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Comorbidity

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We review recent research on the prevalence, causes, and effects of diagnostic comorbidity among the most common groups of child and adolescent psychiatric disorders; anxiety disorders, depressive disorders, attention deficit hyperactivity disorders, oppositional defiant and conduct disorders, and substance abuse. A meta-analysis of representative general population studies provides estimates of the strength of associations between pairs of disorders with narrower confidence intervals than have previously been available. Current evidence convincingly eliminates methodological factors as a major cause of comorbidity. We review the implications of comorbidity for understanding the development of psychopathology and for nosology.

Keywords: Diagnosis, comorbidity, child, adolescent, nosology.

Abbreviations: ADHD: attention deficit hyperactivity disorder; BPD: bipolar disorder; CD: conduct disorder; CI: confidence intervals; ECA: Epidemiologic Catchment Area Study; GAD: generalized anxiety disorder; MDD: major depressive disorder; OAD: overanxious disorder; ODD: oppositional disorders; OR: odds ratios; SAD: separation anxiety disorder.

Introduction

The first quantitative descriptions of general population comorbidity between classes of child and adolescent psychiatric disorders assessed with structured diagnostics appeared only in 1987 (J. C. Anderson, Williams, McGee, & Silva, 1987; Kashani et al., 1987), but since then the number of publications that pay explicit attention to comorbidity has increased exponentially. As a crude index of interest in comorbidity, we conducted a PsycINFO search on the stem "comorb" appearing in the title or abstract fields in citations containing the stems "child" or "adolesc" in any field. No citations appeared for the years before 1986, but in the following years the numbers of citations were: 1986—1, 1987—3, 1988—9, 1989—23, 1990—33, 1991—37, 1992—62, 1993—89, 1994—92, 1995—134, 1996—157, 1997—143. Even this is an underestimate of the increase in attention in comorbidity, first because the PsycINFO database is distinctly patchy in its coverage of the relevant material, and second because it is now commonplace for authors of papers on individual disorders without a special focus on comorbidity to enumerate the rates of other diagnoses in their samples, and to consider the possible impact of comorbidity on their findings. Ten years ago neither of these practices was common. A similar increase in interest in comorbidity is evident in the adult psychiatric literature. It is no accident that in the U.S.A. the most recent national epidemiological study of psychiatric disorders was called the National Comorbidity Survey (Kessler, 1994; Kessler et al., 1994). Indeed, Kendall and Clarkin (1992, p. 833) regard the study of comorbidity as the "premier challenge facing mental health professionals in the 1990s".

As late as 1991, Caron and Rutter (1991), using data from Anderson's work on the Dunedin Longitudinal Study (J. C. Anderson et al., 1987), showed that comorbidity between disorders occurred much more frequently than could be accounted for by the rate of occurrence of the individual disorders in the general population; that is the levels of comorbidity typically seen in the population resulted from *covariation* between disorders (Lilienfeld, Waldman, & Israel, 1994). This is not to say that earlier clinicians and researchers were unaware of the existence of comorbidity. Nothing could be further from the truth; witness the venerable category "mixed disorder of conduct and emotions" in the Tenth Revision of the *International classification of diseases* (ICD-10); or the vast parent questionnaire literature, which showed many years ago that there was substantial overlap among the various factors extracted from large normative samples of children; or work in the 1960s on school phobia showing that depressive symptoms were very common in children with this anxiety disorder (Hersov, 1960a, b). Rather, what has changed is the way in which comorbidity is treated. The purpose of the ICD-10 category of mixed disorder of conduct and emotions was to allow symptomatically mixed states to be allocated a *single* diagnosis. On the other hand, proponents of the factor analytic approach to syndrome definition (e.g. Achenbach, 1966; Arnold & Smeltzer, 1974) developed the idea that patterns of psychopathology were a matter

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of continuous variation along a series of scales, which could, in turn, be grouped together to yield overall levels of psychopathology. From this perspective, comorbidity was seen as an indication of the failure of categorical diagnosis to describe appropriately separable syndromes on the one hand, and an artefact of the failure to recognize the covariation between naturally occurring scalar syndromes on the other.

