The selective injection of contrast media into the right coronary artery of a middle-aged male by Dr F. Mason Sones, Jr, on October 30, 1958 (Figure 1) introduced a new era in cardiovascular medicine that was to revolutionize our understanding and management of the cardiac patient for the remainder of the twentieth century.1,2 As the first reliable in vivo marker for the presence of obstructing coronary lesions, the coronary angiogram not only provided objective evidence to support or refute the clinical diagnosis of angina pectoris but, quite importantly, led to our first studies of the natural history of patients with coronary artery disease (CAD). The purpose of this article is to underscore the crucial role this particular technology played in contributing to the epochal events and discoveries that have characterized the march of progress in the field of cardiology over the past 50 years.

Historical Setting

Sones’ decision to undertake selective visualization of the coronary artery in his patient undergoing catheterization to evaluate mitral regurgitation was, in some measure, the result of a serendipitous event that occurred in his laboratory 2 days earlier. This has been described in detail elsewhere by Dr Willis Hurst3 and entailed a power injection of 40 to 50 cc of Hypaque (Nicomed) was selectively delivered as a bolus into the coronary artery of a middle-aged male by Dr F. Mason Sones, Jr, on October 30, 1958 (Figure 1) introduced a new era in cardiovascular medicine that was to revolutionize our understanding and management of the cardiac patient for the remainder of the twentieth century.1,2 As the first reliable in vivo marker for the presence of obstructing coronary lesions, the coronary angiogram not only provided objective evidence to support or refute the clinical diagnosis of angina pectoris but, quite importantly, led to our first studies of the natural history of patients with coronary artery disease (CAD). The purpose of this article is to underscore the crucial role this particular technology played in contributing to the epochal events and discoveries that have characterized the march of progress in the field of cardiology over the past 50 years.

Historical Setting

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Sosa was quick to offer the following opinion. Mason did not proceed recklessly to a planned selective injection two days later. Rather, it was the calculated decision of a prepared mind made inspite [sic] of the advice of several colleagues including Nobel Laureate, Andre Courmand who had earlier recounted his personal experience of a 100% fatality rate when contrast media was selectively injected in the coronary arteries of dogs. For sometime prior to this event, we had been performing serial injections of 20cc of contrast media under a pressure of 4 kg/cm² into a catheter after its tip was carefully placed in first one and then the other anterior sinus of Valsalva. This insured the introduction of a reasonably large volume of dye into the immediate vicinity of each coronary artery lasting for three to six heart cycles. The resulting arteriogram was considered to be adequate in more than 90% of cases and ventricular arrhythmias, which had been feared as a consequence of transient asymmetrical myocardial hypoxia with this method of delivery, failed to materialize. I have always felt his experience with this inadvertent selective opacification merely convinced him that the human coronary circulation was not the same as the canine’s and that fatal ventricular arrhythmias would not invariably occur.

It is clear from other writings that Sones was equally convinced that the non-selective method of aortic root injection to study the coronary circulation entailed significant risk without the benefit of the added clarity provided by selective injections. He was referring to studies of the coronary circulation carried out by other pioneers using aortic root injections enhanced by acetylcholine ventricular arrest, as in the case of Lehman et al,4 by occlusion aortography, as proposed by Dotter and Frische,5 or by phasic dye injections, as demonstrated by Richard and Thal.6 Lastly, no history of the development of coronary arteriography would be complete without acknowledging the important contributions of Drs Judkins7 and Amplatz.8 Both of these radiologists used the Seldinger percutaneous technique9 to gain access to the femoral artery. Independently, they designed preformed catheters, the conformity of which sought out the ostia of either the left or right coronary artery as well as facilitating access to the left ventricle. It was these preformed catheters that...
made successful engagement of the coronary ostia a much easier process that required far less training than the Sones’ technique, which required much more time to become skillful. Undoubtedly, this facilitated the widespread dispersion of angiography as a diagnostic technique throughout the cardiology and radiology communities.

Contributions of the Fifties and Sixties
The major contributions attributed to the first 2 decades of coronary arteriography are listed in Table 1. As might be anticipated, the earliest patients to undergo this new and riskier diagnostic procedure were mostly gravely ill patients referred to one of the few tertiary institutions in the country that had the resources to install and develop this high-cost technology. A multicenter collaboration reported the annual mortality rates among 1596 patients hospitalized with CAD who underwent coronary angiography in the mid 1960s and who were followed-up for 5 years.10,11 The annual mortality rate was generally 2% to 4% for patients with single-vessel disease, 7% to 8% for 2-vessel disease, and 12% for 3-vessel disease.

