflet of the mitral valve (MV). Normally, both the noncoronary (NC) and the left coronary (LC) leaflets of the aortic valve are in fibrous continuity with the mitral valve. Normally, the left coronary-noncoronary commissure of the aortic valve sits above the middle of the anterior mitral leaflet. By contrast, in this case of tetralogy, the left coronary-noncoronary commissure sits above the rightmost portion of the anterior mitral leaflet—where it intersects with the left ventricular septal surface. Thus, in TOF, the aortic valve typically is mildly abnormally located: both at its mitral approximation posteriorly, inferiorly, and leftward; and at the deviated infundibular septum anteriorly, superiorly, and rightward.

conal septum) is determined by the severity of the expansile growth failure of the infundibulum. When infundibular expansile growth failure is severe, then the floor of the infundibular outflow tract is high, very close to the infundibular free wall, resulting in a very tight (stenotic) or even an atretic infundibular outflow tract (Figs. 14 and 15, respectively).

But when expansile growth of the infundibulum is greater, then the right ventricular outflow tract floor is lower, further away from the infundibular outflow tract roof, resulting in less severe right ventricular outflow tract stenosis (Figs. 12 and 13).

The more severe the failure of infundibular expansile growth is, the lower, more left-sided, and more posterior the pulmonary valve is. The architectural function of growth and development of the subpulmonary infundibulum is to elevate the pulmonary valve superiorly and to carry it anteriorly above the anterior right ventricle. When expansile growth and development of the subpulmonary infundibulum is normal—including its “back door,” the pulmonary valve—then the right ventricular outflow tract is nonobstructive.

Equally important is resorption of the subaortic infundibular free wall, which makes possible aortic-mitral approxi-

mation and aortic-mitral direct fibrous continuity (with no interposed subaortic conal free wall myocardium) (Fig. 17).

Thus, the abnormal location of the pulmonary valve in tetralogy is also of great hemodynamic significance. Its degree of abnormality in location correlates directly with the degree of subnormality of infundibular expansile growth.

TOF is a subnormality: a failure of the normal expansile growth of the subpulmonary infundibulum, with a reciprocal failure of fully normal aortic-mitral approximation. Tetralogy is a partial failure of “Mother Nature’s” arterial switch operation. Expansile growth and development of the subpulmonary infundibulum, plus resorption of the subaortic infundibular free wall (thought to be accomplished by apoptosis or programmed cell death) converts a Taussig-Bing-like origin of both great arteries above the developing right ventricle into normally related, aligned, and connected great arteries. This developmental arterial switch was one of our crucial adaptations to air breathing and land living: a four-chambered heart with separate pulmonary and systemic circulations. In tetralogy, the arterial switch is *almost* normal.

Figure 18 summarizes a previously unpublished morphometric study of neonatal (first month of life) TOF ($n = 16$), compared with age-matched normal heart controls. This study was conducted with Drs. Keishi Kadoba, Maurizio Rubino, and Renzo Pessotto, all cardiac surgeons, when we were privileged to have them as fellows in the Cardiac Registry, the Cardiac Pathology Laboratory of Children’s Hospital Boston. We chose only *neonatal* cases of tetralogy so that the results of morphometry would be influenced as little as possible by postnatal changes.

On May 15, 1993, the database of the Cardiac Registry consisted of 2,965 autopsied cases of congenital heart disease, of which 407 had tetralogy of Fallot (14%; Table 1). Tetralogy was the fifth most common anatomic type of congenital heart disease in the Cardiac Registry, right behind TGA ($n = 442$; 15% of this series of autopsied congenital

Table 1 Autopsied Cases of Congenital Heart Disease: The Top 15 Anatomic Types ($n = 2,965$ patients)

	No.	%
1. Ventricular septal defect	1,077	36
2. Atrial septal defect, secundum	745	25
3. Patent ductus arteriosus (>2 weeks)	557	19
4. Transposition of the great arteries	442	15
5. Tetralogy of Fallot	407	14
6. Aortic stenosis	358	12
7. Coarctation of the aorta	356	12
8. Persistent left superior vena cava	345	12
9. Completely common atrioventricular canal	343	12
10. Pulmonary stenosis	304	10
11. Bicuspid aortic valve	240	8
12. Bicuspid pulmonary valve	238	8
13. Double-outlet right ventricle	233	8
14. Anomalous pulmonary venous return	223	8
15. Aortic atresia, valvar	207	7

