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A Unified Biosocial Theory of Personality and its Role in the Development of Anxiety States

C. Robert Cloninger

From Department of Psychiatry and Genetics, Washington University School of Medicine and Jewish Hospital, 216 So. Kingshighway Blvd, St. Louis, MO 63110, U.S.A.

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Summary

A general theory of heritable personality traits and their neurobiological basis is described. Three independent dimensions of personality are defined and related to heritable variation in patterns of response to specific types of environmental stimuli: *(1)* 'novelty seeking' is due to a heritable tendency toward frequent exploratory activity and intense excitement in response to novel stimuli; *(2)* 'harm avoidance' is due to a heritable tendency to respond intensely to aversive stimuli and to learn to avoid punishment, novelty, and non-reward passively; and *(3)* 'reward dependence' is due to a heritable tendency to respond intensely to reward and succorance and to learn to maintain rewarded behavior. Evidence suggests that variation in each dimension is strongly correlated with activity in a specific central monoaminergic pathway: novelty seeking with low basal dopaminergic activity, harm avoidance with high serotonergic activity, and reward dependence with low basal noradrenergic activity. These neurobiological dimensions interact to give rise to integrated patterns of differential responses to punishment, reward, and novelty. The combination of high novelty seeking, high reward dependence, and low harm avoidance (histrionic personality) or the combination of high harm avoidance, low reward dependence, and low novelty seeking (obsessional personality) are each associated with information-processing patterns that lead to unreliable discrimination of safe and dangerous situations and hence to chronic anxiety. In individuals with high novelty seeking, chronic anxiety is characterized by global uneasiness or alarm without specific premonitory cues, frequent bodily pains due to low pain and sensation thresholds, low sedation threshold, and slow fatigability. In contrast, in individuals with high harm avoidance, chronic anxiety is characterized by frequent anticipatory worries based on specific cues, high pain and sedation thresholds, and easy fatigability. In response to frustrative non-reward, individuals with high reward dependence are susceptible to compensatory noradrenergic hyperactivity and hence acute or recurrent states of agitated dysphoria associated with reward-seeking behaviors such as overeating and increased sexual activity. Specific predictions are made about normal personality development as well as the development and familial aggregation of anxiety, somatoform, depressive and personality disorders. These predictions are compared with available information, and recommendations are made for future research.

Recent progress in our knowledge of the pathogenesis and phenomenology of chronic anxiety states has been extensive but poorly integrated. Multiple syndromes of chronic anxiety have been distinguished that are associated with differences in clinical symptoms, personality traits, pharmacological treatments, and family history[1, 2]. Clinical and longitudinal studies have revealed important information about the developmental course of these disorders[3, 4, 5]. Family, twin, and adoption studies have shown that these disorders are relatively distinct in terms of both genetic and environmental antecedents[1–11]. Advances in cognitive psychology and psychophysiology have revealed differences in information processing, conditioning responses, and other aspects of learning in individuals with these syndromes and related personality traits[12]. Likewise pharmacological treatments have been developed that show relative specificity for different syndromes and hence some clues to their underlying neurochemical basis[13]. Despite the progress in these individual fields, there has been little integration of the findings in terms of a unified theory that accounts for both neurobiological and psychosocial processes[14].

In order to understand the complex pathway from genotype to phenotype in various environmental milieux, we must specify developmental or epigenetic models that integrate the findings of clinical and genetic studies with work on intervening physiological and cognitive processes and on pharmacological treatment. In this article I will describe a tentative synthesis of available information for the two syndromes of chronic anxiety designated as 'cognitive anxiety' and 'somatic anxiety'[2]. These chronic anxiety syndromes are distinguished from panic disorder and other states of acute or recurrent reactive dysphoria. The syndromes of cognitive anxiety and somatic anxiety are prototypes of the 'anxiety disorders' and 'somatoform disorders' in the third edition of the Diagnostic and Statistical Manual (DSM-III) of the American Psychiatric Association[15]. These syndromes are each associated with chronic or recurrent anxiety leading to extensive health care utilization and disability. However, they differ in associated personality traits, information processing, conditioning responses to punishment and reward, psychophysiological characteristics, and responses to psychoactive drugs. Accordingly a comprehensive etiological model of anxiety must account for the development of psychological distress and disability in each condition and must include a general theory of personality.

In this article I will begin by describing the two chronic anxiety syndromes and then outline an ethological perspective on the role of genetic predisposition and learning in the adaptive responses of organisms to danger and novelty. Next I will describe how individual differences in information processing patterns influence the ability to discriminate safe from dangerous situations and hence susceptibility to chronic anxiety. Then I review available information about the neurobiological basis of these information processing patterns and develop an explicit model that accounts for observed genetic and environmental influences on individual differences in personality

and learning patterns. Reactive dysphoria is defined and distinguished from panic disorder and from other forms of agitated depression. Next a developmental theory of personality is described that is testable in terms of predictions about the longitudinal course of personality change with experience and in terms of associations among personality traits, anxiety, somatization, and depression both within individuals and within families. The predictions are compared to available information and recommendations are made for future research to test and extend the theory.

Two Syndromes of Chronic Anxiety

Factor and cluster analyses of signs and symptoms of anxiety have consistently identified two distinct syndromes or sets of features that tend to occur together in the general population and in psychiatric patients[2, 16]. These syndromes are often called 'cognitive anxiety' and 'somatic anxiety' due to the relative prominence of psychological and physiological disturbances. These two syndromes have been demonstrated repeatedly by ratings of anxiety and somatization in psychiatric patients in the United States, England, France, and Sweden[16–20], college students with test anxiety[21], and psychology clients and normal controls[22, 23]. 'Cognitive or psychic anxiety' refers to anticipatory apprehension, ruminative worrying, social anxiety and insecurity, difficulty in muscular relaxation, and slow recuperation after stress or illness. In contrast, 'somatic anxiety' refers to diverse bodily aches, pains, and frequent autonomic disturbances together with distractibility and a global feeling of alarm and uneasiness that is not associated with specific precipitants or premonitory cues. Several distinguishing features are summarized in Table 1.

These names are somewhat misleading because each group of patients is characterized by both psychological and physical complaints. Complaints of nervousness and cardiorespiratory symptoms are frequent in both syndromes, as shown in studies of anxiety neurosis[13, 24] and somatization disorder or Briquet's syndrome[25]. However, patients with somatic anxiety manifest prominent and diverse bodily pains whereas the physical complaints of patients with cognitive anxiety involve fatigue, muscle tension, and slow recuperation from minor illness[2]. The psychological distress of patients with 'cognitive anxiety' involves avoidance of novelty and anticipation of harm contingent on specific warning signals. In contrast, the psychological distress of patients with 'somatic anxiety' involves a vague feeling of alarm and global uneasiness without specific premonitory cues. Somatic anxiety is also often associated with novelty seeking and impulsive action rather than activity that is inhibited by apprehensive reflection and novelty avoidance[16, 26].

Jung[27] first noted that two groups of patients with chronic anxiety could be distinguished by their associated personality traits of introversion and extraversion. Schalling developed separate rating scales for somatic and cognitive anxiety to test

Table 1. Distinguishing Features of Two Chronic Anxiety Syndromes

Characteristic Feature	*Type of Syndrome*	
	Cognitive Anxiety	*Somatic Anxiety*
Anticipation of harm from specific cues	Frequent (anticipatory worry)	Infrequent (global alarm)
Fatigability	Rapid	Slow
Muscular Relaxability	Slow	Rapid
Novelty-seeking	Low	High
Pain Sensitivity	Low	High
Sedation Threshold	High	Low

this. Ratings of somatic and cognitive anxiety were substantially correlated (shared variance of about 40 per cent), but each was associated with different personality traits as predicted by theories of Jung[27] and Eysenck[28]. Somatic anxiety was positively correlated with impulsivity ($r = 0{\cdot}4$) and other scales associated with criminality and antisocial behavior. In contrast, cognitive anxiety was negatively correlated with sociability, impulsivity, and other scales associated with criminality. More recently, in the Stockholm Adoption Study a positive genetic association between somatic anxiety and criminality has been demonstrated in biological relatives separated by adoption in infancy in both women[10] and men[29]. In contrast a negative genetic relationship was observed between cognitive anxiety and criminality: adopted men with cognitive anxiety have significantly fewer biological relatives with criminality than other adoptees[29].

As expected from their differences in personality traits, patients with these two syndromes differ in their patterns of information processing, learning, drug responses. Cognitive anxiety is prominent in patients with anxiety disorders and neurotic depressions who have a high threshold for sedation and a low tolerance for stimulants or physiological stress[28–32]. In contrast, patients with high somatic anxiety tend to have low pain and sensation thresholds[33], low sedation thresholds and improved performance on some perceptual tasks in response to stimulants or novelty[28–32]. Individuals with high cognitive anxiety learn to avoid aversive stimuli passively more readily than others, but do not learn to maintain rewarded behavior more easily[34]. The anxiolytic effects of benzodiazepines in humans are highly correlated with their ability to diminish conditioned avoidance in animal species from bony fishes to man[34, 35]. Benzodiazepines are an effective pharmacological treatment for prominent cognitive anxiety[36]. Catecholaminergic drugs, such as stimulants and monoamine oxidase inhibitors may be useful in the pharmacological treatment of high somatic anxiety, but benzodiazepines have little long-term benefit[37–39]. These differences are striking and

suggest that it may be important to consider the adaptive function of avoidance learning and its role in the pathogenesis of anxiety.

Defensive Responses to Danger and Novelty

Nearly all animals from lower invertebrates to man inherit a tendency to be alerted and frightened by sudden and strong stimuli such as loud noises, bright lights, or unfamiliar objects. However, all animals have fixed limits to the amount of information they can process at any time so significant stimuli must be filtered out from irrelevant stimuli for an organism to function successfully. If an animal reacts unselectively to all harmless stimuli, then other more significant stimuli cannot receive the intensity of response that they may require. Consequently animals have evolved so that they habituate to harmless stimuli in a way that is generally adaptive[40, 41].

Habituation is learning to disregard stimuli that are without significance to an animal, that is, neutral stimuli that are not associated with either punishment or reward. This benefits the organism by screening out 'noise' and focusing attention on more critical variables. It is often regarded as the simplest form of learning and as a fundamental property of nearly all life forms. The potential for habituation is highly specific, depending on both the individual's genetic predisposition and the stimulus. For example, if a non-domesticated animal is repeatedly exposed to a potentially harmful stimulus (such as a predator) without being harmed, habituation does not readily occur and, depending on the psychological system measured, may never habituate. Responses to dangerous stimuli are often likely to have a genetically determined resistance to habituation because of the evolutionary advantage of such mechanisms for survival and reproduction, as first noted by Darwin[42].

Resistance to habituation is seen in the genetic preparedness of man to develop avoidance responses and fear of particular stimuli such as snakes and thunderstorms. Many anxiety-prone individuals are observed to have a reduced tendency for some physiological responses (*e.g.*, responses measured by galvanic skin conductance) to habituate to repeated stimuli[43]. Poor habituation of galvanic skin responses is characteristic of patients with chronic anxiety, whether this is cognitive anxiety or somatic anxiety (as in Briquet's syndrome)[44]. Also normal subjects who are made anxious by threat of shock or by impending examinations show delayed habituation of their galvanic skin responses. This results in their maintaining a high level of perceptual sensitivity.

Vigilance is defined as a state of readiness to respond to critical external or internal events[45]. Vigilance plays a vital role in maintaining safety and is fundamental to survival. Vigilance and habituation are inversely related: resistance to habituation leads to a state of vigilance or high perceptual sensitivity. Sweat gland responses of students habituate more slowly to stimuli with a high phobic potential in man, such as

pictures of snakes and spiders, than to neutral stimuli, such as pictures of houses[46]. When an electric shock preceeded exposure to pictures of snakes, conditioned sweat gland responses were acquired after a single trial and extinguished slowly. High vigilance and resistance to habituation, as seen in many anxiety-prone individuals, is associated with rapid and strong passive avoidance learning.

Avoidance Learning and Anticipatory Anxiety

Freud[47] and Pavlov[48] noted that inborn defensive responses can be modified by experience. Each independently recognized that the ability to predict the future occurrence of dangerous situations from warning signals would be biologically adaptive. Pavlov carried out classical associative learning experiments in which neutral stimuli predicted aversive stimuli, and found that animals could be conditioned so that defensive responses were elicited by the previously neutral cues. Such classical conditioning has been demonstrated in a wide variety of animals from lower invertebrates to man. In higher vertebrates, total decortication does not impair classical conditioning, which is thought to involve changes primarily in the brain stem and limbic system. These parts of the brain are much the same in man as in lower vertebrates that first appeared 300 to 500 million years ago.

Aversive conditioning paradigms have been suggested as a model for acute anticipatory anxiety[28, 49–51]. In people with acute anticipatory anxiety, a specific premonitory signal or cue is thought to predict the occurrence of punishment, danger, or frustrative non-reward. This is analogous to aversive conditioning paradigms in which neutral (conditioned) stimuli predict aversive (unconditioned) stimuli[49]. Thus aversive conditioning paradigms are a model for the acquisition of fears.

In sea snails, Kandel and associates have shown that classical associative learning leads to pre-synaptic facilitation of the amount of neurotransmitter released in specific sensory neurons in response to the conditioned stimulus. Such work begins to specify the underlying cellular and molecular events associated with associative learning, but others have questioned the relevance of associative learning in invertebrates to humans because of the massive influence of the neocortex on information processing and related difficulty in controlling the significance and salience of stimuli in conditioning trials. These neocortical influences will be considered later.

In any case, such anticipatory anxiety is usually transient or acute and is specific for particular situations. It cannot readily serve as a model for chronic anxiety in which there is persistent tension that is not consistently associated with actual danger.

Sensitization and Chronic Anxiety

Sensitization is an elementary form of nonassociative learning in which an animal

learns to strengthen its defensive reactions and to respond defensively to other previously neutral stimuli after exposure to unpredictable aversive stimuli[40]. Exposure to repeated and unpredictable aversive stimuli leads to sensitization, that is, the enhancement or facilitation of the reactions to unidentifiable threat. Sensitization leads to the disinhibition of habituated responses and to the enhancement of non-habituated responses[49], and slows habituation in subsequent conditioning. Kandel and his associates found in sea snails that long-term sensitization led to pre-synaptic facilitation of the amount of neurotransmitter released at synaptic terminals of sensory neurons. Related structural changes also occur with sensitization: the incidence and size of active zones of varicosities at pre-synaptic axon terminals are increased in sensitized animals[52].

Sensitization may be analogous to chronic 'free-floating' anxiety in humans in which feelings of tension and nervousness cannot be related to obvious external threats[49]. Repeated exposure to an aversive stimulus *with* a warning signal or cue leads to acute anticipatory anxiety in response to the cue, whereas repeated exposure to an aversive stimulus *without* a warning stimulus leads to long-term sensitization or chronic anxiety.

Seligman has noted that when aversive events are unpredictable, safety is also unpredictable. In the absence of a safety signal, most vertebrate animals including man remain in a state of chronic anxiety[50].

The unpredictability of aversive stimuli or the unreliability of warning signals can arise in either of two general ways. First, premonitory signals are not present or cannot be reliably recognized by the threatened individual. Second, premonitory signals are ever present or the individual remains highly vigilant (*i.e.*, sensitive in perceiving and predicting danger) even though danger is actually rare. Either extreme hypovigilance or extreme hypervigilance leads to unreliable assessment of risk such that an individual cannot identify safe situations accurately.

Individuals with chronic cognitive anxiety have an 'obsessional' information processing style characterized by hypervigilance and extreme sensitivity in recognizing contingent relationships and perceiving potential danger[52]. In contrast, individuals with chronic somatic anxiety have a 'histrionic' or 'hysterical' information processing pattern characterized by hypovigilance, distractibility, difficulty recognizing temporal or contingent relationships, and difficulty distinguishing targeted from non-targeted stimuli[11, 53–55]. Several distinguishing characteristics of these information processing patterns are summarized in Table 2.

These two different cognitive patterns represent two general ways that information processing can lead to unreliable discrimination of safety and threat, and hence to chronic anxiety. This is summarized in Figure 1.

Novel stimuli elicit orienting responses in which the individual becomes more alert and vigilant. Individuals with histrionic cognitive patterns tend to seek novelty, which

Table 2. Distinguishing Features of Two Patterns of Information Processing

Perceptual Characteristic	*Information-Processing Pattern*	
	Obsessional	*Histrionic*
Distractibility	Low	High
Attention to detail	High	Low
Sensitivity/vigilance	High	Low
Speed and Accuracy	High	Low
Intensity Reactance*	Reducing	Augmenting
Integrating/Organizing	Good	Poor
Decision making	Analytical	Intuitive

*Tendency to augment or reduce the perceived intensity of incoming sensory signals with increasing stimulus intensity.

is adaptive for them by increasing vigilance and perceptual sensitivity[56]. Individuals with obsessional cognitive patterns tend to avoid novelty because exposure to unfamiliar settings and stimuli is maladaptive for them. They seek routine familiar ritualized behavior, which is adaptive for them by reducing vigilance. Hypervigilant information processing is associated with easy fatigability (or subvalidity in Sjöbring's terminology[59]).

In addition to perceptual sensitivity, another aspect of vigilance that may influence the behavioral expression of anxiety is the mechanism by which response criteria are set or shifted. Individuals may be equal in their ability to distinguish targeted from non-targeted stimuli but differ in their willingness to report or accept their judgment of

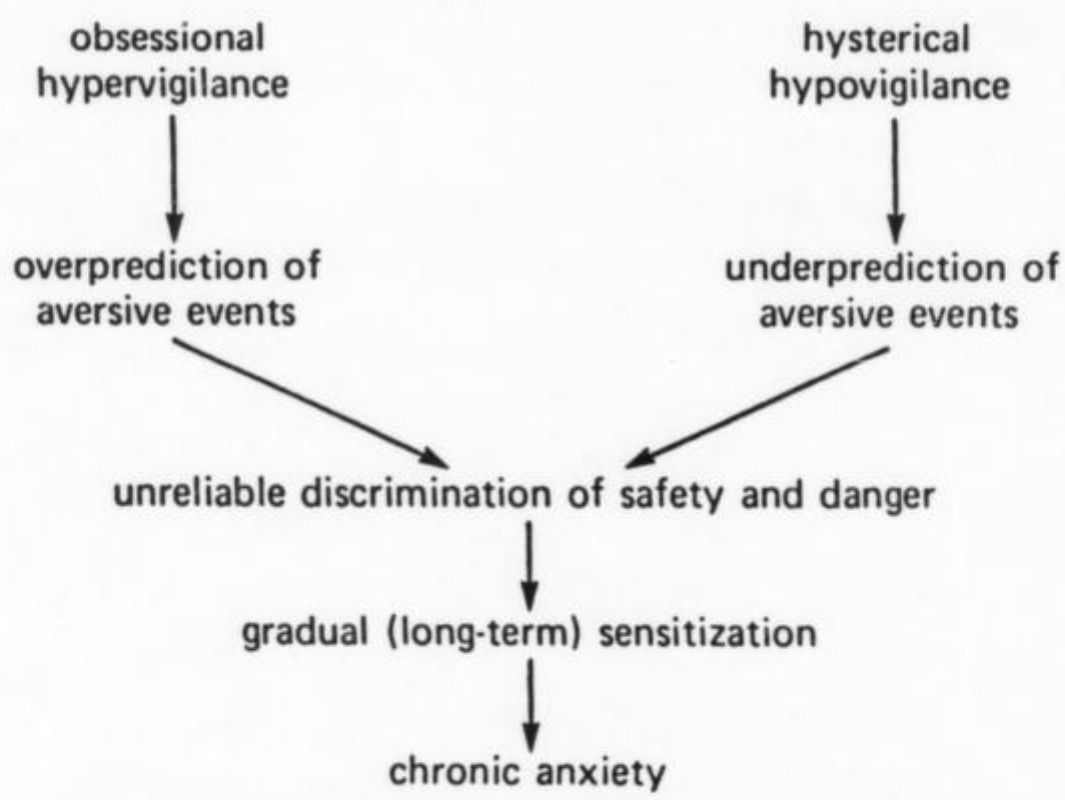

Fig. 1. Information processing and chronic anxiety

that perception. A prominent characteristic of individuals with obsessive-compulsive disorders whom I have treated is that they cannot accept uncertainty. In other words, they are not only hypervigilant but also have a nearly perfect response criterion. In my patients this has often led to rumination and checking behaviors or rituals in an attempt to assure certainty[cf 34]. However, such perceptual characteristics have not been studied systematically with objective tests in clinical samples, and such work is needed before any conclusions can be drawn.

