Neurobiology, Cellular and Molecular Biology, and Psychosomatic Medicine

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Last year in New York the American Psychosomatic Society celebrated its first 50 years. In this presidential address at the beginning of our second half-century, I want to share with you some ideas—perhaps even some visions—for the next 50 years. My major message is that optimal growth in our understanding of how biopsychosocial factors interact in the etiology and course of human disease will come only if our research incorporates theories and techniques from neurobiology and cellular and molecular biology (Fig. 1).

First a roadmap to describe from whence we come and where we are heading. As shown in Figure 1, some people have personality traits that cause them to react to their environments in ways that are harmful when repeated over and over during the course of everyday life. These reactions cause the brain to influence (via neural and endocrine “motor” messages to target organs) peripheral bodily functions in ways that, over the years, set in motion processes leading to disease and death. Inasmuch as it has provided the framework for my thinking, I shall use the research on hostility and its health-damaging effects to convey my main points.

The research on hostility began with Type A. Without Friedman and Rosenman’s pioneering work (1) showing a constellation of traits, including time urgency and hostility, to identify persons at high risk of developing coronary disease, I probably wouldn’t be delivering this presidential address; or, if so, not on the topic I have chosen. As we now know, it seems that only the hostility-related aspects of Type A are coronary prone. Beginning with our 1980 study (2), we found that scores on a 50-item hostility scale (Ho) correlated positively with coronary artery disease (CAD) severity. In fact, Ho scores correlated with CAD independently of Type A and just as strongly as Type A; and in women as well as men. Because the Ho scale is part of the Minnesota Multiphasic Personality Inventory (MMPI), it has been possible for several groups to re-score old MMPIs for the Ho scale and show, as Shekelle and co-workers did in the Western Electric Study (3), that Ho scores predicted increased CHD risk. Interestingly, those with high Ho scores were also more likely to die of all causes, including cancer. Another study of this sort was done at University of North Carolina and Duke by Dr. John Barefoot, who followed up 253 doctors who had taken the MMPI in medical school 25 years ago (4). Those with higher Ho scores in medical school were nearly seven times more likely to be dead by age 50 than their less hostile counterparts. Some studies (5–7) have failed to find the Ho scale predicting health outcomes. However, many additional studies using other self-report measures of hostility and related constructs, especially behavioral assessments of interview data (8), make a strong case that hostility does predict increased risk of coronary disease as well as all-cause mortality.

Results from laboratory studies increase our confidence that hostility is health-damaging by documenting its biological plausibility as a risk factor. In Dr. Edward Suarez’s study (9), harassment produced significantly greater cardiovascular hyperreactivity in the high Ho-scoring subjects. Another important finding of this study was that only in the high hostile subjects were high anger and irritation ratings significantly associated with enhanced cardiovascular reactivity. For low hostile subjects, becoming irritated when harassed was uncorrelated with reactivity. As Suarez et al. (10) reported recently, persons with high Ho scores show increased sympathetic reactivity not only in the lab when being harassed, but also when they are going about their normal activities in a typical day. For more detailed information about biological mechanisms of hostility’s effects on health, I refer you to Dr. Tim Smith’s excellent recent review (8). We have also found that cholesterol levels correlate positively with plasma epinephrine responses to a mental stressor in high Ho subjects, whereas the opposite holds in low Ho subjects (11). The explanation for this finding is not readily apparent.

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PRESIDENTIAL ADDRESS

One potential underlying mechanism that presages some of the points I will be making about our need to apply principles and techniques of cellular and molecular biology is shown in Figure 2.

As shown in the upper part of Figure 2, we interpret the positive correlation between epinephrine responses and cholesterol levels in the high Ho subjects as reflecting the effect of their increased epinephrine release to stimulate mobilization of fat that is then converted to cholesterol. In contrast, as shown in the lower part of Figure 2, among the low Ho subjects, who do not experience sympathetic hyperreactivity, an elevated cholesterol stems mainly from diet and genetic factors. Therefore, in the low Ho subjects, when dietary and genetic factors produce elevated cholesterol it causes, as has been documented in animal studies (12), an upregulation of beta receptors. This in turn, causes a decrease in catecholamine release, accounting for the negative correlation between cholesterol level and epinephrine reactivity in low Ho subjects. This feedback from upregulated beta receptors to reduce catecholamine release would not occur in high Ho subjects with elevated cholesterol, because their primary “lesion” of increased sympathetic nervous system (SNS) reactivity produces large catecholamine responses that have a direct “downregulating” effect on beta receptors. This prevents cholesterol from causing a beta-receptor upregulation, and the resultant dampening of catecholamine release in high Ho subjects, thereby precluding the negative correlation between cholesterol and catecholamine release that is observed in low hostile subjects.