From the outset, the motion studies afforded by cineangiography permitted dynamic visualization of the contracting left ventricle. This gave rise to an appreciation of the regional wall motion abnormalities that are so characteristically associated with the location of an obstructing coronary artery lesion. The ventriculogram performed in association with the coronary angiogram thus provided some of our earliest understanding of left ventricular dysfunction that found its expression in the now-familiar Greek terms akinesia, dyskinesia, hypokinesia, asynergy, etc.12 The work of Dodge and his co-workers13 in developing left ventricular volume estimates also permitted a quantification of the degree of ventricular dysfunction by the application of the concept of ejection fraction. The early angiographic studies of Sones also demonstrated the inadequacy of the internal mammary implant operation of Vineberg, which was the only surgical procedure directed at alleviating the symptoms of CAD that had a tolerable mortality risk.14 Postoperative coronary arteriography carried out during the first year after a Vineberg operation in a substantial number of patients revealed that collateral vessels between the implant site and the myocardium could be visualized in only 54% of patients studied. These observations by Sones no doubt stimulated the development of the saphenous vein bypass graft operation (CABG) by his colleague at the Cleveland Clinic, Dr Rene Favaloro.15 The first successful visualization of an aorto-coronary vein graft was accomplished in May 1967 (Figure 2).

Contributions of the Seventies
The principle contributions of this decade are listed in Table 2. The clinical results of the CABG operation were so dramatic that by the early 1970s it was one of the most

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**TABLE 1. Contributions of Coronary Angiography in the 1950s and 1960s**

<table>
<thead>
<tr>
<th>1950s</th>
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<tr>
<td>Selective coronary arteriography introduced by F. Mason Sones, Jr, MD</td>
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<td>The first human studies using this in vivo marker for severity and extent of CAD</td>
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<td>Earliest natural history studies of proven CAD</td>
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<td>Dynamic visualization of LV performance</td>
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<td>Revealed limitations of the Vineberg operation</td>
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<td>Demonstration of prompt and complete revascularization by CABG</td>
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**TABLE 2. Contributions of the 1970s**

<table>
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<tr>
<td>Refinement of natural history studies of unoperated CAD patients</td>
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<td>Discovery of the benefit of CABG vs Med Rx in subsets of patients</td>
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<td>Delineation of coronary vasospasm and Prinzmetal’s angina</td>
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<td>Significance of coronary pathoanatomy (ulceration, thrombus, dissection, aneurysm, muscle bridge, collateral vessels)</td>
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<tr>
<td>Introduction of PTCA and delineation of restenosis</td>
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<td>First angiographic evidence of clot lysis in a coronary vessel</td>
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common surgical procedures performed in the United States.\textsuperscript{16,17} The demand for proof of superiority over the non-surgical treatment of coronary patients resulted in the formation of 3 separate randomized controlled trials, each of which left its own memorable lesson for the practicing clinician.\textsuperscript{18–20} The US Veterans Administration Study\textsuperscript{18} established the role of coronary surgery for the management of left main coronary lesions. The European Trial\textsuperscript{19} showed better survivorship for patients undergoing CABG compared with those undergoing medical treatment if the patient had either 2-vessel disease, with 1 of the vessels being the left anterior descending coronary artery, or 3-vessel disease. The National Heart, Lung, and Blood Institute-sponsored Coronary Artery Surgery Study (CASS), undertaken in this country, failed to show surgical benefit after 5 years of follow-up in its randomized arm of mostly mild to asymptomatic patients.\textsuperscript{20} In a subset of patients with 3-vessel disease and impaired ventricular function, there was a significant improvement in survival among patients randomized to the surgical arm.

