Suicide Research

Overview and Introduction

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This volume of the *Annals* contains the proceedings of a workshop on suicide research sponsored by the National Institute of Mental Health and the American Suicide Foundation. The workshop presented the latest research in suicide from preclinical, clinical neuroscience, and treatment perspectives. The preclinical section provides information on new methodologies in basic research that have promise for uncovering mechanisms that may underlie suicide. The clinical neuroscience section discusses recent research studies in adult suicide on the neurobiological substrates of suicide risk, taking advantage of powerful methods available in molecular biology and modern neuroscience. The treatment section addresses challenges involved in the development of treatments that specifically reduce suicide risk and discusses the evidence for efficacy of current pharmacological and nonpharmacological treatments in preventing adult suicide. Thus, this volume describes the most promising suicide research findings over the last decade since publication of a previous comprehensive volume on suicide research.[1]

HISTORICAL BACKGROUND

Attitudes toward acts of self-destruction and personal sacrifice are rooted in theology and classical Greek and Roman philosophy. The views in these ancient references are embedded in the fundamental conceptualization of human relationships to others and to God. In these accounts of self-destruction and human sacrifice, themes of personal responsibility, morality, and prohibition are portrayed. The idea of suicide did not always have the same meaning that it has in contemporary Western society. According to the Oxford English Dictionary, the word *suicide* first appears as an English word around 1651.

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The nineteenth century brought a new way of viewing suicide. In essence, the change appears to have resulted from viewing suicide in theological, moral, philosophical, and legal terms to seeing suicide as a social, medical, psychological, and statistical problem. The sociological and psychological perspectives constitute the two main threads for the contemporary study of suicide. These perspectives originated around the turn of the twentieth century and have been associated with Emile Durkheim (1858-1917) and Sigmund Freud (1856-1939), respectively. One hundred years ago Durkheim's *Le Suicide*[2] established a model for sociological investigations of suicide and suggested that suicide occurred when there was a breakdown of external social controls. He proposed a theory of four kinds of suicide, each a result of the person's relationships or ties to society. Whereas Durkheim thought of society in terms of society's influences on the individual, Freud[3] was the father of a psychological explanation postulating that suicide was essentially the outcome of an intrapsychic struggle. For Freud and other psychoanalysts, suicide represented unconscious hostility directed toward the introjected (ambivalently viewed) loved object. The view that suicide can be traced to intrapsychic processes represented the growing focus on internal mechanisms for suicidality. A concentration on internal causes led to the notion in the 1950s that "depression and resultant suicidal behavior have an exclusively organic etiology."[4] It is now well accepted that such a narrow view of the etiology of suicide is inappropriate. A more complete conceptualization is a multidimensional model comprising overlapping psychosocial, biologic, genetic, psychiatric, and temperament/personality domains (*e.g.*, Blumenthal[5]).

MODERN SUICIDE RESEARCH

Today, suicide is one of the most significant public health threats in the United States. In 1994 suicide was the ninth leading cause of death in the United States (among the general population). It claims more than 30,000 lives each year and is the third leading cause of death among young people, aged 15-24 years. The costs and consequences of suicide in the United States are far-reaching and devastating, both financially and socially. It is the sixth leading cause of years of potential life lost before the age of 65. To respond to this major public health problem, we must increase systematic research efforts to identify high-risk groups, understand etiology, and develop effective treatment and prevention strategies. In the past, most research on suicide risk has focused on the role of psychological and sociocultural factors that are clearly important in determining risk. However, efforts aimed at identifying the potentially suicidal individual using demographic, social, developmental, and psychological factors offer too weak a prediction to be of substantial clinical utility. It is believed

that a biological perspective, which has grown out of the expanding research on the biochemical bases of mood disorders, is a promising approach to suicide research. It can assist in the investigation of risk factors that predispose a person to suicidal behavior and that increase understanding of etiology, treatment, and, ultimately, prevention.

