Apathy: A Neuropsychiatric Syndrome

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Traditionally, apathy has been viewed as a symptom indicating loss of interest or emotions. This paper evaluates evidence that neuropsychiatric disorders also produce a syndrome of apathy. Both the symptom and the syndrome of apathy are of conceptual interest because they signify loss of motivation. An apathy syndrome is defined as a syndrome of primary motivational loss, that is, loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness. Loss of motivation due to disturbance of intellect, emotion, or level of consciousness defines the symptom of apathy. Neuropsychiatric literature dealing with apathy is reviewed within the framework of three approaches to defining the concept of a syndrome. Clinical and investigative approaches for evaluating apathy when it occurs in association with other syndromes are described.

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The term *apathy* describes the lack of motivation seen in a variety of neuropsychiatric disorders.[1] It is employed by clinicians to describe such familiar attributes as loss of interests, loss of emotions, flattening of affect, or loss of energy. This usage, which is also reflected in scales, factor analytic studies, and clinical descriptions (reviewed by Marin[1]), suggests that apathy is a symptom or dimension of behavior. It does not, however, directly address either the definition of apathy or its nosological status. Indeed, apathy per se only recently has been the object of research,[1-6] and this work has dealt primarily with evaluating the validity of apathy as a dimension of behavior, rather than with considering its nosological status.

Although it has been proposed that apathy may be a valid clinical syndrome,[1] criteria for evaluating this position have not been described. DSM-III-R defines a syndrome as a group of symptoms that covary, and, yet, DSM-III-R uses the term to refer to some disorders that consist only of a single symptom (e.g., organic amnestic disorder). Others have suggested that a syndrome requires heterogeneity among the symptoms comprising the syndrome (R. Jacob, J. Mezzich, J. Zubin, May, 1990, personal communication). A third approach to defining a syndrome emphasizes the presence of a common physiological mechanism (as, for example, in congestive heart failure); the various etiologies of the syndrome produce symptoms through this mechanism. This definition, like

the others, has its own weaknesses, but also its advantages.[7]

The primary purpose of discussing these definitions is to provide a conceptual framework for evaluating evidence that apathy represents a neuropsychiatric syndrome. In the process, it will be possible to indicate some of the neuropsychiatric disorders in which apathy occurs, to describe some of the variations in its phenomenology, and to suggest some of its underlying mechanisms. Thus, after a brief introduction to the proposed definition of apathy, the general nosological problem of defining a syndrome will be discussed. The three definitions of syndrome that have been introduced above will be presented, and their strengths and weaknesses will be specified. Next, neuropsychiatric literature supporting apathy as a syndrome will be evaluated with respect to these three definitions. In considering these various approaches to defining a syndrome, the purpose is not to answer definitively the question of whether there is a correct or preferred definition. It is expected that experts will differ in their conception of a syndrome according to their theoretical inclinations and investigative purposes. Rather, the intention is to ask, if we were to regard one of these definitions as preferable, could we then say that apathy should be regarded as a syndrome according to the criteria of that definition? In the last section, clinical and investigative strategies for distinguishing the symptom and syndrome of apathy will be described.

DEFINITION OF APATHY

Etymologically, apathy derives from the Greek, "pathos," meaning passions. Reference to lack of passion—that is, to apathy—may have its source in Hippocrates,[8] who states in his *Sacred Disease:*

> Madness comes from moistness. . . . The corruption of the brain is caused not only by phlegm but by bile. You may distinguish them thus. Those who are mad through phlegm are quiet, and neither shout nor make a disturbance; those maddened through bile are noisy, evildoers, and restless, always doing something inopportune [p. 15].

Conventionally, apathy is defined as a lack of interest or emotion. When the clinical features defined as apathy (discussed below) are considered, however, it is apparent that apathy embraces not simply interests and emotions, but a variety of other psychological features that, in the author's view, can be conceptualized best as lack of motivation. It is for this reason that apathy, whether it refers to a symptom or a syndrome, denotes loss of motivation.

This definition seems consistent with the way clinicians use the term. For example, a schizophrenic with negative symptoms may be characterized as apathetic from a syndromic standpoint because of lack of interests, poor initiative, flat affect, lack of engagement with psychosocial events, etc. The same definition of apathy is applicable to the depressed patient who shows apathy. However, the fact that the depressed subject is dysphoric, i.e., in emotional pain, suggests that from an overall or syndromic standpoint it may be misleading to characterize the depressed patient as apathetic; it is illogical to characterize someone in emotional pain as lacking in "passions." This contrasts with the schizophrenic patient who shows exclusively negative symptoms. In the absence of dysphoria, the schizophrenic's overall behavioral state can be accurately described as apathetic. For the depressed individual, the presence of dysphoria complicates the interpretation of motivational loss. This will be discussed further below.

Similar caveats apply to interpreting the presence of apathy when it occurs in dementia and delirium. Lack of interests in a person with dementia might be attributable to the inability of a demented individual to think in a logical or effective manner. Therefore, the lack of interests that one sees in some demented individuals may be due to the cognitive impairment that defines dementia. Similarly, in a delirious patient, lack of interest or emotion may be attributable simply to the fact that the patient shows drowsiness or poor attention, i.e., diminished level of consciousness.