More recently, the study of comorbidity has begun to emerge as an important task in itself, with the recognition that understanding how comorbidity arises may inform our understanding of the development of psychopathology. In effect, rather than being seen simply as a bothersome problem to be ignored, or an embarrassment to categorical diagnosis, or something to be defined away by the use of combined diagnostic categories, comorbidity has emerged as an opportunity for understanding better the development of psychopathology, and as a potential tool for improving nosology. A number of review articles (see, for example Abikoff & Klein, 1992; Achenbach, 1990, 1995; Angold & Costello, 1993; Caron & Rutter, 1991; Hinshaw, Lahey, & Hart, 1993; Kendall, Kortlander, Chansky, & Brady, 1992; D. N. Klein & Riso, 1993; Loeber & Keenan, 1994; Nottelmann & Jensen, 1995; Rutter, 1997) have detailed the importance of taking comorbidity into account for understanding the etiology, course, and treatment of psychiatric disorders, so we will not repeat their arguments. Several of these contributions have also included long lists of possible explanations for comorbidity, and our aim here is to examine research that has addressed the methodological and substantive issues raised by these lists. We shall begin by attempting to clarify some terminology, then move on to a review and meta-analysis of the evidence for associations between the most common child and adolescent psychiatric disorders. The third part of the paper consists of evidence which indicates that comorbidity is not simply a methodological problem. The penultimate and longest section consists of a series of explorations of research findings on pairs of comorbid diagnoses intended to illustrate ways in which comorbidity has been treated in attempts to understand the causes of psychopathology and to refine nosology. Finally, we offer some recommendations for future research on comorbidity. As we pursue this agenda, we shall consider only the most common disorders of children and adolescents—attention deficit hyperactivity disorders (ADHD), oppositional disorders (ODD), conduct disorders (CD), depressive disorders, anxiety disorders, and substance use and abuse. There are two reasons for this. First, only for these disorders is there clear evidence from general population studies that comorbidity is not an artefact of referral. Second, we cannot think of a disorder in which comorbidity has not been reported, and our aim here is to review approaches to understanding comorbidity, rather than to list every paper that has ever reported rates of comorbidity.

Some Terminology

In this section we consider some terms that we think are helpful in talking about comorbidity, and another term that we think is unhelpful.

Disorder and Disease Comorbidity

In many branches of medicine, interest in comorbidity centers on the co-occurrence of two (or more) different *diseases*; for instance, comorbidity between carcinoma of the bronchus and chronic bronchitis. In such cases each individual disease is well established in its own right. Both carcinoma of the bronchus and chronic bronchitis are relatively well defined as clinical entities, their etiologies and pathophysiologies are known to be quite different, and they are treated quite differently. In child and adolescent psychiatry our disease categories are much less well established. We deal mostly with *disorders*, that is, behavioral and psychological syndromes that are deviant from some standard of normality (Angold, 1988). This is an important distinction, because comorbidity between disorders may imply that there is a problem with the classification system, rather than any meaningful association between underlying diseases indexed by that classification. The fact that we are not dealing with clearly validated disease entities does not, however, mean that there is no point studying psychiatric comorbidity. Indeed, the opposite is the case, since understanding the presence of comorbidity between psychiatric conditions offers a means of correcting and validating psychiatric nosology. The key point is that the study of comorbidity does not depend upon the existence of well-validated disease entities, but may actually be particularly informative in the case of poorly validated disorders. If diseases represent the "well-validated" subset of disorders, then the set of explanations of disorder comorbidity is a *superset* of the set of possible explanations of disease comorbidity.

Homotypic vs. Heterotypic Comorbidity

Developmental psychopathologists are used to the concepts of homotypic and heterotypic continuity. The first refers to continuity of some phenomenon over time in a form that changes relatively little. For instance, the fact that depressed adolescents are more likely than nondepressed adolescents to be depressed in adulthood points to a degree of homotypic continuity in depression. Heterotypic continuity, on the other hand, refers to a continuous process that generates manifestations of *different* forms over time. Thus, the finding from the Dunedin Longitudinal Study (McGee, Feehan, Williams, & Anderson, 1992) that disruptive behaviour disorders in girls predicted emotional disorders several years later is evidence for heterotypic continuity between disruptive and emotional disorders in girls. By analogy, studies of comorbidity may be seen as being of two types: (1) those that examine comorbidity between disorders within a diagnostic grouping (such as the co-occurrence of major depression and dysthymia), and (2) those that deal with comorbidity between disorders from different diagnostic groupings (such as depression and conduct disorder). We propose to call the first studies of *homotypic comorbidity* and the second studies of *heterotypic comorbidity*. Just as there is no hard and fast rule about just how similar states have to be over time to be called examples of homotypic continuity, so there can be no rigid distinction between homotypic and heterotypic comorbidity. Nonetheless,

the distinction is useful because the implications of these two types of comorbidity tend to be rather different, and they are rarely addressed in the same paper.

