carries the risk. In phenomenological terms, the studies that have been mentioned up to this point have identified populations at increased risk by using a diagnosis of major depression, various scales that measure symptoms of depression, or the hopelessness item of the General Well-Being Schedule (45). The obvious question is whether the increased risk is associated specifically with the diagnosis of major depression, whether it varies with the severity or chronicity of a depressive state, or whether it can be associated with symptoms of depression in the absence of a diagnosis.

There are only very limited data available to address these distinctions. Lesperance et al. (35) found that in the short term following a heart attack, the risk of death was strongly associated with recurrent major depression, but that a single episode of major depression occurring for the first time after a myocardial infarction was not associated with any increased risk of mortality. Because of the manner in which Frasure-Smith, Lesperance, and colleagues collected their follow-up data, it is not possible to say whether the excess deaths occurred among the patients who were persistently depressed after infarction, whether those who died had a return of their depression before their deaths, or whether the mere occurrence of depression after infarction in those with a history of prior depression marked a group that were at higher risk of death regardless of whether they continued to be depressed. In the long-term studies of Anda et al. (20), Everson et al. (22), and Barefoot and Schroll (23), the higher the symptom scores at baseline, the higher the risk of both developing ischemic heart disease and dying of it. However, it is again not clear whether this increased risk was the result of these individuals merely having more severe symptoms of depression. Alternatively, the higher symptom scores may have identified individuals who were more likely to develop major depression, and the risk was concentrated in those persons who developed major depressive episodes. Everson et al. asserted that hopelessness is a state that can be separated from depression and that this state confers a risk independent of the risk of depression. In general, these remain open issues.

In addition to the studies that have been described to this point, a series of studies from the Netherlands have examined a condition described as vital exhaustion. This state is characterized by lack of energy, increased irritability, and feelings of demoralization (46). Vital exhaustion sounds similar to depression and seems to demonstrate a similar association with cardiovascular disease. In long-term prospective studies it was associated with an increased relative risk of initial myocardial infarction (47), and it was associated with an increase in adverse cardiac events in the year and a half following angioplasty (48). It seems very likely that recurrent major depression and vital exhaustion tap the same underlying process, but the data available do not allow us to test that hypothesis.

Ultimately, it will be established whether these descriptive entities are measuring the same or different processes by identifying the mechanism or mechanisms that lie behind these associations. In the study by Frasure-Smith et al. (37), the excess mortality among post-myocardial infarction patients with depression was due almost exclusively to sudden death. Because sudden death is almost always the result of ventricular arrhythmia, Frasure-Smith et al. investigated whether there was an interaction between depression and postinfarction arrhythmia. There was, in fact, a striking increase in mortality among the postinfarction patients who had both depression and even mild baseline ventricular arrhythmia (37). There is considerable evidence that fluctuations in autonomic nervous system tone influence the risk of ventricular fibrillation and sudden death (49). Changes in autonomic tone have long been considered an integral part of serious depression and the direction of these changes is such that one would anticipate an increase in sudden death (50, 51). This could easily explain a good part of the increased mortality associated with depression following infarction. However, it would be an unlikely explanation for the increased rate of new infarctions seen in depressed individuals initially free of any cardiac disease (20–24, 26).

Increasingly, platelet function has been seen as playing a crucial role in coronary disease, leading from plaque to coronary occlusion and infarction. Noting that platelet receptors were studied as markers for depression, Anda et al. (20) hypothesized that platelet function could represent a mechanism explaining the association between depression and new ischemic disease. This provided the impetus for Musselman et al. (52) to study platelet function in depression. Laghrissi-Thode and colleagues (53) were interested in the potential of selective serotonin-inhibiting antidepressants to influence platelet function because of the ability of these drugs to deplete platelets of serotonin. For this reason they obtained baseline measures of platelet function. Both groups of investigators observed significant abnormalities among drug-free depressed patients. These abnormalities, although not identical, were all associated with an increased propensity for platelets to aggregate and could easily be seen as a reason for the increased rate of new ischemic events associated with depression.

There are also studies of cholesterol and high-density lipoprotein cholesterol which suggest that alterations in lipid metabolism in depressed patients may increase the risk of vascular disease (54).

Before the studies of Musselman and colleagues and Laghrissi-Thode and colleagues, studies of platelet function examined the influence of psychological states (stress, anger, or anxiety) over minutes or hours (55, 56). This distinction between the influence of mood states over very short, intermediate, and long time periods has undoubtedly been a source of some of the confusion that might appear to exist among studies that relate moods and cardiovascular function. Acute mood states are difficult to approach epidemiologically, and the information that does exist tends to be anecdotal. Retrospective studies of individuals who died suddenly suggest that almost one-quarter had experienced such
stantial emotional distress in the period immediately preceding their deaths (57). The Northridge earthquake in Los Angeles provided an opportunity to collect epidemiological evidence about the influence of acute stress on a large number of individuals (58). There was a significant rise in the number of sudden cardiac deaths on the day of the quake. However, there was then an unusually low number of such deaths in the week following the quake, suggesting that acute emotional stress may precipitate cardiac events in people who are already predisposed.