Percentages are all rounded to the nearest whole number. This table lists 5,852 congenital heart malformations that occurred in 2,965 patients; many patients had more than one cardiac anomaly.

heart disease). These data do *not* answer the question, “what is the commonest anatomic type of cyanotic congenital heart disease?” because all anatomic types of TGA were included (ie, congenitally physiologically corrected [often acyanotic] transpositions were not excluded). There are many other findings of interest in this Table, but the need for brevity precludes further comment.

This morphometric study (Fig. 18) of *typical* neonatal TOF was based on 16 of 47 neonatal congenital heart specimens (34%). The following were excluded: absent pulmonary valve ($n = 7$; 15% of neonatal TOF); pulmonary atresia ($n = 4$; 9% of neonatal tetralogy); “complicated” tetralogy with other associated anomalies ($n = 11$; 23% of neonatal tetralogy); and operated patients ($n = 9$; 19% of neonatal tetralogy).

The total sample of tetralogy that was surveyed in this morphometric study was 300 heart specimens, 253 were > 30 days of age (84%), and 47 heart specimens were ≤ 30 days of age (16%). Thus, this morphometric study was based on approximately one third of our cases of neonatal tetralogy ($n = 16$ of 47; 34%) that were regarded as typical and uncomplicated (as above).

The mean age of death was 8 days (normal controls = 10 days, no statistically significant difference). Mean body weight was 2.5 kg (normal controls = 2.8 kg, no significant difference).

The measurements that were made were: dimensions of the ventricles, inflow and outflow; annular circumferences of the atrioventricular and semilunar valves; wall thicknesses of the conus, right ventricular and left ventricular sinuses; length of the conal septum; perimeter of the main pulmonary artery; perimeter of the conus; and the nature aortic-mitral fibrous continuity.

The salient findings may be summarized as follows:

1. The lengths of the right ventricular inflow tract and outflow tract, and of the left ventricular inflow tract and outflow tract in typical neonatal TOF were not statistically significantly different from those dimensions in normal control heart specimens.
2. The thicknesses of the right ventricular sinus free wall and of the left ventricular sinus free wall were not statistically significantly different from normal controls. However, the thickness of the conal free wall was significantly thinner in neonatal tetralogy than in normal controls ($P < .01$). Similarly, the conal septum was significantly thinner in neonatal tetralogy than in normal controls ($P < .01$).
3. The circumferences of the tricuspid and mitral valves in neonatal tetralogy were not statistically significantly different from those in normal controls. The circumferences of the subpulmonary conus in neonatal TOF were much smaller than those found in normal controls ($P < .01$). The circumferences of the pulmonary valve in neonatal tetralogy also were much smaller than those in normal controls ($P < .01$). The circumferences of the aortic valve in neonatal tetralogy were mildly larger than those in normal controls, but these differences did not reach statistical significance. As expected, the cir-

cumferences of the main pulmonary artery in neonatal tetralogy were much smaller than those found in normal controls ($P < .01$).

The conal septal lengths in neonatal TOF were mildly greater than those found in normal controls; however, these differences were not statistically significant. The distances between the pulmonary valve and the tricuspid valve also were greater in neonatal tetralogy than in normal controls, and these differences were statistically significant ($P < .05$).

Although the width of the anterior mitral leaflet in neonatal tetralogy was not significantly different from that in normal controls, the number of patients that had aortic-mitral fibrous continuity consisting of the left coronary leaflet only (rather than the left coronary leaflet and the noncoronary leaflet of the aortic valve) was significantly greater in neonatal TOF than in normal controls ($P < .01$). This finding is shown photographically in Fig. 17.

The calculated cross-sectional areas at the levels of the infundibulum, pulmonary valve, and the main pulmonary artery were all significantly smaller in typical neonatal TOF than in normal control heart specimens ($P < .01$; Fig. 18).

The calculated volume of the infundibulum in typical neonatal tetralogy was also very much less than in normal controls ($P < .01$; Fig. 18).

What Conclusions may be Drawn from the Morphometric Data?