Thus, in the case of dementia, depression, delirium, and other psychiatric syndromes, the critical factor in evaluating the significance of motivational loss, i.e., apathy, is whether the symptoms are attributable to cognitive impairment, emotional distress, or diminished level of consciousness. These considerations underlie the definitions of apathy used in this paper. The syndrome of apathy is defined as primary absence of motivation, that is, lack of motivation not attributable to disturbance of intellect, emotion, or level of consciousness. If loss of motivation is attributable to disturbance of intellect, emotion, or level of consciousness, apathy is considered a symptom. An alternative terminology would be to refer to apathy as primary or secondary, depending on whether it is attributable to some other syndrome. This terminology has its own difficulties, however. For example, to some the distinction will suggest mistakenly that "primary" apathy is a disease entity itself. At present, this seems doubtful. Furthermore, conceptualizing apathy as a syndrome has immediate benefits for clinical discourse because it characterizes the overall clinical presentation of some patients who would not otherwise be described as well.

Since the concept of motivation is central to understanding apathy, it may be helpful to define motivation and to distinguish it from emotion. I will adhere to those traditions in psychology that use the term "motivation" as a superordinate concept referring to the characteristics and determinants of goal-directed behavior. As stated by Atkinson, theories of motivation aim to "develop a conceptual scheme, or theory...which will explain, more adequately than conventional wisdom, what accounts for the direction, vigor, and persistence of an individual's actions" (p 4).[9] Psychological approaches to the study of motivation, of which a number of theoretical directions can be distinguished,[9-12] deal with such concepts as initiation, persistence, level of aspiration, goal-hierarchies, motives, and so on. Biological approaches attempt to correlate these psychological concepts with autonomic, endocrine, physiological, biochemical, or anatomical concepts of brain and general bodily function. These approaches are, therefore, potentially useful in understanding motivational loss, i.e., apathy.

What then about the relationship of apathy to emotions? Diminished interest and emotion define apathy conventionally, and clinicians are clearly influenced by affect, mood, feeling tone, and other emotional descriptors when evaluating whether a patient shows apathy. Their relevance to apathy is that emotional state and, particularly, emotional responsivity provide information regarding the motivational significance of environmental events. Thus, the presence of emotions such as anger, the intensity and duration of their expression, the presence of flat affect, and reports of mood and feeling tone—all of which fall within the domain generally referred to as emotion or affection[13,14]—are relevant to the evaluation of apathy because they are used by clinicians to assess the extent to which the potential incentive or reward features of the environment are of motivational significance to the patient. As a clinical caveat, it is necessary to exclude the presence of disorders of affect that may alter the interpretation or expression of emotional information, e.g., aprosodia or pseudobulbar palsy.[14,15] Absenting such disorders of affect, however, the quality and dynamics (intensity, persistence, or fixity) of emotion are of immediate use in helping us interpret the motivational significance of diminished goal-directed behavior or its cognitive concomitants in thought content (e.g., diminished plans or goals, lack of interests, curiosity, etc.).

The distinction between the overt behavioral, cognitive, and emotional concomitants of goal-directed behavior has direct relevance to the operational definition of apathy (Table 1). In most instances, the presence of apathy is suggested by a deficit—relative to the standards of one's own age, culture, or previous level of functioning—

in the overt behavioral evidence of goal-directed behavior. Thus, apathy may be suggested by diminished productivity, lack of effort, diminished initiative, lack of persistence, and so on. However, inactivity per se is insufficient to diagnose apathy. It is necessary to know that cognitive concomitants of goal-directed behavior (e.g., plans and goals for the future, values and interests, and curiosity) are also diminished. A patient with spinal cord injury or Parkinson's disease may be inactive and, yet, based on thought content, profoundly concerned with her usual roles, responsibilities, or goals in life. Equally important is evaluation of the patient's emotional state. For example, a patient with depression will typically be dysphoric about his inactivity, whereas an apathetic individual would demonstrate indifference, emotional unresponsiveness, or inappropriate cheerfulness. For these reasons, in clinical practice, the diagnosis of an apathy syndrome requires reduction in the overt behavioral, cognitive, and emotional concomitants of

TABLE 1. Criteria for the syndrome of apathy

The syndrome of apathy: lack of motivation that is not attributable to intellectual impairment, emotional distress, or diminished level of consciousness (drowsiness and/or diminished attentional capacity).

A. Lack of motivation, relative to the patient's previous level of functioning or the standards of his or her age and culture, as evidenced by all three of the following:

1. Diminished goal-directed overt behavior as indicated by:
   Lack of productivity
   Lack of effort
   Lack of time spent in activities of interest
   Lack of initiative or perseverance
   Behavioral compliance or dependency on others to structure activity
   Diminished socialization or recreation

2. Diminished goal-directed cognition as indicated by:
   Lack of interests, lack of interest in learning new things, lack of interest in new experiences
   Lack of concern about one's personal, health, or functional problems
   Diminished importance or value attributed to such goal-related domains as socialization, recreation, productivity, initiative, perseverance, curiousity

3. Diminished emotional concomitants of goal-directed behavior as indicated by:
   Unchanging affect
   Lack of emotional responsivity to positive or negative events
   Euphoric or flat affect
   Absence of excitement or emotional intensity

B. Lack of motivation is not attributable to intellectual impairment, emotional distress, or diminished level of consciousness. When lack of motivation is attributable to intellectual impairment, emotional distress, or diminished level of consciousness (drowsiness or diminished attention), then apathy is a *symptom* of some other syndrome such as dementia, delirium, or depression.

