The report by Seiler et al on a clinical trial using granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate the growth of coronary collateral vessels is the temporary culminating point of a long history of research that started in the early 1940s with the observation that the pressure measured in the distal stump of an occluded canine coronary (or femoral or carotid) artery rose as a function of time and was caused by the development of a collateral circulation. Strandness and Schoop and Jahn were probably the first to measure the pressure in the coronary arterial system that was later refined by Scheel. The effects of 2 vasodilating agents, papaverine (a smooth muscle relaxant) and filled catheters were not very precise. Feldman et al and Probst et al were probably the first to measure the pressure in the distal stump of a peripheral artery in the leg of patients for an estimation of residual perfusion.

Almost 30 years after Gregg, my group presented the first systematic analysis of peripheral coronary pressure (PCP), provided a theoretical framework, and described the influence of coronary collateral growth and of collateral blood flow on PCP. This led to the formulation of an electrical analog of the coronary arterial system that was later refined by Scheel et al and Harrison et al. The electrical analog could be displayed on an Apple Macintosh computer and served as a great educational aid for training young cardiologists and physiologists. This was necessary because the complex network of coronary resistances sometimes behaved counterintuitively, but the program helped solve problems of interpretation. A classic case of confusion to the uninitiated is the fall in PCP with increasing collateral blood flow and vice versa.

With the miniaturization of catheter tip manometers, it finally became possible to measure PCP in human patients. Before that, Gruntzig used the method to evaluate the success of balloon dilatation, but measurements by fluid-filled catheters were not very precise. Feldman et al and Probst et al were probably the first to measure PCP for the purpose of estimating collateral blood flow in human patients. By that time, the pioneering work of the animal physiologists was already forgotten.

In 1997, Piek et al published a paper in Circulation in which coronary wedge pressure and collateral flow (by flow wire) were measured during balloon occlusion of a stenosed coronary artery. The effects of 2 vasodilating agents, papaverine and adenosine, were correctly explained. They also showed that the type of collateral vessels, ie, microvascular or macrovascular, markedly influenced the reaction to vasoactive drugs, as predicted by the model. It was a landmark article because it explained the primary data in light of the theoretical framework.

This truly basic work in human coronary pathophysiology was carried further mainly by Pijs et al and Seiler et al. These physiological methods did not revolutionize the diagnosis of coronary artery disease, and most cardiologists continued to rely on angiography. The study of pressure-flow relationships in diseased coronary arteries was more or less regarded as an academic exercise. This opinion may soon change, because the time has come to stimulate the collateral circulation with recombinant angiogenic and arteriogenic growth factors or their genes. This would require a detailed study of the collateral circulation. This was tried before with fibroblast growth factor and vascular endothelial growth factor (VEGF), but the studies were confounded by conceptual and technical limitations. The conceptual limitation was that growth factors were studied that act mainly on endothelial cells (VEGF), and the technical limitation was that methods were used that relied on surrogate end points and did not directly measure collateral pressure and flow.

The present study by Seiler et al overcomes both of these limitations: they studied a growth factor that stimulates arteriogenesis, and they used methods that are directly related to the status of the collateral circulation. Furthermore, they applied a new paradigm, arteriogenesis, that differs from that of angiogenesis in that it tries to substitute the occluded artery with arterial collaterals. It is finally recognized that an occluded epicardial coronary artery cannot be replaced by capillaries, regardless of numbers. Only arterial collaterals come somewhat close to replacing the conductance of a coronary artery.

In a canine heart with a progredient coronary stenosis leading to complete chronic coronary occlusion but not to infarction due to the synchronous growth of collateral channels, the PCP usually reaches 80% of the aortic perfusion pressure under conditions of rest (anesthesia). The ratio of PCP over aortic pressure falls with coronary vasodilatation and remains, ≈6 weeks after chronic occlusion, at 40% of aortic perfusion pressure. This is an indication that collateral growth has not completely restored the conductance of the occluded artery to preocclusive values but rather to only ≈35% (ie, the collateral vessels offer finite resistance). The flow they can deliver is sufficient to avoid ischemia under normal ambulatory conditions but would become limiting under physical exertion. It is presently unknown why the process of arteriogenesis stops prematurely before the optimal adaptation is reached. One explanation could be that the 2 forces which had initiated the growth process, ie, fluid shear stress and tangential wall stress, become normal again soon.
after the growth starts. It would therefore be desirable to prolong the period of growth or to restart it. The discovery of the arteriogenic potency of circulating monocytes offers such a possibility.18 Monocytes produce a host of different growth factors, and when they attach to a transforming vessel, a mixture of factors is released. This may be superior to monotherapy. Arras et al19 reported that increasing the attraction of monocytes to the endothelium of collateral vessels by an infusion of monocyte chemotactic protein-1 increases the speed of growth.

By increasing the life cycle of monocytes with the stem cell factor GM-CSF, the speed of development and the level of adaptation could be increased in experimental animals.20 Seiler et al21 are very circumscript about the effects of GM-CSF on atherosclerosis. It is known that GM-CSF lowers cholesterol levels21; this is also what Seiler et al observed in their treated patients. However, they are cautious not to overestimate this effect because LDL cholesterol remained unchanged. However, experiments in relevant animal models (Watanabe rabbits22) have shown that GM-CSF reduces the plaque surface, and it is not unreasonable to assume that this may also occur in patients. GM-CSF is thus far the only growth factor that has not been accused of being negatively associated with atherosclerosis. Most of the other angiogenic or arteriogenic factors are prothrombic, upregulate tissue factor, activate monocytes with the potential to aggravate atherosclerosis, or are expressed in the vicinity of atherosclerotic plaques.23,24 Russell Ross25 once said that the monocyte may not necessarily be the “bad guy” in atherosclerosis because the transformation of the monocyte/macrophage into atherogenic factors, and when they attach to a transforming vessel, a mixture of factors is released. This may be superior to monotherapy. Arras et al19 reported that increasing the attraction of monocytes to the endothelium of collateral vessels by an infusion of monocyte chemotactic protein-1 increases the speed of growth.

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References

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Therapeutic Arteriogenesis Has Arrived
Wolfgang Schaper

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