Although data on humans are difficult to collect, there are excellent animal models for examining the influence of short-term emotional states on the outcome of myocardial infarction. In animals with deliberately occluded coronary arteries, acute states of anger, stress, and anxiety have all been shown to increase dramatically near-term ventricular arrhythmia and mortality (59–61). There is little reason to doubt that these same intense negative emotional states can have adverse consequences for human beings over the short term. However, the long-term consequences of more chronic anger and anxiety are not entirely clear. As indicated earlier, chronic anxiety, if not specifically panic or phobic anxiety, does not seem to be associated with long-term cardiovascular morbidity. If there is any long-term effect that is independent of depression, the effect is very small (28, 42). The picture with chronic states of anger is less clear. The findings of the available studies have been contradictory and difficult to reconcile (42, 62, 63). Some aspects of hostility probably do relate to the progression of coronary heart disease. What those aspects are, and whether they exert an effect independent of depression, remains speculative.

Another concept of the relation between psychological states and cardiovascular disease involves the so-called type A personality. In the late 1960s and early 1970s, Rosenman, Friedman, and colleagues (64, 65), among others, developed a body of evidence linking a competitive, time-urgent, irritable personality with an increased incidence of myocardial infarction. By the late 1970s, investigators began to have difficulty replicating these earlier observations. In 1987 Booth-Kewley and Friedman (42) analyzed some 55 studies that had examined the relation between personality and cardiovascular disease. Using meta-analysis techniques, they found considerable statistical evidence for the concept of type A personality over a 30-year period. However, the strength of the relationship was modest at best, and there was evidence for a decline in the association over time. They speculated on a number of issues that might have served to weaken the relationship. We would wonder about the increasing use of β blockers moderating processes that were primarily mediated by increased sympathetic outflow. It is interesting that Booth-Kewley and Friedman found that the strongest effect size in the 55 studies they analyzed was not for type A personality or anger but for depression. They commented that “depression appears to be reliably associated with cardiovascular heart disease... but has generally been overlooked” (42). Again, the evidence for an effect of anxiety was weak.

CONCLUSIONS

Regardless of what made the type A effect weaken, whether some form of anger has long-term implications, depression is unquestionably associated with cardiovascular disease. It is hard not to think of this association in terms of depression causing heart disease. The presence of depression preceding the onset of ischemic heart disease in individuals initially free of disease, the greater risk of sudden death among post-myocardial infarction patients with both depression and arrhythmia, and the predisposition to increased platelet aggregation among depressed patients all seem to point to a causal relationship. Yet it is important to remember that what has been demonstrated is an association and not causality. It is conceivable that atherosclerosis could be a cause of both depression and heart disease. Indeed, there is evidence that late-onset depression may be secondary to arteriosclerotic disease in the brain (66, 67). At this point, the source or sources of these associations remain to be determined. Although we suspect that the autonomic nervous system and platelet changes, as well as the health behaviors that are associated with depression, contribute significantly to the relationship with ischemic heart disease, the relationship could easily be a two-way street, where the arteriosclerotic process could also increase the risk of depression.

The other question raised by the relation between depression and mortality is whether successfully treating the depression would reduce the associated mortality. It almost seems obvious that if depression increases the risk of postinfarction mortality, then treating depression should reduce the risk. However, experience has taught that treatments which seem rational can produce very unexpected results. It was clear to cardiologists that ventricular arrhythmia after myocardial infarction predicted death and that antiarrhythmic drugs greatly reduced these arrhythmias. It seemed logical that these antiarrhythmic drugs should reduce this mortality. Nevertheless, when tested, although they eliminated arrhythmias, antiarrhythmic drugs increased mortality (68). Even before we can test whether antidepressants are able to reduce mortality after infarction, we need to test whether these drugs are safe and efficacious in these patients. It is already evident that the tricyclic antidepressants are too risky in this group (69). Tricyclic antidepressant pharmacology strongly resembles that of the recently incriminated antiarrhythmic drugs. The serotonin reuptake inhibitors seem more benign, but the evidence available at this time is scanty at best (70).

Although it remains to be clarified whether any antidepressant treatment will alter this post-myocardial infarction mortality, it is amply clear that depression is strongly associated with more frequent and more malignant cardiovascular disease. In fact, it is likely that depression's effect is not limited to cardiovascular disease...
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