C. Emotional distress is absent or is insufficient to account for the lack of motivation.

goal-directed behavior. The interested reader is referred to a previous publication for further discussion of this definition and its use in differential diagnosis.[1]

DEFINITION OF SYMPTOM, SIGN, AND SYNDROME

Virtually all classifications of psychiatric disorders use symptoms and signs as the clinical constructs for determining the presence of a mental disorder.[16] However, a variety of epistemological problems arise when the process of symptom description[17] and classification[18] is carefully examined. Conclusions about what a patient has said, showed, presented, etc., are structured by the training, education, psychological state, personal development, and culture[19,20] of both the clinician and the patient. Such complexities are particularly salient in psychiatry because of the ways in which observer characteristics and language determine descriptions or, more properly, the constructions and interpretations of what is and what is not the case.

These considerations provide the context for understanding the process of characterizing and classifying psychiatric phenomena. Symptoms and signs remain the conceptual building blocks for describing higher level nosological categories, specifically syndromes and diseases. The concept of symptom is, of course, derived from the realm of general medicine where it names the pain, suffering, or disability that a patient reports. Signs of diseases traditionally are considered the observable features of a clinical disorder and, therefore, are regarded as possessing an objectivity and verifiability that symptoms do not have. Syndromes, on the other hand, are groups of signs and symptoms that have heuristic value for describing, diagnosing, or treating patients, while a disease "implies knowledge of etiology" (p. 29).[16]

We can distinguish the syndrome definitions discussed below according to the answers they provide to two questions: First, do the symptoms comprising a syndrome represent a homogeneous or heterogeneous group of symptoms from a categorical standpoint? Second, must the symptoms defining the syndrome reflect a single pathological mechanism?

Definition 1: The simplest notion of a syndrome is that it is a group of symptoms that constitute a recurring, discriminable pattern. As stated by Spitzer and Endicott[16]:

> A symptom is a condition that may be associated with many different disorders and therefore has only limited power to predict other facts of interest. A syndrome is a collection of symptoms (or signs) that covary and has more power than a

symptom but nevertheless may be associated with a variety of underlying pathophysiological processes [p. 29].

This definition is equivalent to that of DSM-III-R, which states that a syndrome is a "group of symptoms that occur together and that constitute a recognizable condition. 'Syndrome' is less specific than 'disorder' or 'disease.' The term 'disease' generally implies a specific etiology or pathophysiologic process. In DSM-III-R most of the disorders are, in fact, syndromes" (p. 405). Dementia, for instance, is regarded as a syndrome of memory and other intellectual impairments. Some syndromes in DSM-III-R are actually monosymptomatic syndromes, for example, organic amnestic disorder, organic hallucinosis, or simple phobias.

Definition 2: A syndrome is a group of heterogeneous symptoms and, therefore, a group of symptoms whose relationship to each other would not otherwise be considered. The requirement for heterogeneity means that the symptoms defining the syndrome will not be categorically or logically related to each other. Certainly, they should not be synonyms for each other. For example, if anxiety is defined by the symptoms of nervousness, tension, and jitteriness, the attributes of an anxiety syndrome are relatively homogeneous, and, one might argue, synonymous. They would, therefore, suffice for definition 1, but not for definition 2. In fact, since these symptoms are synonymous, it could be argued that they serve only as different labels for the same phenomenon and, therefore, that anxiety is a monosymptomatic syndrome or, simply, a single symptom. By contrast, the diagnosis of delirium conforms to definition 2 because the clinical state in question entails such categorically varied symptoms as memory failure, impaired attention, emotional lability, and visual hallucinations. Similarly, the criteria for major depression embody considerable heterogeneity, e.g., depressed mood, anxiety, weight loss, and insomnia. Reconsidering anxiety as a syndrome, if depressed mood, stomach pains, urinary frequency, and sleep disturbance are added to the profile of anxiety, a more heterogeneous symptom cluster is obtained such that anxiety might now be regarded as a syndrome according to the requirements of definition 2. Definition 2 thus provides a more stringent test for establishing a group of symptoms as a syndrome. It has the disadvantage of excluding monosymptomatic states that have been regarded conventionally as syndromes, e.g., organic amnestic disorder. However, it has the corollary advantage of preventing us from mistaking a symptom for a syndrome when there are multiple synonyms used to label the same phenomenon and from defining a syndrome on the basis of every homogeneous group of symptoms.