I will come back later to the implications of this explanation of the differential cholesterol-catecholamine associations in high and low Ho subjects for how we might begin to apply molecular biological principles and techniques to understand psychosomatic relationships. But first I need to cover just a few more background points. An earlier study (13) found Type A men to show a shorter and less pronounced vagally mediated HR decrease during elicitation of the dive reflex, suggesting weaker para-
sympathetic function in coronary prone persons. This has now been confirmed in a subsequent study (14) finding that the extent to which the EKG T-wave response to isoproterenol is enhanced by atro- pine pretreatment, a measure of the amount of vagal antagonism of SNS effects on the myocardium in the normal state, is strongly correlated with lower scores on several different hostility and anger scales. Thus, subjects with high hostility levels show weaker vagal antagonism of SNS effects on the heart. A paper presented at this meeting by Sloan et al. (15) confirmed this result by showing a negative correlation between Ho scores and a measure of vagal tone (heart period variability) in ambulatory Holter EKG records.

Results from Dr. Ilene Siegler’s UNC Alumni Heart Study (16) will complete the background information. Those students who had higher Ho scores when they were in college in the 1960s show increased risk behaviors 21 to 23 years later. These findings, along with complementary findings from the CARDIA study (17), show that in addition to all the other reasons for hostile persons to have increased health problems, they are also placing themselves at higher risk by eating more, drinking more alcohol, and smoking more cigarettes.

NEUROBIOLOGY AND PSYCHOSOMATIC MEDICINE

Table 1 summarizes the evidence just reviewed. Persons who score high on the Ho scale show a constellation of characteristics that seem to cluster together: increased anger/irritation; increased sympathetic reactivity; decreased parasympathetic function; increased smoking; increased eating; and increased alcohol use. For heuristic purposes only at this stage of our understanding, I am going to call this clustering of characteristics in persons who are identified on the basis of high Ho scores a “hostility syndrome,” which brings us to my first vision for the future: we need to incorporate principles and techniques from neurobiology if psychosomatic medicine is to enjoy another 50 years of progress.

Rather than saying that a hostile personality trait somehow “causes” the clustering of the characteristics making up the hostility syndrome, I am proposing (again for heuristic purposes) that current neurological research findings suggest that all the characteristics in the left column of Table 1 could be the result of a single underlying neurochemical condition: deficient central nervous system (CNS) serotonergic function. Here is a brief review of the evidence supporting this serotonin deficiency hypothesis.

To start with the behavioral manifestations, a considerable body of evidence links increased aggressive behaviors with decreased brain serotonin function. For example, Coccaro et al. (22) found a measure correlated with CNS serotonin function, the prolactin response to fenfluramine, to be negatively correlated with scores on four hostility subscales. In an elegant series of studies, Kyes and co-workers (35, 36) have documented that male cynomolgus monkeys with decreased CNS serotonergic function (indexed by prolactin response to fenfluramine) show more aggressive and fewer affiliative behaviors. These findings are consistent with the mediation of aggressive behaviors in hostile persons by decreased CNS serotonergic function.

Considerable evidence suggests that decreased

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<tr>
<th>Biobehavioral Component</th>
<th>Evidence for Serotonergic Basis</th>
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<tr>
<td>Increased anger and irritation in lab and real world settings (9,18).</td>
<td>CSF 5-HIAA correlates −.78 with and aggression history in men (19). 5HT agents decreased aggression in monkeys (20) and man (21). Prolactin response to fenfluramine correlates negatively with hostility scale scores (22).</td>
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<td>Increased sympathetic nervous system reactivity in lab and real world settings (9,23).</td>
<td>CNS 5HT₁ₙ receptor activation reduces sympathetic outflow (24). Fluoxetine lowers BP in SHR (25). Tryptophan loading reduces sympathetic nerve firing in cats (26).</td>
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<td>Decreased parasympathetic nervous system activation (13–15).</td>
<td>CNS 5HT₁ₙ receptor activation leads to increased vagal outflow (24). Reward property of nicotine is mediated by 5HT₁ receptors (27). Tryptophan (28) &amp; buspiron (29) reduce smoking.</td>
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<td>Increased smoking behavior (3,16–17).</td>
<td>CNS 5HT depletion increases food intake, body weight, and adiposity in rats (30). Fluoxetine reduces eating and weight in rats (31) and humans (32).</td>
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<td>Increased eating and body mass index (16, 17).</td>
<td>CSF 5-HIAA is lower in alcoholics (33). 5HT uptake inhibitors reduce alcohol intake in humans (34).</td>
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<td>Increased alcohol consumption (9,16).</td>
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CNS serotonin function could cause increased SNS outflow. For example, stimulation of one class of serotonin receptors (5HT_{1A}) is known to cause a decrease in SNS outflow (24). Stimulation of these receptors may account for Verrier's finding (28) that enhancing CNS serotonin function via tryptophan loading causes a decrease in cardiac sympathetic nerve firing rate. Animal studies have documented that besides decreased SNS outflow, stimulation of CNS 5HT_{1A} receptors also causes an increase in parasympathetic (PNS) outflow (24). These results indicate that the altered autonomic balance (increased SNS and decreased PNS function) found in hostile persons could be caused by deficient CNS serotoninergic function.