Individuals with chronic anxiety, as measured by high neuroticism scores, were found by Eysenck to have either high or low intelligence. Individuals with average intelligence were under-represented among those with chronic anxiety when intelligence was measured by progressive matrices tests[60]. Eysenck suggested that the progressive matrices tests he used measured skill in perceptual integration rather than efficiency, which may be consistently reduced by increased anxiety. Slater found that obsessional neurotics had higher intelligence than the general population[61] whereas most neurotics had lower intelligence than average[62]. More recently Schalling and associates[16] found that somatic anxiety is associated with low intelligence but not high intelligence, as expected if low perceptual sensitivity contributes to somatic anxiety. Schalling found that somatic complaints and somatic anxiety were strongly negatively correlated with intelligence (−0·4). In contrast, the partial correlation of intelligence with cognitive anxiety when somatic anxiety is held constant is very weakly positive (+0·07) even in tests that may be influenced by reduced efficiency of anxious subjects[16]. These findings support the idea that extreme differences in information processing predispose to chronic anxiety states. However, since personality and perceptual characteristics are themselves correlated, it is uncertain how much intelligence itself contributes after personality characteristics are taken into account.

Sensitization leads to slowed habituation, and chronic anxiety is associated with slowed habituation of some physiological responses whether cognitive or somatic features are prominent[43, 44, 63]. Habituation is slowed in normals made acutely anxious also[63], but it is normal in acute hysteria. This complicates the use of habituation as an index of trait anxiety because habituation is not a fixed or stable trait.

Neurobiological Basis of Cognitive Patterns

Biological Basis of Personality Trait Models

Psychometric studies of personality dimensions by Eysenck and others have consistently included two major dimensions that Eysenck[28] labels neuroticism-stability and introversion-extraversion. More recently it has been demonstrated that there is a third major dimension that is substantially heritable, as well as other variables determined by social learning. The labelling and content of the heritable dimensions is

uncertain, but the existence of three independent dimensions is clearly supported in studies using a wide variety of instruments and theoretical constructs[59, 64–68]. Here I will use neurobiological and genetic studies to help define the genetic structure of the putative trivariate system underlying observed personality variation because the phenotype structure of existing scales do not correspond well to the underlying biogenetic variation[64]. First I will begin with the two phenotypic dimensions that have been most intensely studied: neuroticism-stability and introversion-extraversion.

According to Eysenck's phenotypic model, variation along each of these two dimensions is statistically uncorrelated. However, Gray[34] has pointed out that the effects of anti-anxiety drugs (benzodiazepines, barbiturates, alcohol) and lesions to the prefrontal and cingulate cortex reduce anxiety and increase sociability. This implies that the anti-anxiety treatments consistently have two combined but independent effects on neuroticism and introversion in Eysenck's model. Gray suggests that these biological findings indicate a need to rotate the axes in Eysenck's model to its diagonals, yielding two dimensions that he calls 'anxiety' and 'impulsivity'. Gray suggests that his 'anxiety' dimension reflects variation in a central behavioral inhibition system, which maintains passive avoidant behavior in response to punishment, non-reward, and novelty. The impulsivity dimension is thought to reflect variation in a central behavioral activation system.

Gray's model implies that individuals who are high on either or both of these two dimensions will be susceptible to chronic anxiety (that is, neurotic or unstable in Eysenck's model). Perhaps a more appropriate name for Gray's dimension of anxiety is 'harm avoidance' because his references to anxiety are only appropriate for cognitive, but not somatic, anxiety. It is postulated here that 'harm avoidance' involves a heritable neurobiological tendency to learn to avoid punishment, non-reward, and novelty. Also it will be shown later that individuals who are low in harm avoidance may at times be sociable but are also prone to harmful behavior, including suicidal and aggressive action.

Likewise a more informative name for the dimension of 'impulsivity' is 'novelty seeking' because it indicates the nature of the motivation along this dimension that is suggested in available knowledge of the central 'incentive' and 'reward' system and studies of impulsive individuals that will be considered later. Individuals high in novelty seeking are often active, exploratory, and intensely attracted to novelty and unfamiliar stimuli. Their reaction to novel, unfamiliar stimuli is intense excitement, which can lead to feelings of exhilaration, explosive outbursts, or overstimulation depending on other personality factors and circumstances. Also the name 'novelty seeking' makes clear that biogenetic variation along this dimension exists in a negative feedback relationship with the 'harm avoidance' dimension, so that in the presence of environmental variability the dynamic interaction of the two dimensions leads to observed variability with the phenotype factor structure described by Eysenck.

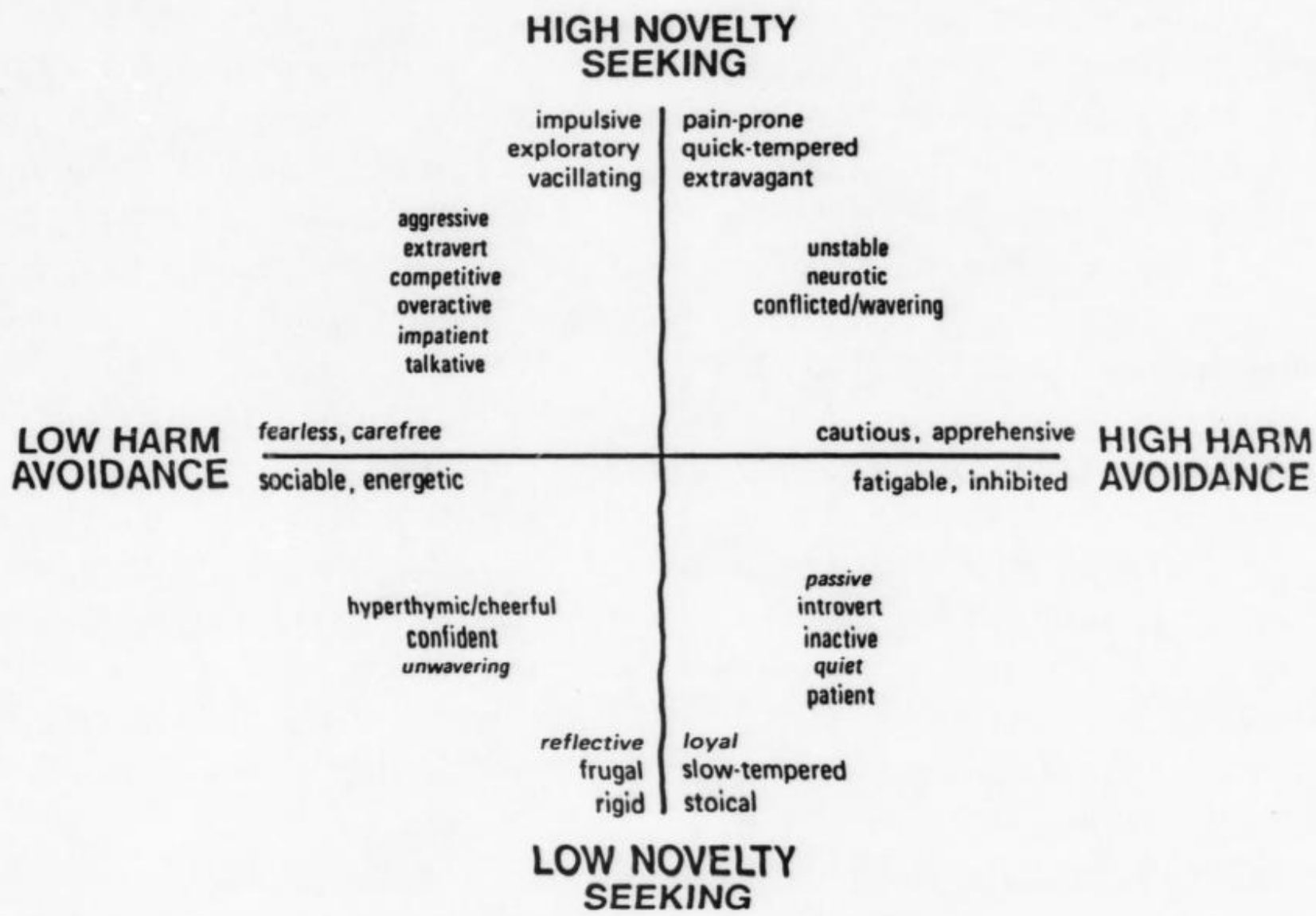

Fig. 2. Interaction of two personality dimensions: harm avoidance and novelty seeking

The two dimensions that are most directly involved in susceptibility to chronic anxiety, 'harm avoidance' and 'novelty seeking', are depicted in Figure 2. The full model and its hypothesized neuroanatomical and neurohumoral basis is considered later in this section. As shown in Figure 2, the harm avoidance dimension varies from extremes of 'inhibited apprehension' (cognitive anxiety or high harm avoidance) to 'carefree sociability' (low harm avoidance). The novelty-seeking dimension varies from extremes of 'pain-prone impulsivity' (high novelty seeking) to 'stoical reflection' (low novelty seeking).

Genetic studies also indicate that extraversion has two distinct components with independent genetic antecedents. These components correspond to the dimensions proposed here: sociability and impulsivity. Eaves and Eysenck[69] carried out a quantitative genetic analysis of twin data about extraversion and found that both genetic and environmental factors contributed substantially to variation in extraversion and its two components sociability and impulsivity. Impulsivity and sociability were found to have genetic antecedents that were largely independent ($r = 0{\cdot}42$), but social and environmental antecedents were largely correlated ($r = 0{\cdot}66$), leading to observed variation with a fairly unitary phenotypic structure. The 9-item measure of impulsivity was dominated by 6 items related to novelty seeking but

included 3 items that appear related to harm avoidance (carefree, careful planning, slow and unhurried), which may account for the partial genetic overlap with sociability (low harm avoidance). This supports the hypothesis presented here that harm avoidance and novelty seeking are genetically independent but that negative feedback interaction will lead to a single phenotypic factor because of the reciprocal effects of novel environmental stimuli. Hence both biological and genetical studies indicate that congenital predisposition to observed variation in temperament or personality varies along the independent dimensions of harm avoidance and novelty seeking illustrated in Figure 2.

In addition, factor analytic studies indicate that there is a third dimension that is independent of harm avoidance and novelty seeking (or extraversion and neuroticism) and which shows substantial heritability[69–72]. In Figure 2 this dimension was assumed to be fixed at the general population average. The models of normal personality variation developed by Sjöbring and Eysenck both posit three dimensions in addition to intelligence. Sjöbring's dimensions of 'validity' and 'solidity' were meant to reflect genetic predisposition to dimensions which are descriptively similar to 'harm avoidance' and 'novelty seeking' respectively[59]. He calls the third dimension 'stability'. Highly 'stable' individuals are socially detached, independent, cool and calculating, low in empathy and sympathy for others, fixed in their own habits, and stable in mood. Furthermore, highly stable individuals are weakly affected by sensory stimulation, limited in their range of interests but are highly prepared, skilled, and attendant to details in what does interest them. They are characteristically analytical, precise, logical, and objective as well as mechanically adroit and physically agile. Individuals who are low in 'stability' are industrious, work hard to please others, are socially empathetic and sympathetic. They are imprecise observers, unobjective and intuitive, strongly affected by sensory stimulation, and often maladroit. According to Sjöbring, these tendencies make the substable individual susceptible to grief and dysthymic reactions when rewards such as social approval and supports that have been associated with the reinforced maintenance of behaviors are withdrawn. Substable individuals need continued rewards, social attachments and support more than do others, and become depressed when these attachments and supports are withdrawn.

Eysenck's third dimension, which he calls tough-mindedness or psychoticism, includes components of social detachment and sensation or novelty seeking. Neuroticism in Eysenck's system appears to include contributions from what Sjöbring calls subvalidity (high harm avoidance), subsolidity (high novelty seeking), and substability (high reward dependence). Hence Eysenck's third dimension of observed variability can be seen as the consequence of the negative feedback relationship between multiple genetically independent components postulated here and by Sjöbring[57]. The third dimension postulated here is called 'reward dependence' and is

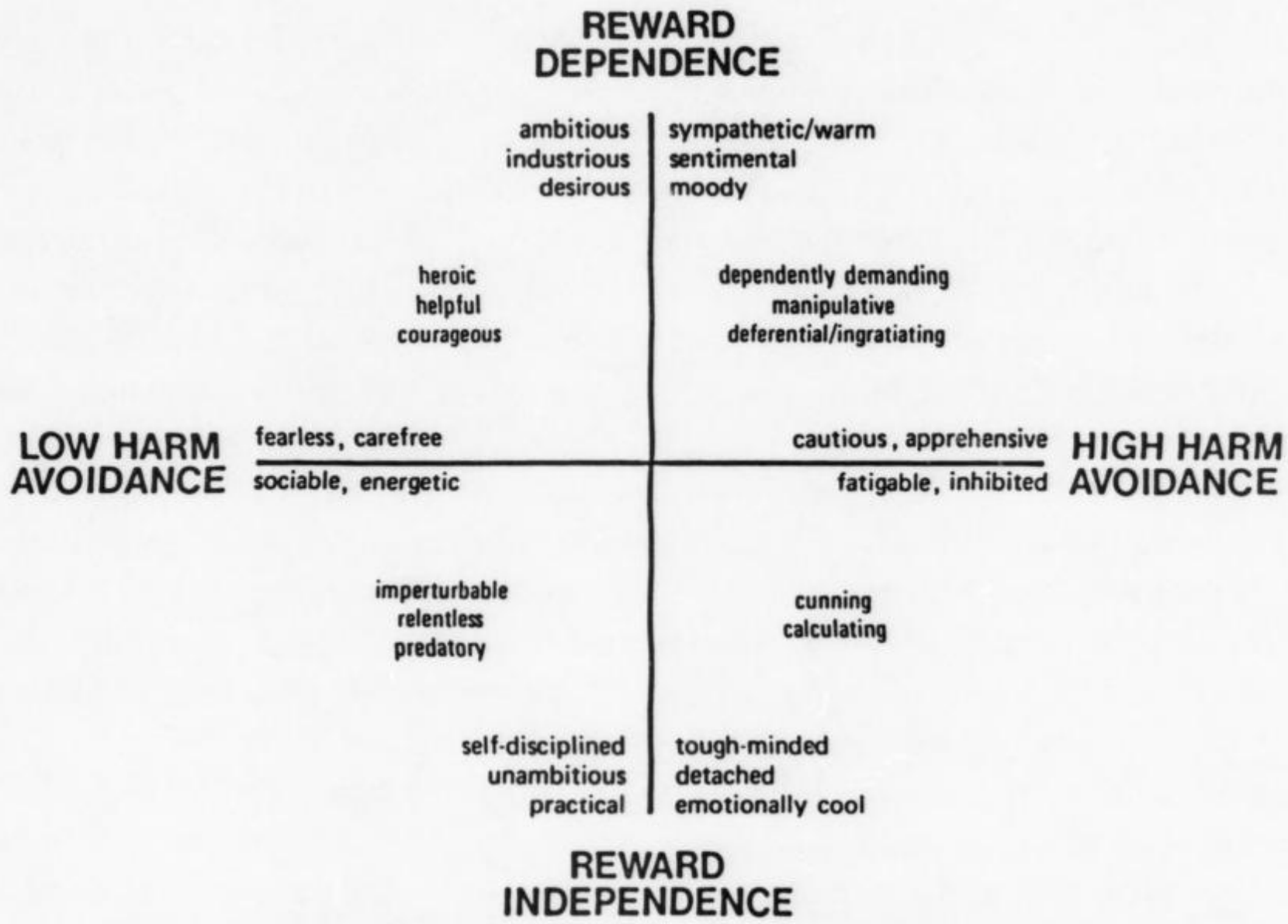

Fig. 3. Interaction of two personality dimensions: harm avoidance and reward dependence

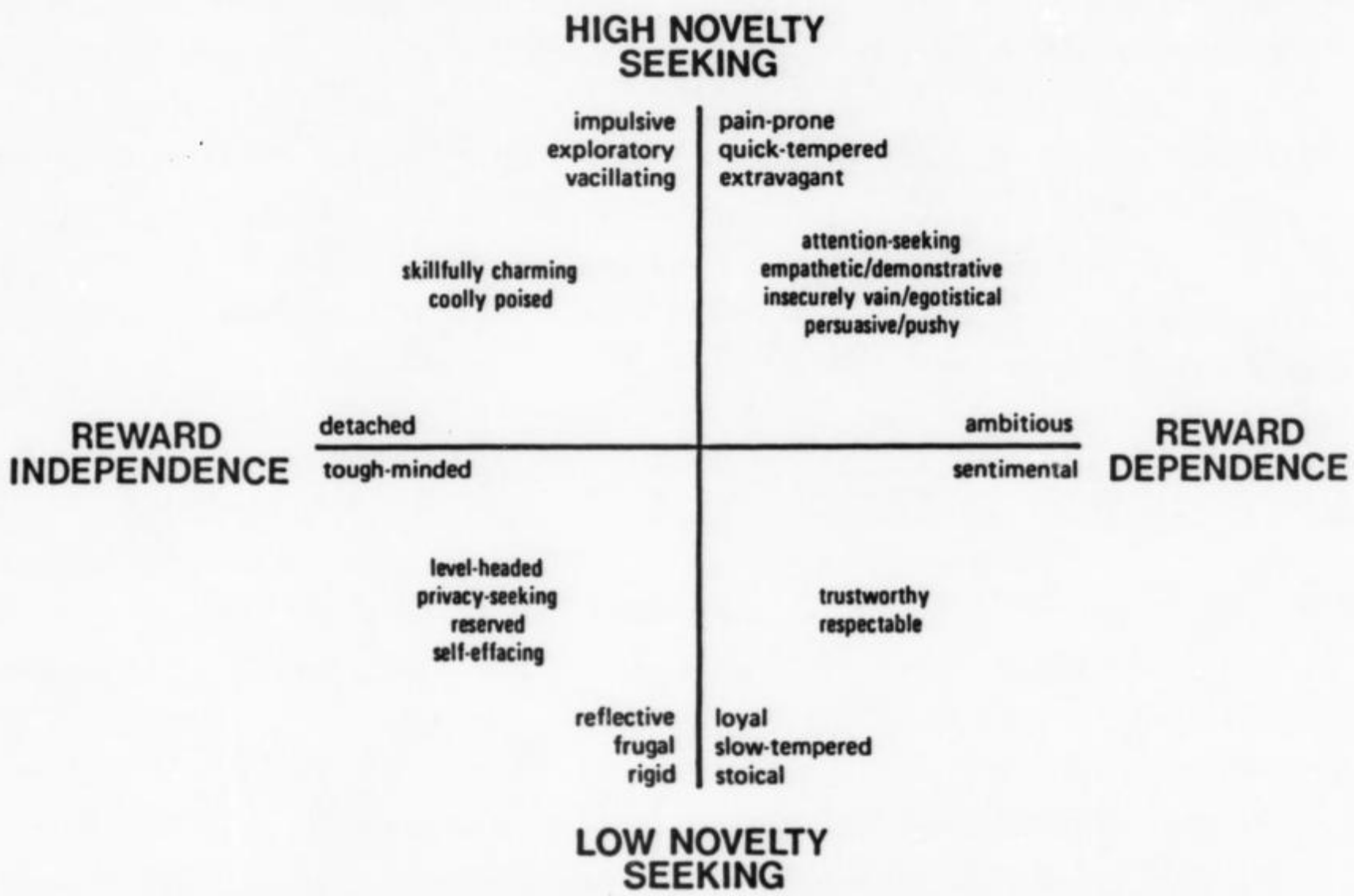

Fig. 4. Interaction of two personality dimensions: reward dependence and novelty seeking

postulated to involve a heritable neurobiological tendency to maintain behavior associated with reward and non-punishment. In man social recognition and approval are highly rewarding and so this dimension is similar to Sjöbring's concept of 'stability'. However, my clinical observations indicated that such individuals are strongly responsive to appetitive pleasures or rewards of all sorts, including food, affection, wealth, power, praise or fame and other things that acquire value as rewards and recognition by social learning. Furthermore, the theoretical basis for personality dimensions hypothesized by Sjöbring is totally different from the biosocial theory developed here.

Variation in 'reward dependence' and its interaction with the other two dimensions is described in Figures 3 and 4. Translations of Sjöbring's concept of stability have described individuals who are high in stability as 'abstract' and those who are low in stability as 'concrete', but these are misleading terms in my clinical experience. Barrett's results with the Marke-Nyman inventory of Sjöbring dimensions also showed that abstractness was poorly correlated with other items relevant to stability[70]. The name 'reward dependence' clarifies the fundamental variable in my clinical experience. Individuals who are reward independent are practical, tough-minded, analytical, shrewd, and realistic. In contrast, those who are reward dependent ('outer directed') are ambitious wishful thinkers, sentimental and impractical, intuitive dreamers who may be idealistic, ingratiating, manipulative or sympathetic depending on influence of other personality dimensions and what will satisfy their appetite for reward. Low reward dependence leads to independence and social detachment that is sometimes characterized as 'schizoid' personality in extreme cases. Individuals with high reward dependence respond intensely to rewards and succorance and seek such support constantly in order to maintain rewarded behavior. As a result they may appear narcissistic, insecure, and vulnerable.

Studies of the central nervous system of man indicate that there are specific neural pathways or networks involved in responses to punishment, reward, and novelty. Available data suggests that variation in each of the three personality dimensions defined here is strongly correlated to variation in one of the three specific monoaminergic pathways (dopaminergic, serotonergic, noradrenergic) in the central nervous system.

The Central 'Punishment'/Behavioral Inhibition System

Gray suggests that the behavioral inhibition system functions as a comparator, checking predicted against actual events, and then interrupting behavior when the unexpected is encountered. He suggests that this system primarily involves the limbic system, including the septo-hippocampal system, the Papez circuit, and the prefrontal cortex, as well as the ascending monoaminergic and cholinergic pathways which innervate these forebrain structures[34].