Familial Comorbidity

Comorbidity occurs not only within individuals; it also occurs within families. For instance, relatives of children with ADHD have higher rates of antisocial personality disorder, hysteria, alcoholism and substance dependence, and unipolar depression (Biederman et al., 1992; Biederman, Faraone, Keenan, Knee, & Tsuang, 1990; Cantwell, 1972; McCormick, 1995; Morrison, 1980). The children of depressed parents clearly have elevated rates of depression compared to the children of the non-depressed, but they are also at higher risk of having anxiety and disruptive behavior disorders (Beardslee et al., 1996; Beidel & Turner, 1997; Decina et al., 1983; Gershon et al., 1985; Grigoroiu-Serbanescu et al., 1991; Grigoroiu-Serbanescu, Christodorescu, Totoescu, & Jipescu, 1991; Hammen, 1992; Hammen et al., 1987; D. W. Klein & Depue, 1985; Last, Hersen, Kazdin, Francis, & Grubb, 1987; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; J. M. McClellan, Rubert, Reichler, & Sylvester, 1990; Merikangas, Prusoff, & Weissman, 1988; Moreau, Weissman, & Warner, 1990; Morrison & Stewart, 1971; Nurnberger et al., 1988; Orvaschel, 1990; Orvaschel, Walsh-Allis, Ye, & Walsh, 1988; Sylvester, Hyde, & Reichler, 1988; Turner, Beidel, & Costello, 1987; Warner, Mufson, & Weissman, 1995; Weissman, Fendrich, Warner, & Wickramaratne, 1992; Welner, Welner, McCrary, & Leonard, 1977). Children of parents with "pure" anxiety disorders have been found to have little but anxiety disorders, whereas those with depressed or mixed anxious-depressed parents have a much wider range of disorders (Beidel & Turner, 1997). Whether these effects are attributable to genes or environments or both, consideration of comorbidity has proved to be very important for family genetic studies of psychopathology. As we shall see below, family genetic methods provide some powerful tools for unraveling the meaning of patterns of comorbidity observed in individuals. However, it should not be supposed that shared risk necessarily implies that what were thought to be two disorders are in reality one. The often quoted example of the various disease risks associated with smoking serves here (e.g. Rutter, 1994). No-one wants to claim that chronic bronchitis and myocardial infarction are the same disease, though both occur much more frequently in smokers. But, to pursue the analogy a little further, what about atherosclerotic stroke and myocardial infarction? In this case, there are many similarities in pathogenesis, but the affected organ varies. We could argue that these are alternative manifestations of the same disease, but from the perspective of differential diagnosis in the emergency room, it is more helpful to be thinking about "diseases of the brain" when a stroke patient comes in, and "diseases of the heart" when the patient complains of crushing central chest pain. Certainly the treatment of the two conditions will differ in many ways. The point here is that "diseases" are not obvious "natural" categories in any branch of medicine (D. N. Klein & Riso, 1993), and that boundary problems abound in relation to medical disease, just as they do in mental disease. Rather, diseases (or disorders) are groupings of phenomena established over time by their utility for describing and organizing those phenomena and responses to them. Furthermore, comorbidity between entirely "unrelated" physical diseases is very common, especially in older adults. We are now used to data reporting *lifetime* rates of psychiatric comorbidity. How many of us have *not* had at least two different sorts of physical disease in our lives? In old age, simultaneous comorbidity is also the norm, as any family practitioner know. For instance, most 90-year-old men with osteoarthritis will also have prostate cancer. So there is nothing particularly special about comorbidity among psychiatric disorders in this respect.

If we were to find that some pair of disorders, say depression and anxiety, was associated with identical risk factors, brain correlates, relapse rates, and treatment responses, insofar as it was in our power to measure them, perhaps it would be right to call them instances of the same disorder. But that would still leave unanswered the important question of why some people present with this disorder in the form of a major depression, whereas others never have such an episode. It is hard to believe that the phenomenological differences between depressed and anxious people are generated by some purely random process, and even if they were, we would still want to know where the "randomizer" was and how it worked. Thus, even if many, or even all, examples of "comorbidity" turn out to be alternative expressions of some unitary underlying psychopathological process or processes, the phenomenon currently called "comorbidity" will still need explaining.

Concurrent vs. Successive Comorbidity

One problem with the term "comorbidity" is that it has been used to include a multitude of different temporal relationships amongst disorders. Whereas some child and adolescent studies have considered disorders co-occurring over a relatively short span of time, others have reported rates of co-occurrence over 6 months, 1 year, 3 years, or the individual's lifetime to date. Clearly such different time spans will allow very different types of temporal relationships between comorbid disorders. For instance, comorbidity between current disorders at the time of assessment means that both must be present at the same time. Although their times of onset and offset may not be coterminous, during some period they must have been present concurrently. We propose to label such co-occurrence *concurrent comorbidity*. The two disorders "run together", perhaps not only in time but in phenomenology.