PRECLINICAL RESEARCH

Preclinical models can be used to examine relevant biological systems in greater depth in order to address hypotheses, interpret clinical findings, and aid in directing future clinical neurobiological and treatment research. It is important to determine what new tools and conceptual advances in the basic neuroscience provide the most promising opportunities for clinical neurobiological and treatment studies of suicide. Although there are no experimental models of suicidal behavior in animals, there are some preclinical models that are relevant to the study of suicide. Furthermore, insights might be gained from naturalistic observations.

Stories of abnormal behavior patterns, presumably indicative of animal suicide, are based on folklore and are frequently mythical, or are anecdotal and anthropomorphized to a degree. An early scientific account of animal suicide is from Aristotle. In his *History of Animals,* a horse is described who ran away and threw himself down a precipice. A number of legendary accounts of animal self-injury and suicide have been noted by Einsidler and Hankoff.[6] These include a horse who fell down on purpose and dashed itself to bits, dogs and horses who pine and die in the absence of their masters, and a scorpion who was said to have stung itself to death when placed within a ring of burning coals. It is unlikely, however, that in these instances animals possess a conceptualization of death that is thought to be critical. We cannot use the definition of suicide as voluntarily and intentionally taking one's own life and apply it to animals. There has been little scientific study of animal suicide. However, ethological observations derived from the zoological literature may shed some light on the study of self-destructive behavior. Identifying underlying mechanisms involved in the natural life events in the home environment of some animal species may be helpful in understanding analogous processes involved in unusual responses to life events in humans. The Arctic lemming is the proverbial form of "suicidal behavior" in the natural setting of animals. Lemmings have been described as possessing an irresistible compulsion to march into the sea, from which no lemming has ever been known to come back. Their large-scale migration is presumably in response to overpopulation when there is intense competition for mates, space for burrows, and food. Most likely, overcrowding results in stress as the main response for migration, and lemmings do not migrate in order to commit suicide. Behavioral abnormalities including self-mutilation have

been observed in veterinary practice and in a variety of zoo animals.[7] Self-mutilation has been noted in a macaque[8] and rhesus monkey,[9] and unexplained sudden deaths have occurred in several animal species, including rats,[10] dolphins,[11] deer, and rabbits.[12] These examples most likely represent a response to stress and are transitional between true naturalistic animal behaviors and laboratory models, inasmuch as they are externally imposed. They nevertheless demonstrate that in animals, as in humans, stress-causing situations, such as confinement and crowding, can result in self-destructive and self-endangering behavior.

Laboratory-based animal models have been extensively used for modeling psychiatric illnesses or for producing specific pharmacological or anatomical manipulations of the central nervous system. However, surprisingly little attention has been paid to the modeling of self-destructive or suicidal behaviors. In the evaluation of any laboratory-based animal model, it is essential to establish validation criteria as general standards that the model must adhere to. The validating criteria for animal models of depression (see reviews by Geyer and Markou[13] and Willner[14]) can be applied to suicide and virtually any other form of psychopathology. These criteria include face validity (how well the model resembles suicide from behavioral and physiological viewpoints), predictive validity (the ability of drugs used in the treatment of suicide to modify the behavior in the model), construct validity (similarities in underlying processes between the model and suicide, specifying common biochemical mechanisms), etiological validity (similarities in the etiologies of the model phenomenon with suicide), convergent validity (high correlations with other models that attempt to measure the same construct), and discriminant validity (low correlations with other models that assess different phenomena).