The importance of limbic structures has been supported by recent research on benzodiazepine receptors[73]. Specific high-affinity benzodiazepine receptors have been identified in the brains of all animal species phylogenetically superior to the shark. The highest densities of benzodiazepine receptors are found in cortical and limbic forebrain areas. There is an initial decrease in the number of benzodiazepine receptors in the cerebral cortex and hippocampus of rats following acute stress, and this is followed by a rebound increase that is most prominent in the hippocampus[74]. Rodents selectively bred for a high defecation score in a bright unfamiliar environment (an index of emotionality) have fewer benzodiazepine receptors in the hypothalamus and hippocampus than animals selected for a low defecation score[75, 76]. Also specific lesions of limbic structures reproduce most of the behavioral effects of benzodiazepines[73].

The affinity of different benzodiazepines for the receptor is highly correlated ($r = 0{\cdot}78$) with their ability to reduce inhibition of behavior suppressed by contingent punishment[77]. Stein has summarized extensive information that benzodiazepines disinhibit passive avoidance conditioning by GABA-ergic inhibition of the activity of serotonergic neurons originating in the dorsal raphe nuclei[35]. Ascending serotonergic projections from the dorsal raphe nuclei to the substantia nigra inhibit nigro-striatal dopaminergic neurons, and are essential for conditioned inhibition of activity by punishment and non-reward[78].

Accordingly it is postulated that harm avoidance is positively correlated with facility in passive avoidance learning and with turnover of serotonin and its metabolites in the brain and cerebrospinal fluid. Thus subjects who are highly predisposed to avoid harm (and hence are most susceptible to acute anticipatory anxiety and chronic cognitive anxiety) are supposed to learn passive avoidant responses readily and strongly and to have high basal levels of serotonergic activity in the behavioral inhibition system. In contrast, subjects who have a weak predisposition to avoid harm are supposed to be poor at passive avoidance learning and to have low levels of serotonergic activity in the behavioral inhibition system. This is directly supported by studies of the association between harm avoidant behavior and the cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid(5-HIAA), the major metabolite of serotonin. These are reviewed in detail later in this section.

The Central 'Incentive'/Behavioral Activation System

The discovery that local brain stimulation can have reward-like properties led to studies of sites associated with self-stimulation. Self-stimulation at the sites of dopaminergic neurons is rapid and accompanied by marked locomotor activation, whereas many brain areas such as cortex, thalamus, and cerebellum do not support self-stimulation[79]. Dopaminergic cell bodies in the ventral tegmentum have ascending projections to the striatum, nucleus accumbens, and frontal and limbic cortex.

Available data indicate that the dopaminergic pathways serve an 'incentive' function to activate exploration, pursuit, and approach to rewards and environmental stimuli associated with rewards[79]. Noradrenergic neurons from the locus coeruleus are supposed to be involved in reinforcement of rewarded behavior, rather than in the initial activation of approach or exploratory behavior. In relation to the model of personality traits proposed here, it is postulated that low basal dopaminergic activity would be associated with frequent exploratory activity and more intense responses to novel stimuli[80], but normal conditioning to punishment or reward[81]. In particular, it is postulated that novelty seeking is associated with low basal dopaminergic activity[82, 83]. Direct supporting findings are discussed later in this section along with a detailed review of central modulation of pain sensitivity.

Central 'Reward'/Behavioral Maintenance System

Noradrenergic neurons in the dorsal bundle arising from the locus coeruleus are believed to be involved in the maintenance of behavior by reward ('positive reinforcement') or non-punishment ('negative reinforcement')[79]. Ascending noradrenergic pathways arise from the locus coeruleus and project to limbic structures including the amygdala, septum, and hippocampus as well as cerebral cortex. This noradrenergic system is regulated by the alpha-2 pre-synaptic receptor in a negative feedback inhibition. Electrical stimulation of the locus coeruleus of monkeys induces a state of agitated dysphoria associated with self-grooming behavior[79]. A similar state is induced by administering alpha-2 adrenergic receptor antagonists such as yohimbine and by administering beta carboline, and these states of agitated dysphoria are also associated with increased plasma cortisol levels[84]. Similarly human depressives show more variability in indices of basal noradrenergic output, such as plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol (MHPG), and elevated cortisol levels compared to normals[85]. Clonidine, an alpha-2 adrenergic agonist, transiently relieves the dysphoria and decreases cortisol to normal levels; growth hormone, plasma MHPG, and heart rate responses to clonidine have been found reduced in depressives compared to controls, all suggesting reduced alpha-2 adrenergic responsiveness[85].

In contrast to these dysphoric states that are associated with a rise in plasma cortisol and intensification by imipramine pretreatment, panic attacks induced by lactate are not consistently associated with a rise in plasma cortisol and are blocked by imipramine pretreatment (DF Klein, personal communication, 1986). Panic attacks can be precipitated by lactate infusions in about 70 per cent of patients with panic disorder, but only rarely in normals or patients with other anxiety or somatoform disorders[86, 87]. The mechanism by which lactate infusion induces panic attacks in these patients is uncertain: the direct effects of lactate suggested by Pitts and McClure have been called into doubt by later work showing that panic attacks

could also be triggered by other means of inducing somatic symptoms of anxiety such as breathing in high CO_2 environment, strenuous exercise, or infusion of isoproterenol which does not cross the blood-brain barrier[87].

It is possible that these different treatments trigger panic attacks by conditioned phobic responses to particular physiological signals similar to those experienced in suffocation, but not all individuals appear to be equally susceptible to acquiring such responses. Furthermore, at least some patients have the abrupt onset of spontaneous panic attacks and only subsequently developed chronic anxiety as a consequence of sensitization by recurrent unpredictable panic attacks[13]. This suggests that panic attacks may involve defective regulatory mechanisms of vital functions that are independent of other mechanisms of harm avoidance. Klein suggests that these mechanisms are normally involved in the regulation of responses to asphyxia or separation, events that both require a sudden outcry and appeal for help[13].

Recent PET studies indicating asymmetric blood flow (left < right) to the parahippocampal gyrus support such a role for vigilance functions in the generation of panic attacks[88], and may eventually help clarify why some patients with chronic anxiety are more susceptible to panic attacks than others.

The susceptibility to conditioned maintenance of behavior appears to vary independently of susceptibility to panic attacks as well as of harm avoidance and novelty seeking. The name for variation in this third dimension of personality is called 'reward dependence' here in order to indicate the nature of the motivation along this dimension and its relation to conditioned learning responses. Individuals who are high in reward dependence form strong social attachments, are warmly sentimental, attempt to be pleasing and ingratiating, and have greater 'dependency' needs. Their ambition for rewards in the form of power, wealth, food, affection or recognition tends to be insatiable in extreme cases and so that they may be described as addicted or 'dependent' on rewards. In contrast, individuals who are low in reward dependence are independent, emotionally cool, and socially detached. It is postulated that individuals who are highly reward dependent are more strongly influenced by positive and negative reinforcement, *i.e.* they are generally more susceptible to conditioning that is contingent on reward or non-punishment. Hence it is postulated that fixedness in reward-seeking behavior is negatively correlated with variation in basal noradrenergic activity in the central reward system. In other words, low basal noradrenergic activity is associated with more intense responses to rewards and hence better maintenance (resistance to extinction) of rewarded behavior.

According to this model, in some individuals (specifically those with low basal noradrenergic activity and 'high reward dependence'), but not others (specifically those with high basal noradrenergic activity and 'low reward dependence'), reduction in rewards or approval leads to compensatory rebound activation of noradrenergic activity and hence to agitated dysphoria. This dimension is presumed to be relevant to

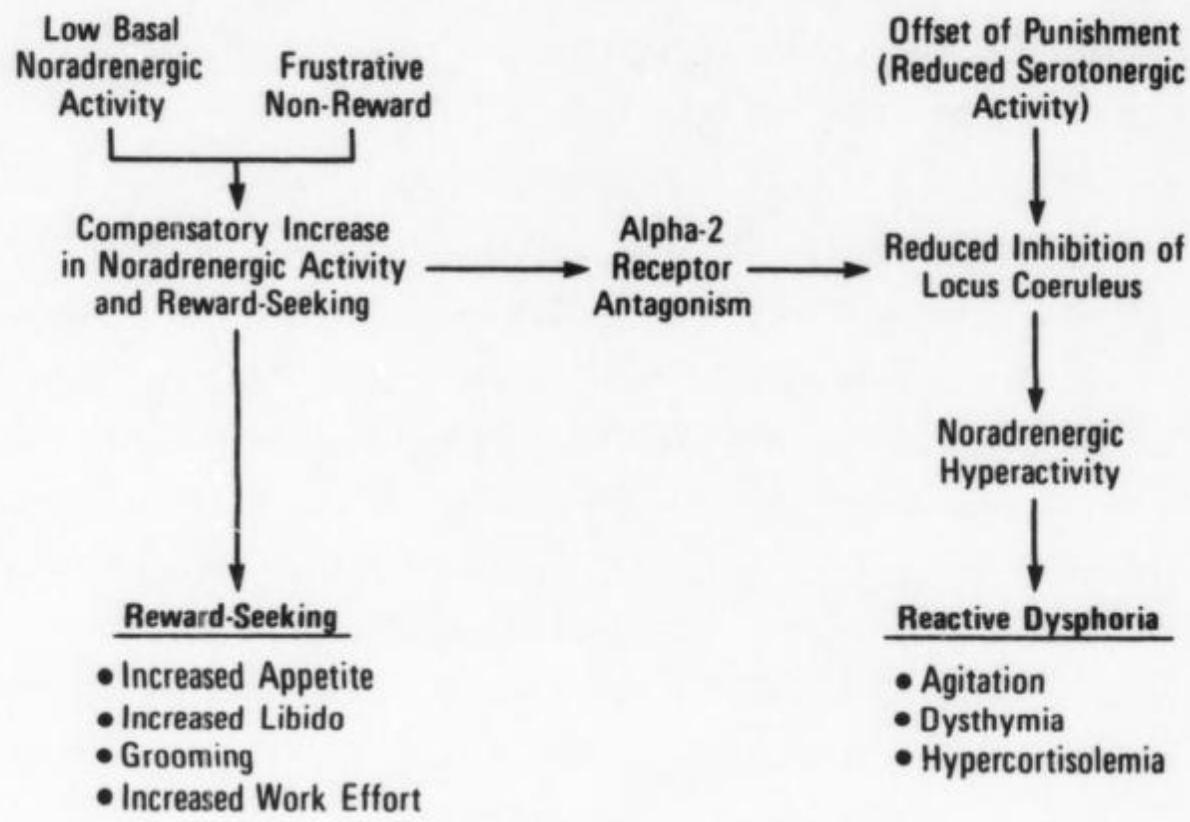

Fig. 5. Proposed mechanisms underlying "reactive dysphoria"

susceptibility to reactive forms of agitated depression associated with reactive hypercortisolemia as described earlier. Such reactive states of agitated depression associated with rebound noradrenergic hyperactivity and hypercortisolemia will be referred to as 'reactive dysphoria'.

Agitated dysphoric states due to noradrenergic hyperactivity can occur in several ways, as illustrated in Figure 5. These include direct stimulation of the locus coeruleus and reduced inhibition of noradrenergic activity due to alpha-2 receptor antagonists or reduced alpha-2 receptor responsivity. Likewise individuals with low basal noradrenergic activity are 'reward-dependent' and in such cases frustrative non-reward is supposed to precipitate compensatory rebound activation of noradrenergic activity as well as increased reward-seeking behavior. Other factors will modulate the compensatory responses. Use of alpha-2 receptor agonists may interfere with the compensatory function of rebound noradrenergic facilitation, and so does not lead to lasting clinical benefit[85]. Serotonergic projections from cell bodies in the mid-pons inhibit the locus coeruleus, and so high harm avoidance (which is associated with high serotonergic activity) may reduce susceptibility to excessive rebound activation of the locus coeruleus. Furthermore, it is postulated that low novelty seeking may reduce activation of compensatory reward-seeking behavior, and so increases susceptibility to reactive dysphoria to some extent. Hence susceptibility to reactive dysphoria is primarily determined by high reward dependence and reduced somewhat by high harm avoidance and high novelty seeking.

This model implies that genetic susceptibility to chronic anxiety is not the same as that to reactive dysphoria, but both anxiety and dysphoric states may be associated in

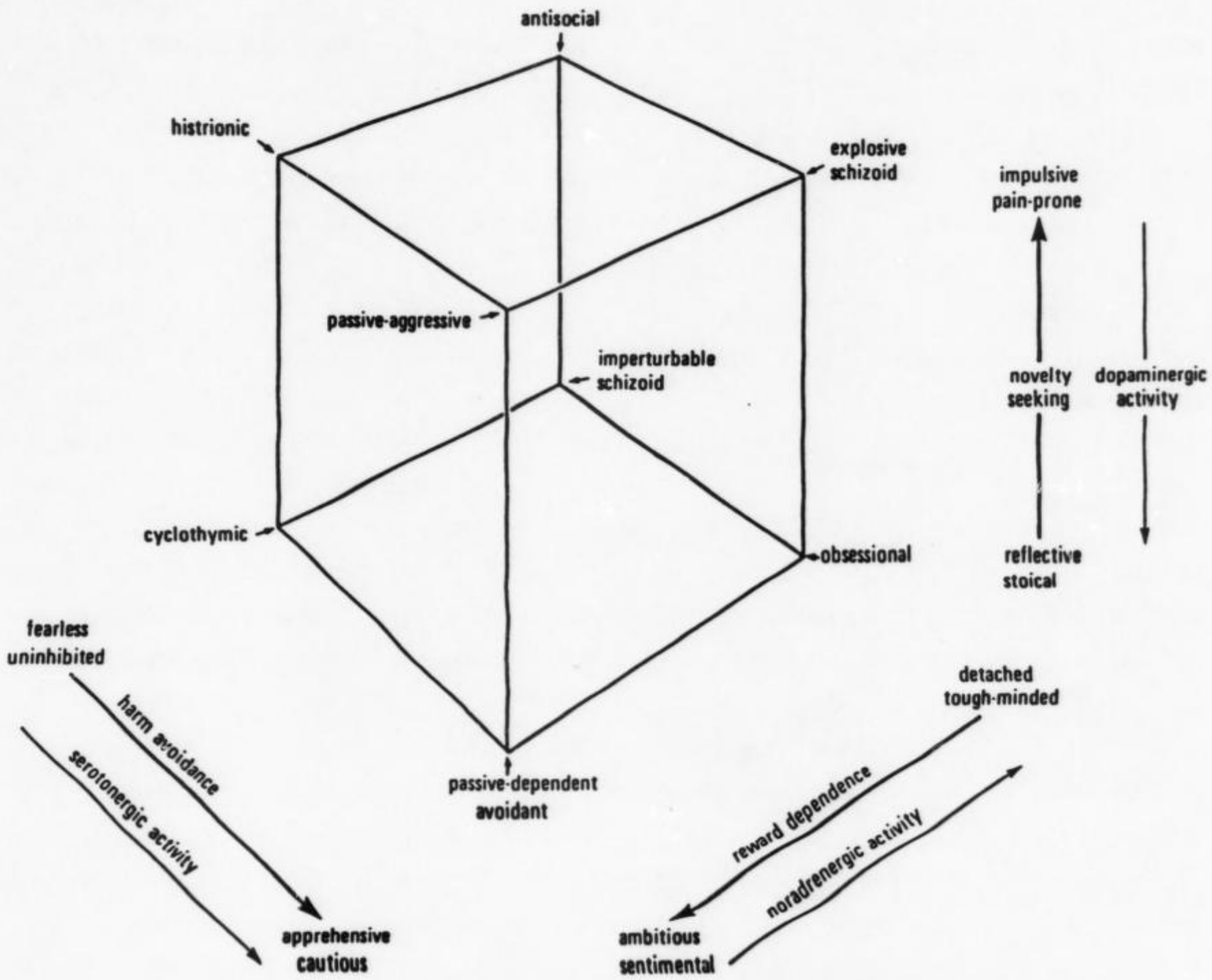

Fig. 6. Three-way interaction of personality and monoaminergic transmission

individuals and potentially in families due to the common environmental influences of punishment and non-reward. The overall relationship of the three postulated dimensions of personality and monoaminergic neurotransmission is summarized in Figure 6.

Central Modulation of Pain Sensitivity

Pain tolerance is markedly different in chronic cognitive anxiety and in chronic somatic anxiety. High frequency of complaints of diverse bodily pains in chronic somatic anxiety is associated with higher sensitivity to pain than in other anxiety states[33]. Accordingly it is critical to the hypothesis presented here to relate variation in pain sensitivity to the dimensions of personality and neurotransmitters systems described here.

Both ascending and descending monoaminergic pathways in the central nervous system perform modulatory functions that are important in nociceptive transmission. Ascending dopaminergic pathways include projections to frontal and limbic cortical

areas, so that reduced ascending dopaminergic activity may be associated with weak cortical and reticular inhibition of sensory input and motor outflow[26, 89]. Negative feedback relations between the frontal cortex and the reticular activating system suggest that frontal disinhibition leads to reduced sensation and pain thresholds, as well as the distractibility, motor restlessness, and autonomic disturbances characteristic of somatic anxiety.

The functions of the monoaminergic pathways in this negative feedback system are carried out in interaction with CNS neuropeptides, including endorphins and substance P, which modulate nociceptive neurotransmission. Beta-endorphin or low doses of morphine produce hyperactivity accompanied by sniffing and gnawing in the rat. These effects are similar to those produced by amphetamines, which facilitate dopaminergic activity[79]. In contrast, descending serotonergic pathways from the caudal raphe magnus in the brain stem to the ventral and dorsal horns of the spinal cord inhibit nociception. Hence these relationships suggest that low dopaminergic activity may be associated with increased pain sensitivity whereas high serotonergic activity is associated with decreased pain sensitivity.

It has been suggested that 'fear inhibits pain' allowing defensive responses that are not handicapped by pain[90]. On the other hand, it would be adaptive for novelty seeking to be associated with increased sensitivity to pain, which may signal the organism to the need for defensive responses. In other words, according to the model developed here, pain sensitivity is expected to be positively correlated with novelty seeking and negatively correlated with harm avoidance. This hypothesis leads to the predictions that pain sensitivity is highest for patients with high novelty seeking and low harm avoidance, intermediate for patients with either low harm avoidance or high novelty seeking, and lowest for patients with low novelty seeking and high harm avoidance. Furthermore, this model predicts that pain sensitivity should be negatively correlated with central dopaminergic activity since low ascending dopaminergic activity leads to high novelty seeking and pain sensitivity. Also pain sensitivity should be negatively correlated with central serotonergic activity since low ascending serotonergic activity is associated with low harm avoidance and low descending serotonergic activity is associated with high pain sensitivity.

These predictions are supported by an important series of studies that have extended early work by Petrie on the basis of individual variation in pain sensitivity[91]. Petrie showed that individuals have a characteristic perceptual reactance to either augment or reduce perceived stimuli using a kinesthetic figural after-effect test. More recently averaged evoked potentials have provided a more reliable index of perceptual reactance, measured as the tendency to augment or reduce the intensity of incoming sensory signals with increasing stimulus intensity. This can be measured by the slope of the amplitude of averaged EEG responses evoked by increasing stimulus intensity as suggested by Buchsbaum and von Knorring (see[82]). Augmenters have been shown

to be more sensitive to painful stimuli and stressful psychological events[91, 92] have more intense orienting responses to novel stimuli[80], and lower endorphin levels in their cerebrospinal fluid[93]. Augmentation is strongly associated with novelty and sensation seeking as measured by the Zuckerman Sensation Seeking Scale, particularly the disinhibition subscale which appears to be a composite of high novelty seeking, low harm avoidance, and possibly social detachment (low reward dependence)[94].

In response to acute alcohol ingestion, reducers show little change in ability to control stimulus intensity, but augmenters show a decrease in augmentation or show reduction[91]. Alcoholics were found to be augmenters significantly more often than normals or depressives (85 per cent versus 50 per cent)[95].

Furthermore, an important study by von Knorring and his associates[82] showed that pain sensitivity and tendency toward augmentation were negatively correlated with CSF levels of homovanillic acid (HVA) and 5-HIAA as predicted by the model described here. The tendency toward augmenting was most strongly correlated with reduced dopaminergic turnover ($r = -0{\cdot}52$) in 22 heterogeneous psychiatric patients[81]. This strong relationship is particularly striking when it is recalled that the heritability of scores on sensation seeking and augmenting tendencies are also about 0·58 to 0·69. This implies that most heritable variation of augmenting, novelty seeking, and dopaminergic turnover is shared. Also patients with chronic pain were found to have low dopaminergic and serotonergic turnover in studies of HVA, 5-HIAA, and the serotonin precursor tryptophan[96].

Most attention has been directed at studies of the dopaminergic and serotonergic systems, but it is unlikely that novelty seeking and harm avoidance are sufficient to explain all variation in pain sensitivity. When antisocial subjects with high novelty seeking and low harm avoidance are also selected for a lifelong history of resistance to anxiety and depression and low social attachment ('primary psychopaths'), they are found to have low pain thresholds[81]. In contrast, other individuals with high novelty seeking, low harm avoidance, and high reward dependence have high pain thresholds. Also individuals with high reward dependence, described as relentless 'workaholics', have been found to be susceptible to chronic pain[97]. Altogether these observations suggest that each of the three dimensions described here influence pain sensitivity.