When considering reports of lifetime comorbidity, the disorders in question may never have been present simultaneously, but may have occurred widely separated in time. When two disorders do not overlap in time, we suggest that the term *successive comorbidity* could be used. At least it would be helpful to know more about the degree to which comorbidity represents the occurrence of multiple disorders in succession as opposed to multiple disorders occurring at the same points in time. Data from the Oregon Adolescent Depression Project (Rohde,

Lewinsohn, & Seeley, 1991) indicate that current (and, therefore, necessarily *con*current) and lifetime comorbidity rates can be very different. For instance, they found that the odds ratio (OR) for current comorbidity between unipolar depression and any other diagnosis was 9.6; that for lifetime comorbidity was only 2.8. This implies that adolescents who had formerly been depressed, but were not currently depressed, were unlikely also to have had other disorders. However, studies of rates of concurrent comorbidity in younger children do not support this implication (see Table 3). This suggests that lifetime recall probably underestimates comorbidity rates quite substantially. One obvious problem here is that estimates of lifetime comorbidity rely upon individuals remembering the symptoms of two separate disorders. The only way to avoid this apparent problem is to measure concurrent and successive comorbidity *prospectively* in longitudinal studies.

Primary vs. Secondary Disorders

The distinction between primary and secondary depressions was introduced by Woodruff, Murphy, and Herjanic (1967), and has been taken up by some child and adolescent researchers (G. A. Carlson & Cantwell, 1979, 1980; R. C. Friedman, Hurt, Clarkin, & Corn, 1983; Geller, Chestnut, Miller, Price, & Yates, 1985; Puig-Antich, 1982). A primary affective disorder is one occurring in a person who has not had a preceding nonaffective psychiatric illness. A secondary affective disorder is one occurring in a patient who has had a preexisting, diagnosable, nonaffective, psychiatric illness. However, we find that this is a confusing terminological distinction because it diverges from the meanings of primary and secondary in medicine in general and reduces the complex issue of relationships over time to a dichotomy. In the rest of medicine, a secondary condition is *caused* by a primary condition. For instance, renal failure secondary to a myocardial infarction generally results from hypoperfusion of the kidneys caused by a catastrophic drop in blood pressure following the infarction. No-one would think of calling a heart attack secondary to chicken pox just because the latter occurred first. The issue of whether a later-occurring psychiatric disorder is caused by an earlier disorder is one we shall take up later, but so far none of the common psychiatric comorbidities has been shown to result from one disorder causing another. The second problem with the primary/secondary distinction is that it is a poor representation of the complex questions concerning timing that are key to developmental psychopathology. We seek to identify characteristic pathological processes that operate over developmental time, and just finding out which disorder occurred first hardly does justice to this quest (although it may be a start).

The Uses of General Population Surveys and Clinical Studies in Research on Comorbidity

In this section we consider the pros and cons of using clinical and community-based samples to provide information about comorbidity. Many of studies of comorbidity in clinical samples have been published recently, making it imperative that we clearly understand the limitations of clinical samples for this purpose. The problem, of course, is that clinical samples are anything but representative of individuals with the disorder in the general population. Individuals presenting to specialty treatment settings have more severe symptomatology, are more impaired, and come from families that feel more burdened by their children's problems, than are individuals with psychiatric disorders who do not present for treatment (see, e.g., Angold, Messer, et al., 1998). In the Great Smoky Mountains Study, a community study of children's mental health service use, we found that comorbid individuals were more than twice as likely to be receiving psychiatric services as individuals with only a single diagnosis (Costello et al., 1996).

This means that clinical studies are of no use for providing unbiased prevalence or incidence rates of comorbidity, or unbiased estimates of risk factors for comorbidity. The only exception to this rule occurs when most individuals with a disorder can be expected to present for treatment. So, for instance, a local or regional autism treatment program might have among its patients a reasonably representative sample of autistic people, but even where there is no referral bias whatsoever, clinical samples will produce *incorrect* estimates of the strength of the association between disorders. We point this out because some studies of clinical samples have reported that there was no greater association than expected by chance between particular pairs of disorder, and these results have then been quoted by others and contrasted with other studies where a significant association was found. Consider a neater world than ours, where there were just three disorders, A, B, and C, each of which occurred in 10% of the population. A always occurs alone. Half of those with B also have C, and half of those with C have B. If we were to take a general population sample of 100 people, we would expect to see the relationship between B and C appearing as in Table 1. From this table we can compute a joint odds ratio describing the strength of the relationship between B and C. It yields an OR value of 17. With a sample of 100, this is a highly significant effect ($p = .0003$).