Definition 3: A syndrome is a group of symptoms that have a shared pathological mechanism. This definition, which is found, for example, in the introductory chapter of MacBryde's textbook of medicine, states that if "characteristic groupings of signs and symptoms (syndromes) are recognized, the anatomical location of the cause may be suggested ... or the organ or tissue or system involved."[7] Thus, a stroke syndrome consisting of right hemiparesis and nonfluent aphasia suggests infarction of the anterior left cerebral hemisphere, although it should be pointed out that the etiology of such a syndrome of hemispheric infarction is not implied. For example, the cause of the stroke may be embolism, thrombosis, hemorrhage, etc. In the case of delirium, which is a well-recognized neuropsychiatric syndrome, it is understood that the symptom cluster that defines the syndrome has a common pathological mechanism: delirium implies the presence of organic brain dysfunction. However, the specific location and nature of this dysfunction is not implied.[21] Thus, the syndrome of delirium has heuristic value for diagnosing etiology, but is not to be equated with the diagnosis of a disease entity. Furthermore, the information it provides regarding pathological mechanism ("organic brain dysfunction") is important but relatively nonspecific if compared, for example, to the specificity of information about mechanism implied by the syndrome of congestive heart failure. Thus, in our current state of knowledge, the requirement of definition 3 for a shared mechanism represents a goal rather than a prerequisite in most, if not all, instances.

In summary, each of these approaches to defining a syndrome has strengths and weaknesses. Definition 1 helps us to identify distinctive groups of symptoms. The symptoms may or may not be categorically related to each other, but may nevertheless constitute a recognizable pattern that has heuristic value for patient care. Its weakness is that it does not guard against instances in which the symptoms are synonymous labels for the same phenomenon; thus, it admits the presence of monosymptomatic syndromes, thereby blurring the boundary between a symptom and a syndrome. Definition 2 aids patient care, as do the other definitions, but it has specific heuristic value because it attaches meaning to attributes whose interrelationship as part of a recurring pattern would otherwise be overlooked. Its limitation is that some symptom clusters (monosymptomatic syndromes) usually thought of as having syndromic status would not meet the heterogeneity criterion, e.g., organic amnestic disorder. Definition 3 requires that the symptoms comprising a syndrome reflect a shared pathological mechanism. Its virtue is the emphasis on the elucidation of mechanism. Yet, its strength in this regard is also its weakness, for, if strictly applied, definition 3 prevents

clinicians from characterizing a patient in syndromic terms until there is sufficient knowledge to specify pathogenetic mechanism. In such situations, we would then face the problem that patients could only be described in terms of symptoms, which would defeat the purpose of defining patterns of symptoms in the first place. Thus, the recognition of a symptom cluster as a syndrome is often useful precisely because it may lead to new knowledge about mechanism, treatment, etc. But to require such information in advance defeats the purpose of identifying syndromes.

EVIDENCE THAT APATHY IS A SYNDROME

The three definitions of a syndrome will now be used to organize pertinent aspects of the literature describing apathy.

Definition 1: Apathy is a syndrome defined by a group of related symptoms. There are a number of disorders that have been described in such a way that the overall clinical picture may be specified as a group of symptoms that can be characterized overall as apathy (Table 2). A vivid example is Bleuler's[22] description of the loss of affectivity seen in chronic schizophrenia:

> Many schizophrenics. . . sit about the institutions to which they are confined with expressionless faces, hunched up, the image of indifference. They permit themselves to be dressed and undressed like automatons, to be led from their customary place of inactivity to the messhall, and back again without expressing any sign of satisfaction or dissatisfaction. They do not even seem to react to injuries inflicted on them by other patients [p. 40].

A variety of terms have been used to describe the same phenomena, including flat affect,[23] amotivational syn-

TABLE 2. Psychological and clinical states that may produce apathy syndromes

Schizophrenia (type II or negative symptoms)
Frontal lobe injury
Postpsychotic depression
Frontoparietal right hemisphere infarction
Cingulate gyrus/supplementary motor area infarction
Amphetamine or cocaine withdrawal
Parkinson's disease and other states of catecholamine hypoactivity, especially dopaminergic hypoactivity (e.g., neuroleptic-induced akinesia)
Lack of environmental incentive or reward, as in role loss, institutionalization, and other states of environmental deficiency
Loss of elementary sensory or motor capacity, including hearing and vision
"Apathetic" hyperthyroidism
Serotonergic hyperactivity, possible[68]

drome,[24] emotional blunting,[25] negative symptoms,[26] and type II schizophrenia.[27] Regardless of the term used, the "signs and symptoms" of the state described are similar: the patient shows a diminution in initiative or goal-directed behavior and an absence of emotional responsivity to events that are related to the patient's needs or goals.

In schizophrenia and other disorders producing apathy, therefore, one may find such symptoms as lack of initiative; inactivity; social withdrawal; lack of interests; lack of goals and plans; behavioral and emotional unresponsiveness to success or failure (i.e., diminished response to positive or negative reinforcement); behavioral compliance; lack of persistence; anergy; diminished concern about others; decreased effort; diminished intensity, range, and duration of emotional reactions; flat or inappropriately cheerful affect; and diminished spontaneous speech, gesture, or movement.