It is postulated that pain sensitivity increases with high novelty seeking, low harm avoidance, and high reward dependence. Each of these dimensions contributes to augmenting perceptual reactance and together define what is clinically recognized as a histrionic personality whereas the opposite pattern is associated with reducing perceptual reactance and obsessional personality. Pain sensitivity involves the interaction of all three dimensions, but is useful in discriminating patients with cognitive and somatic anxiety because of the opposite direction of effects of each dimension on susceptibility to these syndromes.

Neocortical Contributions and Direct Biochemical Studies

In humans, the prefrontal and cingulate regions of the neocortex play an important role that is not developed in other animals. Lesions of these areas have been used successfully in the treatment of chronic anxiety[98]. Gray[34] has described the importance of such neocortical influences, which allow verbally coded information to influence expectancies. Destruction of the prefrontal and cingulate regions are not uniformly beneficial in chronic anxiety states, however. Such surgical treatments are most effective in patients with the cognitive anxiety syndrome and not in chronic anxiety in somatoform disorders associated with impulsivity, such as Briquet's syndrome. Recently Flor-Henry *et al.*[99] compared neuropsychological function in psychiatric patients with Briquet's syndrome with that in other patient groups matched for age, sex, handedness, and full-scale intelligence quotient (IQ) scores. Compared to normal controls, the Briquet's patients had a bilateral and symmetrical pattern of frontal lobe impairment. This anterior cerebral impairment was substantially greater than posterior cerebral impairment, but the Briquet's patients exhibited some bilateral posterior temporal deficits in most cases also. The patients with Briquet's syndrome had greater dominant hemisphere impairment than schizophrenics. Similar patterns of bilateral frontal lobe dysfunction are also found in antisocial personality[100]. Gorenstein suggests that the major cognitive deficit is the failure to modulate dominant response sets—that is, a tendency to persist with ongoing activities whether or not they remain appropriate. This is consistent with the view that individuals susceptible to somatic anxiety, such as Briquet's syndrome and antisocial personality, are characterized by both poor passive avoidance learning (low harm avoidance) and high novelty seeking as shown in Figure 2.

The findings that both antisocial personality and Briquet's syndrome have associated neuropsychological deficits that are similar to those observed in patients with bilateral frontal lobe lesions and/or lesions of the septum and hippocampus is especially important because family and adoption studies indicate that these disorders are usually different expressions of the same underlying genetic predisposition[5, 10, 101–103]. In other words, the clinical differences are largely state-dependent or determined by sex and related experiential variables. This difference will be discussed in more detail later. For our present purposes, the similarities between antisocial personality and Briquet's syndrome suggest that studies of subjects with antisocial personality who are not anxious may provide information about the characteristics of individuals who are susceptible to somatic anxiety but who have not been sensitized by prior experience. Such individuals show low anticipatory anxiety, high impulsivity, avoid monotony and seek novelty, and learn to avoid aversive stimuli poorly but learn positively reinforced tasks well[26]. They show little increase in electrodermal activity in anticipation of an aversive stimulus but are readily able to acquire anticipatory heart

rate and digital vasomotor responses[81]. In addition, the recovery time for skin conductance responses is inversely correlated with the severity of antisocial behavior. However, the cardiovascular and vasomotor responses are not diminished, and impulsivity is positively correlated with somatic anxiety. The slow recovery time for skin conductance responses has been interpreted as indicative of slow fear reduction when making avoidance responses to conditioned noxious stimuli: passive avoidance learning is impaired in such subjects because reinforcement by fear reduction is delayed[104].

Fowles[105] has reviewed extensive evidence indicating that in humans skin conductance responses are closely related to the behavioral inhibition system described by Gray. Reduced harm avoidant behavior and poor passive avoidance learning is associated with reduced serotonergic turnover in the human brain, as measured by cerebrospinal fluid levels of the major metabolite of serotonin, 5-hydroxyindoleacetic acid[83, 103, 106, 107]. The relationship between serotonergic dysfunction and impaired harm avoidance is strong: the correlation between cerebrospinal levels of 5-HIAA and aggressive behavior was large ($r = -0{\cdot}78$) in a study of military men with a variety of interpersonal adjustment problems but no major psychiatric illness[106]. A strong relationship has also been observed between suicidal behavior in depressives and low serotonergic activity in studies of depressives[108, 109], and this has also been associated with a family history of alcoholism[110]. Linnoila *et al.*[83] have emphasized the association between low serotonergic turnover and impulsive-aggressive traits in patients with personality disorder. However, his subjects were all violent criminals and so had behavioral signs of both low harm avoidance and high novelty seeking. Studies of CSF 5-HIAA in depressives have revealed correlations between suicidal behavior[108, 109] but not impulsivity as measured by low solidity in the Marke-Nyman scale[109].

In studies of a heterogeneous population of psychiatric patients, CSF 5-HIAA was significantly lower in patients who had made violent suicide attempts, but did not differ between suicide attempters who had taken drug overdoses and non-attempters. Furthermore, CSF 5-HIAA was negatively correlated with scores on the 'validity' scale in the Marke-Nyman Temperament Inventory[109]. In other words, individuals with high serotonergic turnover had low validity scores, indicating asthenic temperament or a tendency to weakness and fatigue accompanied by hypersensitivity. In contrast, individuals with low 5-HIAA had high validity scores, indicating high energy levels and a capacity for carrying out work with ease[59]. This scale was originally developed to distinguish 'subvalid' patients with high cognitive anxiety (psychasthenics and neurasthenics) from others. Studies of monoamine metabolites in individuals with personality disorders without depression revealed associations with aggressivity or scores on psychopathic deviance on the MMPI[106, 107]. Some studies fail to find an association between serotonergic activity and individual suicidal or violent

acts themselves[110]. Altogether these findings indicate that low serotonin turnover is consistently related to low harm avoidance rather than impulsivity, novelty seeking, or violent behavior itself.

In addition impulsive violent criminals have been found to have lower levels of the dopamine metabolite homovanillic acid than do individuals with non-impulsive personality disorders[83]. This further supports the hypothesis that low activity in dopaminergic pathways is associated with impulsivity, novelty seeking, as well as low pain tolerance[81]. In contrast levels of the norepinephrine metabolite methoxyhydroxyphenylglycol (MHPG) have not been consistently related to harm avoidance or novelty seeking, possibly varying with the mood state[85, 106, 110].

Dopaminergic pathways are involved in the brain's incentive system[79], and the tendency of impulsive patients toward exploration of the unknown and stimulation of novelty can be interpreted as a compensatory mechanism that improves alertness and perceptual sensitivity[26, 58]. Low dopaminergic activity is associated with more intense orienting responses to novel stimuli and a tendency to augment electrocortical responses with increasing stimulus intensity, as described earlier. Treatment of individuals with impulsivity and somatic anxiety with dopaminergic agonists[38, 39] leads to improvement whereas benzodiazepines, barbiturates, and alcohol usually lead to no change or deterioration in the long run[39].

In studies of intelligence, antisocial subjects often have poorer verbal than performance scores, but this is not invariable[103, 112]. In one detailed study of performance on Wechsler Adult Intelligence Scale subtests, subjects with antisocial personality had lower scores on information, comprehension and arithmetic of the verbal scale, and the picture completion subtest of the performance scale compared to subjects with other personality disorders; this suggested that a fundamental feature in antisocial personality was a lack of general alertness, interest and intellectual curiosity[112]. However, it appears from factor analytic studies of personality variables that such restricted intellectual interest is associated with low reward dependence rather than novelty seeking, and the variable findings of past studies may be due to failure to control for this particular personality variable.

Relationship Between Personality and Cognitive Style

The information-processing patterns described earlier as 'histrionic' and 'obsessional' appear to be extreme and opposite composites of the personality dimensions of novelty seeking, reward dependence, and harm avoidance. 'Histrionic' personality or information-processing is a combination of high novelty seeking, high reward dependence, and low harm avoidance: these are all associated with an augmenting perceptual reactance and lead to distractibility, hypovigilance, inattention to detail, low perceptual speed and accuracy, difficulty integrating and organizing information,

intuitive decision making, wide range of interests, strong responses to sensory stimulation. In contrast, 'obsessional' personality is a combination of high harm avoidance with low reward dependence and low novelty seeking: these are all associated with a reducing perceptual reactance and lead to hypervigilance, attention to detail, limited range of interests but high degree of preparedness and skill, objectivity and detachment, excellent analytical skill to organize and integrate observations but weak responses to sensory stimulation.

Thus variation in the reward dependence dimension influences the susceptibility of individuals with high novelty seeking or high harm avoidance to develop chronic anxiety. High reward dependence and low harm avoidance increase the risk of underpredicting aversive events and hence predispose to chronic somatic anxiety in individuals with high novelty seeking. In contrast, this pattern of effects is reversed in individuals with high harm avoidance: low reward dependence and low novelty seeking increase the risk of overpredicting danger and predispose to chronic cognitive anxiety.

The relationship of traditional categorical terms for personality disorders and various combinations of the personality dimensions described here are summarized in Figure 6. It is useful to distinguish between histrionic personality and antisocial personality ('primary psychopathy') in terms of reward dependence because high reward dependence is associated with an augmenting perceptual reactance and pain sensitivity whereas low reward dependence is associated with reducing perceptual reactance and pain tolerance. Borderline personality has a pattern similar to that of histrionic personality in many cases, but reward dependence may be more prominent than novelty seeking in borderlines whereas novelty seeking is somewhat more prominent in histrionic personality. Likewise avoidant personality has a pattern similar to that of passive-dependent personality, but harm avoidance is more prominent than reward dependence. Needless to say, such distinctions have not been consistently applied in the past because there has been no general theory of personality on which to base the distinctions.

Furthermore, it should be remembered that extreme combinations are not necessarily maladaptive. For example, individuals with high novelty seeking, low harm avoidance, and low reward dependence may be well adapted to successfully carrying out exploration of highly dangerous tasks, as illustrated vividly in the autobiography of the fighter/test pilot General Chuck Yeager who first traveled faster than the speed of sound[113]. Such individuals are well adapted to combat and exploration of the unknown and highly resistant to anxiety and dysthymic reactions. However, without consistent discipline, such individuals may also show aggressive antisocial behavior when their interests and goals differ from those of others around them.

It is expected that variation along each dimension is approximately normally

distributed due to polygenic inheritance. This means that most individuals will have intermediate values rather than extreme values. For example, most individuals with high novelty seeking and low harm avoidance will have intermediate values on reward dependence so that individuals at the extremes designated as histrionic personality and antisocial personality will be rare. Individuals with histrionic personality are supposed to be most susceptible to Briquet's syndrome, whereas those with antisocial personality as defined here are supposed to be most susceptible to conduct disorders. However, most people with high novelty seeking and low harm avoidance will be susceptible to conduct disorders, somatic anxiety, and dysthymia to varying degrees. Actual behavior will depend on social learning, experience, and environmental circumstances as well as temperamental predisposition.

Relationship of Chronic Anxiety and Reactive Dysphoria

In the model proposed here, non-reward or punishment lead to reduced maintenance of rewarded behaviors and dysthymic states, particularly in those who are high in reward dependence. Non-reward or punishment can also lead to increased apprehension and inhibition of behavior, particularly in those who are high in harm avoidance. Consequently the environmental antecedents of such demoralization responses (*i.e.*, increased anxiety and reduced industry) are correlated, and both acute anxiety and learned helplessness will tend to occur together because of the environmental effects.

However, the pattern of genetic influences on chronic anxiety and dysthymic disorders is more complex because high reward dependence predisposes to chronic somatic anxiety and reactive dysphoria whereas low reward dependence predisposes to chronic cognitive anxiety. This proposed differential effect of reward dependence implies that most individuals with chronic somatic anxiety will have greater susceptibility to the dysphoric effects of non-reward than either individuals without anxiety or those with chronic cognitive anxiety. Conversely chronic cognitive anxiety will be associated with reduced genetic susceptibility to reactive dysphoria. Consequently it is predicted that chronic somatic anxiety, but not chronic cognitive anxiety, will be associated with increased genetic susceptibility to reactive dysphoria.

This prediction is supported by studies of depressive comorbidity in Briquet's syndrome and anxiety neurosis in the relatives of psychiatric outpatients[3]. Briquet's syndrome appears to be a chronic syndrome of severe chronic somatic anxiety, reactive dysphoria, and abnormal sick role behavior that is most likely to arise as a complication of histrionic personality, particularly when the abnormal sick role behavior is reinforced[11]. Psychiatric patients themselves often seek treatment because of depression but their relatives are not such a biased sample. Among relatives, individuals with anxiety neurosis are rarely depressed, whereas individuals with

Table 3. Patterns of Susceptibility to Dysphoria by Personality Type

*Personality Type**	*Somatic Anxiety*	*Cognitive Anxiety*	*Reactive Dysphoria*
Histrionic (NhR)	++++	–	+++
Antisocial (Nhr)	+++	–	–
Passive-aggressive (NHR)	++	+	++
Explosive schizoid (NHr)	+	++	–
Passive-dependent (nHR)	–	+++	+
Obsessional (nHr)	–	++++	–
Cyclothymic (nhR)	–	–	++++
Imperturbable schizoid (nhr)	–	–	–

*The combination of personality traits is indicated in parentheses: Novelty seeking (N or n), harm avoidance (H or h), and Reward dependence (R or r) with capital letters indicating high values and lower case letters low values.

Briquet's syndrome or somatization disorder nearly always have a history of depressive reactions. Among 22 relatives with Briquet's syndrome, 63·6 per cent also had a definite depressive disorder compared to 9·0 per cent of 1,112 relatives with neither Briquet's syndrome or anxiety neurosis. In contrast, 9·6 per cent of 115 relatives with anxiety neurosis also had a history of a definite depressive disorder, suggesting that susceptibility to anxiety neurosis and depression are not significantly correlated. Furthermore, even a lifetime history of ever being 'depressed, sad, or despondent' to an extent associated with any disability or treatment occurred in 86·4 per cent of Briquet's patients, 41·7 per cent of anxiety neurotics, and 31·8 per cent of other relatives in the Washington University Clinic Study (Cloninger, Guze, Clayton, Martin, unpublished data). If the environmental antecedents are positively correlated, then the genetic antecedents must be negatively correlated in order to yield a negligible correlation overall. However, the separation of genetic and environmental effects will require more detailed analysis including large-scale adoption data.

More specific semi-quantitative predictions about patterns of susceptibility to various dysphoric states are summarized in Table 3 according to individual personality types. The predictions about somatic anxiety assume it is based on high novelty seeking primarily and reduced by high harm avoidance and/or low reward dependence. The predictions about cognitive anxiety assume it is based on high harm avoidance primarily and reduced by high novelty seeking and/or high reward dependence. The predictions about reactive dysphoria assume it is based on reward dependence primarily and reduced by high harm avoidance and, to a lesser extent, high novelty seeking. The predicted patterns suggest that extensive comorbidity is

likely; however, this comorbidity is not random but related to interaction of the various personality dimensions.

The prediction about histrionic personality is also supported by studies of dysthymic disorders which are designated as 'character-spectrum' disorder by Akiskal[114]. The latter individuals have early onset of dysphoria in response to romantic disappointments and some other types of separation events. They have a lifelong history of histrionic traits and somatic anxiety[114]. In response to loss of rewards these histrionic individuals develop 'atypical' depressions that are often but not invariably associated with 'reverse vegetative symptoms' including motor restlessness (rather than psychomotor retardation) and engage in reward-seeking behaviors such as increased sexual activity (rather than loss of libido), overeating or bulimea (rather than loss of appetite), frequent grooming (rather than poor hygiene), and/or gambling. They also show prominent increases in pain sensitivity and complaints of bodily pains, conversion and phobic symptoms. Such patients respond well to medications that facilitate monoaminergic transmission such as inhibitors of monoamine oxidases[115, 116].

Klein distinguishes individuals with reactive depressions associated with high reward dependence in ways that are equivalent to whether they have low novelty seeking ('atypical' depressives) or high novelty seeking ('histrionic or borderline personalities') (Klein personal communication, 1986). In Figure 6 the individuals designated as having 'cyclothymic' and 'passive-dependent' personalities have high reward dependence and low novelty seeking, so individuals along the line between these polar extremes are supposed to be susceptible to 'atypical depression'. Those who are most similar to passive-dependent personality, *i.e.*, with high harm avoidance, are supposed to also be most susceptible to cognitive anxiety whereas those who are most similar to cyclothymic personality are most susceptible to reactive dysphoria. Whether anxiety or depression occur first or ever is supposed to depend on both environmental events and the personality variation. Consequently, the distinction between primary and secondary affective disorder may be of limited value in such individuals since experience cannot be standardized. This underscores the importance of attention to stable personality traits rather than symptoms alone.

Dysphoric reactions, cognitive anxiety, and somatic anxiety may all concur. Individuals with the combination of high reward dependence, high harm avoidance, and high novelty seeking ('passive-aggressive' personality) are predicted to be susceptible to both depressive reactions to frustrative non-reward and to chronic anxiety with some cognitive apprehension and prominent painful somatization. These predictions are strongly supported by descriptive longitudinal studies of passive-aggressive personality[117]. This is vividly illustrated in detail in Caro's biography of Lyndon Johnson, whose depressions occurred when his ambitions for political power and attention were frustrated despite his manipulations[118]. Mostly

these reactive dysphorias were brief and relieved by increased support, praise, or other rewards, but others required hospitalization.

Likewise individuals with high reward dependence, low novelty seeking, and low harm avoidance satisfy the usual descriptions of cyclothymic personality in that they are energetic, carefree, cheerful, overconfident, boastful, industrious, and warmly sentimental and moody. They also are expected to be courageous and frugal and their depressions are not autonomous but reactive. Hence it may be possible to distinguish individuals with such extreme personality differences from others with autonomous bipolar mood disorders.

It must be emphasized that there are other types of affective disorders that appear to be etiologically unrelated to variation in personality dimensions described here. The agitated depressions related to reward dependence are reactive to frustrative non-reward, whereas other 'autonomous' depressions cannot be relieved by environmental manipulation. In other words, other effective disorders show 'lack of reactivity'. Since there are endogenous genetic antecedents of personality, the term 'autonomous' mood disorders is preferable to the more common term 'endogenous'. Such autonomous mood disorders may be common, so that overall the relationship between mood disorders other than 'character-spectrum' or 'atypical' subgroups is weak and questionable[119]. Events associated with mood disorders may in turn lead to both transient and permanent changes in personality (see next section) so that the clinical separation of distinct subgroups is notoriously difficult without comprehensive developmental information. Suggestions for future research are discussed later.

Maturation Function of Long-Term Sensitization

In the model proposed here harm avoidance has reciprocal feed-back interactions with novelty seeking and reward dependence. Heritable tendencies to low dopaminergic activity and to low noradrenergic activity lead to novelty seeking and reward seeking behaviors respectively. In contrast, a heritable tendency to high serotonergic activity is supposed to lead to avoidance of novelty and risk of harm. The search for reward and novelty will tend to expose an individual to risk, and acute feed-back interaction with the serotonergic behavioral inhibition system leads to immediate short-term adaptation.

This acute or short-term adaptation is augmented over the long-term development of an individual by the effects of long-term exposure to aversive stimuli. As noted previously, exposure to repeated unpredictable aversive experiences leads to long-term sensitization. Sensitization leads to facilitation of neurotransmitter release generally, that is, for both habituated and non-habituated responses. This facilitation of neurotransmitter activity leads to an overall inhibition of novelty and reward seeking because novelty seeking and reward seeking are associated with low monoaminergic

activity, whereas harm avoidance is associated with high monoaminergic activity. In other words, it is postulated here that long-term sensitization decreases novelty and reward seeking by facilitation of all three monoaminergic neurotransmitters, which in turn decreases novelty seeking and reward dependence and increases harm avoidance.

With increasing age, exposure to aversive experiences, and firm and consistent discipline, an individual will tend to reduce novelty seeking and reward-dependence and to be more cautious and inhibited, less exploratory and innovative and flexible, more independent and less responsive to social pressures and other rewards (power, wealth, recognition). This pattern of adaptive change due to long-term sensitization and/or age-dependent biological processes is collectively described as 'maturation', and is primarily of benefit to those who are initially high in novelty seeking and/or reward dependence and low in harm avoidance. Conversely, individuals who are initially high in harm avoidance are expected to function with least discomfort in supportive, non-threatening environments.

This hypothesis is supported by the consistent observation that risk-taking behavior decreases with increasing age[120–122], whereas symptoms of anxiety increase with age and symptoms of bodily pain gradually increase and then decrease partially. Long-term experience with adversity tends to be associated with rigidity and concern for safety and security rather than innovation and risk taking. Hyperactivity and aggressiveness tend to decrease with age. Also sensitivity to peer pressures and 'ambition' tend to 'burn out' or decrease with age, particularly following long-term experiences with adversity. It is unknown to what extent such 'maturation' is due to age-dependent biological processes other than long-term sensitization, but the finding that strict and consistent discipline and stable childhood attachments facilitates the maturation process[103, 120] does suggest that maturation is at least partially dependent on experience and not just age.