Now suppose that we have a perfect clinical system

Table 1
Hypothetical Co-distribution of B and C in 100 Children in the General Population

	C absent	C present
B absent	85	5
B present	5	5

Table 2
Resulting Co-distribution of B and C in 100 Children in the Perfect Clinic

	C absent	C present
B absent	40	20
B present	20	20

that identifies all individuals with a disorder and leaves out everyone without a disorder. In other words, there is no referral bias whatsoever. Given the population base rates, we expect 40% of clinic patients to have nothing but A, and 60% to have B or C or both. Let us now take a clinic sample of 100 children and look at the relationship between B and C; it will be as shown in Table 2. Notice that in Table 2 we have exactly *correct* estimates of the *proportions* of individuals with B who also have C and vice versa, because there is no Berkson's bias or referral bias. However, when we compute the joint OR, it is only 2 and this is "not significant" ($p = .1$). Even in this perfect world an attempt to estimate the strength or "statistical significance" of associations between disorders from clinical populations is misleading. We have, therefore, not considered clinic-based studies in our discussion of the strengths of associations between disorders.

Given this unavoidable situation, what use are clinical samples for the study of comorbidity? The answer is that they are very useful when their limitations are appreciated:

(1) When the target groups to which one wishes to generalize one's results are other clinical samples, then clinical research may provide more useful information than will general population studies. For instance, the clinical literature on comorbidity of depression with other diagnoses has indicated that, in clinical settings, when an individual presents with CD it is important to make a careful assessment of the possibility that the individual is also suffering from depression (Puig-Antich, 1982).
(2) When a disorder is rare, there may be no epidemiological studies of sufficient size to inform us about its associations with other disorders. In these circumstances, clinical studies may provide the only available data on associations with other disorders. For instance, there is a dearth of diagnostic general population studies of comorbidity in obsessive-compulsive disorder or the eating disorders. The clinical data, however, indicate that these are conditions associated with considerable diagnostic comorbidity, and thereby point to the need for general population studies to address this issue in relation to their etiologies and development. Even when a disorder is relatively common, there may simply be no general population data published on its associations with other disorders. None of the recent diagnostic general population studies has, for instance, reported rates of comorbidity with enuresis. Here clinical studies provide an important laboratory for the development of hypotheses about the nature of individual disorders and the associations between disorders.

However, one must remain aware that in clinic samples apparent correlates of disorder may actually be correlates of *referral* rather than true associations with the disorder itself. An example is the association between ADHD and mania. Farone et al. (1997b) have said that the "co-occurrence of attention deficit hyperactivity disorder (ADHD) and bipolar disorder (BPD) is not a rare event. Clinical studies of children and adolescents show that rates of ADHD range from 57% to 98% in bipolar patients (Borchardt & Berstein, 1995; Geller, Sun, Zimmerman, Frazier, & Williams, 1995; West, McElroy, Strakowski, Keck, & McConville, 1995; West et al., 1996; Wozniak et al., 1995) and rates of BPD range from 11% to 22% in ADHD patients (Biederman, Faraone, & Mick, 1996; Butler, Arredondo, & McCloskey, 1995)". In his commentary on the Faraone et al. paper, Werry (1997) points out that "we do not want to see a massive overdiagnosis of ADHD as BPD, nor as comorbid disorders" (see also J. McClellan, 1998). If we take as the proposed rate of BPD in ADHD the mean of the two available estimates, we have a rate of 16.5%. If we take the general population rate of DSM ADHD to be 5%, then we would expect the rate of comorbid mania and ADHD in the general population to be 0.825%. The National Comorbidity Survey (Kessler et al., 1994) gives the lifetime prevalence of mania as 1.6%. If these clinical rates are correct, then over half of the lifetime cases of disorders involving mania have already had their onsets by late childhood, in association with ADHD. Of course, this is not impossible, but it would mean that the estimates of lifetime rates of BPD, estimated in the Oregon Adolescent Depression Project at two time points 1 year apart, for older adolescents, of 0.58% and 0.72%, were underestimates of the total lifetime prevalence of BPD by late adolescence. It would also suggest that all or nearly all cases of BPD would have had ADHD, whereas only 11% did so (Lewinsohn, Klein, & Seeley, 1995). As we have seen, even the clinical studies of juvenile BPD do not support this contention. In the Great Smoky Mountains Study (Costello et al., 1996), only 6 children or adolescents out of 1420 were observed to have been in a manic or hypomanic episode during the 3 months preceding any 1 of 4 annual interviews (a weighted population prevalence rate of 0.41%), whereas 92 (weighted 3.4%) met criteria for ADHD in at least one wave. Only one subject had both a manic episode and met criteria for ADHD, giving weighted population estimates of 0.9% for the rate of mania in those with ADHD (vs. 0.39% in those without ADHD), and a rate of 7% for ADHD in those with mania (vs. 3% in those without mania). Neither of these studies proves that there is no association between ADHD and BPD; indeed, given the ubiquity of comorbidity amongst other diagnoses, it would be surprising if there were not. They do, however, seriously challenge the notion that "co-occurrence of attention deficit hyperactivity disorder (ADHD) and bipolar disorder (BPD) is not a rare event". Both studies indicate that the co-occurrence of these disorders in the general population is a *very rare* event. On the other hand it is easy to see how their co-occurrence would be very likely to result in referral to specialist services at a major center with a particular interest in such problems. The point here is not to condemn

clinical studies of rates of comorbidity, but to sound a warning about their interpretation. In following up this question, Faraone and his colleagues (Faraone et al., 1997b) have produced evidence from a family study that comorbid ADHD and BPD may indeed be familially distinct from other forms of ADHD. It may be rare, but at present it appears that it does exist. As we have already said, in the absence of epidemiologic data, such clinical studies can be an important stimulus to research.

