When we first entered this scientific area about 10 years ago, we did not fully appreciate the emotional content of discussions involving chocolate. Contacts between medical scientists and the lay press tend to be sporadic. When chocolate is the issue, however, the lay press interest becomes intense and widespread. We have participated in many dozens, probably hundreds, of interviews about our research into the vascular effects of cocoa. Two questions inevitably emerge. The first is, “Is there some way of identifying which chocolate available for purchase is especially good for you?” The second is, “Does this mean that chocolate is a health food?” Reporters have been, almost without exception, rather disappointed by our response to each question.

The use of the word “dark” in dark chocolate, prominent in the title of this article, the article it accompanies, and on chocolate bar wrappers in high-end groceries around the world is symptomatic of this interest in identifying a simple, reliable, and inexpensive assay for what is good in chocolate. What makes it healthy? As is stated clearly in the report by Flammer et al in this issue of Circulation, we have probably identified the major chemical mediators: the subclass of flavonoids called flavanols, including especially the monomers epicatechin and catechin, and possibly proanthocyanidins and metabolites. All cocoa is created flavanol-rich. It is primarily the processing of natural cocoa solids into cocoa powder or into confectionary chocolate that determines whether a final product is flavanol-rich or -poor. Because flavanols are bitter, manufacturers have often treated natural cocoa with processing techniques that necessarily destroy the flavanols as they enrich flavor and improve consistency.

The use of the term “dark chocolate” is misleading: There is nothing about the color of the chocolate that will tell you the flavanol content. One of the key places in the manufacturing chain where significant loss of flavanols occurs, after fermentation, is an alkalization step called dutching. The Dutchman van Houten discovered 200 years ago that adding alkali-potash to cocoa nibs would enhance the taste, texture, and appearance of the cocoa. Dutched cocoa has the bitterness eliminated, together with most of the active flavanols.

One relatively underreported effect of alkalization is, in fact, darkening of cocoa, so that a very dark chocolate might be essentially devoid of flavanols. If the industry wants us to use chocolate as a health food, then they will have to change their behavior. Specifically, what the world needs is a label on each package that describes the flavanol content of the chocolate. It should be obvious that the percent of cocoa, like the color of chocolate, does not represent a measure of flavanols at all. The medical community should encourage the industry to participate. Probably the most effective mechanism is for the lay press to stop talking about dark chocolate or percent cocoa and start discussing flavanol content.

A second issue involves chocolate as a health food. We like chocolate, and the average person eats a great deal of it every year. Although there is little evidence to indicate that chocolate is a cause of obesity, weight loss in the presence of a high chocolate intake, necessarily rich in fat and sugar, will be very difficult. Here, however, there is good news. Cocoa—as opposed to chocolate—is prepared by squeezing out the fat. Indeed this fat, called cocoa butter, although known as white chocolate, is not really chocolate at all. The resultant cocoa powder retains all the flavor of chocolate but is much lower in calories. Although no commercially available cocoa has a high flavanol content because of extensive processing, it is clear that natural cocoa powder can be a health food.

Evidence that flavanol-rich cocoa contributes to well-being is convincing among the Kuna Indians living off the coast of Panama. Our interest in the vascular benefits of cocoa began with this population, which has no increase in blood pressure with age and a very low incidence of hypertension. Because their protection is lost on migration to Panama City, the relevant factors are more likely environmental than genetic. Kuna living on the islands drink at least 5 cups of cocoa with extraordinarily high flavanol-content every day; in contrast, mainland drinkers consume cocoa from grocery stores as devoid of flavanols as the cocoa available commercially in most of the developed world.

Abundant evidence indicates that flavanol-rich cocoa acting on nitric oxide synthesis and perhaps degradation has a profound influence on the blood supply of the extremities and a similar influence on the blood supply of the brain. The study by Flammer et al adds coronary circulation to that list, a very important addition. Twenty-two cardiac transplant recipients undergoing routine angiography were randomized to receive acute doses of either flavanol-rich chocolate or to a control substance devoid of flavanols. Only the active product induced coronary vasodilation, improvement in vascular function, and a decrease in platelet adhesion, accompanied by a reduction in measures of oxidative stress. The nitric oxide dependence of the vasodilator response to cocoa was
demonstrated in our early study of natural flavanol-rich cocoa administered to healthy humans (Figure).