Continuing with other aspects of the hostility syndrome, there is evidence that the reward properties of nicotine may be mediated by the 5HT_{2} receptor (27), and serotonergic drugs are being increasingly used as an aid to smoking cessation (28, 29). Decreased CNS serotonin function has been found in extensive research (30–32) to be associated with increased eating behavior. There is also very extensive and convincing evidence that weak brain serotonin function contributes to increased alcohol consumption (33, 34).

Based on the foregoing review, I offer for your consideration, and hopefully as a stimulus for your future research efforts, a parsimonious, although speculative explanation of the clustering of the behavioral and physiological characteristics that make up the hostility syndrome (and hence account for its health-damaging effects). All stem from a common CNS “lesion:” deficient serotoninergic function.

Before proceeding may I add that I am not unaware of how simplistic this hypothesis may seem at first blush. For example, deficient CNS serotonergic function has been implicated in depression (37), and the question might be posed, how can a deficiency in a single neurotransmitter be responsible for both a personality trait (hostility) and a clinical disorder (depression)? Another complication, and one that might explain how serotonergic deficiency could have multiple consequences, stems from the multiple interactions of the serotonin system with other neurotransmitter systems. For example, serotonin and catecholamine systems can have opposite actions on the same function and may compete for the same target areas in the CNS (38). One person could have a hostile personality whereas another becomes depressed as a result of serotonin deficiency depending on the status of other neurotransmitter systems with which serotonin interacts. Or perhaps the potential for different manifestations of serotonin deficiency in different individuals is a reflection of the multiple subtypes of serotonin receptors, many of which seem to have opposing effects (39). Additional research will be required before we shall be able to conclude whether the hostility syndrome is actually a serotonin deficiency syndrome.

Despite these potential complications standing in the way of a proposed CNS serotonin deficiency as responsible for the clustering of health-damaging characteristics making up the hostility syndrome, I am still attracted to this hypothesis by its parsimony, as well as its inductive and heuristic nature.

Additional support for the serotonin deficiency hypothesis comes from a consideration of recent research linking low cholesterol with certain types of mortality. Muldoon et al. (40) in their review of the cholesterol lowering trials found an increase in nonillness mortality, chiefly that due to accidents, suicide, and violence, in the cholesterol-lowering groups. Cohort studies have found a similar increase in violent deaths among persons with low cholesterol levels (41). In a fascinating series of studies, the group at Bowman Gray and Pittsburgh led by Kaplan, Manuck and others (42, 43) have documented that monkeys with low cholesterol levels exhibit more aggressive and fewer affiliative behaviors than their high cholesterol counterparts. Moreover, these investigators propose that the “antisocial” behavioral effects of low cholesterol are mediated by reduced CNS serotonin function, as indexed by both smaller prolactin responses to fenfluramine and lower CSF 5HIAA levels in animals with lower cholesterol levels.

Direct support for this explanation comes from Engelberg (44), who cites evidence showing decreased brain serotonin receptor numbers in the setting of low cholesterol as providing a specific mechanism whereby low cholesterol could bring about a brain serotonin deficiency state leading to the behavioral changes that predispose to violent forms of death.

In contrast to the preceding scenario, where decreased CNS serotonergic function and the consequent behavioral changes are secondary to decreased cholesterol concentrations, in the hostility syndrome it seems more likely that low CNS serotonergic function is the primary state, whether because of early environmental influences on development or to genetic factors, that leads to behavioral and physiologic changes.

If additional research confirms that a serotonin deficiency is the cause of the hostility syndrome, it would have far-reaching implications for prevention and treatment of the medical disorders to which
hostile persons are prone. There is a growing proliferation of drugs that enhance CNS serotonin function, including selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, paroxetine, and fluvoxamine) and specific serotonin receptor agonists, e.g., buspirone. Although developed with treatment of psychiatric disorders in mind, it may soon become evident to all that these agents could have an equally, if not more important application in preventing the health-damaging consequences of the hostility syndrome.