(3) When one is concerned with identifying potential risk factors, case-control designs are often appropriately employed. Cases of a particular disorder may be identified from clinical samples and compared with "normal" controls and/or cases of other disorders and/or cases of mixed disorders. Some very informative work abut the implications or comorbidity (see below) has been done in this way. As always, the concern is the degree to which the findings from such studies generalize to the whole universe of cases of the disorders in question. One must recognize that clinical research of this sort may be quite misleading. The classic example is given by Berkson (1946), who showed that the supposed association between gall bladder disease and diabetes, which had led some to undertake cholecystectomies for the treatment of diabetes, was the spurious statistical result of the independent disease-specific probabilities for treatment (note that Berkson's bias does *not* refer either to "selection bias" or to situations in which comorbidity results in a probability of treatment for comorbid cases that is higher than expected on the basis of the individual disease-specific probabilities for treatment). On the other hand, it would be foolish to ignore the results of clinical research on comorbidity on the grounds that the results are almost certain to suffer from unknown effects of sampling bias. The proper response is to recognize the problems and move on to research designs that overcome them. Indeed, in a number of areas, the clinical studies of comorbidity have pushed well ahead of the general population data, and epidemiologists need to be refocused from documenting rates of association between disorders on to considering the implications of those associations for etiology and development.

(4) Very little developmental epidemiological work has been done on the implications of comorbidity for the development and outcomes of psychiatric disorders. With the same caveats as already mentioned, a group of interesting clinical studies is the source for most of the work in this important area. Diagnostic, longitudinal, general population studies large enough to allow the identification of effects of the presence of one disorder upon another are expensive and time-consuming to conduct, difficult to keep funded, and very thin on the ground. It is to be hoped that those that do exist will be used to address some of the comorbidity issues raised by the rapidly expanding clinical literature.

The Contribution of "Empirically Derived Syndromes" to the Study of Comorbidity

Before moving on to a review of the literature on comorbidity based on the DSM in its various recent revisions (American Psychiatric Association, 1980, 1987, 1994), we briefly consider two other lines of research, one using symptom scales, and the other the ICD (World Health Organization, 1993) taxonomy.

A very large body of literature based on parent questionnaires has established at least seven highly replicable factor-analytically derived syndromes that can be applied to boys and girls of all ages. The most frequently used version identifies seven syndromes found in both genders (aggressive, anxious/depressed, attention problems, delinquent, schizoid, somatic complaints, and withdrawn), and two gender-specific syndromes labeled socially inept (boys) and mean (girls) (Achenbach, Conners, Quay, Verhulst, & Howell, 1989). These "narrow-band syndromes" can be grouped statistically into two "broad-band syndromes" labeled "internalizing" and "externalizing", which correspond broadly to what have long been called emotional and behavioral disorders. It is also well established that the internalizing and externalizing syndromes are correlated with one another (Garnefski & Diekstra, 1997; McConaughy & Achenbach, 1994). In other words, there is unassailable evidence of "comorbidity" between statistically derived syndromes.

Looking within syndromes, we also see that they often do not conform to the structure of individual diagnoses in the ICD or DSM systems. For instance, the aggressive syndrome includes "ADHD" items like talking too much and impulsivity, and mood-related items like sulking, irritability, and changeable mood; the anxious/depressed syndrome includes, as its name suggests, a mixture of depressive and anxiety symptoms; the delinquent syndrome includes use of alcohol and drugs; the withdrawn syndrome includes depressed mood and anxiety symptoms like shyness and self-consciousness. Thus, within syndromes we see that the statistical structure of symptomatology implies what, from a diagnostic perspective, is called comorbidity. Whether one looks across or within statistically derived psychopathological syndromes, there are structural relationships indicating that such syndromes are not statistically independent of one another and that the content of individual syndromes consists of mixtures of different "types" of symptoms. All this was clearly established before the child and adolescent diagnostic literature began to pay much serious research attention to comorbidity as a topic for investigation.