TOF is characterized by underdevelopment of the subpulmonary infundibulum in a 3-dimensional or volumetric sense.

Our findings also confirm the observations of Becker and Anderson⁴¹ that the *length* of the conal septum in TOF often is normal (not smaller than normal).³⁹

This is why we have been emphasizing the importance of *expansile* or *centrifugal* growth and development of the subpulmonary infundibulum normally, and conversely the importance of the absence or underdevelopment of expansile or centrifugal growth and development of the infundibulum as the morphogenetic cause of TOF.⁷ The problem in tetralogy is not the length of the conus or the conal septum. Instead, the problem is a failure of normal expansile growth of the subpulmonary infundibulum, resulting in a low-volume and hence obstructive pulmonary outflow tract.⁷ Consequently, the “floor” of the right ventricular outflow tract is too close to the “roof” of the right ventricular outflow tract, resulting in subpulmonary infundibular obstruction (stenosis or atresia), with or without involvement of the pulmonary valve (Figs. 9, 10, and 12-15).

Because the subpulmonary conus is too small in 3 dimensions, it does not expand rightward, posteriorly, and inferiorly enough to largely fill—with the help of the membranous septum—the interventricular foramen. Persistent patency of the interventricular foramen results in the typical malalignment VSD of TOF (Figs. 10-16).

However, it must be added that the conal septum in tetralogy can be much shorter than normal. Indeed, when Dr. Aldo Castañeda was operating in Mexico City as a visiting professor, he encountered TOF with absence of

the infundibular (conal) septum, resulting in direct fibrous continuity between the pulmonary and the aortic valves. Since that time, we have referred to tetralogy with absence of the conal septum as the “Mexican type of TOF.”

How Can One Understand this Uncommon, but Surgically Important Associated Malformation?

It is surgically important because in VSD patch placement the surgeon must be very careful not to traumatize the right coronary leaflet of the aortic valve, which is abnormally vulnerable to needle and suture trauma because of the absence of the interposed muscular conal septum.

Absence of the conal septum (ie, conal septal defect) is much more common in Asiatic populations than it is in white or black populations. Amerindian populations are thought to be “overseas Chinese,” via the Bering land bridge during the last Ice Age—about 10,000 years ago and quite possibly earlier. This anthropologic hypothesis may help to explain the finding of subpulmonary and subaortic VSD in TOF in American “Indian” populations, related to great underdevelopment or absence of the infundibular septum.

The understanding of what TOF really is (underdevelopment of the subpulmonary conus in a 3-dimensional or volumetric sense)⁷ has been of considerable diagnostic and surgical importance. Diagnostically, it makes possible the recognition and appropriate surgical treatment of TOF, even when there is no demonstrable right ventricular outflow tract gradient. For example, TOF can be associated with cor triatriatum⁷ or other congenital or acquired causes of pulmonary arterial hypertension that mask the presence of a pulmonary outflow tract gradient that would otherwise be demonstrable. Solution: Just look at the angiocardiograms (or other imaging studies); the small-volume infundibulum is diagnostic.⁷

How Can One Understand TOF With Absence of Pulmonary Valve Leaflets?

Malseptation of the great arteries and infundibulum at the expense of the pulmonary outflow tract and favoring the aortic outflow tract (ie, resulting in a stenotic subpulmonary infundibulum and a small main pulmonary artery, and a reciprocally wide open aortic outflow tract and a large ascending aorta) makes no sense in tetralogy with absent pulmonary valve leaflets.⁴⁸ Why? Because, when the pulmonary valve leaflets are absent, although the subpulmonary infundibulum is restrictively small and hence stenotic, the main pulmonary artery is typically huge (we think for hemodynamic reasons; a very large systolic-diastolic volume change because of free pulmonary regurgitation). But it is very difficult to explain these anatomic findings on the basis of the classical trunco-conal malseptation hypothesis (ie, malseptation at the infundibular level at the expense of the pulmonary outflow tract), resulting in pulmonary infundibular stenosis; but malseptation in the *opposite* direction at the great arterial level—at the expense of the aorta and favoring the pulmonary artery, to “explain” the huge main pulmonary artery and

the much smaller ascending aorta. In other words, the classical malseptation hypothesis suggests that infundibular and great arterial malseptations have occurred in *opposite* directions: at the expense of the pulmonary outflow tract at the infundibular level; but at the expense of the aorta at the great arterial level.