Sensitization is not an anachronistic phenomenon, but an important mechanism for long-term adaptation or maturation. The development of excessive sensitization and hence chronic anxiety is a consequence of unreliable perceptual processes, maladaptive social learning and other exogenous factors beyond the control of the individual, not simply excessive deviation in the normal personality dimensions themselves.

When sensitization becomes excessive, then chronic anxiety arises along with other changes predicted by the model described here. Facilitation of serotonergic transmission leads to chronic anxiety manifest as increased worrying, apprehension, and social insecurity. Facilitation of dopaminergic transmission leads to decreased pain sensitivity, decreased frequency of conversion reactions, and decreased novelty seeking manifest as decreased inpulsivity, reduced innovativeness and flexibility, and increased rigidity. Facilitation of noradrenergic transmission leads to decreased reward dependence manifest as reduced industriousness, reduced ambition, and

increased social detachment ('burn out' or 'demoralization'). Seligman has described such chronic anxiety and demoralization as a result of long-term sensitization[50].

The most distinctive prediction of the model described here is that increasing sensitization should lead to decrements in pain sensitivity even in individuals who initially have prominent novelty seeking and unusually high pain sensitivity. This is supported by the observation in female psychiatric outpatients that the frequency of bodily pains and other somatic complaints reaches a peak in their early twenties and then gradually declines with age[123, 124]. However, even after sensitization and the decrement in pain sensitivity, individuals with high novelty seeking are likely to remain high on this dimension and more sensitive to pain compared to the population average. Similarly conversion reactions are most common in early adulthood and then gradually decline with age[11]. Further information about the longitudinal development of chronic anxiety syndromes is considered later.

Bidirectional Interaction of Conditioning and Cognitive Awareness

It has been argued that all human learning is based on insightful awareness and that there is no evidence of classical or operant conditioning in man[125]. The role of awareness in associative learning remains inconclusive, and this is not surprising: the interconnections of cortex with more primitive parts of the brain lead to awareness of processes even when the awareness follows the initiation of responses. Nevertheless it is untenable that man is incapable of the more primitive forms of learning because the human brain still includes the more primitive structures. This is confirmed by the high correlation of the anxiolytic effects of benzodiazepines and barbiturates with their effects in avoidance learning in lower animals from teleost fish to rodents and chimps. The genetic preparedness of man for phobic responses to certain types of stimuli like snakes also supports persistent conditioning mechanisms.

Nevertheless, the well developed neocortex of man makes possible additional learning mechanisms and modifies the more primitive mechanisms. Not all learning is associative in man or other animals. Chimps and others show insight learning in which there is a perceptual restructuring or reorganization of relationships without any change in association or contingency, as in tool making or use of mnemonics. Man can also use information that is verbally transmitted and encoded to modify the significance and salience of stimuli in his internal or external environment and thereby modify his behavior. It is certain that in man classical and operant conditioning are inadequate accounts of learning and adaptation to environmental influences in man.

The relationships among neocortex and other brain structures are not unidirectional. Conscious evaluations or expectancies about the significance of a stimulus influence the rate of habituation in conditioning trials[41]. Similar subjective influences on potential reinforcers make studies of operant learning difficult in

humans: what is reinforcing varies between individuals with sex, personality, expectancy sets, and other social factors. Sex and expectancy sets such as locus of control (*i.e.*, attitude or expectancy about an individual's own efficacy in influencing the environment) are associated with differences in habituation responses. Thus, insight learning or attitudes modify the salience and significance of experiential stimuli.

On the other hand, conditioned responses influence conscious thoughts, Specifically conditioned responses may lead to 'automatic' thoughts, as described by Beck and Emery[126], which are illogical and catastrophizing. Automatic thoughts may either arise from conscious insightful processes and modify associative learning, or they may reflect and intellectualize conditioned responses. This formulation differs from that of Beck, who seems to regard anxiogenic cognitions as anachronistic primary phenomena.

Cognitive therapy or cingulumotomy may modify the conscious cortical processes that contribute to the enhancement of some conditioned responses. Eysenck has noted that neurotic fears are more highly resistant to extinction than is expected from experiments with lower animals. He refers to the increased conditioned responding when the unconditioned stimulus is no longer presented as 'incubation' or 'enhancement'[51]. He postulates that the physiological changes associated with the conditioned response become their own unconditioned stimulus, resulting in increased conditioned response strength. A cognitive perspective of this phenomenon is that the images and expectancies set up the vicious cycle of a self-fulfilling prophecy[126]. Conditioning takes place to both external and internal stimuli. It is essential to recall that we do not respond to the stimuli as they really are in the environment but as we perceive and summarize what is given. Such information processing can involve much restructuring.

Longitudinal Development and Stability of Chronic Anxiety Syndromes

Longitudinal studies indicate that both chronic anxiety states (either somatic or cognitive) develop gradually and then fluctuate in intensity but are moderately stable. A recent prospective blind follow-up of a random sample of 500 psychiatric outpatients indicates such gradual development and moderate stability in panic disorder, somatization disorder, and other primary anxiety states[3,4].

Table 4 summarizes information about the age of onset of various anxiety features based on personal interviews and medical records of 32 outpatients with a final diagnosis of panic disorder. Nervousness and simple or social phobias often began in childhood (N = 9, 28 per cent) and nearly always by the late teens (N = 28, 88 per cent). The average age of onset of palpitations and/or dyspnea was 20 years. Panic attacks typically began a couple of years later, often coincident with depressed mood

Table 4. Natural History of Panic Disorder Among Probands

Symptom	*Affected N(%)*	*Age of onset (yrs ±SD)*
Nervousness	32 (100%)	12·41 ± 6·07
Simple phobias	27 (84%)	18·46 ± 12·99
Social phobias	9 (28%)	18·48 ± 15·81
Palpitations/dyspnea	32 (100%)	20·53 ± 10·72
Panic attacks	32 (100%)	22·30 ± 10·54
Agoraphobia	5 (16%)	23·40 ± 8·82
Obsessions/compulsions	7 (22%)	27·43 ± 12·71
Depressed mood	31 (97%)	28·94 ± 14·26
Depressive syndrome	24 (75%)	31·25 ± 14·15

(N = 12, 38 per cent). A full depressive syndrome, when it appeared, usually began about a decade later. Agoraphobia always followed the onset of panic attacks. Obsessions and compulsions were mild in these subjects and usually followed the onset of panic attacks.

Somatization disorder or Briquet's syndrome also develops gradually. It is rarely diagnosable before age 14[127]. In the majority of cases characteristic somatic symptoms begin during adolescence and full criteria are satisfied by age 25[11, 25, 128]. The histrionic information processing pattern and histrionic personality traits are usually recognizable during adolescence in those cases (about 70 per cent) in whom they are ever prominent[101]. Kimble and associates[129] found histrionic personality and Briquet's syndrome highly correlated in adult women, but noted that teenage girls with histrionic personality rarely fulfilled the criteria for Briquet's syndrome. Guze and associates[130] found among psychiatric clinic patients that the number of symptoms characteristic of Briquet's syndrome peaked during the twenties, followed by a gradual decline. In men, there was a gradual increase in the number of symptoms with age, reaching a peak in the fifties and then declining. Similar findings have been observed in Swedish psychiatric outpatients[124].

Patients with somatization disorder are more likely to have a history of juvenile antisocial behavior[123] or adult criminality[101] than patients with cognitive anxiety disorders. There is also an association between antisocial behavior and somatization in biological relatives[10], and this will be discussed more later.

The intensity of somatization is only moderately stable in psychiatric outpatients. The correlation between the number of symptoms characteristic of somatization disorder over a 6 to 12 year follow-interval was slightly over 0·5. Measures of concordance for specific categorical diagnoses are also only fair for either

somatoform or anxiety disorders. In a blind prospective study the intraclass correlation (kappa coefficient) was 0·30 for any primary anxiety disorder diagnosis[3] and 0·35 for a diagnosis of somatization disorder or Briquet's syndrome[4].

Such gradual development and moderate stability of symptomatic distress is expected according to the proposed role of long-term sensitization in the development of chronic anxiety. The observations that the information processing deficits are noticeable at an early age and that early signs of tendencies to be sensitive and apprehensive (in cognitive anxiety disorders) or impulsive and antisocial (in somatic anxiety disorders) suggest that such behaviors are closer to the underlying genetic predisposition than the full chronic anxiety state itself.

According to the developmental model proposed here, patients who are most susceptible to pure cognitive anxiety are high in harm avoidance but not novelty seeking, whereas those who are most susceptible to pure somatic anxiety are high in novelty seeking but not harm avoidance. Individuals who are high in both harm avoidance and novelty seeking have conflicting responses to novelty and are predisposed to be unstable neurotics with mixed cognitive and somatic anxiety. In early childhood, individuals who condition easily to aversive stimuli (*i.e.*, are high in harm avoidance) are expected to have skin conductance responses that habituate slowly to repeated stimuli whereas those who condition poorly to aversive stimuli (*i.e.*, are low in harm avoidance) are expected to habituate readily. It follows that children who are predisposed to the different anxiety syndromes should differ in their habituation responses. However, after long-term sensitization the habituation responses of patients with chronic anxiety are expected to be slow regardless of their tendencies prior to conditioning. This means that combined family and longitudinal studies are critical in testing and evaluating such hypotheses: family studies permit identification and prospective longitudinal study of high risk individuals as well as evaluation of patterns of inheritance.

Genetic Predisposition to Chronic Anxiety

Animal Studies

Animal studies permit artificial selection experiments that are not possible in man. These can reveal important information about the genetic systems that influence central brain systems that are essentially the same in man and most other vertebrates. The harm avoidance dimension which reflects variability in responses to 'aversive' stimuli such as punishment, non-reward, or novel, unfamiliar environments is expected to be comparable in man and other vertebrates. As noted earlier, there is a high correlation between anxiolytic properties of benzodiazepines in man and their ability to disinhibit avoidant learning in other vertebrates[35, 73].

Rats and mice have been selectively bred for indices of emotional reactivity in their

open field behavior. Broadhurst carried out two-directional selection of rats for high and low defecation scores in a brightly illuminated unfamiliar environment[131]. He took the defecation score in a novel unprotected environment as an index of emotional reactivity, and called the resulting strains the Maudsley Emotionally Reactive and Non-reactive rats. According to the model proposed in this article, this experiment should be relevant to the harm avoidance dimension. This is supported by findings that a correlated response to selection for defecation scores in a novel environment was that the reactive rats had fewer benzodiazepine receptors in the hypothalamus and hippocampus than nonreactive rats[75]. The benzodiazepine binding sites are part of a complex including the receptor for gamma-aminobutyric acid, which is an inhibitory neurotransmitter that suppresses serotonergic activity; hence lower numbers of benzodiazepine receptors is associated with greater serotonergic activity and presumably enhanced avoidance learning. The same difference in benzodiazepine receptors was found in a inbred strain of mice characterized as 'anxious'[76]. The divergence between the lines over successive generations of selection is strong evidence for genetic contributions to reactivity to novel, unprotected environments. The continued divergence over more than 12 generations suggests that there are many genes contributing to this trait, implying polygenic inheritance.

Similar results have been obtained in mice, and indicate that there is a negative correlation between genetic factors associated with fearfulness (defecation scores) and exploratory activity[132], as expected according to the model proposed here. The BALB/c strain of mice shows high fearfulness (high defecation scores) and low exploratory open-field activity whereas the C-57BL/6 strain shows lower fearfulness and higher exploratory activity. Defries *et al.*[132] selectively bred a cross of these two strains for high and low activity over 30 generations producing two strains with no overlap in activity. A correlated genetic response was an inverse relationship between activity and defecation scores. This negative correlation supports the model proposed here since high activity is expected with high novelty seeking and low harm avoidance whereas the converse pattern is expected to minimize activity levels. Other work indicates that whole brain dopamine and HVA levels are low in C-57 mice and high in the BALB strain[133, 134], as expected from the proposed inverse relationship between dopamine and exploratory activity. Also BALB's have higher brain stem serotonergic activity[135]. Brain site and age effects on noradrenergic activity are complex and variable in relation to exploratory activity[134, 135].

Selection experiments have been carried out on various forms of learning and of aggressive behavior in rodents, including predatory aggression and 'affective aggression', such as fighting induced by painful shocks or isolation (see ref. [136]). Such selection has demonstrated substantial genetic effects for both avoidance learning[137] and aggressive behavior[138, 139]. It appears from biochemical studies that susceptibility to aggressive behavior involves multiple monoaminergic systems. It does appear that

overall dopaminergic and noradrenergic activity is different in aggressive and non-aggressive strains[39, 134, 138], but it has not been possible to specify particular brain systems that are indirectly affected by such selection. This variability in neurotransmitter activity is consistent with the hypothesis presented earlier that aggressivity is a composite of low harm avoidance and either high novelty seeking ('affective aggression' as in Figure 2) or low reward dependence ('predatory aggression') as in Figure 3 (see refs. [39, 134]).

Inheritance of Human Perceptual Skills

The personality variables described here are associated to some extent with differences in perceptual skills and performance on tests of intelligence. Since it is postulated that these personality variables are heritable, it is relevant to determine whether the perceptual skills themselves are heritable. Evaluations of the inheritance of generalized intelligence suggest substantial genetic contributions whether they are based on twins, adoptees, or multiple kinship relationships. Controversy persists over the proportion of overall variability that is genetic, which has varied from 30 to 80 per cent depending on type of test, sample, and alternative analytical assumptions (see ref. [140]).

Tests that measure variation in the ability for perceptual organization and interpretation may be of more relevance than tests of general intelligence or scholastic achievement. In studies intended to identify distinct perceptual skills, Thurstone developed a number of tests that require the subject to impose a perceptual reorganization on presented material in order to perceive 'meaning' and perform well on the test[141]. Thurstone suggested that differences in such information processing ability influenced personality trait development. Vandenberg evaluated the heritability of a variety of tests of perceptual skill in a study of 45 monozygotic and 37 dizygotic like-sexed twins of high school age[142]. Heritability estimates varied from 33 to 67 per cent on 16 tests of perceptual ability. The most highly heritable variation occurred in performance on tests requiring perceptual reorganization, such as identification of 'concealed figures' or 'hidden words' in which subjects identify a geometrical design imbedded in other designs or four letter words in a page of continuous letters. Somewhat lower heritability occurred for skill in judging size constancy or detecting flickering of lights (critical flicker fusion test). Tests of perceptual speed, which require speed and accuracy in recognizing similarity and differences between objects or symbols, were least heritable. Subsequent studies have confirmed substantial heritability even in perceptual speed: correlations in three studies range from 0·68 to 0·80 for MZ twins and from 0·34 to 0·55 for DZ twins, giving polygenic heritability estimates around 35 per cent[143]. Altogether these results suggest that genetic factors contribute to variation in information processing skills, and this variation is evident in adolescents.

Inheritance of Personality Traits

Twin and family studies indicate that measures of many personality traits and temperament factors, such as impulsivity, sociability, industry/persistence, tough-mindedness, and neuroticism are heritable[69, 72, 142, 144–147] with genetic factors accounting for 40 to 60 per cent of overall variability on most indices in adolescence. Analyses of the genetic and environmental structure of Eysenck's three dimensional model of neuroticism, extraversion-introversion, and psychoticism revealed that the phenotypic structure did not correspond well with the underlying genetic structure[64]. This was also shown by Eaves and Eysenck who carried out a detailed analysis of sociability and impulsivity in twins. Genetic factors were largely independent between these two dimensions whereas environmental influences were largely shared[69]. A quantitative model assuming additive polygenic effects, random mating, and non-familial environmental effects was adequate to describe the inheritance of impulsivity and sociability.

Environmental variability and sex differences increase with age on personality traits. For example, studies of men and women in Norway showed large sex differences in the inheritance of hysterical and oral personality traits. Torgersen[65] found substantial genetic contributions to hysterical personality traits in women and to oral personality traits in men. Hysterical personality traits include exhibitionism and aggressiveness (cf. novelty seeking) whereas oral traits included dependency, introversion, and fear of sickness, aggression and disasters (cf. harm avoidance and reward dependence). Age and sex must be taken into account in studies of the inheritance of such traits, particularly in adults.

Personality traits are weakly correlated with measures of cognitive skills such as perceptual speed. For example, perceptual speed has correlations of about +0·3 with obsessional traits like orderliness or introversion and about −0·3 with histrionic traits like impulsivity[148].

Inheritance of Self-Reported Anxiety

Using the Minnesota Multiphasic Personality Inventory, the heritability of hypochondriasis and psychasthenia is low among adolescent twins[149] but is substantial in adult adopted twins[150]. In a recent study of adult twins, the correlations between monozygotic co-twins who had been reared apart were significant for both hypochondriasis ($r = 0{\cdot}30$) and psychasthenia ($r = 0{\cdot}51$)[150]. Earlier studies that had suggested that such traits were not heritable were carried out in adolescents who had seldom had time to develop chronic anxiety symptoms. This supports the developmental model described earlier in which heritable personality traits predispose to the development of chronic anxiety following long-term sensitization. The long time

required for sensitization means that the genetic contributions to chronic anxiety are not apparent until adulthood in most people.

Twin and Family Studies of Chronic Anxiety Disorders

Early family history studies suggested that from 15 to 22 per cent of first degree relatives of probands with chronic anxiety neurosis had the same disorder (see [3]), compared to an estimated lifetime risk of 2 to 5 per cent in the general population. However, these early studies were open to criticism because of the lack of blind assessment, uniform assessment procedures, explicit diagnostic criteria, and did not distinguish panic disorder from other primary anxiety states. An exception was the blind study of a heterogeneous consecutive sample of same-sexed twins at the Maudsley Hospital by Slater and Shields (see [151]). The probandwise concordance rate for definite anxiety neurosis was 41 per cent in 17 monozygotic twins compared to 4 per cent of 28 dizygotic twins. When the diagnostic criterion is broadened to include any blind diagnosis mentioning anxiety, the concordance was 65 per cent of 20 monozygotic twins and 13 per cent of 40 dizygotic twins[151]. These differences in concordance according to degree of genetic relationship suggest the importance of genetic contributions to predisposition to some chronic anxiety states in adults.

The findings of Slater and Shields have been confirmed and extended by recent family and twin studies that used explicit diagnostic criteria. In the Washington University Clinic Study of 500 psychiatric outpatients and their relatives, anxiety neurosis was defined as a disorder manifest by recurrent panic attacks (panic disorder) or chronic nervousness plus recurrent palpitations and/or dyspnea (other anxiety neurosis) in the absence of pre-existing psychiatric disorders[3]. The prevalence of a blind diagnosis of definite anxiety neurosis (panic disorder or other anxiety neurosis) was 8 per cent in 141 first degree relatives of probands with anxiety neurosis compared to 1·9 per cent in 1,084 first degree relatives of proband with other diagnoses. When the criteria were broadened to include probable and questionable cases, the prevalence was increased to 14 per cent in the relatives of anxiety neurosis probands compared to 6·5 per cent in the relatives of other probands. The findings in first degree relatives in the Washington University study are similar to those in the Maudsley Hospital study, which used similar sampling and blind assessment of a heterogeneous sample.

The Washington University study also noted that the familial aggregation of anxiety neurosis was largely accounted for by the families of probands with recurrent panic attacks complicated by agoraphobia. However, the affected relatives in these families had mostly recurrent panic attacks without agoraphobia or occasionally other mild anxiety states. This suggested the possibility that panic disorder and other anxiety disorders (such as generalized anxiety disorder in DSM-III) segregated in different families. Stated another way, not all individuals with chronic anxiety are

susceptible to developing panic attacks. Other psychiatric disorders including primary depression and alcoholism did not aggregate in families with anxiety disorders, suggesting striking diagnostic specificity.

Subsequently Torgersen[6, 7] has carried out a twin study in Norway that also suggests that familial recurrence risks are related to severity of illness and the presence of panic attacks. He identified 39 monozygotic and 40 dizygotic twins with neurosis from medical records and a twin registry. The ratio of the monozygotic to dizygotic concordance increased with severity of illness in the index twin: the ratio was less than one for those identified from clinics and greater than one for those who had a psychiatric hospitalization. The less frequent male pairs were also more likely to be concordant than female pairs. Torgersen also found that twins who had a history of panic attacks were more likely to be concordant than those without such attacks. When the probands had panic disorder, 31 per cent of 13 monozygotic co-twins had panic attacks compared to none of 16 dizygotic co-twins (two of these did have generalized anxiety disorder). In contrast, when the probands had generalized anxiety disorder (no panic attacks) 16 per cent of 12 monozygotic co-twins and 10 per cent of 20 dizygotic co-twins had the same diagnosis. Panic disorder and generalized anxiety disorder did not significantly aggregate in either the Washington University study or the Norwegian twin study. This suggests that there are specific familial factors that contribute to susceptibility to panic attacks that are not common to all types of anxiety disorder. However, patients who eventually develop recurrent panic attacks often experience other aspects of anxiety for several years prior to their first panic attack, so in family studies where age and experience of relatives is variable there is always a limited amount of aggregation of subjects with and without panic attacks.