The Contribution of ICD-based Studies

The Isle of Wight and associated epidemiological studies (Graham & Rutter, 1973; Rutter, Tizard, & Whitmore, 1970), which pioneered the use of structured psychiatric interviewing in epidemiological studies of child psychopathology, used a taxonomy based on the ICD; one that differed from DSM-III in several ways. Most important for our discussion here is the use of a

specific "mixed disorder" category for children defined by the presence of both conduct disorder and emotional or neurotic disorders. Mixed disorder was the third most common diagnosis in this population when the children were first interviewed at age 10 to 11 years (Rutter & Graham, 1966) and also when the children were re-interviewed at age 14–15 years (Graham & Rutter, 1973). Mixed disorder was diagnosed 14 times more often than would be expected from the prevalence of the separate disorders at age 10–11, and 8 times more often at age 14–15. In a similar study carried out in an inner-London borough, all disorders were diagnosed more frequently than on the Isle of Wight, while mixed disorders were three times more common than expected by chance.

Similar findings were reported from a partial replication of the Isle of Wight study carried out in Mannheim, Germany, on 1486 children born in 1970. Mixed disorders were nine times more common than expected by chance at age 8, and four times more common at age 13, when they were the third most common diagnosis (Esser, Schmidt, & Woerner, 1990; Laucht & Schmidt, 1987). Vikan (1985), using the Isle of Wight interview and the ICD classification with 1510 Norwegian children, also reported that mixed disorders were the third most prevalent diagnosis; more frequent than the prevalence of either conduct or neurotic disorders alone would predict. Fombonne's French study (1994) gives numbers of children with mixed disorders of conduct and emotions suggesting that comorbidity occurred much more frequently than chance would predict, but because of sampling stratification and the need to use weights for computing prevalence and co-occurrence statistics, this cannot be confirmed from the reported data.

Thus, long before the advent of the DSM-III, comorbidity was recognized as being so much a feature of child and adolescent psychopathology that it was not regarded as "comorbidity" in the sense of an association between disorders, but as the basis for a particular class of disorders.

Rates of Diagnostic Comorbidity from General Population Surveys Using the DSM

In this section we review the literature on comorbidity generated by the use of the DSM, in its three most recent editions.

Table 3 lists recent community studies that have used standardized psychiatric interviews with parents and children to generate diagnoses according to the DSM-III, DSM-III-R, or DSM-IV and have reported rates of comorbidity between disorders in such a way as to permit us to determine the joint OR for the pairs of disorders or types of disorder. We concentrate on four types of disorder; depressive disorders, anxiety disorders, ADHD, and ODD and CD—all but two studies provided only figures for combined ODD/CD. Most studies did not provide data on substance abuse disorders, so these are omitted. One paper on comorbidity from the Oregon Adolescent Depression Project (Lewinsohn et al., 1993) reported lifetime comorbidity rates for a combined diagnostic group including ADHD, ODD, and CD, and so those results have not been reported in the table; rather, we have used the current diagnostic data reported in Rohde et al. (1991), where CD and ODD were combined, apparently without ADHD, which they do not consider at all. Here obsessive-compulsive disorders were included in the anxiety disorders group, but since these were very uncommon compared with other anxiety disorders (Lewinsohn et al., 1993), we did not allow this difference from other studies to preclude anxiety comorbidity data from this study from inclusion in Table 3. The report from the Virginia Twin Study of Adolescent Behavioral Development (Simonoff et al., 1997) also presented some problems for this analysis. First, raw data on comorbidity rates were only presented for a subset of the combinations considered here. Though OR and confidence intervals (CI) for a wider range of combinations are provided, these also did not consider groupings of diagnoses that parallel those in most other studies. Data on CD and ODD were reported separately and we selected the more prevalent of the two disorders (CD) to represent this grouping. Similarly, separation anxiety disorder, overanxious disorder, simple phobia, agoraphobia, and social phobia were all reported separately. Again we chose the most prevalent (overanxious disorder) to represent the anxiety disorders. In all cases relating to this study we considered rates of comorbidity for diagnoses associated with impairment (separate figures for diagnoses without impairment were also reported by these authors).

The two pioneering papers in this literature (Anderson et al., 1987; Kashani et al., 1987) employed the very helpful practice of presenting their comorbidity data in the form of Venn diagrams, with the numbers of individuals in each pure or comorbid group. The publications associated with the Dunedin study have continued the practice. The critical issue here is not the diagram (although it is a convenient and comprehensible way to present data that otherwise require a relatively complex contingency table), but the provision of all the information pertinent to calculating correlational statistics and their CI. Formal tests of whether comorbidity exceeds the level expected by chance are rare in the published literature. Bird and his colleagues computed the phi agreement statistic (the equivalent of the Pearson correlation coefficient for a 2-by-2 table). Caron and Rutter (1991) showed that the association of disorders was much higher than that expected by chance for the 11-year-olds from the Dunedin Study. Drs Hector Bird and Patricia Cohen kindly computed associational statistics from their datasets for inclusion in our 1985 review of depressive comorbidity (Angold & Costello, 1993), and those figures have been included here, and the contributions from the Virginia Twin Study (Simonoff et al., 1997) and the Christchurch Health and Development Study (Fergusson, Horwood, & Lynskey, 1993a) provided CI around OR for comorbidity. We computed all the other ORs and CI in the table from data provided in the relevant papers. Since several studies have reported separately on comorbidity from different waves of data collection, we broke out data from the Great Smoky Mountains Study by wave, although elsewhere comorbidity in this study has been reported across waves (Angold, Erkanli, Egger, & Costello, 1998). We strongly recommend that papers on comorbidity include all the