The foregoing is just one example of why we think the classical malseptation hypothesis to explain the morphogenesis of TOF is erroneous, and should be replaced with the infundibular underdevelopment hypothesis that is supported by the data (Fig. 18).

A related therapeutic point is so clinically important that it merits brief reiteration. The anatomic and developmental understanding that the essence of TOF is a low-volume infundibulum⁷ has also played an important role in revolutionizing the surgical management of patients with TOF.⁴⁰ Extensive right ventricular myocardial resection proximal (upstream) relative to the infundibular obstruction has been abandoned in favor of adequate right ventricular outflow tract reconstruction with transannular patching when necessary.⁴⁰ Restoration of the right ventricular outflow tract volume, with little or no myocardial resection, has led to great improvement in postoperative outcomes for patients with tetralogy. This improved understanding has also helped to make possible the strategy of surgical repair at any age postnatally, even in the neonatal period—whenever the patient needs it; and the avoidance, whenever possible, of palliative surgery—because repair is preferable to palliation, and one operation is better than two or more.⁴⁰

A previously unknown form of TOF was described in 1988 by Foran and colleagues,⁴² and its successful surgical repair was reported in 1995 by Santini and associates.⁴³ The rare feature of this type of tetralogy is that the infundibulum and the great arteries are inverted, or in mirror image compared with the usual type of tetralogy. Although the viscera and atria were in situs solitus (the usual, noninverted anatomic organization), and the usual D-loop ventricles were present, resulting in the expected atrioventricular concordance, the stenotic (or atretic) pulmonary outflow tract originated from the right ventricle—but to the *right* of the ascending aorta (instead of the left of the ascending aorta, which is normal) (Fig. 19).^{42,43} The ascending aorta originated from the left ventricle and overrode the ventricular septum, as is usual in tetralogy. In the posteroanterior projection, the tightly stenotic pulmonary outflow tract is seen best in Fig. 21, whereas left-sided aorta and the right aortic arch are best visualized in Fig. 19.

In the left lateral projection of this selective right ventricular injection (Fig. 20), the angiocardiographic picture looks almost like that in typical TOF {S,D,S}.

However, the fact that this patient has TOF {S,D,I} is obvious when one views the posteroanterior projections (Figs. 19 and 21), because the aorta arises to the *left* of the pulmonary artery (rather than to the right of the pulmonary artery, which is characteristic of solitus normally related great arteries).^{7,23,42}

The aortic valve is much lower than the pulmonary valve (Fig. 20), accurately suggesting that aortic-mitral fibrous

Table 2 Cardiac Segments in Tetralogy of Fallot (n = 100 autopsied cases)

{S,D,S}	97
{l,D,S}	2
{l,L,l}	1

continuity is present. The pulmonary outflow tract stenosis involves the infundibulum and the pulmonary valve (Fig. 20).

There is one important finding in the lateral projection that one might easily overlook. The right coronary artery is running right across the pulmonary outflow tract, exactly where a surgeon might want to place an infundibulotomy (Fig. 20).

In TOF {S,D,l}, the right coronary artery *always* runs across the obstructive pulmonary outflow tract. Why? Because with infundibuloarterial inversion as in {S,D,l}, the ascending aorta lies to the left and the pulmonary outflow tract lies to the right (Figs. 19 and 21). In order for the right coronary artery to reach the right atrioventricular groove, the right coronary artery “must” cross the pulmonary outflow tract from left to right. Santini, Jonas, Sanders, and Van Praagh⁴³ reported that in an 8-month-old girl, it was possible to repair TOF {S,D,l} *without a conduit*; the latter is a non-trivial detail. Thus, TOF {S,D,l} essentially “always” has a right coronary artery at increased risk of surgical trauma.^{42,43}

In TOF, associated anomalies can be of decisive importance to surgical outcome: cor triatriatum⁷; pulmonary sequestration⁷; left ventricular outflow tract obstruction caused by adherence of the mitral valve to the left ventricular septal surface⁴⁴; discrete fibrous subaortic stenosis⁴⁵; VSD obstruc-