A syndrome similar to that described by Bleuler is suggested by descriptions of patients with postpsychotic depression. According to Floru et al.,[28] postpsychotic depression is "seldom expressed by genuine deep melancholy or depressive contents but frequently by apathy." They use the terms, "lack of vital impulse" and "lack of desire," citing a number of German publications that contain related ideas. Steinberg et al.[29] described postpsychotic patients as having a "wooden" demeanor, while Wildroe[30] highlighted their lack of initiative. "Neurasthenic" features, noted by Kayton,[31] are relevant because lack of energy is often considered a feature of neurasthenic as well as of apathetic patients. McGlashan and Carpenter[32] remarked on the paucity of spontaneous speech seen in such patients. Undoubtedly, patients with postpsychotic "depression" may show elevated ratings on depression rating scales.[33] Nevertheless, these observations suggest that at least some such patients may be better characterized as apathetic than depressed. Furthermore, consideration of this differential diagnosis raises the possibility that such elevated depression ratings in postpsychotic "depression" may be due to the apathetic features rather than to the dysphoric features evaluated in depression rating scales. To test this hypothesis using the Hamilton Rating Scale, for example, one would hypothesize that the elevated total scores in postpsychotic depression would be more due to lack of interests, lack of energy, psychomotor retardation, and, perhaps, lack of insight, whereas major depression or other dysphoric affective states would be characterized more by depressed mood, guilt, suicidal ideation, difficulty falling asleep, and anxiety.

While psychomotor retardation is often thought of as a feature of depressive disorders, the defining features of the syndrome—slowing of mental processes and behav-

ior—may be seen in normal aging as well as a variety of other clinical disorders, including Parkinson's disease, progressive supranuclear palsy, Huntington's disease, Wilson's disease, frontal lobe injury, and akinetic mutism.[34] Since slowing per se does not imply loss of motivation, psychomotor retardation does not necessarily represent an apathetic syndrome. On the other hand, many of the associated features of psychomotor retardation are consistent with apathy, including diminished initiative, loss of interest, lack of energy, and flat affect. If the patient with psychomotor retardation reports emotional unresponsiveness or indifference, then the syndrome of psychomotor retardation may also be regarded as an apathy syndrome. If the mood is dysphoric, however, it may be difficult to determine whether apathy represents an associated symptom or a syndrome. Strategies for making this differential diagnosis are discussed in the last section of the paper.

The author has pointed out elsewhere[1] that apathy may occur when individuals are deprived of their usual sources of incentive or reward motivation. In otherwise normal individuals, such apathy occurs in response to role changes, such as retirement or other phase-of-life transitions. Since such people are otherwise functioning normally, it is questionable whether they should be characterized as apathetic by clinical standards. Occasionally, however, such individuals will present for treatment because of concern about their lack of interests or initiative, wondering if they are depressed when, in fact, they are apathetic. On the other hand, loss of reward or incentive motivation can reach clinical levels, such as in institutionalism or in sensory loss in the elderly. When this occurs in the absence of depressive features, the appropriate diagnosis may be apathy rather than depression.[35]

Akinetic mutism presents an unusual cause of apathy syndromes. While such patients are usually characterized as mute, akinetic, and abulic, an apathetic state may occur if they improve sufficiently. This possibility is illustrated by a patient of Damasio and VanHoesen[36] who was recovering from unilateral infarction of the cingulate gyrus, supplementary motor area, and mesial motor area. In addition to contralateral hemiparesis, she showed "a state of aspontaneity and nonlateralized neglect of most stimuli." When she regained her ability to speak, she reported that prior to recovery she had had "'nothing to say.' Her mind was 'empty.' 'Nothing mattered.' She apparently was able to follow our conversations even during the early period of illness, but felt no 'will' to reply to our questions. In the period after discharge she continued to note a feeling of tranquility and relative lack of concern."

Similar apathetic states occur in victims of right hemisphere stroke who have been described[37–40] as showing

lack of emotional concern, lack of emotional expression, and inappropriate cheerfulness or flat affect. Differential diagnosis of such affective symptoms includes aprosodias, which are impairments in the ability to express or understand affective information through nonlinguistic aspects of speech.[15] Since aprosodias are impairments in the processing and expression of affective information, such patients should not show deficits in goal-directed behavior and goal-related cognitions and, therefore, would not be regarded as having the syndrome of apathy.

A last example of an apathy syndrome is exemplified by patients with bilateral lesions of the amygdala and anterior temporal lobes, who have been described[41] as showing "blunted affect, apathy, and pet-like compliance," a syndrome thought to resemble the Kluver-Bucy syndrome in temporal lobectomized monkeys.