Nevertheless, the limited overlap of panic disorder and generalized anxiety disorder in families excludes the possibility that panic disorder is simply a more severe form of a single disorder: in this case, severe (*i.e.*, panic disorder) probands would have more relatives with the mild (generalized anxiety disorder) form than do mild probands[152]. It is still possible that the development of panic disorder requires both a specific susceptibility to panic attacks and a more severe degree of sensitization for its expression than is typical of most cases of chronic anxiety. Under this hypothesis, panic probands would also tend to have greater tendency to harm avoidance and/or more threatening experiences than patients with generalized anxiety disorder. There is some support for this based on retrospective childhood histories of being apprehensive[3, 14, 153].

Several well designed interview studies of panic disorder have been carried out in Iowa. The major methodological difference from other studies is that only definite cases were selected as probands and these were compared to relatives of normal controls. The other studies were based on consecutive series of heterogeneous cases so that the possibilities for halo effects in assessment were less than in the Iowa

case-control studies. Using DSM-III criteria strictly, Crowe and associates[8] found that 61 per cent of 41 index families had panic disorder in at least one first-degree relative. The morbid risk in first degree relatives was 17·3 per cent for definite panic disorder in panic disorder probands compared to 1·8 per cent in relatives of normal controls. Some additional relatives had some panic attacks but not enough for a definite diagnosis: 7·4 per cent of the relatives of panic disorder probands and 0·4 per cent of control relatives. Other psychiatric disorders, including generalized anxiety disorder, primary unipolar depression, and alcoholism did not aggregate with panic disorder in these families. Carey has suggested that the higher morbid risks observed in the Iowa studies compared to those at Washington University or Maudsley Hospital may be related to differences in the selection of definite or severe probands and possible halo effects in assessment due to case-control design[151].

Harris *et al.*[154] further evaluated the relationship of panic disorder and agoraphobia in a family interview study in Iowa. All the agoraphobic probands had a history of recurrent panic attacks. The families of panic disorder patients had a morbidity risk of 20·5 per cent for panic disorder and 1·9 per cent for agoraphobia. In contrast the families of agoraphobics had a morbidity risk of 7·7 per cent for panic disorder and 8·6 per cent for agoraphobia. The risks were 4·2 per cent for each diagnosis in the control relatives. Thus the risk of being affected with panic disorder or agoraphobia was about the same in the two groups of families, but the relatives of agoraphobics were likely to have their panic attacks complicated by agoraphobia. This suggests that agoraphobia shows familial specificity rather than being simply a non-specific complication of severe recurrent panic attacks.

There was a high prevalence of school phobias or separation anxiety in the childhood histories of patients with panic disorder, particularly those who develop agoraphobia[155]. A history of school phobia or separation anxiety may be a predictor of which panic disorder patients are most likely to develop agoraphobia. However, Roth has emphasized that this association has low predictive power in the general population because most school phobics do not show psychopathology as adults[14].

Because of its relative clinical homogeneity and its strong familial aggregation and specificity, many investigators have considered the possibility of Mendelian inheritance in panic disorder. Pedigree analyses have been carried out to test alternative hypotheses about the mode of inheritance of panic disorder, including polygenic models and monogenic models.

In a study of 15 families, Pauls *et al.*[156] found a predominance of affected ancestral relatives occurred on either the paternal or maternal side of the family, but not on both sides. This is more likely with monogenic transmission than with polygenic transmission, but such patterns often reflect the artifact that the extent of information is seldom comparable on both sides of the family. Pedigree analysis was also carried out on 19 families that included the 15 used in the ancestral analysis. This showed

compatibility with monogenic transmission but did not exclude alternative hypotheses[157]. Crowe *et al.*[8] later carried out analyses that also took into account the sex differences in the family data that the earlier analyses had neglected. Both polygenic and monogenic models fit the data satisfactorily and neither could be excluded. Hence the results of published pedigree data do not permit discrimination of monogenic and multifactorial models.

Artificial selection experiments in animals suggest that polygenic models should be considered likely in chronic anxiety disorders in general. Nevertheless, specific clinical phenomena such as panic attacks or agoraphobia may be due to relatively specific genetic susceptibility factors even if overall susceptibility to chronic anxiety states has a more complex multifactorial etiology. For example, Wernicke-Korsakoff syndrome is a neuropsychiatric complication of malnutrition in alcoholism and anorexia nervosa. It is associated with a defective transketolase enzyme with a low affinity for binding thiamine. Reduced dietary intake of thiamine, as is common in alcoholics, triggers the onset of signs of Wernicke-Korsakoff syndrome in those who have the transketolase defect, which is thought to be due to a relatively common mutation at a single gene locus that is inherited as an autosomal recessive[158]. Similarly susceptibility to panic attacks may be a specific neuropsychiatric complication of chronic anxiety that has a relatively simple etiology in addition to the multifactorial basis of chronic anxiety states. Future pedigree analyses should consider mixed models in which there is multifactorial variation in the background of each genotype at a single locus that has a large effect on particular clinical subtypes. The multifactorial background should allow for both polygenic effects and cultural inheritance or social learning, and explicit models have been developed for this purpose[159, 160].

Family and Adoption Studies of Somatization

The families of patients with chronic somatic anxiety are strikingly different than those of patients with chronic cognitive anxiety. Early family studies of patients with Briquet's syndrome observed that 10 to 20 per cent of the female first degree relatives had the same disorder, a 5- to 10-fold increase over the lifetime risk of the disorder in women in the general population[161]. The male relatives of women with Briquet's syndrome also showed an increased risk of antisocial personality. Quantitative genetic analyses showed that the same familial factors predisposed to both Briquet's syndrome and antisocial personality in most cases[102]. In the same families, men developed antisocial personality whereas women developed somatization disorder when their familial predisposition was mild and antisocial personality when their predisposition was severe[102]. These early studies were done with structured interviews and explicit behavioral criteria, but they were not blind. Recently, a blind family interview study has confirmed the familial nature of Briquet's syndrome or somatization disorder in women and also the association with antisocial personality in

male and female relatives[4, 5, 11]. This is consistent with the hypothesis presented earlier that both somatic anxiety and impulsivity are associated with high novelty-seeking. Subjects with antisocial personality also tend to have poor avoidance learning associated with low harm avoidance. Low harm avoidance may also be characteristic of Briquet's syndrome in view of its association with frequent suicide attempts, aggressivity, and other antisocial behavior.

Familial aggregation could be due to genetic factors, environmental influences, or both. Recently an adoption study of somatoform disorders in Sweden has shown that the contributions of both genetic and environmental influences are substantial[10]. Two relatively discrete types of somatoform disorders were distinguished in 859 Swedish women using comprehensive lifetime medical records[1]. One of these disorders, called high-frequency somatization, was characterized by frequent headaches, backaches, gastrointestinal and gynecologic complaints associated with extensive psychiatric disability. Extensive overlap with Briquet's syndrome was suggested by available psychiatric evaluations. Women who were adopted-away at an early age had a 5-fold increase in high-frequency somatization if their biological parents had impulsive aggressive behavior as shown by registrations for violent crimes and frequent alcohol abuse that did not require treatment compared to the adopted-away children of other parents (10 versus 2 per cent). This is consistent with the hypothesis that this disorder is associated with a predisposition to both high novelty seeking and low harm avoidance. This is further supported by the recent finding that these female somatizers have low CSF 5-HIAA and low platelet monoamine oxidase (MAO) activity[162].

The second somatoform disorder, called diversiform somatization, was characterized by less frequent but a similar range of diverse bodily pains and infrequent psychiatric treatment. Adopted-away women with diversiform somatization were more than twice as frequent (31 versus 14 per cent) if their biological fathers had a history of non-violent property crime in the absence of alcohol abuse or a history of early onset alcoholism complicated by criminality[10]. These non-violent property crimes were mostly petty thefts and other impulsive acts that did not involve risk of personal injury to self or others. Similarly the subgroup of male alcoholics associated with diversiform somatization had registered behavior suggesting high novelty seeking and this has recently been confirmed by personality tests indicating high impulsivity and sensation seeking[163]. Interestingly, these alcoholics also had low activity of platelet monoamine oxidase[163], as expected in individuals predicted to have low brain monoamine turnover since the monoamine oxidase in platelets is the predominant one in brain (MAO B)[164].

Creed Abell and his associates have recently demonstrated that MAO B is localized in brain serotonergic cells including the nucleus raphe dorsalis and nucleus centralis superior whereas MAO A is localized in catecholaminergic (*i.e.*, dopaminergic and noradrenergic) neurons[165]. This may appear surprising because serotonin is

preferentially deaminated by MAO A and not MAO B[165]. However, this is consistent with observed associations of MAO B activity with serotonergic activity and personality[164]. In mice and men low brain and platelet MAO B activity is associated with low serotonergic activity[133]. MAO B preferentially metabolizes phenylethylamine, an endogenously produced neurotransmitter that is structurally the same as amphetamine except for a single methyl group. Low serotonergic and low MAO B activity are likely to be associated with higher levels of phenylethylamine. According to the model proposed here low serotonergic activity should differentiate aggressive criminals from other criminals, and hence it would be predicted that phenylethylamine levels should be higher in violent criminals than non-violent criminals. In fact this has been observed by Sandler *et al.*[166], who proposed that phenylethylamine overproduction may be a compensatory response to reduce aggressive behavior.

These findings support the hypothesis presented earlier that high novelty seeking is associated with somatic anxiety and impulsivity. When this is combined with a predisposition to low harm avoidance and poor avoidance learning, there is increased frequency of somatization and increased psychosocial disability as in the full Briquet's syndrome. A similar picture may arise when an individual with high novelty seeking but average harm avoidance begins to abuse 'anti-anxiety' drugs like alcohol. Such drug abuse artificially reduces harm avoidance and impairs avoidance learning by suppression of serotonergic activity.

Admixture analysis of quantitative scores discriminating the two types of male somatizers indicated that they were relatively discrete subtypes rather simply differing in severity of illness. The model of personality predisposition described here involves quantitative variation along three continuous dimensions. However, actual behavior involves the interaction of both these dimensional temperament variables with qualitatively distinct environmental events. Different types of developmental experiences were observed for each type of disorder in adoptees and also often differed by the sex of the adoptee. For example, criminality, but not somatization, was associated with multiple temporary placements in childhood and other indicators of inconsistent discipline or unstable caretaking. The effect of such discrete exogenous factors on the dimensional personality variables is to produce 'relatively' discrete categories with some underlying overlap but recognizable natural boundaries in terms of actual behavior.

A recent study of somatization in 807 adopted Swedish men indicated that most men with prominent somatization have features characteristic of the cognitive anxiety syndrome[2, 167]. Such 'asthenic' male somatizers had infrequent bodily pains but recuperate slowly from minor illness and are often disabled with complaints of fatigue and weakness. Cross-fostering analyses indicated that both genetic and environmental factors contributed substantially[167]. Such asthenic men had significantly fewer biological parents with criminality than did normal men or women. This indicates that

male and female relatives[4, 5, 11]. This is consistent with the hypothesis presented earlier that both somatic anxiety and impulsivity are associated with high novelty-seeking. Subjects with antisocial personality also tend to have poor avoidance learning associated with low harm avoidance. Low harm avoidance may also be characteristic of Briquet's syndrome in view of its association with frequent suicide attempts, aggressivity, and other antisocial behavior.

Familial aggregation could be due to genetic factors, environmental influences, or both. Recently an adoption study of somatoform disorders in Sweden has shown that the contributions of both genetic and environmental influences are substantial[10]. Two relatively discrete types of somatoform disorders were distinguished in 859 Swedish women using comprehensive lifetime medical records[1]. One of these disorders, called high-frequency somatization, was characterized by frequent headaches, backaches, gastrointestinal and gynecologic complaints associated with extensive psychiatric disability. Extensive overlap with Briquet's syndrome was suggested by available psychiatric evaluations. Women who were adopted-away at an early age had a 5-fold increase in high-frequency somatization if their biological parents had impulsive aggressive behavior as shown by registrations for violent crimes and frequent alcohol abuse that did not require treatment compared to the adopted-away children of other parents (10 versus 2 per cent). This is consistent with the hypothesis that this disorder is associated with a predisposition to both high novelty seeking and low harm avoidance. This is further supported by the recent finding that these female somatizers have low CSF 5-HIAA and low platelet monoamine oxidase (MAO) activity[162].

The second somatoform disorder, called diversiform somatization, was characterized by less frequent but a similar range of diverse bodily pains and infrequent psychiatric treatment. Adopted-away women with diversiform somatization were more than twice as frequent (31 versus 14 per cent) if their biological fathers had a history of non-violent property crime in the absence of alcohol abuse or a history of early onset alcoholism complicated by criminality[10]. These non-violent property crimes were mostly petty thefts and other impulsive acts that did not involve risk of personal injury to self or others. Similarly the subgroup of male alcoholics associated with diversiform somatization had registered behavior suggesting high novelty seeking and this has recently been confirmed by personality tests indicating high impulsivity and sensation seeking[163]. Interestingly, these alcoholics also had low activity of platelet monoamine oxidase[163], as expected in individuals predicted to have low brain monoamine turnover since the monoamine oxidase in platelets is the predominant one in brain (MAO B)[164].

Creed Abell and his associates have recently demonstrated that MAO B is localized in brain serotonergic cells including the nucleus raphe dorsalis and nucleus centralis superior whereas MAO A is localized in catecholaminergic (*i.e.*, dopaminergic and noradrenergic) neurons[165]. This may appear surprising because serotonin is

preferentially deaminated by MAO A and not MAO B[165]. However, this is consistent with observed associations of MAO B activity with serotonergic activity and personality[164]. In mice and men low brain and platelet MAO B activity is associated with low serotonergic activity[133]. MAO B preferentially metabolizes phenylethylamine, an endogenously produced neurotransmitter that is structurally the same as amphetamine except for a single methyl group. Low serotonergic and low MAO B activity are likely to be associated with higher levels of phenylethylamine. According to the model proposed here low serotonergic activity should differentiate aggressive criminals from other criminals, and hence it would be predicted that phenylethylamine levels should be higher in violent criminals than non-violent criminals. In fact this has been observed by Sandler *et al.*[166], who proposed that phenylethylamine overproduction may be a compensatory response to reduce aggressive behavior.

These findings support the hypothesis presented earlier that high novelty seeking is associated with somatic anxiety and impulsivity. When this is combined with a predisposition to low harm avoidance and poor avoidance learning, there is increased frequency of somatization and increased psychosocial disability as in the full Briquet's syndrome. A similar picture may arise when an individual with high novelty seeking but average harm avoidance begins to abuse 'anti-anxiety' drugs like alcohol. Such drug abuse artificially reduces harm avoidance and impairs avoidance learning by suppression of serotonergic activity.

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high cognitive anxiety is negatively correlated with genetic antecedents of impulsivity or criminality, as expected according to the hypothesis that cognitive anxiety is associated with an extremely strong predisposition toward harm avoidance and low novelty seeking. This also indicates that genetic factors cannot be ignored in the etiology of chronic cognitive anxiety in adults.

Overview of the Developmental Model

In this article I have attempted a synthesis of available information about the development of chronic anxiety by integrating relevant information from several different fields including genetics (human, animal, and evolutionary studies), psychology (learning theory, cognitive psychology, psychophysiology, personality theory), and psychiatry (nosology, psychopharmacology, longitudinal research). I felt that the discipline of having to reconcile disparate observations about phenomena as different as anxiety and somatoform disorders helped to obtain a more robust etiological model to guide future research and practice than would have been achieved otherwise. The model that emerges indicates that there is systematic interaction of biological and social factors in the developmental pathway from genotype to phenotype.

According to the theory developed here, predisposition to chronic anxiety is determined by heritable differences between individuals in traits called 'harm avoidance', 'novelty seeking', and 'reward dependence'. Individuals who are predisposed to be highly harm avoidant easily acquire conditioned avoidant responses to aversive stimuli, which makes them especially susceptible to becoming fearful, apprehensive, and worried. Individuals who have little predisposition to harm avoidance show poor avoidance learning to aversive stimuli, which allows them to be carefree and sociable often but also reduces their resistance to activities that increase the risk of personal injury. Animal and human studies suggest that variation in this dimension is influenced by polygenic factors that modify the activity of serotonergic neurons in a central behavioral inhibition system. This is supported by anatomical and pharmacological studies as well as measurement of serotonin turnover by cerebrospinal fluid studies of patients with personality disorders and suicidal behavior.

A predisposition to high harm avoidance is also associated with high vigilance and reduced habituation to potentially dangerous situations. When this is combined with low reward dependence and low novelty seeking, individuals have excellent skill in recognizing hidden threats and contingent relationships and so tend to overestimate potential risks in ordinary circumstances. Because there are few situations that are totally safe, such individuals will become sensitized, *i.e.*, develop chronic anxiety in which there is prominent anticipatory anxiety, ruminative worrying, and social introversion. Such chronic anxiety associated with high harm avoidance is recognized

in the syndrome of chronic cognitive anxiety, which is often prominent in patients with generalized anxiety disorder, panic disorder, obsessional personalities/disorders, and some neurotic depressions. There appear to be additional specific genetic antecedents that lead to familial specificity of such disorders. For example, family and twin studies indicate that there are relatively specific susceptibility factors for panic attacks and agoraphobia.

In contrast to such cognitive anxiety states, individuals with a strong predisposition to novelty seeking have a tendency toward both impulsivity and somatic anxiety with frequent bodily pains according to the theory developed here. They may engage in impulsive criminal acts against property but are unlikely to risk personal injury in the absence of low harm avoidance. Such individuals can maintain rewarded behaviors when adequately motivated, but they prefer exploratory activity and pursuit of novel thrills, pleasures, and adventures. It is hypothesized here that such impulsive individuals tend to have low activity in the central dopaminergic pathways that project from the ventral tegmentum to the striatum, nucleus accumbens, and frontal and limbic cortex. These ascending projections appear to have an 'incentive' function to activate approach toward environmental stimuli that are potentially associated with rewards. Low activity in this system in individuals with high novelty seeking is suggested by findings of low levels of the dopamine metabolite homovanillic acid in their cerebrospinal fluid, a tendency to seek out novel stimuli which increase perceptual sensitivity, and a tendency to augment the amplitude of sensory input. This may predispose to hyperactivity, excitability, impulsivity, low pain and sensation thresholds, and susceptibility to conversion reactions at times of stress via negative feedback relationships between the cortex and the reticular activating system[26, 89].

Individuals with high reward dependence are supposed to respond more intensely to rewards than do others, and so maintain rewarded behaviors more strongly. This is associated with their being ambitious, industrious, and affectively warm as well as moody. Frustrative non-reward precipitates compensatory need to increase reward seeking behavior as well as rebound noradrenergic hyperactivity which leads to reactive dysphoric state associated with hypercortisolemia. Such reactive dysphoric states may be acute or recurrent. Susceptibility to such reactive dysphoria depends primarily on high reward dependence but is reduced by high harm avoidance and high novelty seeking.

Individuals with high novelty seeking, high reward-dependence, and low harm avoidance ('histrionic personality') tend to be distractible and hypovigilant. This information processing pattern is supposed to lead such individuals to be unreliable in predicting when they will be exposed to potentially aversive stimuli. Consequently such individuals are likely to be sensitized by unpredicted aversive stimuli and may 'mature' as a result of long term sensitization which facilitates monoaminergic neurotransmission. However, excessive sensitization may lead to a chronic anxiety

state associated with prominent somatization, particularly diverse bodily pains. When sensitized, the skin conductance responses of such individuals habituate poorly to repeated stimuli (as do individuals with a tendency to cognitive anxiety) but they still have pain and sensation thresholds that are lower than those of patients with cognitive anxiety.

Adoption studies suggest that relatively discrete disorders arise depending on interactions between continuously distributed personality traits and discrete types of environmental events. Women have a higher threshold for antisocial behavior and a lower threshold for somatic anxiety than do men. High novelty seeking in combination with average levels of harm avoidance predispose to somatic anxiety and/or impulsive criminal acts that are unlikely to involve personal injury. High harm avoidance in combination with average levels of novelty seeking predispose to cognitive anxiety with frequent disability from fatigue and weakness and slow recuperation from stress or minor illness. High novelty seeking and low harm avoidance together lead to aggressive impulsive behavior and frequent somatization, as seen in Briquet's syndrome and some forms of antisocial personality with aggressive conduct[168]. When individuals with high novelty seeking abuse alcohol and other drugs that reduce harm avoidance, they are likely to develop aggressive impulsive behavior and/or more frequent somatization.

Chronic anxiety states develop gradually over many years. In the case of individuals with high novelty seeking and low harm avoidance, there is a marked change in habituation responses as a result of long-term sensitization. According to the theory developed here, they are congenitally poor in aversive conditioning and their skin conductance responses habituate rapidly to aversive stimuli. Although patients with acute conversion reactions have rapid responses, patients with chronic somatic anxiety (as in Briquet's syndrome) after sensitization habituate poorly to repeated stimuli[44], as do patients with chronic or acute cognitive anxiety[43]. Available findings are limited to cross-sectional comparisons of different groups. Direct tests of these predicted changes in longitudinal family studies are warranted.