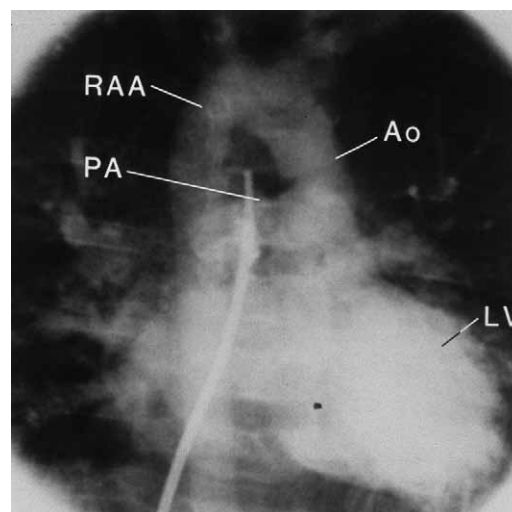


Figure 19 Angiocardiography in TOF {S,D,l}, posteroanterior projection. Ao, ascending aorta; LV, morphologically left ventricle; PA, main pulmonary artery; RAA, right aortic arch. (Reprinted with permission from Santini et al.⁴³)

tion⁴⁶; aortic valvar stenosis⁴⁷; and absence of pulmonary valve leaflets.⁴⁸

Because associated malformation in patients with tetralogy may be unexpected, and can be of great clinical importance to patient outcomes, we did a study of the problem (previously unpublished) based on 100 postmortem cases. (Consequently, the number of cases = the percent of the series.)

Time frame. The autopsies of patients with TOF were randomly selected from the 1980s and the 1990s (sex: males 48, females 47, unknown 5). Age at death postnatally (n = 90): median 6.75 months, ranging from 6.5 hours to 48 years. There were also 10 fetuses.

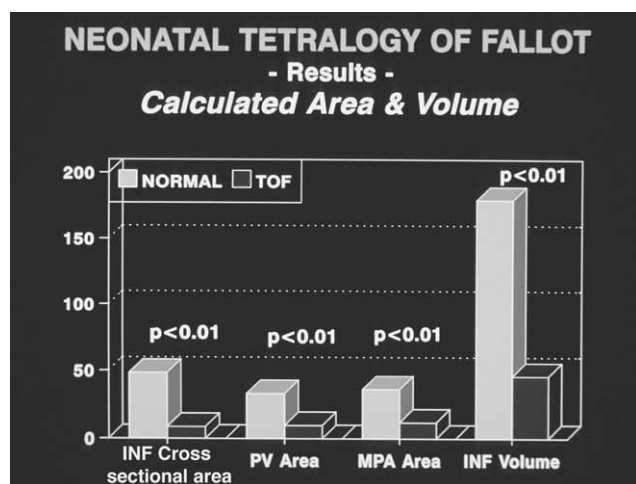


Figure 18 Morphometry of TOF in the neonatal period, prior to the development of acquired postnatal changes: calculated cross sectional areas of the infundibulum (Inf), of the pulmonary valve (PV), and of the main pulmonary artery (MPA), compared statistically with normal control heart specimens; and calculated infundibular volume, compared statistically with normal controls. Morphometry showed that all of these measurements were statistically significantly smaller in neonatal TOF than in normal controls. ($P < .01$ for all measurements.)

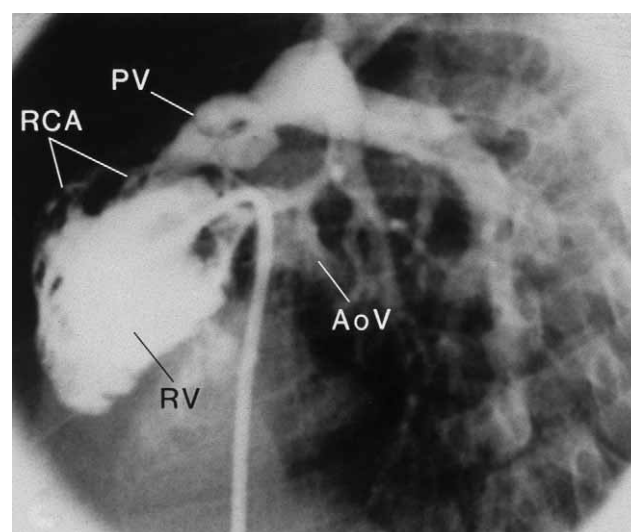


Figure 20 Angiocardiography in TOF {S,D,l}, selective right ventricular injection, left lateral projection. AoV, aortic valve; PV, pulmonary valve; RCA, right coronary artery; RV, morphologically right ventricle. (Reprinted with permission from Santini et al.⁴³)