Definition 2: Apathy is a syndrome composed of a heterogeneous group of symptoms. The so-called frontal lobe syndromes are perhaps the best-known cause of apathy arising from neurological damage. Characterizing such patients in global behavioral terms of any sort is undoubtedly an oversimplification.[42] However, it frequently has been noted that such patients show impairment in initiative and perseverance. Similarly, they seem unconcerned and unengaged with their social and interpersonal environment. For these reasons, frontal lobe damaged patients are said to show "an underlying background of abulia and apathy,"[43] which is consistent with definition 1. Inclusion of frontal lobe syndromes with definition 2 is suggested by descriptions of such patients' affective states. Some frontal lobe patients show flat affect, while others show silly or euphoric affect. Such patients also may show impulsivity, irritability, and sometimes rage.[44] From the vantage of an apathy syndrome that meets the criterion of definition 2, it is clear that these symptoms introduce categorical differences into the features defining a frontal lobe syndrome. For example, it is paradoxical to consider flat affect and euphoric affect parts of the same syndrome because they suggest categorically different affective states, euphoria implying elevation of mood and the preservation of the capacity for pleasure, flat affect suggesting an absence of emotional expression and hedonic capacity. Similarly, being apathetic and, at the same time, angry are logically contradictory, since anger by convention implies intense concern, objection, or protest in response to some event or issue, while apathy implies the opposite (i.e., lack of concern, complacency, behavioral compliance, etc.). Similar contrasts with apathy apply to the symptoms of irritability, demandingness, and agitation. When this combination of behaviors occurs in other disorders, for example, with Alzheimer's disease,[45] Huntington's disease,[4] or progressive supranuclear palsy,[46] the same type of problem arises.

Resolving these contradictions requires complementing the logical analysis of the symptoms with clinical considerations. Flat and euphoric affect are both consistent with apathy because both, when used to characterize a patient's usual affective state, imply that the patient fails to show evidence of distress or concern when untoward events occur. Anger, irritability, agitation, or sadness are compatible with apathy if their intensity and duration are diminished. On the other hand, to the extent that such emotions dominate the clinical picture, the "background of abulia and apathy" will be absent and it will no longer be appropriate to characterize a patient as apathetic from a syndromic standpoint. To the extent that flat, shallow, or euphoric affect are present, apathy is suggested.

To summarize, normal emotional responses are integrated into goal-directed behavior and show amplitude and persistence that is in keeping with the goals (purposes, values, concerns, interests, etc.) embodied in thought and overt behavior. To the extent that emotion is superficial, lacking in intensity, unsustained, or unresponsive to negative or positive events, the behavioral state in question is consistent with apathy. For example, if a patient with a frontal lobe syndrome or Alzheimer's disease becomes sad, it may be misleading to characterize this patient as depressed from a syndromic standpoint. If the sadness is superficial or transient, apathy is suggested. If it is persistent and intense, it suggests depression. Similar analyses apply to the interpretation of sexual behavior, anger, and other behaviors not usually considered features of apathy.

Definition 3: Apathy is a syndrome characterized by a group of symptoms having a shared pathological basis. The applicability of this definition depends on knowledge about the mechanisms of apathy. Since reliable measurement of apathy has been reported only recently,[2-5] we have only suggestive information about the biological correlates of apathy per se. Clearly, neurobehavioral and neuropsychological analyses of frontal lobe function provide a fertile source for interpretating apathy, based on the frontal lobe effect on drive, sequencing, and the so-called executive functions, such as anticipation, goal-setting, planning, and monitoring.[42]

From a neurochemical standpoint, it may be noteworthy that functional deficiency of dopaminergic systems has been postulated to underlie a number of disorders causing apathy, including neuroleptic-induced akinesia,[47] negative symptoms in schizophrenia,[26,27] postpsychotic depression,[28-32] subcortical dementing diseases

such as Parkinson's disease,[48] and frontal lobe syndromes.[49] Flat affect, lack of initiative, psychomotor slowing, and other features associated with apathy have been noted in these disorders as well as in depression.[50,51] Such clinical and neurochemical parallels may apply to akinetic mutism[52] and to other stroke syndromes involving more delimited midline diencephalic structures.[53]

Given the multiplicity of neurotransmitter systems that are now recognized, it is doubtful that a hypothesis as simple as this will prove sufficient. However, the clinical similarity among these disorders with respect to the symptoms and signs that comprise apathy does suggest that this symptom cluster may have heuristic value for identifying a common biological basis for the motivational loss seen in these disorders.

Other mechanisms of apathy may be pertinent to other disorders. For example, Alzheimer's disease is associated with damage, not only to the hippocampus, but also to the amygdala and contiguous structures.[54,55] The role of the amygdala and closely interconnected temporal-diencephalic subsystems in producing apathy[41] is suggested by the Kluver-Bucy syndrome in monkeys and by the taming observed in other species of animals with anterior temporal damage.[56] The tameness, hypoemotionality, and altered responses to food seen with bilateral removal of the amygdala in monkeys may reflect an inability to associate sensory events with positive or negative reinforcement.[56,57] Experimental evidence that such amygdalectomized animals are unable to associate environmental stimuli with reward or punishment may be understandable in terms of the amygdala's connectivity.[56] Input to the amygdala includes multiple sources of highly processed cortical input, while its output provides a means for influencing motor and autonomic systems, as well as limbic structures influencing memory[56] and cerebral cortex.[58,59] In functional anatomical terms, the failure to associate environmental events with previous sources of reinforcement would, in part, reflect the disruption of a neural system that permits sensory information to influence and to be integrated with the organism's drive states as represented in and organized by midline limbic system structures. From a clinical standpoint, such failure to make appropriate motor and emotional responses to motivationally important environmental events would present as a deficit in goal-directed behavior occurring in the absence of intellectual deficits, emotional distress, or diminished level of consciousness, i.e., apathy.