How large is the influence on the coronary vasculature? We suspect that the study design used may have led to an underestimate of the magnitude of the effect. In studies on the extremities, the response to a single acute dose is small compared with the response over several days of sustained exposure. This study examined the response to a single dose after 2 hours, and thus probably underestimated the contribution of flavanols in cocoa to the state of the vasculature.

The precise chemical mediators responsible for the vascular effects of chocolate and cocoa remain somewhat ambiguous. Flammer et al quite appropriately cite a recently published study by Schroeter et al, who performed a simple experiment. In the same individuals, Schroeter et al examined the vascular response of the extremities to flavanol-rich cocoa with a known epicatechin and catechin content. They then examined the response to synthetic epicatechin and catechin administered in graded dose. The parallel responses to quantities of flavanol in cocoa and to synthetic epicatechin indicated that epicatechin was probably the dominant, if not the sole, mediator. Despite the unambiguous outcome, there are still questions left to be resolved. Schroeter et al also examined the response to a single acute dose. It is possible that responses to doses administered over days, which lead to an unambiguous enhanced vascular response, might involve more than epicatechin. The major mystery factor is the procyanidins, which are polymerized chains of epicatechin and catechin, and which represent the vast majority of the polyphenol content of cocoa. In vitro the procyanidins, indeed, have more bioactivity on isolated blood vessels than does epicatechin or catechin. When cocoa is ingested, the monomer and dimer of epicatechin appear in plasma, but larger oligomeric fractions do not appear. The idea that prolonged intake of chocolate or cocoa leads to a change in the metabolism of procyanidins is an interesting possibility. At the moment, this might be a theoretical construct, but it would not be surprising if some enterprising person or organization tried to develop either a food additive or a drug based on these observations, and at that time these considerations would be central.

Oxidative stress is mentioned in the article by Flammer et al as a possible mechanistic pathway. Certainly, the phenolics in chocolate and cocoa are antioxidant, and nitric oxide is thought to play a prominent role in the oxidative stress story. If we contrast diabetes, a condition in which glycosolated hemoglobin measurement has given us a very powerful tool for examining glycemic control, a striking difference emerges. We have many candidates for chemical measurement of oxidative stress, but none can match glycosolated hemoglobin for information content. We do not know if there is a hierarchy; whether different measures provide more compelling information than others; or whether, indeed, there is a single measure that provides us useful information. In this study, Flammer et al quantified isoprostaglandin F2 alpha as their index of isoprostane status. Their simultaneous measurement of the TRAP and FRAP assays certainly lends credence to the results. If cocoa ingestion indeed reduces coronary events, as indicated by a substantial literature, this issue will become very important as future studies are designed.

Another feature of study design will involve the question of the appropriate control group. The solution to that problem has had many novel strategies. One solution involved the chewing and swallowing of air. Other studies have used white chocolate as a control: The only thing that white chocolate and chocolate have in common is their source, as white chocolate is not truly chocolate at all. It is probably more important and appropriate to match the control beverage on the basis of the content of caffeine and theobromine, agents that have potentially prominent vascular effects and could influence the outcome of studies. In the study by Flammer et al, the control is not well defined except to be called “cocoa-free chocolate.” In reality there cannot be such an entity, but standards for chocolate differ across the globe.
The rapidly growing literature in this field raises some interesting possibilities. At what stage will the community begin to augment short-term assessments of physiological phenomena and epidemiological reports with randomized control trials designed prospectively to ascertain whether cocoa imparts cardiovascular benefits? There are surely sufficient epidemiological data to warrant such studies.\textsuperscript{10,11} The classic model for studies on therapeutics is that adopted by the pharmaceutical industry. The support of such studies represents a reasonable investment because their intellectual property is protected. Indeed, their market size and share is largely determined by the outcome of such studies. In the case of the nutrition industry, however, a positive study does not create intellectual property, and there is no way for a company to justify the expenditure as an investment. This is a problem we have to overcome if we are to obtain the evidence that we need to make appropriate recommendations to the community.

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**References**


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