It is unlikely that a single model will satisfy all these validity criteria, and in most cases different types of validity are relevant depending on the nature and the desired purpose of the test. For example, face validity was the primary concern for some of the earlier reports of self-injurious behaviors in monkeys after isolation-induced social separation[15] and self-injury in a variety of nonhuman species induced by temporal lobe lesions,[16] caffeine,[17] clonidine,[18] or caudate nuclei lesions.[19] It has been argued that some other models have good face validity because there is similarity between signs of depression and the behavioral characteristics of either learned-helpless animals[20] or animals that have learned to despair.[21] The strategy of mimicking the salient symptoms of depression would only be meaningful if the strong association between depression and suicide could be shown to apply to the animal model. Thus far, this has not been accomplished. More recent preclinical studies have shifted attention away from assessing face validity to the evaluation of predictive, construct, and etiological validity. This has been motivated by recognition of the difficulties in mimicking in animals the intentional and voluntary aspects of suicide and

cross-species homology in behavioral and neurobiological characteristics. The preclinical papers in this volume (Kraemer *et al.*, Higley and Linnoila, Kaplan *et al.*, Hen (Brunner and Hen), and Lopez *et al.*) represent the shift in focus toward a better understanding of processes and mechanisms common to animals and humans. A major shift has occurred away from depression to aggression and impulsivity as behavioral features more relevant for suicidal behavior that is operationalized as a subtype of aggression. This shift is crucial because aggression and impulsivity can be studied in animal models.

CLINICAL NEUROSCIENCE RESEARCH

It is hoped that understanding the neuroscientific substrates of suicidal behavior will lead to increased predictability in at-risk individuals, better diagnosis, and the development of more effective treatment and prevention strategies. In essence, the major task is to provide a road map of brain functioning and neurochemistry correlated with suicidal behavior, taking advantage of the powerful modern methods of molecular biology, quantitative morphometrics, and neurochemistry. Additional impetus for the neurobiological study of suicide comes from the implications of a genetic contribution to the risk for suicidal acts (Roy *et al.*, this volume).

The two main strategies used to study the neurobiology of suicide are neuroendocrine challenges (*e.g.*, HPA axis) and neurotransmitter (*e.g.*, serotonin) measures. Neuroendocrine systems have not been as intensively investigated as the neurotransmitter systems. Nevertheless, neuroendocrine studies are noteworthy in representing some of the initial endeavors to identify biological correlates of suicide.

The earliest report of a biological abnormality derives from the observation of metabolic abnormalities and adrenocortical dysfunction in a seriously suicidal patient with Cushing's syndrome (among whom emotional and mental disturbances are frequent).[22] Subsequent reports in Cushing's syndrome also suggested endocrine abnormalities in suicide. For example, a female patient with a mental disorder accompanying Cushing's syndrome experienced a remission of suicidal ideation and risk after receiving deep X-ray therapy to the pituitary gland.[23] More recently, a study of 35 individuals with Cushing's syndrome revealed that six (17%) patients had recurrent suicidal thoughts, and two (7%) of these had made suicide attempts since the onset of their hypercortisolism.[24] Although endocrine profiles with ACTH and urinary-free cortisol are not presented for patients with suicidal ideation or suicide attempts, those with the most severe depressive clinical presentations had persistently and significantly elevated ACTH levels.[24] These data support the hypothesis that suicidal behavior, at least in a subgroup of patients with hypercortisolism, may be

associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.

The possibility that hyperactivity of the HPA axis might have a special relationship to suicidal behavior was initially suggested by investigators of the National Institute of Mental Health who observed elevated urinary 17-hydroxycorticosteroids, an indirect measure of daily cortisol production, in patients who later committed suicide.[25,26] However, several subsequent studies investigating this association have yielded mixed results.[27-29] In addition, investigations of relationships between suicidal behavior and plasma cortisol levels, before and after administration of dexamethasone, have also yielded contradictory results. Most studies found higher rates of nonsuppression on the dexamethasone suppression test (DST) in patients who had attempted or completed suicide compared to nonsuicide attempters.[30-33] There are, however, some negative studies reporting no association of recent suicidal behavior and nonsuppression of DST.[34,35] More recently, suicide victims have been found to have reduced binding of corticotropin-releasing factor (CRF) in the frontal cortex.[36] Inasmuch as it is thought that CRF hypersecretion is the basis of cortisol dysregulation in depression, this finding is consistent with the hypothesis that CRF is hypersecreted in depression with resulting receptor downregulation.