The right cerebral hemisphere lesions responsible for neglect and for the indifference reaction[37-40,58,59] may point to a mechanism for apathy that in some ways is analogous to the mechanisms hypothesized with respect to the amygdala. Functional anatomic interpretations of

the right hemisphere's role in directed attention have been offered by many authors.[58-62] The formulation of Mesulam[58,59] is used here as an illustration. According to Mesulam, studies of the connectivity of the parietal lobe in monkeys, specifically the inferior parietal lobule, indicate that it receives highly processed multimodal sensory input and has reciprocal connections with the limbic system, although these interconnections are with the cingulate and retrosplenial cortex and, therefore, by contrast to the amygdala, provide a higher level "motivational map for the distribution of interest and expectancy." This region of the parietal lobe also has reciprocal connections with the frontal eye fields and other structures thought to be important for head- and eye-orienting responses comprising directed attention. This connectivity has been interpreted as providing a functional anatomical basis for the prominent role of the parietal lobe and the interconnected structures (frontal lobe and cingulum) in the control of attention to extrapersonal space.[58] The apathy of right hemisphere damaged patients may also be understandable in terms of these anatomical relationships. As in the case of the amygdala, destruction of the parietal, frontal, or limbic cortical regions involved in this system would disrupt the organism's capacity to respond adaptively to potential sources of reward because the organism's motivational state would not be integrated with sensory and motor systems.

Predictably, these considerations indicate that there is not a single pathogenic mechanism for apathy. On the other hand, they do suggest that apathy may have heuristic value in leading us to consider a delimited group of neural systems. Studying the correlates of apathy at multiple levels of behavioral analysis may also help to identify subtypes of apathy whose distinguishing features in behavioral or neuropsychological terms will be predictive of these different mechanisms. Thus, multiple causes of apathy are associated with flat affect. These disorders may be associated with functional hypoactivity of dopamine systems, e.g., type II schizophrenia, postpsychotic depression, Parkinson's disease, psychomotor retardation, and neuroleptic-induced akinesia. On the other hand, euphoria or inappropriate cheerfulness occurs in some patients with Alzheimer's disease, Pick's disease, frontal lobe injury, or right hemisphere stroke. In these instances, there may be impairment of neurological structures (amygdala, prefrontal cortex, temporo-parietal cortex) critical for the integration of the organism's motivational status with sensory and motor systems. In the presence of intact dopaminergic innervation, emotional reactivity is present (i.e., affect is not flat), but its intensity and duration are not regulated by the reinforcement value of socioenvironmental events.

CLASSIFICATION OF APATHY IN ASSOCIATION WITH OTHER SYNDROMES

The rationale for describing a patient as showing an apathy syndrome is apparent when loss of motivation characterizes a patient's overall behavioral state and does so more accurately than other more familiar syndromes, such as depression, delirium, or dementia. But what about the instances in which loss of motivation occurs in association with other syndromes? Nosologically, in such circumstances clinicians have traditionally treated apathy as a symptom rather than as a syndrome. In other words, the loss of motivation seen in such patients is attributed to the other diagnosable syndrome, e.g., delirium.

Although it might seem confusing to regard apathy as a symptom or a syndrome in different circumstances, such variation in the use of clinical terms is quite usual. The term "depression" is a good example. Depression is sometimes used to describe a symptom and at other times a syndrome. It is proposed, therefore, that apathy should be regarded nosologically as a symptom or as a syndrome, depending on whether the motivational loss is due to some other syndrome. This distinction provides assistance in answering the question posed above. For classificatory purposes, when apathy occurs in association with other disorders, the distinction between apathy as a symptom and apathy as a syndrome depends on the clinician's assessment of its cause. If the apathy is due to a patient's emotional distress, intellectual deficits, or level of consciousness, then it represents a symptom. If not, it represents an apathy syndrome co-occurring with another syndrome and, therefore, requires an additional diagnosis. For example, one might diagnose dementia and apathy in a patient with Parkinson's disease or Huntington's disease.

This approach may seem simple in principle, but its application is undoubtedly difficult. How is a clinician to determine whether loss of motivation is in fact attributable to a patient's cognitive deficits, emotional distress, or diminished level of consciousness. Two answers should be considered. The first, a conventional clinical approach, is that this problem is not unique to the differential diagnosis of apathy and that, as clinicians, we make such evaluations frequently. The differential diagnosis of dementia is a case in point. DSM-III-R states that in the diagnosis of dementia an etiological factor must be demonstrable or, if not, "an etiological factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., Major Depression accounting for cognitive impairment" (p. 107). In other words, diagnosing dementia in the presence of depres-

sive symptoms requires the clinician to exercise the same judgment as that discussed with respect to apathy. Although it may seem simple to decide whether major depression accounts for cognitive impairment, it is apparent from the attention given to this topic[63,64] that, while important, it is not easily accomplished. Ongoing attempts to validate clinical,[63] neuropsychological,[65,66] or sleep electroencephalographic[67] approaches to understanding mixed states of depression and dementia bespeak the uncertainty that surrounds this differentiation.