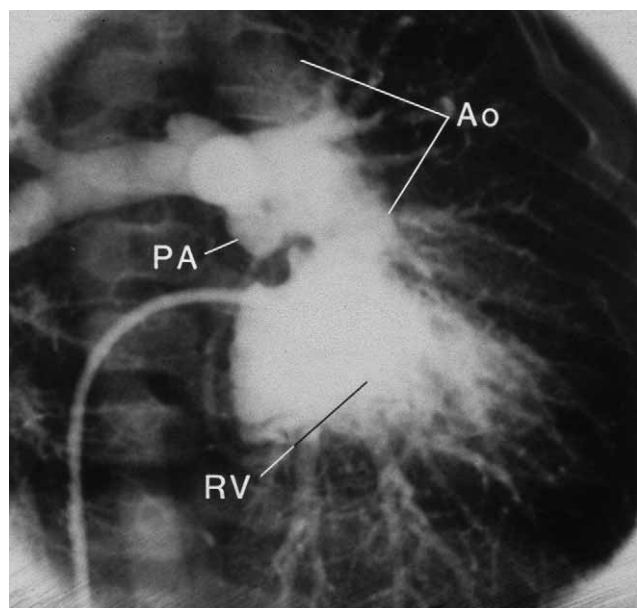


Figure 21 Angiocardiography in TOF {S,D,I}, selective right ventricular injection, posteroanterior projection. Angiocardiographic interpretation: the viscera and atria are in situs solitus (note the right-sided position of the inferior vena caval catheter in Figs. 19 and 21). A right-handed D-loop right ventricle (RV) is present, with atrioventricular concordance (Fig. 21). The great arteries are inverted, with ascending aorta to the left and main pulmonary artery to the right (Figs. 19 and 21). The great arteries are inverted normally related, with an inferior and posterior aortic valve, an anterior and superior pulmonary valve (Fig. 20), and with the main pulmonary artery passing to the right of the ascending aorta (Figs. 19 and 21). There is infundibular and valvar pulmonary outflow tract stenosis typical of tetralogy of Fallot (Fig. 20), without aortic outflow tract stenosis. The right coronary artery runs across the stenotic pulmonary outflow tract (Figs. 20 and 21). Hence, the diagnosis is tetralogy of Fallot with visceratrial situs solitus, concordant D-loop ventricles, and inverted normally related great arteries (briefly, TOF {S,D,I} with moderately severe pulmonary outflow tract stenosis, and with the right coronary artery running across the stenotic pulmonary outflow tract—which should be expected because of the isolated infundibulo-arterial inversion, with the ascending aorta lying to the left of the pulmonary outflow tract and with the right ventricle in a normally right-sided location. Ao, ascending aorta; PA, main pulmonary artery; RV, right ventricle. (Reprinted with permission from Santini et al.⁴³)

Findings. The great majority (97%) had the usual segmental anatomy, ie, {S,D,S},* with situs solitus of the viscera and atria {S,-,-}, D-loop ventricles {S,D,-}, and solitus normally related great arteries {S,D,S} (Table 2). In this, the typical form of tetralogy, the great arteries are conventionally regarded as being solitus normally related—as long as there is aortic-mitral fibrous continuity, which may be tenuous, despite considerable aortic valvar overriding. As noted above, the great arteries really are *almost* normally related in typical tetralogy. (When there is no aortic-mitral fibrous continuity because of the interposition of subaortic conal free wall mus-

cle, and if the aortic valve arises predominantly or entirely above the right ventricle, then we and most others make the diagnosis of DORV, not TOF.)

In TOF {S,D,S}, the atrioventricular and the ventriculoarterial alignments are both *conventionally* regarded as concordant (appropriate). It is customary to “wink” at the aortic overriding above the right ventricle as long as aortic-mitral fibrous continuity, however tenuous, is present.