We have already witnessed what can be seen in retrospect as a massive, but uncontrolled “clinical trial” of serotonin enhancement pharmacotherapy to improve psychological well-being. That is, before its withdrawal because of a contamination causing a febrile illness, tryptophan (the amino acid precursor to serotonin) was self-prescribed by many Americans as a “natural tranquilizer.” Littman and co-workers have conducted a more conventional clinical trial and found buspirone (a partial agonist for the 5HT1A receptor) to reduce Type A behavior, hostility, and perceived stress in cardiac patients (45).

**CELLULAR AND MOLECULAR BIOLOGY AND PSYCHOSOMATIC MEDICINE**

Figure 3 provides another summary and presents a model that points to my second vision for psychosomatic medicine's second half-century. As reviewed thus far, epidemiological research has shown that hostility increases risk of dying from all causes, including coronary disease and cancer. Other epidemiological studies have identified increased eating, smoking, and alcohol consumption as behavioral consequences of hostility that could play a role in these illnesses. Experimental studies have identified increased sympathetic reactivity, particularly that associated with high cholesterol levels, and decreased parasympathetic function as biological characteristics that could also be contributing to disease risk. And as I have just suggested, all of these health-damaging hostility syndrome components could be the result of a serotonin deficiency in the central nervous system.

The model in Figure 3 points to another body of knowledge that I believe psychosomatic medicine will need to use in the future. While I have focused thus far on events related to serotonin function inside the head as important for understanding psychosomatic mechanisms of disease, it will also be important to understand how differences in brain serotonergic function are translated into disease at the level of peripheral organ systems. As shown in Figure 3, the biobehavioral characteristics of the hostility syndrome could very well contribute to etiology and pathogenesis of disease via effects on the cellular and molecular biology of macrophage activation.

To illustrate this idea, I shall draw upon my Duke colleague, Dolph Adams’ review (46) of the exciting and brave new world of macrophage activation to posit two pathways via which increased cholesterol in the setting of increased sympathetic agonists could influence macrophage activation in ways that would lead to increased pathogenesis of medical disorders like coronary atherosclerosis and cancer.

First, as Adams (46) notes, increased oxidized low-density lipoprotein (LDL) has well-known effects that affect the cellular and molecular events of activation in ways to make the macrophage more likely to speed development of both atherosclerosis and tumors. A second pathway involves high cholesterol’s amplification, via upregulation of beta receptors on the macrophage, of the effects of increased catecholamines on macrophage activation. These catecholamine effects on macrophage activation mimic in most respects those of oxidized LDL (46). This conflation of the effects of elevated cholesterol and catecholamines (both of which are found in hostile persons) would be expected, therefore, to accelerate atherogenesis via effects on the molecular biology of macrophage activation that add to the effects of oxidized LDL.

We have performed a preliminary and somewhat crude test of this hypothesis using the Egyptian sand rat model of cholesterol-induced atherosclerosis. When fed a high cholesterol diet the Egyptian sand rat develops typical early atherosclerotic lesions after 6 to 8 months (47). These lesions contain macrophage- and smooth muscle-derived foam cells that are typical of the early atherosclerotic lesion. It

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**Fig. 3.** Summary model illustrating proposed effects of low brain serotonin on biobehavioral parameters that can affect macrophage activation in ways that potentiate atherogenesis and tumorogenesis.
takes 6 months on the high cholesterol diet to develop these lesions. If sand rats are placed on the high cholesterol diet for only 2 months, no lipid accumulates in the arterial wall and only a few isolated foci of intimal hyperplasia can be observed. After 2 months on the same high cholesterol diet, but with the addition of high catecholamines maintained by subcutaneously implanted osmotic minipumps, we found (48) that the combination of high cholesterol and high catecholamines leads in only two months to pathology that with high cholesterol alone takes 6 months to develop. This result is consistent with the hypothesized synergistic effects of the combination of high cholesterol and catecholamines acting on atherogenesis via effects on macrophage activation. Our future collaborative work with Dr. Adams will be aimed at identifying the specific changes in the cellular and molecular biology of macrophage activation that are responsible for the accelerated atherogenesis observed in sand rats maintained on high levels of both cholesterol and catecholamines.

As with the serotonin deficiency hypothesis I advanced to explain the clustering of characteristics of the hostility syndrome, I am aware that I have only scratched the surface in proposing how using the theories and techniques of cellular and molecular biology might enhance future research in psychosomatic medicine. Many more factors (e.g., plasminogen activation inhibitors, platelet activation, cytokines, natural killer cell activity, and the like) apart from the macrophage are important contributors to both atherogenesis and tumorigenesis.