Returning to the problem of deciding the cause of a patient's apathy, the conventional clinical approach entails asking clinicians to make a similar clinical judgment. A delirious patient would not be given the diagnosis of apathy if the loss of motivation was clearly related to the fact that the patient was too drowsy or inattentive to organize behavior effectively. A demented patient would not be diagnosed with the syndrome of apathy if he or she lacked the problem-solving capacities to devise a plan for obtaining some goal, such as how to prepare a meal or balance a checkbook. Analogously, a depressed patient who professed a disinterest in socializing or working because he or she was "just too depressed to do anything" would not be said to present with the syndrome of apathy. On the other hand, to the extent that major depression is associated with loss of motivation not attributed to dysphoria per se (a possibility worthy of consideration if one considers psychomotor retardation a state of diminished motivation or if one considers the role of dopaminergic systems in depression[48-51]), then apathy may be a valid syndromic descriptor.

The second approach to evaluating the causative relationship between apathy and associated disorders is to take an investigative approach. Here apathy is treated as a dimension of behavior, that is, as a continuous, quantifiable variable that is measured reliably. Given a reliable and valid means for measuring apathy, correlational or experimental methods could be used to examine the relationship between apathy and other variables of interest.[1,2] Thus, one would measure or experimentally manipulate apathy in a population of interest and then show that the variance in apathy occurs independently of the potential covariates, e.g., depression, cognitive impairment, or attentional disturbance.

CONCLUSIONS

The value of terms used to describe or classify clinical phenomena derives from their use in facilitating communication about patients, in predicting pathological mechanism, etiology, prognosis, or treatment response, and in generating new knowledge.[16] The starting point

for proposing that apathy has validity as a syndrome is that it helps clinicians recognize that some patients are better characterized as apathetic than by some other recognized syndrome. In other words, characterizing such patients as apathetic is immediately useful in a clinical setting because it facilitates the classification of such individuals into recognizable groups that may be useful in assessment and treatment.

If we reconsider the three definitions of a syndrome discussed in this paper, these benefits suggest that the concept of an apathy syndrome at least meets the requirements of definition 1. The clinical characteristics of apathetic patients described here provide numerous symptoms that appropriately are considered to comprise the syndrome of apathy. Such symptoms are readily assembled into an assessment device for evaluating apathy.[2]

In the author's view, apathy does fulfill the heterogeneity requirement of definition 2. Not only is there heterogeneity among the symptoms referred to by apathy (i.e., apathetic patients may be affectively flat, euphoric, or irritable), but interpreting apathy in terms of diminished motivation explains how clinicians can characterize patients as apathetic in the face of seemingly nonapathetic symptoms. Specifically, it is proposed that diminished intensity or duration of emotional responses distinguishes apathetic from nonapathetic emotional responses. At the same time, the definition of an apathy syndrome helps us understand why diminished intensity and duration of emotional responses, as in, for example, flattened affect, are not sufficient to diagnose apathy. A person may manifest diminished emotional expression without necessarily losing interest or involvement in usual sources of gratification, i.e., without losing motivation. For example, aprosodias impair emotional expression without deficits in goal-directed behavior.[15] Further, not all patients showing masked facies due to Parkinson's disease are apathetic; thus, the suggestive term "masked." Similarly, an obsessional patient who overvalues emotional control but who remains highly achievement-oriented may be emotionally unexpressive but highly productive.

The applicability of definition 3 is problematic for apathy but probably not more so than for other psychiatric syndromes. Multiple possible mechanisms for dementia, depression, and delirium—each a well-recognized psychiatric syndrome—are readily gleaned from the neuropsychiatric literature, but, in general, the validity of these mechanisms is uncertain at this time. This uncertainty, however, does not diminish the usefulness of these syndromic concepts. On the contrary, the fact that they define symptom clusters that are readily investigated contributes to our assessment of their heuristic value. Brief consideration of the etiologies of apathy suggests a variety of pathological mechanisms at multiple levels of behavioral organization. Defining apathy as lack of motivation suggests that multiple socioenvironmental influences on apathy deserve investigation, as, for example, the influence of residence in nursing homes or in other institutions.[35] It also suggests that the mechanisms of apathy may be illuminated by the vast literature of experimental psychology dealing with theories of motivation.[9-12] Further, from a biological standpoint, anatomical, physiological, and biochemical approaches warrant consideration. Neurobehavioral interpretations of the structures whose dysfunction produces apathy— right cerebral hemisphere, frontal lobes, amygdala, midline diencephalic regions—suggest explanations of apathy based on such concepts as reinforcement value of sensory information, integration of motivational state with sensory and motor representations of extrapersonal space, and executive functions of the frontal lobe. Correlations with neurotransmitter function, particularly dopaminergic systems, is also suggested by the neuropsychiatric disorders that cause apathy. To the extent that apathy has validity at multiple levels of behavioral organization, diverse treatments can be envisioned.

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