Of nearly equal importance to the CASS randomized trial were the data collected in its registry arm, which was composed of 23,338 patients who underwent coronary angiography to determine whether or not they had angiographically demonstrable CAD, regardless of their symptoms. The specific therapy received by these individuals was determined solely by the individual treating physician and was not in anyway randomized. The subsequent 5-year follow-up of these patients created one of the largest existing observational databanks on CAD. Of its many seminal contributions, perhaps the most widely cited article relates to the natural history of patients with CAD who were treated nonoperatively. The CASS registry indicates annual mortality rates of 1.5%, 3.0%, and 5.0% for patients with 1, 2, and 3-vessel disease, respectively, who remain unrevascularized.\textsuperscript{21} These data are more than 20 years old and must be interpreted with caution because of the well-documented beneficial effects of therapies that were not available in the CASS era. These therapies include present day therapy using statin class of drugs, antiplatelet therapy, and the use of angiotensin-converting enzyme inhibitors that have been shown to reduce subsequent cardiovascular events, independent of their blood pressure lowering effects. Similarly, surgical techniques have improved over the past 2 decades, and surgical survival has increased with more extensive use of the internal thoracic artery compared with the use of saphenous vein grafts that were used in 80% of the CASS patients.

In the later years of this decade, the coronary angiogram provided evidence that the clinical manifestations of severe myocardial ischemia, including acute myocardial infarction, could result from severe, flow-limiting coronary artery vasospasm in the absence of any anatomic lesion.\textsuperscript{22} This observation by Oliva and colleagues validated the hypothesis originally postulated 2 decades earlier by Prinzmetal.\textsuperscript{23}

Overshadowing all of the events of the 1970s, however, was the report of Dr Andreas Gruntzig et al\textsuperscript{24} in September 1977 describing an entirely new method of achieving coronary revascularization by the endovascular dilation of an obstructing lesion that he referred to as percutaneous transluminal coronary angioplasty (PTCA). The coronary angiogram provided the road map necessary for the successful development and expansion of this technology, particularly to patients with multivessel disease. Early on, the angiogram also unmasked the principal limitation of this revolutionary technology, the problem of coronary restenosis at the site of the lesion originally dilated.\textsuperscript{25} Finally, in this decade, the seeds were sewn for the thrombolytic era that was to follow by the rather audacious maneuver performed in Goettingen, Germany by Dr Peter Rentrop and colleagues.\textsuperscript{26} He achieved and documented the successful reperfusion of the left anterior descending coronary artery of a middle aged man by first recanalizing the occluding thrombus with a guidewire and then infusing the proteolytic enzyme streptokinase directly into the artery.

**Contributions of the Eighties**

Commencing in 1980 and extending for more than a decade, the coronary angiogram earned credit for influencing present day thought in 3 basic areas (Table 3). First among these were the observations by DeWood et al\textsuperscript{27} that obstructing clots were present in the coronary arteries of patients early in the course of acute myocardial infarction and that this thrombus showed spontaneous partial dissolution over the first 24 hours. Angiographic observations taken from patients undergoing coronary arteriography within the first 24 hours of the onset of symptoms with the aim of undergoing early coronary bypass surgery provided the evidence that spontaneous fibrinolysis occurred in man and laid the foundation for the earliest studies on clot lysis by fibrinolytic agents.\textsuperscript{28,29} The coronary angiogram was thus the cornerstone for all of the efforts directed at reperfusion therapy for acute myocardial infarction that are as intense today as they were 20 years ago. Additionally, the angiogram was able to provide a road map of the distal portions of an acutely occluded coronary artery by means of collateral filling, thus allowing the balloon catheter to be used as a mechanical means of establishing coronary reperfusion in the setting of acute myocardial infarction. This operation was first carried out in 1982 by Meyer and colleagues in Germany.\textsuperscript{30} From then until now a heated debate has existed over which of the 2 methods of reperfusion provides the greatest benefit for the management of a patient with an acute myocardial infarction.\textsuperscript{31} More than 2 dozen randomized, controlled trials have been undertaken since the initial study reported 15 years ago by O’Neil and colleagues\textsuperscript{32} in an attempt to resolve this dispute.\textsuperscript{31} It is only now, as we begin the 21st century and the sixth decade of using selective coronary arteriography that, with the aid

<table>
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<th>TABLE 3. Contributions of the 1980s</th>
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<tr>
<td>Dawn of the thrombolytic era, with the demonstration of spontaneous fibrinolysis during 24 hrs of acute occlusions</td>
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<td>Plaque regression studies uncovering the clinical benefits of statin fibrinolysis during 24 hrs of acute occlusions</td>
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<tr>
<td>Delineation of the pathogenesis of acute myocardial infarction from studies outlining angiographic progression to myocardial infarction</td>
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<td>Estimates of coronary flow using TIMI flow grades and TIMI frame rates</td>
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<td>Comparisons of PCI vs CABG for revascularization outcomes</td>
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of other imaging techniques, it would seem that the use of percutaneous coronary interventions (PCI) is emerging as the superior method.33