The majority of clinical neurobiological studies of suicide have concentrated on the serotonin (5-HT) system. A rationale for the intensive study of 5-HT is that it occupies a key role in other-directed aggression and impulsivity as well as a variety of other physiologic and behavioral functions of animals. The link between other-directed aggression/impulsivity and inner-directed aggression (*i.e.*, self-destructive and suicidal behavior) has been frequently commented upon. Serotonergic function bears a similar relationship to aggression in animal models of aggression[37] and clinical studies of suicide and aggression. Although remarkable progress has been made in clarifying the role of the serotonin (5-HT) system in suicide, the basic neurobiology of suicide risk has yet to be elucidated, and a distinct and complete constellation of neurochemical/neuroanatomical deficits in suicide has yet to be identified.

Most 5-HT studies of suicide attempters have demonstrated abnormalities in related 5-HT indices, leading to the hypothesis that reduced serotonergic activity is associated with increased suicide risk (see review by Mann[38]). The first study of the relationship between 5-HT function and attempted suicide comes from a cerebrospinal fluid (CSF) study of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of 5-HT, in depressive illness.[39,40] The finding that CSF 5-HIAA concentration was bimodally distributed in depressed patients generated interest in discovering clinical correlates of the two modes of the CSF 5-HIAA distribution (Åsberg, this volume). It was noted that a history of serious suicide attempts was associated with low CSF 5-HIAA concentration, in particu-

lar, when violent methods were employed. It has been pointed out that the failure to show uniformly low 5-HT function in studies of suicide attempters may be due to the complexity of attempted suicide and the difficulties in controlling and assessing numerous variables in behaving subjects. Studies of 5-HT turnover in suicide attempters have also employed the platelet serotonin transporter, and 5-HT_{2A} receptor and neuroendocrine strategies (Pandey, this volume). Alterations in the serotonergic system in the brain of suicide victims also supports the hypothesis that reduced serotonergic activity is associated with increased suicide risk (see review by Mann *et al.*[41]). The first neurochemical studies of suicide completers involved the measurement of monoamines and their metabolites in brain tissue. Similar to the majority of studies showing low CSF 5-HIAA in attempters, brain stem levels of 5-HT and 5-HIAA are also reduced in most studies of suicide victims. Paralleling the CSF 5-HIAA findings in attempters, this reduction in brain stem 5-HT and in 5-HIAA is independent of psychiatric diagnosis, occurring in suicide attempters in several diagnostic groups (major depression, schizophrenia, personality disorders, and alcoholism). Postmortem brain stem measurements of 5-HT and 5-HIAA are difficult to interpret because of lack of stability after death, anatomical heterogeneity, and uncertainty about the mechanisms (synthesis, transport, catabolism) accounting for brain levels. Investigators have therefore turned their attention to measurement of postsynaptic receptors or transporter sites in discrete brain regions of suicide victims (Kleinman (Bachus *et al.*), Stockmeier, Ordway, Rajkowska, and Arango *et al.*, this volume). These postmortem studies will provide the necessary information for the eventual application to *in vivo* imaging studies in suicide attempters and at-risk individuals.

CLINICAL THERAPEUTICS

The earliest treatment approaches to suicide were based on the dominant views of the origin and causes of suicide rather than strict empirical evidence. These views are embodied in sociologic, psychologic, and psychosocial theories, and with minor modifications they could also be generalized to other forms of psychopathology. The sociological treatment approach targets the individual's response to the social milieu. One of the earliest psychological treatment approaches had a psychodynamic emphasis concentrating on intrapsychic conflicts where suicide is "aggression turned inward." Other psychotherapeutic approaches have enlarged the possible internal dynamics that predispose to suicide and have also addressed an interpersonal component. The psychosocial treatment approach recognizes the importance of the individual and the social milieu, and emphasizes inner conflict as well as situational stresses, such as physical illness or disturbed interpersonal relations. Treatment inter-

ventions derived from these views have been limited in their effectiveness and do not seem to be very helpful in the prevention of suicide.