TOF {I,D,S} is so rare that there is no widely accepted name for this unfamiliar segmental set or combination (Table 2). Perhaps the least confusing approach to diagnostic designation is simply to spell out the segmental anatomy segment-by-segment and alignment by alignment: TOF with situs inversus of the viscera and atria, discordant D-loop ventricles with discordant atrioventricular alignments, and solitus normally related great arteries (complicated by tetralogy, as stated at the outset). It may well be helpful to draw a diagram to point out that the left-sided right atrium (RA) opens into the left-sided left ventricle (LV), and that the right-sided left atrium (LA) opens into the right-sided right ventricle (RV). Hence, there is atrioventricular discordance; but there is only one intersegmental discordance—because the ventriculoarterial alignments are concordant.

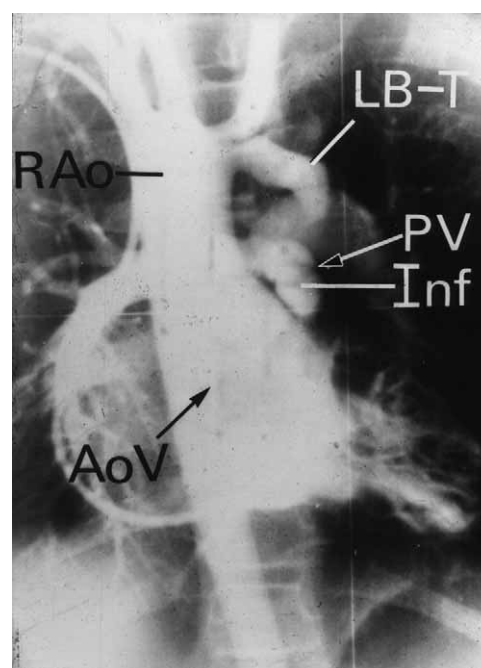


Figure 22 Angiocardiogram in typical TOF {S,D,S}, selective right ventricular injection, posteroanterior projection. The infundibulo-arterial part of the heart is *not* inverted. The small-volume infundibulum (Inf), the small pulmonary valve (PV), and the small main pulmonary artery pass to the *left* of the large ascending aorta—not to the right of the ascending aorta (as in Figs. 19 and 21). The large aortic valve (AoV) is low, typical of normally related great arteries. A right aortic arch (RAo) is also present, with mirror-image branching of the brachiocephalic arteries and a left-sided classical Blalock-Taussig shunt (LB-T). The essence of TOF—a small-volume infundibulum, with its sequelae—is well seen.

*Braces { } mean the set of.

Table 3 Associated Malformations in Tetralogy of Fallot (n = 100 postmortem cases)

	No.
Pulmonary atresia	37
Secundum atrial septal defect	
Pentalogy of Fallot (common atrium, 5)	35
Multiple congenital anomalies	29
Right aortic arch	28
Aortopulmonary collateral arteries	26
Persistent left or right	
Superior vena cava (LSVC 15, RSVC 1)	16
Patent ductus arteriosus	13
Absent ductus arteriosus	12
Completely common atrioventricular canal (Type C, 6; Type A, 1; NOS, 2)	9
Down's syndrome (Familial, 2)	8
Aberrant right or left subclavian artery	8
Anomalous muscle bundles of the right ventricle	8
Absent pulmonary valvar leaflets syndrome	6
Restrictive ventricular septal defect	5
Additional muscular ventricular septal defects	5
Ectopia cardis (complete thoracic, 1; thoracoabdominal, 3)	4
Familial congenital heart disease	4
Myxomatous aortic valve	4
Aortic regurgitation	4
Bicuspid aortic valve	3
Coronary sinus septal defect	3
Single left coronary artery	3
Trisomy 18	2
Tricuspid stenosis	2
Parachute mitral valve	2
Superior vena cava to left atrium because of unroofed coronary sinus	2
Chromosomal anomalies	2
Twins	2
Conjoined twin	1
Aortic stenosis, valvar	1
Partially anomalous pulmonary venous connection	1
Turner's syndrome	1
Noonan's syndrome	1
Klinefelter's syndrome	1
Thick-walled and small-chambered right ventricle, with restrictive ventricular septal defect	1
Sinusoids between right ventricle and right coronary artery, with restrictive ventricular septal defect	1
Small anterolateral papillary muscle group of left ventricle	1
Dextrocardia, ie, predominantly right-sided heart	1
Mesocardia	1
Heterotaxy with polysplenia syndrome	1
Quadricuspid aortic valve	1
Vascular ring formed by right aortic arch, aberrant left subclavian artery, and left-sided patent ductus arteriosus	1
Intussusception of left atrial appendage, ie, inside-out appendage producing supramitral stenosis	1
Congenital mitral stenosis	1
Absence of conal septum	1
Hypertrophy of conal septum	1