The second basic area to be influenced by coronary angiography in this decade came after the Nobel-caliber work by Brown and Goldstein34 on lipid transport that led to the introduction of hepatic hydroxymethyl glutaryl coenzyme A reductase-agents to clinical medicine. There was intense interest focused on regression studies of atherosclerotic lesions in response to vigorous lipid lowering therapy.35 Central to the majority of these studies was the use of computerized measurements of the severity of angiographic lesions taken over time. The near universal finding of all these studies was the surprising evidence of a rather negligible regression of the anatomic lesion but a powerful reduction in subsequent clinical cardiovascular events.36 In this instance, the coronary angiogram, coupled with subsequent clinical follow-up, altered our fundamental concepts of the evolution of atherogenesis and materially influenced lipid-lowering therapy throughout the world.

Using high arteriographic magnification and computer-assisted measurements of the coronary arteries of 32 patients receiving intracoronary streptokinase during acute myocardial infarction, Brown and colleagues37 were the first to suggest that mild to moderate stenoses were frequently the anatomic lesion but a powerful reduction in subsequent clinical cardiovascular events.36 In this instance, the coronary angiogram, coupled with subsequent clinical follow-up, altered our fundamental concepts of the evolution of atherogenesis and materially influenced lipid-lowering therapy throughout the world.

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Contributions of the Nineties
After 5 decades of intense use, the coronary arteriogram continues to reign over all other coronary imaging techniques for the management of CAD and play an integral role in the development of newer technology, as summarized in Table 4. It played a lesser role in the development of the endovascular scaffold device known as a stent than it did in establishing the preferred pharmacotherapeutic agents to be used in association with the implantation of stents. As an intravascular prosthesis, many believed that warfarin anticoagulation would be required but, in fact, it was demonstrated that antiplatelet therapy using ticlopidine and clopidogrel were superior to the coumarin drugs in preventing stent thrombosis.42

The dispersion of contrast media throughout the myocardium once it has passed through the epicardial coronary arteries has been referred to as the “myocardial blush.” Recent efforts to quantify this phenomenon have been helpful in assessing the influence of drugs such as the glycoprotein Ilb/IIIa inhibitors on the microcirculation. Similarly, the coronary angiogram has recently delineated heretofore unknown entities, such as late stent thrombosis and skip areas of radiation effect (candy-wrapper effect) attributable to one of the latest coronary interventions, brachytherapy.43 The cardiac catheter is now used regularly to introduce newer intracoronary devices such as intravascular ultrasound, velocity probes, gene probes, and eluting catheters.

Conclusion
It is to be anticipated that new technology will eventually replace the utilitarian functions of the coronary angiogram, but as of this moment in medicine, after having served as the 1 indispensable form of coronary imaging for 5 successive decades, coronary angiography has provided more than “lumenology”; indeed, it has served cardiology as the lumen de lumine, the light of lights.

Epilogue
It should be noted that throughout this 50-year march of progress, coronary arteriography was found to have certain risks, complications, and limitations unique to the procedure itself. From the outset, the Sones’ technique required an arteriotomy, the repair of which was often beyond the capabilities of the non-surgically trained cardiologist. The preformed catheters introduced by Judkins that greatly simplified the technique were so successful in reaching the coronary ostia they often sprang from a position in the aortic arch and embedded themselves into the coronary artery, resulting in acute dissection or obstruction of flow. Often times, this was not recognized by the inexperienced operator who found these catheters extremely easy to use. Fibrin emboli, initially a problem related to exchanging multiple catheters over guidewires, led to greater use of heparin during the procedure. Inter- and intra-observer variations in estimating the severity of stenoses led to the use of calipers and eventually computerized edge detection techniques to more precisely quantify these measurements. The technological advances made in this field have matched the pace of progress and, collectively, stand as an appropriate monument to the vision and spirit of the pioneers who began it all a half century ago.

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<td>Establishment of the stent era</td>
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<td>Studies of the coronary microcirculation by myocardial blush</td>
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<tr>
<td>Brachytherapy, late stent thrombosis, and pharmacotherapy</td>
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<td>The coronary catheter and newer imaging devices (intravascular ultrasound, MRI)</td>
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References


The Coronary Angiogram and Its Seminal Contributions to Cardiovascular Medicine Over Five Decades
Thomas J. Ryan

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