Comparison to Other Personality Models

There have been many efforts to develop a comprehensive model of personality, and the resulting theories differ markedly from one another. It is beyond the scope of the present paper to describe even the major theories, but this has been presented by Hall and Lindzey[169] and Wiggins[170]. Wiggins described three clusters of theories. One cluster includes the neo-Freudians whose theories emphasize the salient influence of social and cultural determinants of behavior. This cluster includes Adler, Fromm, Horney, and Sullivan. A second cluster includes the self theorists who emphasize the importance of judging behavior in the context of the total organismic unit and

recognizing that humans are organisms who seek to achieve personally defined purposes. This cluster includes Angyal, Goldstein, Rogers, and Allport. The priority of organismic purpose was principally challenged by behaviorists such as Skinner, who emphasized that patterns of behavior are always learned or acquired through the experience of rewards and punishment. A third group emphasizes the importance of personality structure with a formal framework of mechanisms or traits that take into account genetic and biological determinants of behavior but tend not to emphasize learning processes or social and situational influences. This group is highly heterogeneous and includes Freud, Sheldon, Jung, Murray, Eysenck, Gray, and Tellegen.

The theory discribed here attempts to unify these different emphases into a developmental model that accounts for neurobiological, psychosocial, and learning processes in a balanced comprehensive manner. It recognizes that there are biogenetically distinct dimensions underlying personality variation that are moderately heritable and moderately stable across time and situations. However, learning and social influences are as important as biological and genetic influences in shaping the development of personality. Different neurobiological dimensions interact with one another to produce integrated patterns of response to punishment, reward, and novelty that may be modified by socially-influenced patterns of cognitive assessment in different situations. Such a unified model is needed to account for available information about neurobiology, learning, and personality structure.

Personality traits are not invariantly stable across time or situations, as has been emphasized by situationist theorists like Mischel[171]. Mischel observed that individuals behave rather inconsistently in different situations, leading him to challenge the central tenet of trait theories that assume that an individual's behavior is highly predictable and consistent regardless of situational influences. Studies that correlate behavioral ratings in one specific situation with those in another situation are seldom correlated more than 0·3[172], but self-reports or aggregated ratings across a variety of situations are often moderately or highly reliable in test-retest studies[173]. Studies that try to partition variance to personality traits, to situations, or to their interaction find that most variability is attributable to the interaction of personality and situations rather than either alone[172, 174]. The theory presented here is an interactional model in which behavior is seen as an integrated pattern of responses to situational cues and the multiple neurobiological processes underlying personality variation. The response to environmental stimuli necessarily involves the interaction of multiple underlying biogenetic dimensions so that the structure of environmental influences on personality is necessarily different from the genetic structure. For example, novel stimuli elicit an integrated response involving predispositions toward novelty seeking (which activates approach to novel stimuli) and harm avoidance (which inhibits behavior involving novel stimuli that may be dangerous). Likewise rewards and non-punishment (or

punishment and non-reward) elicit integrated responses involving predispositions toward reward dependence and harm avoidance. Thus environmental variability contributing to harm avoidance is correlated with each of the other two dimensions. As a result the structure of environmental contributions to personality is not the same as the underlying genetic structure. Consequently biogenetic, environmental, and phenotypic variation must be considered separately. Futhermore, novelty can only be defined in relation to prior experience so situational and experiential factors must be as carefully specified as observed personality traits.

The models of Eysenck, Gray, and Tellegen all posit three dimensions of personality besides intelligence, but are distinct from the theory described here. Tellegen has recently presented a concise comparison of his model with that of Gray and Eysenck[173]. Factor analytic studies of variation on self-report inventories of personality produce remarkably consistent descriptions of the phenotypic structure. Tellegen labels factors obtained from his Multidimensional Personality Questionnaire (MPQ) as positive emotionality, negative emotionality, and constraint. He indicates that in practice these correspond closely to extraversion, neuroticism, and psychoticism as measured by Eysenck's Personality Questionnaire (EPQ), despite differences with Eysenck's original theoretical constructs and earlier measures of extraversion and neuroticism. Eysenck's recent measure of extraversion emphasizes sociability items whereas impulsivity items from older measures are included with psychoticism. Tellegen suggests that his phenotypic dimensions correspond to the three neurobiological systems postulated by Gray.

Gray proposes that there are three emotional systems in brain, each with its separate behavioral function. Gray suggests that the behavioral activation system, mediated by Olds' reward system, is said to control active approach and avoidance behavior in response to signals of reward and non-punishment. Gray suggests that this underlies behavioral variation which he labels as 'impulsivity'. The second system, the behavioral inhibition system, mediated by the septo-hippocampal 'stop' system described earlier here, regulates extinction and passive avoidance in response to signals of punishment and frustrative non-reward. Gray suggests that this underlies behavioral variation which he labels as 'anxiety'. The third system, the fight/flight system involving amygdalo-hypothalamo-midbrain structures, is said to control escape and defensive aggressive behavior in response to unconditioned (rather than conditioned signals of) punishment and non-reward. Gray has suggested that this corresponds to Eysenck's psychoticism dimension. Tellegen accepts these putative systems as plausible substrates for the phenotypic dimensions he observes, but objects to the 'impulsivity' label for the behavior associated with sensitivity to reward signals. Tellegen feels that sensitivity to rewards would be associated with what he calls high positive emotionality, not with impulsivity.

The models of Gray and Tellegen differ from that described here in at least two

fundamental ways. First of all, Gray neglects the distinction between the 'incentive' aspects of behavioral activation that are mediated by dopaminergic neurons and the 'maintenance' or 'reinforcement' aspects that are mediated by noradrenergic neurons[79]. As a consequence Gray attempts to account for impulsivity as sensitivity to rewards, to which Tellegen objects quite reasonably. In my model, reward dependence is genetically independent from novelty seeking, which is associated with impulsivity, low constraint, easy distractibility, and frequent exploratory behavior.

The second fundamental difference is that Gray and Telegen implicitly assume that the observed phenotypic structure of personality corresponds with the underlying biogenetic variation. Actually Gray uses biological data to criticize the phenotypic rotation of Eysenck, but then recommends another phenotypic rotation rather than recognizing that the biogenetic structure does not correspond to the natural phenotypic structure. My model specifies the genetic structure and predicts correlated environmental variation between these genetic dimensions, which consequently leads to different genetic and phenotypic structures. Eaves and Eysenck[69] have clearly shown in pedigree analyses that the genetic and phenotypic factor structures are different. This observed difference between the genetic and phenotypic structures is predicted by my model because the behavioral inhibition system modulates both novelty seeking and reward seeking behaviors.

As a consequence of the interaction of harm avoidance with the other two genetic dimensions, phenotypic variation consistently involves a general neuroticism (or negative emotionality) factor with harm avoidance as the major determinant and lesser positive contributions from both novelty seeking and reward dependence. The orthogonal factor analyses of phenotypic variation also include an extraversion factor with a major determinant from high reward dependence consistently and lesser contributions from various combinations of harm avoidance and novelty seeking; the combination of low harm avoidance and high novelty seeking gives impulsivity (as in Eysenck's original extraversion scale) whereas the combination of low harm avoidance and low novelty seeking gives hyperthymia (as in Tellegen's positive emotionality factor). The third orthogonal phenotypic factor depends on the other two and gives rise to much semantic confusion because of labelling problems. Consistently novelty seeking is the major determinant of the dimension but the direction of the contributions of reward dependence and novelty seeking may be the same or different. An obsessional versus histrionic factor may arise with a major contribution from low novelty seeking and lesser contributions from high harm avoidance and low reward dependence or social detachment (as in Tellegen's high constraint or low impulsiveness factor). Alternatively an antisocial versus passive-dependent factor may arise when high novelty seeking is combined with low harm avoidance and low reward dependence (giving high toughmindedness, social detachment or antisociality as in Eysenck's psychoticism scale) versus low novelty seeking combined with high harm

avoidance and high reward dependence (giving low antisociality or high passive-dependence). These phenotypic factors represent different behavioral strategies for integrating the influences of the three underlying biogenetic dimensions in response to environmental challenge, but the choice of ways of combining the direction of effects for novelty seeking and reward dependence is rather arbitrary in three dimensional space. As a result I have preferred to define my model in terms of underlying genetic dimensions and to explain the pattern of interactions between genetic dimensions in response to environmental challenge.

The model proposed here is descriptively most similar to that of Sjöbring, who also emphasized the importance of specifying the underlying genetic structure. However, the theoretical basis of my model is totally different from that of Sjöbring[59], who developed his speculative ideas without access to information from recent advances in neurobiology. There are substantial descriptive differences also because clinical ratings are guided by Sjöbring's theoretical constructs rather than empirical descriptive studies. For example, low solidity is similar to high novelty seeking except distractibility and exploratory behavior are not described as characteristic of low solidity, as they are of high novelty seeking. Validity is similar to low harm avoidance except that validity is associated with high confidence but not necessarily high risk-taking. Stability is similar to low reward dependence except that stability is associated with facility with abstract thinking whereas this is not necessarily true of reward dependence. As noted earlier, empirical results with personal interviews and self-report instruments support the dimensional descriptions presented here.

Implications for Future Research

These findings indicate that the developmental pathway to chronic anxiety states is complex, involving heritable differences between individuals in neurobiological systems that influence personality, information processing, and acquisition of adaptive responses to environmental and social circumstances. There may be relatively specific genetic susceptibility factors for particular phenomena such as panic attacks and certain types of phobic responses, but these must be considered against the multifactorial background that is involved in their development.

Progress in understanding anxiety states will be handicapped if attention is restricted to self-reported symptoms or cross-sectional signs. Measurements are needed at several levels of observation. These include *(1)* clinical ratings of behavior and symptoms; *(2)* ratings of personality traits relevant to novelty-seeking, harm avoidance, and reward dependence; *(3)* measures of information processing including tests of neuropsychological function and performance on vigilance tasks; *(4)* performance in habituation and conditioning experiments for a range of incentive conditions and types of stimuli; *(5)* measures of neurotransmitter function and

responses to biochemical challenges; and (6) genetic data. Both observational and self-report information is likely to be valuable. Recent advances in brain imaging techniques to assess regional brain function are promising because specific predictions are made about particular pathways in the theory developed here. This allows advances in our knowledge of neurophysiology and neuropharmacology to be integrated with developmental studies.

Longitudinal family studies offer particular promise for testing such development theories like that described here. Family studies identify individuals at high risk who can be followed longitudinally on multiple measures. Predictions can be tested over time within individuals and also across individuals within and between families.

Anxiety was early recognized to involve adaptive defensive responses to the environment[42, 47, 48]. The maintenance of susceptibility to chronic anxiety in man should not be seen as anachronistic as some have suggested[120]. Either extreme hypervigilance or extreme hypovigilance lead to impaired ability to distinguish dangerous circumstances from safe situations and hence to make reliable predictions. Maintenance of the related genetic variability is likely in the population because of balanced selection against either extreme.

Social learning of attitudes and expectancy sets may modify responses as suggested by cognitive therapists. However, twin and adoption studies in man and artificial selection experiments in animals strongly indicate that genetic and neurobiological variation that influence older parts of the vertebrate brain make fundamental contributions to predisposition to chronic anxiety states. We need to take into account the bidirectional interaction between neocortical influences and conditioned responses of the limbic system. Hence both social learning and genetic influences must be considered[10, 11, 159].

Studies of either genetic factors or life events alone are each severely limited because we need to evaluate heritable differences between individuals in their adaptive responses to challenges from varying external and internal environmental stimuli. This requires a developmental analysis of individuals both within and between families. Life event research is greatly handicapped by the inevitable confounding of what is given in experience with the individual's processing of and adaptation to what is given. In other words, stimulus and response become inextricably confounded when individuals vary in their response predisposition and their expectancies of the salience and significance of the same events. However, measurement of 'expressed emotion' involving recurrent critical attitudes towards family members may provide a practical index of the probability that an individual will be subject to repetitive aversive conditioning, and this can be experimentally modified[175, 176].

Likewise genes do not determine the phenotype directly. Genetic factors influence the pattern of response to nongenetic stimuli, and the resulting expression will vary due to epigenetic variables such as age, sex, social status, and other aspects of

experience. Relatively specific genes may be involved in susceptibility to specific neuropsychiatric complications of chronic anxiety such as panic attacks or other particular phobic response patterns like agoraphobia. However, even for such specific phenomena it is valuable to take into account the multifactorial system that influences development of the state in which the latent susceptibility to such complications can be expressed. Given the non-Mendelian patterns, delayed age of onset, and variable expression that are characteristic of all the chronic anxiety disorders, it is important to recognize that chronic anxiety states and related personality traits have a complex developmental pathway.

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References

1. Clonniger CR, Sigvardsson S, von Knorring A-L and Bohman M. An adoption study of somatoform disorders. II. Identification of two discrete somatoform disorders. Arch Gen Psychiatry 1984; 41: 863–871.
2. Sigvardsson S, Bohman M, von Knorring A-L and Cloninger CR. Symptom patterns and causes of somatization in men. I. Differentiation of two discrete disorders. Genetic Epidem 1986; 3: 153–170.
3. Cloninger CR, Martin RL, Clayton PJ and Guze SB. A blind follow-up and family study of anxiety neurosis: Preliminary analysis of the St. Louis 500. In Klein DF and Rabkin J (Eds). Anxiety: New Research and Changing Concepts. New York, Raven Press, 137–150, 1981.
4. Cloninger CR, Martin RL, Guze SB and Clayton PJ. Somatization in Men and Women: A prospective follow-up and family study. Am J Psychiatry, 1986; 43: 873–878.
5. Guze SB, Cloninger CR, Martin RL and Clayton PJ. A follow-up and family study of Briquet's syndrome. Br J Psychiatry, In press, 1986.
6. Torgersen S. Genetics of neurosis: The effects of sampling variation upon the twin concordance ratio. Br J Psychiatry 1983a; 142: 126–132.
7. Torgersen S. Genetic factors in anxiety disorders. Arch Gen Psychiatry 1983b; 40: 155–162.
8. Crowe RR. The genetics of panic disorder and agoraphobia. Psychiatric Dev 1985; 2: 171–186.

9. Sigvardsson S, von Knorring A-L, Bohman M and Cloninger CR. An adoption study of somatoform disorders. I. The relationship of somatization to psychiatric disability. Arch Gen Psychiatry 1984; 41: 853–862.
10. Bohman M, Cloninger CR, von Knorring A-L and Sigvardsson S. An adoption study of somatoform disorders. III. Cross-fostering analysis and genetic relationship to alcoholism and criminality. Arch Gen Psychiatry 1984; 41: 872–878.
11. Cloninger CR. Somatoform and Dissociative Disorders. In Winokur G and Clayton PJ (Eds). Medical Basis of Psychiatry. New York, W. B. Saunders Co, In press, 1986b.
12. Gale A and Edwards JA. Physiological Correlates of Human Behavior. III. Individual Differences and Psychopathology. New York, Academic Press, 1983.
13. Klein DF. Anxiety Reconceptualized. In Klein DF and Rabkin J (Eds). New York, Raven Press 1981. 41: 872–878, 1984.
14. Roth M. Agoraphobia, Panic Disorder and Generalized Anxiety Disorder: Some implications of Recent Advances. Psychiatric Dev 1984; 2: 31–52.
15. American Psychiatric Association Task Force on Nomenclature and Statistics. Diagnostic and Statistical Manual, 3rd edition (DSM-III). Washington DC, American Psychiatric Association, 1980.
16. Schalling D, Cronholm B, Åsberg M and Espmark S. Ratings of psychic and somatic anxiety indicants—interrater reliability and relations to personality variables. Acta Psychiatr Scand 1973; 49: 353–368.
17. Hamilton M. The assessment of anxiety by rating. Br J Med Psychol 1960; 23: 56–62.
18. Buss AH. Two anxiety factors in psychiatric patients. J Abnorm Soc Psychol 1960; 23: 56–62.
19. Fenz WD and Epstein S. Manifest anxiety: unifactorial or multifactorial composition? Percept Motor Skills 1965; 20: 773–780.
20. de Bonis M. Etude factorielle de la symptomatologie subjective de l'anxiete. Rev Psychol Appl 1968; 18: 177–187.
21. Morris LW, Davis MA and Hutchings CH. Cognitive and emotional components of anxiety: Literature review and a revised worry-emotionality scale. J Educational Psychol 1981; 73: 541–555.
22. Lehrer PM and Woolfolk RL. Self-report assessment of anxiety: Somatic, cognitive, and behavioral modalities. Behav Assessment 1982; 4: 167–177.
23. Tamaren AJ, Corney RM and Allen TW. Assessment of cognitive and somatic anxiety. Behav Assessment 1985; 7: 197–202.
24. Woodruff RA Jr, Guze SB and Clayton PJ. Anxiety Neurosis among psychiatric outpatients. Compr Psychiatry 1972; 13: 165–170.
25. Perley MJ and Guze SB. Hysteria—the stability and usefulness of clinical criteria. N Engl J Med 1962; 266: 421–426.
26. Schalling D. Psychopathy-related personality variables and the psychophysiology of socialization. In Hare RD and Schalling D (Eds). Psychopathic Behavior: Approaches to Research. New York, John Wiley & Sons, pp. 85–106, 1978.
27. Jung CG. Psychologische Typen (1921), reprinted in English in De Laszlo (Ed): The Basic writings of C. G. Jung, New York, 1959.
28. Eysenck HJ. The Biological Basis of Personality. Springfield, Illinois, Charles C. Thomas, 1967.
29. Cloninger CR, von Knorring A-L, Sigvardsson S and Bohman M. Symptoms patterns and causes of somatization in men. II. Genetic and environmental independence from somatization in women. Genetic Epidem 1986; 3: 171–186.

30. Shagass C and Jones AL. A neurophysiological test for psychiatric diagnosis: Results in 750 patients. Am J Psychiatry 1958; 114: 1002–1009.
31. Shagass C and Kerenyi AB. Neurophysiologic studies of personality. J Nerv Ment Dis 126: 141–147.
32. Perez-Reyes M. Differences in sedative susceptibility between types of depression: clinical and neurophysiological significance. In Williams TA, Katz MM and Shield JA Jr (Eds): Recent Advances in the Psychobiology of the Depressive Illnesses. Washington DC, US Gov Printing Office, 1972, pp 119–130.
33. Bianchi GN. Patterns of hypochondriasis. A principal components analysis. Br J Psychiatry 1973; 122: 541–548.
34. Gray JA. Anxiety, Personality and the Brain, in Physiological Correlates of Human Behavior. III. Individual Differences and Psychopathology. In Gale H and Edwards JA (Eds). New York, Academic Press, 1983, pp. 31–43.
35. Stein L. Behavioral pharmacology of benzodiazepines. In Klein DF and Rabkin J (Eds). New York, Raven Press, 1981, pp. 201–214.
36. Insel TR, Ninan PT, Aloi J, Jimerson DC, Skolnick P and Paul SM. A benzodiazepine receptor-mediated model of anxiety. Arch Gen Psychiatry 1984; 41: 741–750.
37. Wheatley D. General Practitioner Clinical Trials: Chlordiazepoxide in anxiety states. 2. long-term study. Practitioner 1965; 195: 692–695.
38. Wender PH, Reimherr FW and Wood DR. Attention deficit disorder ("Minimal brain dysfunction") in adults: A replication study of diagnosis and drug treatment. Arch Gen Psychiatry 1981; 38: 449–456.
39. Cloninger CR. Pharmacological Approaches to the treatment of antisocial behavior. In Hippius H, Winokur G (Eds). Psychopharmacology Vol 1, Part 2: Clinical Psychopharmacology. Amsterdam, Excerpta Medica, 1983, pp. 353–370.
40. Dilger WC. Animal Behavior. Encyclopedia Britannica, Vol 2: 804–814, 1980.
41. O'Gorman JG. Habituation and Personality. In Gale A and Edwards JA (Eds). Physiological Correlates of Human Behavior. III. Individual Differences and Psychopathology. New York, Academic Press, 1983, pp. 45–62.
42. Darwin C. The Expression of the Emotions in Man and Animals. New York, D Appleton & Co, 1873.
43. Lader M. Anxiety and Depression. In Gale A and Edwards JA (Eds). Physiological Correlates of Human Behavior. III. Individual Differences and Psychopathology. New York, Academic Press, 1983, pp. 155–169.
44. Mears R and Horvath TB. 'Acute' and 'chronic' hysteria. Br J Psychiatry 121: 653–657, 1972.
45. Parasuraman R. Vigilance, arousal and effort. In Gale A and Edwards JA (Eds). Physiological Correlates of Human Behavior. II. Attention and Performance. New York, Academic Press, 1983, pp. 35–56.
46. Öhman A, Eriksson A, Fredriksson M, Hugdahl K and Olofsson C. Habituation of the electrodermal orienting reaction to potentially phobic and supposedly neutral stimuli in normal human subjects. Biol Psychol 1974; 2: 85–93.
47. Freud S. Inhibitions, symptoms and anxiety (1926), in Standard Edition of the Complete Psychological Works of Sigmund Freud. London, Hogarth Press, 1964.
48. Pavlov IP. Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Translated and Edited by Anrep GV. London, Oxford University Press, 1927.
49. Kandel ER. From metapsychology to molecular biology: explorations into the nature of anxiety. Am J Psychiatry 1983; 140: 1277–1293.