Table 3 Continued

	No.
Visceroatrial situs discordance {IS,D,S}, ie, situs inversus of abdominal viscera, with solitus atria, and appropriate venous connections with the atria	1
Absence of main pulmonary artery, right pulmonary artery, left pulmonary artery, and both ductus arteriosi	1
<i>Ductus</i> is a 4 th declension masculine noun (Latin); hence, the plural is <i>ductus arteriosi</i> .	
Abbreviations: LSVC, left superior vena cava; NOS, not otherwise specified; RSVC, right superior vena cava.	

Consequently, patients with TOF {I,D,S} have two good reasons to be cyanotic: (1) they have TOF; and (2) they have one intersegmental discordance at the atrioventricular level which also physiologically uncorrects their systemic and pulmonary venous circulations. The morphologically right atrium and the aorta valve are ipsilateral—both left-sided; and the morphologically left atrium and the pulmonary valve also are ipsilateral—both right-sided. Thus, unoxygenated caval blood and the aorta are same-sided, as are the oxygenated pulmonary venous blood stream and the pulmonary artery; hence, blue blood flows to the aorta (even without tetralogy), and bright red blood goes unnecessarily back to the lungs.

Trying for a short verbal name for TOF {I,D,S}, perhaps “noninverted TOF, with ventricular noninversion, in visceroatrial situs inversus.” However, this designation is not brief, and I am not sure it would be clear to those who had never heard of this rare form of tetralogy. So perhaps “TOF {I,D,S}” will suffice, at least for the moment. This designation is brief, and if one understands segmental anatomy, it is also clear.

Surgically, patients with TOF {I,D,S} need (1) a standard repair of TOF, as in tetralogy {S,D,S}; and (2) a mirror-image atrial switch procedure (Senning or Mustard)—because the systemic and pulmonary venous circulations are “transposed” (physiologically uncorrected), in turn because there also is atrioventricular discordance, as the segmental anatomy indicates: tetralogy {I,D,S}.

To the best of my knowledge, this is the first time that TOF {I,D,S} has ever been reported. Most pediatric cardiologists and cardiac surgeons do not know that there is a rare form of TOF that therapeutically requires not only a standard TOF repair, but also requires a mirror-image atrial switch operation. In other words, TOF rarely can occur with atrioventricular discordance (Table 2).

TOF {I,L,I} is also rare (1% of this series), but at least its common verbal name is clear and generally understood: “TOF in situs inversus totalis” (Table 2). As the segmental anatomy indicates, there is the combination of visceroatrial situs inversus {I,-}, with concordant L-loop ventricles {I,L,-}, and inverted normally related great arteries {I,L,I}. The infundibulum, great arteries, and ventricular septum are also afflicted with TOF; hence, TOF {I,L,I}. The atrioventricular and ventriculoarterial alignments are both concordant.

We did not encounter TOF {S,D,I}^{42,43} in this series of 100 randomly selected cases (Figs. 18-20, and 22). Thus, the mental addition of TOF {S,D,I} to Table 2 would make this summary of the anatomic types of segmental set that can occur in tetralogy more complete.

Thus, TOF is an anomaly that happens to hearts with normally related great arteries—be they solitus normally related or inverted normally related. The ventricular anatomy may be D-loop or L-loop. And the viscera and atria may be solitus or inversus (Table 2). Other associated malformations are summarized in Table 3.

Table 3 offers the seldom-presented “big picture”—a detailed look at how tetralogy of Fallot really occurs, often with other diagnostically and surgically important associated malformations.

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