My choice of macrophage activation to illustrate the importance of cellular and molecular biology for psychosomatic medicine’s next 50 years was not a casual one, however. As Adams notes in his review (46), current thinking in cellular and molecular biology accords a key role to altered macrophage activation in the initiation and progression of the atherosclerotic plaque; and it is the activated macrophage that is essential to start the cascade of events in the immune system that ultimately determine whether tumor cells thrive or die. Therefore, incorporation in psychosomatic research of new knowledge regarding the cellular and molecular biology of macrophage activation will clearly enhance our understanding of how psychosocial factors like hostility contribute to the pathogenesis and course of major killers like coronary atherosclerosis and cancer.

Let me summarize my first two points. Low CNS serotonin function has effects on biology and behavior that could be responsible for both the biobehavioral traits and consequent high rates of disease and death that have been found associated with high hostility. To test this hypothesis and eventually to apply the knowledge gained to develop more effective means of prevention and treatment, we need to incorporate the growing knowledge from the fields of neurobiology and biological psychiatry into our psychosomatic thinking and research.

In work currently in progress at Duke, for example, we are evaluating the prolactin response to fenfluramine of high versus low hostile subjects; if high hostile subjects show a reduced prolactin response, it will constitute direct evidence supporting the hypothesis that serotonin deficiency is responsible for the clustering of health-damaging traits that make up the hostility syndrome. Such a result would point the way to clinical trials evaluating serotonin-enhancing pharmacologic agents in both the primary and secondary prevention of hostility-related diseases.

We also need to bring to bear the growing understanding of disease processes that come from cellular and molecular biology. If such psychosomatic constructs as hostility are indeed involved in the pathogenesis of coronary disease and cancer, it will surely be via effects occurring at the cellular and molecular levels. Therefore, we should be able to learn more about pathogenic mechanisms whereby psychosocial factors (I have used hostility as an example) lead to disease by applying the principles and techniques of molecular biology in our research. The studies we are now conducting with Dr. Adams to understand how cholesterol and catecholamines interact to influence macrophage activation are one example of such a combined approach. If successful, this research could point the way to specific pharmacologic probes that would prevent or slow, at the level of the macrophage, the health-damaging effects of the hostility syndrome.

SOME FINAL THOUGHTS

Over the past 50 years psychosomatic medicine has come of age. We are now poised to apply new knowledge from neurobiology and cellular and molecular biology during the next 50 years, so that we can realize the promise of what we have learned about psychosomatic relationships during our first 50 years.

In closing, I want to change the focus from that taken thus far in this presidential address, from one honing in on ever more particular molecular factors inside the body to one that considers instead the

implications of our research for the world outside the body—for society at large.

In this regard, we have recently begun to ask whether a hostile personality could affect a person's attitudes and behaviors in ways that have the potential to harm the health of society. To begin to answer this question, in three independent samples on whom we had hostility scores we asked whether during the period leading up to the Persian Gulf War in January 1991, subjects had favored bombing Baghdad or letting the economic sanctions have longer to work. As we reported recently [49], in all three samples three fourths of those with higher hostility scores favored the bombing option, whereas three fourths of those with lower scores favored giving economic sanctions longer to work.

Thus, it seems that the same personality trait—hostility—that imposes increased risk of personal health problems also influences opinions on matters of public policy in ways that could also harm social and political health. I am not sure just how the implications of this influence, assuming it is confirmed in future research, will play out. Just as we need input from colleagues in neurobiology and cellular and molecular biology to understand how personality affects physical health, so also might we need help from our colleagues in the social sciences to understand and make use of knowledge regarding the impact of personality on social and political health.

I envision an important and broad role for psychosomatic medicine across a number of specialized fields of endeavor during the next 50 years. On our horizons loom potential findings and applications in neurobiology, cellular and molecular biology, and social research. I am confident that many members of our Society will pursue these exciting possibilities.

I am also confident that in at least some specialized fields, the work of psychosomaticists will have society-wide implications. To illustrate just how broad is this vision, let me say in closing that my own investigations in hostility research have led me increasingly to resonate to these words attributed to the Chinese philosopher Lao-Tse:

If there is to be peace in the world, there must be peace in the nations.

If there is to be peace in the nations, there must be peace in the cities.

If there is to be peace in the cities, there must be peace between neighbors.

If there is to be peace between neighbors, there must be peace in the home.

If there is to be peace in the home, there must be peace in the heart.

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REFERENCES
1. Friedman M, Rosenman RH: Type A Behavior and Your Heart. Greenwich, CT, Fawcett, 1974

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