50. Seligman MEP. Helplessness. San Francisco, WH Freeman, 1975.
51. Eysenck HJ: The conditioning model of neurosis. Behav and Brain Sci 1979; 2: 155–166.
52. Bailey CH and Chen MC. Morphological basis of long-term habituation and sensitization in Aplysia. Science 1983; 220: 91–93.
53. Shapiro D. Neurotic Styles. New York, Basic Books, 1965.
54. Horowitz MJ (Ed). Hysterical Personality. New York, Jason Aronson, Inc, 1977.
55. Bendefeldt F, Miller LL and Ludwig AM. Cognitive hysteria. Arch Gen Psychiatry 1976; 33: 1250–1254.
56. Ludwig AM. Hysteria: a neurobiological theory. Arch Gen Psychiatry 1972; 27: 771–786.
57. Almgren PEN, Nordgren L and Skantze H. A retrospective study of operationally defined hysterics. Br J Psychiatry 1978; 132: 670–673.
58. Siddle DAT, Kuiack M and Kroese BS. The orienting reflex. In Gale A and Edwards JA (Eds). Physiological Correlates of Human Behavior. II. Attention and Performance. New York, Academic Press, 1983, pp. 149–170.
59. Sjöbring H. Personality Structure and development: A model and its application. Acta Psychiatr Scand Suppl 1973; 244.
60. Eysenck HJ: Neurosis and intelligence. Lancet 2: 362–368, 1943.
61. Slater E and Slater P. A heuristic theory of neurosis. J Neurol Psychiatry 1944; 7: 49–55.
62. Slater E. The Neurotic Constitution: A statistical study of two thousand neurotic soldiers. J Neurol Psychiatry 1943; 6: 1–16.
63. Lader MH. Psychophysiology of anxiety. In Lader M (Ed). Studies of Anxiety. Br J Psychiatry Special Pub No. 3, 1969.
64. Martin NG, Eaves LJ and Fulker DW. The genetical relationship of impulsiveness and sensation seeking to Eysenck's personality dimensions. Acta Genet Med Gemellol (Roma). 1979; 28: 197–210.
65. Torgersen S. The oral, obsessive, and hysterical personality syndromes: A study of hereditary and environmental factors by means of the twin method. Arch Gen Psychiatry 1980; 37: 1272–1277.
66. McCrae RR, Costa PT Jr and Arenberg D. Constancy of adult personality structure in males: longitudinal, cross-sectional and times-of-measurement analyses. J Gerontol 1980; 35: 877–883.
67. Gajar AH and Hale RL. Factor analysis of the Quay-Peterson Behavior Problem Checklist across racially different exceptional children. J Psychol 1982; 112: 287–293.
68. Flynn PM and McMahon RC. An examination of the factor structure of the Millon Clinical Multiaxial Inventory. J Pers Assess 1984; 48: 308–311.
69. Eaves L and Eysenck HJ. The nature of extraversion: a genetical analysis. J Per Soc Psychol 1975; 32: 102–112.
70. Barrett JE Jr. Use of the M-N-T Inventory (Sjöbring Personality Dimensions) on an American Population. Acta Psychiatr Scand 1972; 48; 501–509.
71. Barrett JE Jr. Sjöbring Personality Dimensions: Norms for some American populations. Acta Psychiatr Scand 1975; 52: 107–115.
72. Loehlin JC. Are personality traits differentially heritable? Behav Genet 1982; 12: 417–428.
73. Dantzer R. Benzodiazepines and the limbic system. In Trimble MR and Zarifian E (Eds). Psychopharmacology of the limbic system. New York, Oxford University Press, 1984, pp. 148–163.
74. Medina JH, Novas ML and De Robertis E. Changes in benzodiazepine receptors by acute stress: different effect of chronic diazepam or RO 15–1788 treatment. Eur J Pharmacol 1983; 96: 181–185.

75. Robertson HA, Martin IL and Candy JM. Differences in benzodiazepine receptor binding in Maudsley reactive and Maudsley non-reactive rats. Eur J Pharmacol 1978; 50: 455–457.
76. Robertson HA. Benzodiazepine receptors in 'emotional' and 'non-emotional' mice: comparison of four strains. Eur J Pharmacol 1979; 56: 163–6.
77. Sepinwall J and Cook L. Mechanism of action of the benzodiazepines: behavioral aspects. Fed Proc 1980; 39: 3021–31.
78. Thiebot M-H, Hamon M and Soubrie P. Serotonergic neurones and anxiety-related behavior in rats. In Trimble MR and Zarifian E (Eds). Psychopharmacology of the limbic system. New York, Oxford University Press, 1984, pp. 164–174.
79. Crow TJ and Deakin JFW. Neurohumoral transmission, behavior, and mental disorder, in Handbook of Psychiatry, Vol 5: The Scientific Foundations of Psychiatry, Shepherd M (Ed). Cambridge, Cambridge University Press, 1985, pp. 137–182.
80. Neary RS and Zuckerman M. Sensation seeking, trait and state anxiety, and electrodermal orienting reflex. Psychophysiology 1976; 13: 205–211.
81. Hare RD and Schalling D (Eds). Psychopathic Behavior: Theory and Research. New York, John Wiley & Sons, 1978.
82. von Knorring L, Monakhov K and Perris C. Augmenting/reducing: an adaptive switch mechanism to cope with incoming signals in healthy subjects and psychiatric patients. Neuropsychobiology 1978; 4: 150–179.
83. Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R and Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. Life Sciences 1983; 33: 2609–2614.
84. Crawley JN, Ninan PT and Pickar D *et al.* Neuropharmacological antagonism of the beta-carboline-induced 'anxiety' response in rhesus monkeys. J Neurosci 1985; 5: 477–485.
85. Siever LJ and Uhde TW. New studies and perspectives on the noradrenergic receptor system in depression: effects of the alpha 2-adrenergic agonist clonidine. Biol Psychiatry 1984; 19: 131–156.
86. Pitts FN Jr and McClure JN Jr. Lactate metabolism in anxiety neurosis. N Engl J Med 1967; 277: 1328–1336.
87. Liebowitz MR, Gorman JM and Fyer AJ *et al.* Lactate provocation of panic attacks. Arch Gen Psychiatry 1985; 42: 709–722.
88. Reiman EM, Raichle ME, Butler FK, Herscovitch P and Robins E. A focal brain abnormality in panic disorder, a severe form of anxiety. Nature 1984; 310: 683–685.
89. Cloninger CR. The link between hysteria and sociopathy: an integrative model of pathogenesis based on clinical, genetic, and neurophysiological observations. In Akiskal HS and Webb WL (Eds). Psychiatric Diagnosis: Explorations of biological predictors. New York, Spectrum, Inc, pp. 189–218, 1978.
90. Bolles RC and Fanselow MS. A perceptual-defensive-recuperative model of fear and pain. Behav Brain Sci 1980; 3: 291–323.
91. Petri A. Individuality in Pain and Suffering. Chicago, University of Chicago Press, 1967.
92. von Knorring L, Espvall M and Perris C. Averaged evoked responses, pain measures and personality variables in patients with depressive disorders. Acta Psychiatr Scand 1974; Suppl 225, 99–108.
93. von Knorring L, Almay BGL, Johansson F and Terenius L. Endorphins in CSF of chronic pain patients, in relation to augmenting-reducing response in visual average evoked response. Neuropsychobiology 1979; 5: 322–326.

94. Zuckerman M. Sensation Seeking. In Gale A and Edwards JA (Eds). Physiological Correlates of Human Behavior, Volume 3: Individual Differences and Psychopathology. New York, Academic Press, 1983, pp. 99–119.
95. von Knorring L. Visual average evoked response in patients suffering from alcoholism. Neuropsychobiology 1976; 2: 233–238.
96. Gottfries CG, von Knorring L and Perris C. Neurophysiological measures related to levels of 5-HIAA, HVA, and tryptophan in CSF of psychiatric patients. Neuropsychobiology 1976; 2: 1–8.
97. Blumer D and Heilbronn M. Chronic pain as a variant of depressive disease: The pain-prone disorder. J Nerv Ment Dis 1982; 170: 381–406.
98. Powell GE. Brain and Personality. London, Saxon House, 1979.
99. Flor-Henry P, Fromm-Auch D, Tapper M, Schopflocher D. A neuropsychological study of the stable syndrome of hysteria. Biol Psychiatry 1981; 16: 601–626.
100. Gorenstein EE. Frontal lobe functions in psychopaths. J Abnorm Psychol 1982; 91: 368–379.
101. Cloninger CR and Guze SB. Psychiatric illness and female criminality: the role of sociopathy and hysteria in the antisocial woman. Am J Psychiatry 1970; 127: 303–311.
102. Cloninger CR, Reich T and Guze SB. The multifactorial model of disease transmission. III. Familial relationship between sociopathy and hysteria (Briquet's syndrome). Br J Psychiatry 1975; 127: 11–22.
103. Cloninger CR. Biology of antisocial behavior. In Hippius H and Winokur G (Eds). Psychopharmacology, Vol 2, Part 2: Clinical Psychopharmacology. Amsterdam, Elsevier, In press 1986.
104. Mednick SA. Autonomic nervous system recovery and psychopathology. Scand J Behav Ther 1975; 4: 55–59.
105. Fowles D. The three arousal model: Implications of Gray's two-factor learning theory for heart rate, electrodermal activity and psychopathy. Psychophysiology 1980; 17: 87–104.
106. Brown GL, Goodwin FK, Ballenger JC, Goyer PF and Major LF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1979; 1: 131–139.
107. Brown GL, Ebert MH and Goyer PF *et al.* Aggression, suicide, and serotonin. Relationships to CSF amine metabolites. Am J Psychiatry 1982; 139: 741–746.
108. Åsberg M, Bertilsson L and Martensson B. CSF monoamine metabolites, depression, and suicide. Adv Biochem Psychopharmacol 1984; 39: 87–97.
109. Banki CM and Arato M. Amine metabolites, neuroendocrine findings, and personality dimensions as correlates of suicidal behavior. Psychiatry Res 1983; 10: 253–261.
110. Rosenthal NE, Davenport Y, Cowdry RW, Webster MH and Goodwin FK. Monoamine metabolites in cerebrospinal fluid of depressive subgroups. Psychiatry Res 1980; 2: 113–9.
111. Roy-Byrne P, Post RM, Rubinow DR, Linnoila M, Savard R and Davis D. CSF 5HIAA and Personal and Family history of suicide in affectively ill patients: A negative study. Psychiatry Res 1983; 10: 263–274.
112. Virkkunen M and Luukkonen P. WAIS performance in antisocial personality (disorder). Acta Psychiatr Scand 1977; 55: 220–224.
113. Yeager C and Janos L. Yeager. New York, Bantam Books, 1985.
114. Akiskal HS. Dysthymic Disorder: Psyschopathology of proposed chronic depressive subtypes. Am J Psychiatry 1983; 140: 11–20.
115. West ED and Dally PJ. Effects of iproniazid in depressive syndromes. BMJ 1959; 1: 1491–1494.
116. Sheehan DV, Ballenger J and Jacobson. Relative efficacy of monoamine oxidase inhibitors and tricyclic antidepressants in the treatment of endogenous anxiety. In Klein DF and Rabkin JG

(Eds). Anxiety: New Research and changing Concepts. New York, Raven Press, 1981, pp. 47–68.

117. Small IF, Small JG, Alig VB and Moore DF. Passive-aggressive personality disorder: A search for a syndrome. Am J Psychiatry 1970; 126: 973–983.
118. Caro RA. The years of Lyndon Johnson: The path to power. New York, Random House, 1982.
119. Akiskal HS, Hirschfeld RMA and Ywerevanian BI. The relationship of personality to affective disorders. Arch Gen Psychiatry 1983; 40: 801–810.
120. Robins L. Deviant Children Grown Up. Baltimore: Williams and Wilkins, 1966.
121. Guze SB. Criminality and Psychiatric Disorders. New York: Oxford University Press, 1976.
122. Martin RL, Cloninger CR and Guze SB. Female criminality and the prediction of recidivism: A prospective six year follow-up. Arch Gen Psychiatry 1978; 35: 207–214.
123. Guze SB, Woodruff RA Jr and Clayton PJ. Hysteria and antisocial behavior: Further evidence of an association. Am J Psychiatry 1971; 127: 957–960.
124. Lindberg BJ and Lindegard B. Studies of hysteroid personality attitude. Acta Psychiatr Scand 1963; 39: 170–180.
125. Brewer WF. There is no convincing evidence for operant or classical conditioning in adult humans. In Neimer J and Palermo D (Eds). Cognition and the Symbolic Processes. Hillside, NJ, Erlbaum, 1974.
126. Beck AT and Emery G with Greenberg RL. Anxiety Disorders and Phobias: A Cognitive Perspective. New York, Basic Books, 1985.
127. Robins E and O'Neal P. Clinical features of hysteria in children. The Nervous Child 1953; 10: 246–271.
128. Purtell JJ, Robins E and Cohen ME. Observations on clinical aspects of hysteria. JAMA 1951; 146: 901–909.
129. Kimble R, Williams JG and Agras S. A comparison of two methods of diagnosing hysteria. Am J Psychiatry 1975; 132: 1197–1199.
130. Guze SB, Woodruff RA Jr and Clayton PJ. Sex, age, and the diagnosis of hysteria (Briquet's syndrome). Am J Psychiatry 1973; 129: 745–748.
131. Broadhurst PL. The Maudsley reactive and non-reactive strains of rats: A survey. Behav Genet 1975; 5: 299–319.
132. DeFries JC, Gervais MC and Thomas EA. Response to 30 generations of selection for open-field activity in laboratory mice. Behav Genet 1978; 8: 3–14.
133. Oreland L and Fowler C. Brain and platelet monoamine oxidase activities in relation to central monoaminergic activity in mice and man. Excerpta Medica, International Congress Series 1982; 564: 312–320.
134. Bernard BK, Finkelstein ER and Everett GM. Alterations in mouse aggressive behavior and brain monoamine dynamics as a function of age. Physiol and Behav 1975; 15: 731–736.
135. Sudak HS and Maas JW. Central nervous system serotonin and norepinephrine localization in emotional and non-emotional strains in mice. Nature 1964; 203: 1254–1256.
136. Sprott RL and Staats J. Behavioral studies using genetically defined mice—A bibliography (July 1973–July 1976). Behav Genet 1978; 8: 183–206.
137. Durcan MJ, Wraight KB and Fulker DW. The current status of two sublines of the Roman High and Low Avoidance Strains. Behav Genet 1984; 14: 559–570.
138. Eichelman B, Elliot GR and Barchas JD. Biochemical, pharmacological, and genetic aspects of aggression. In Hamburg DA and Trudeau MB (Eds). Biobehavioral aspects of aggression. New York, Alan R Liss, 1981, pp. 51–84.

139. Van Oortmerssen GA and Bakker TC. Artificial selection for short and long attack latencies in wild Mas musculus domesticus. Behav Genet 1981; 11: 115–126.
140. Horn JM, Loehlin JC and Willerman L. Aspects of the inheritance of intellectual abilities. Behav Genet 1982; 12: 479–516.
141. Thurstone LL. A factorial study of perception. Chicago, University of Chicago Press, 1949.
142. Vandenberg SG. The hereditary abilities study: hereditary components in a psychological test battery. Am J Hum Genet 1962; 14: 220–237.
143. Rose RJ, Miller JZ, Dumont-Driscoll M and Evans MM. Twin-family studies of perceptual speed ability. Behav Genet 1979; 9: 71–86.
144. Plomin R. A twin and family study of personality in young children. J Psychol 1976; 94: 233–5.
145. Carey G, Goldsmith HH, Tellegen A and Gottesman II. Genetics and personality inventories: The limits of replication with twin data. Behav Genet 1978; 8: 299–313.
146. Floderus-Myrhed B, Pedersen N and Rasmuson I. Assessment of heritability for personality, based on a short form of the Eysenck Personality Inventory: A study of 12,898 Twin pairs. Behav Genet 1980; 10: 153–162.
147. Fulker DW. The genetic and environmental architecture of psychoticism, extraversion and neuroticism. In Eysenck HJ (Ed). A Model for Personality. New York, Springer Verlag, 1981.
148. Nagoshi CT, Johnson RC and Ahern FM. *et al.* Correlations of measures of personality and of cognitive abilities within and across generations. Behav Genet 1982; 12: 327–342.
149. Gottesman II. Differential inheritance of the psychoneuroses. Eugenics Quart 1962; 9: 223–227.
150. Gottesman II, Bouchard TJ and Carey G. MMPI findings in the Minnesota Study of twins reared apart. Proceedings of the Fourteenth Annual meeting of the Behavior Genetics Association, Indiana University, May 1984.
151. Carey G and Gottesman II. Twin and Family studies of anxiety, phobic, and obsessive disorders. In Klein DF and Rabkin J (Eds). Anxiety: New Research and Changing Concepts. New York, Raven Press, 1981, pp. 117–136.
152. Reich T, Cloninger CR and Guze SB. The multifactorial model of disease transmission. I. Description of the model and its use in psychiatry. Br J Psychiatry 1975; 127: 1–10.
153. Noyes R, Clancy J, Hoenk PR and Slyman DJ. The prognosis of anxiety neurosis. Arch Gen Psychiatry 1978; 35: 173–178.
154. Harris EL, Noyes R, Crowe RR and Chaundhry DR. A family study of agoraphobia: Report of a pilot study. Arch Gen Psychiatry 1983; 40: 1061–1064.
155. Gittelman R and Klein DF. Relationship between separation anxiety and panic and agoraphobic disorders. Psychopathology 1984; 17: 56–65.
156. Pauls DL, Crowe RR and Noyes R. Distribution of ancestral secondary cases in anxiety neurosis (panic disorder). J Affect Disord 1979; 1: 287–290.
157. Pauls DL, Bucher KD, Crowe RR and Noyes R. A genetic study of panic disorder pedigrees. Am J Hum Genet 1980; 31: 639–644.
158. McKusick VA. Mendelian Inheritance in Man. Baltimore, Johns Hopkins University Press, 1983.
159. Cloninger CR, Rice J and Reich T. Multifactorial inheritance with cultural transmission and assortative mating. II. A general model of combined polygenic and cultural inheritance. Am J Hum Genet 1979; 31: 176–198.
160. Cloninger CR, Rao DC, Rice J, Reich T and Morton NE. A defense of path analysis in genetic epidemiology. Am J Hum Genet 1983; 35: 733–756.
161. Woerner PI and Guze SB. A family and marital study of hysteria. Br J Psychiatry 1968; 114: 161–168.

162. von Knorring L, Oreland L and von Knorring A-L. Personality traits and psychopathology related to platelet MAO Activity. Proceedings of IV World Congress of Biological Psychiatry, Shagass C (Ed). New York, Elsevier, 1986; pp 530–532.
163. von Knorring A-L, Bohman M, von Knorring L and Oreland L. Platelet Monoamine oxidase as a biological marker in subgroups of alcoholism. Acta Psychiatr Scand 1985; 72: 51–58.
164. Cloninger CR, von Knorring L and Oreland L. Pentameric distribution of platelet monoamine oxidase activity. Psychiatry Res 1985; 15: 133–143.
165. Westlund KD, Denney RM, Kochersperger LM, Rose RM and Abell CW. Distinct MAO A and MAO B Populations in the primate brain. Science 1985; 230: 181–183.
166. Sandler M, Ruthven CRJ, Goodwin BL, Field H and Matthews R. Phenylethylamine overproduction in aggressive psychopaths. Lancet 1978; 2: 1269–72.
167. Cloninger CR, von Knorring A-L, Sigvardsson S and Bohman M. Symptom patterns and causes of somatization in men. II. Genetic and environmental independence from somatization in women. Genetic Epidem 1986; 3: 171–186.
168. Virkkunen M. Insulin secretion during the glucose tolerance test in antisocial personality. Br J Psychiatry 1983; 142: 598–604.
169. Hall CS and Lindzey G. Theories of Personality. John Wiley, Chichester, 1957.
170. Wiggins JS. Personality and Prediction: Principles of Personality Assessment. Addison-Wesley, Reading, Massachusetts, 1973.
171. Mischel W. Toward a cognitive social learning reconceptualization of personality. Psychol Rev 1973; 80: 252–283.
172. Powell GE. Personality: In McGuffin P, Shanks MF, Hodgson RJ: The Scientific Principles of Psychopathology. Grune & Stratton, New York, 1984, pp. 409–446.
173. Tellegen A. Structures of Mood and Personality and their relevance to assessing anxiety, with an emphasis on self-report, In Tuma AH, Maser J (Eds): Anxiety and The Anxiety Disorders. Lawrence Erlbaum Associates, Hillsdale, NJ, 1985, pp. 681–706.
174. Bowers KS. Situationism in psychology: an analysis and a critique. Psychol Rev 1973; 80: 307–336.
175. Leff J, Kuipers L, Berkowitz R and Sturgeon D. A controlled trial of social intervention in the families of schizophrenic patients: two year follow up. Br J Psychiatry 1985; 146: 594–600.
176. Liberman RP, Evans CC. Behavioral rehabilitation for chronic mental patients. J Clin Psychopharmacol 1985; 5: 88–148.