More modern strategies for the treatment of suicide come from the psychiatric, neurobiologic/clinical psychopharmacological and cognitive-behavioral fields (see Fawcett *et al.*, Linehan, Montgomery, and Tondo *et al.*, this volume). The ideal focus should be primary prevention, and interventions should be multidisciplinary. Treatment of suicidal patients is based on an understanding of the risk factors for suicide, a set of general management principles for suicidal patients, and the treatment of the associated psychiatric disorder. Specific treatment is directed at the underlying psychiatric disorder responsible for suicidal symptomatology. With the explosion of knowledge on the neurobiologic substrates underlying psychopathology, a neurobiological perspective can improve identification of suicidal persons and hence offers promise for new prevention strategies. The development of more novel pharmacotherapeutic approaches for suicidal patients depends, at least in part, on advances in clinical neuroscience to determine the neurobiological mechanisms underlying the threshold for suicidal behavior. Based on neurobiological abnormalities, there may be a suicidal subgroup of patients with a serotonergic deficiency in whom serotonergic enhancement may be most beneficial. Preclinical basic research models relevant to suicide may one day also inform treatment research to the extent that they assist in uncovering mechanisms underlying suicide.

In the past decade, increasing attention has been paid to cognitive factors that may contribute to suicidal behavior. The impetus for examining the role of cognitive processing in suicide has come largely from the paradigm shift in behavior therapy to the cognitive domain and, indirectly, from research on cognitive aspects of depression and suicide. Cognitive therapy, developed as a result of empirical investigations with depressed patients, has received attention because of its demonstrated efficacy in the treatment of unipolar depression. Beck and colleagues[42] have shown an association of hopelessness and impaired problem solving in suicidal patients that may have been sensitive to cognitive therapy.

One caveat that must be kept in mind is that there is no single reason why individuals commit suicide, and suicide is the outcome of multiple influences that bear on it. Therefore, a single treatment approach may be effective often, but sometimes a combination of treatments that matches the individual needs to be employed. Additionally, other avenues of study are also relevant to suicide treatment research. In the future, designing treatments for the specific susceptibility to suicidal acts, apart from the associated psychiatric illness, may represent an important approach. There has been some interest in ameliorating the conditions that theoretically would predispose an individual to suicidal behavior by attempting to reduce suicidal ideation. In a similar way, it would be useful to design treatment modalities that might specifically address how to reduce

impulsive-aggressive behavior and other high-risk personality traits. Drug development research aimed at the design of specific antisuicidal agents is similar to the strategy of developing "serenics," a new category of specific antiaggressive drugs based on 5-HT agonist activity.

By and large, there has been little progress in the development of effective treatments for suicidal behavior, at least relative to the advances that have occurred in the therapeutics of mood disorders and other major psychiatric disorders. This is due, at least in part, to the belief that it is ethically unsound to include a suicidal patient in a randomized trial that might require withholding treatment. The consequence associated with this practice of excluding suicidal patients from clinical treatment trials is a lack of data on this group and is discussed elsewhere in this volume (Linehan). Another factor that has hindered suicide treatment research is the absence of a sensitive and specific predictor of suicide that allows identification of a high-risk group. This state of affairs represents a strong rationale for many of the neurobiological studies presented in greater detail in this volume.

An important theme underlying current suicide research is that suicide risk factors are drawn from multiple domains (demographic, social, psychological, developmental, psychiatric, genetic, and biologic) demanding a multidisciplinary approach for their study. Close collaboration of basic and clinical scientists is required for the development of the most promising preclinical models to guide clinical investigations, identification of specific neurobiologic abnormalities in suicidal patients, and the translation of these findings into clinically useful applications.

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