Table 3
Rates of Diagnosis and Comorbidity in General Population Studies

Study (DSM)	*N*	Age	Time frame	Pop. rate of a (%)	Pop. rate of b (%)	Rate of a in b (%)	Rate of a in not b (%)	Rate of b in a (%)	Rate of b in not a (%)	OR	CI	*p*
a = ADHD, b = CD/ODD												
1 (III)	792	11	1 yr	6.7	9.1	34.7	4.4	47.2	7.1	11.6	6.3–21.5	***
2 (III)	943	15	1 yr	2.1	9.0	4.7	1.9	20.0	8.8	2.6	0.9–8.0	***
5 (III)	278	7–11	6 mo	2.3	9.8	13.0	1.2	54.6	8.7	12.6	3.6–44.1	***
6 (IIIR)	278	12–18	6 mo	12.2	13.9	41.0	7.5	46.9	9.4	8.6	3.8–48.7	***
11 (III)	222	9–16	6 mo	10.0	10.5	35.7	—	93.0	—	phi = .47	—	***
12 (IIIR)	1015	9–13	3 mo	1.9	5.2	11.8	1.3	33.3	4.7	10.2	4.5–22.3	***
13 (IV)	970	10–14	3 mo	1.0	4.8	7.5	0.69	35.5	4.5	11.7	4.9–28.2	***
14 (IV)	928	11–15	3 mo	0.9	3.3	5.8	0.7	22.1	3.1	8.7	2.0–37.9	**
15 (IV)	820	12–16	3 mo	0.6	2.9	3.1	0.6	13.9	3.6	5.6	0.7–44.6	n.s.
16 (IIIR)	323	9–13	3 mo	1.3	6.6	4.8	1.0	25.0	6.3	4.9	0.5–49.6	n.s.
17 (IV)	317	10–14	3 mo	1.3	8.3	7.7	0.7	50.0	7.7	11.9	1.6–88.4	*
18 (IV)	304	11–15	3 mo	1.0	5.0	13.3	0.35	67.0	4.4	43.7	3.7–513	**
19 (IV)	289	12–16	3 mo	0.4	4.2	8.3	0.0	100.0	3.9	—	—	—
20 (IIIR)	986	15	6 mo	4.8	10.8	—	—	—	—	26.8	13.7–52.4	*
21 (IIIR)	2762	8–16	3 mo	1.4	4.3	—	—	—	—	3.2	0.9–8.7	n.s.
a = ADHD, b = Depression												
1 (III)	792	11	1 yr	6.7	1.8	57.1	6.5	15.1	0.91	19.3	6.4–58.2	***
2 (III)	943	15	1 yr	2.1	4.2	2.5	2.1	5.0	4.2	1.2	0.2–9.1	n.s.
5 (III)	278	7–11	1 yr	2.3	1.6	13.5	2.2	9.1	1.4	7.1	0.7–72.9	n.s.
6 (IIIR)	278	12–18	6 mo	12.2	4.2	25.2	11.6	8.7	3.6	2.6	0.8–8.3	n.s.
7 (IIIR)	776	9–18	1 yr	12.0	3.4	46.2	10.8	12.9	2.1	7.1	3.7–16.5	***
8 (IIIR)	776	11–20	1 yr	7.6	2.8	22.7	7.2	8.5	2.3	3.8	1.3–10.9	**
11 (III)	222	9–16	6 mo	10.0	8.0	13.0	—	44.5	—	37.1	—	**
12 (IIIR)	1015	9–13	3 mo	1.9	1.5	15.5	1.6	12.8	1.3	11.1	3.6–33.3	***
13 (IV)	970	10–14	3 mo	1.0	3.0	2.4	1.0	7.2	3.0	2.5	0.5–11.7	n.s.
14 (IV)	928	11–15	3 mo	0.9	3.2	3.5	0.8	13.2	3.1	7.7	1.0–22.5	n.s.
15 (IV)	820	12–16	3 mo	0.6	2.7	0.0	0.7	0.0	2.7	—	—	—
16 (IIIR)	323	9–13	3 mo	1.3	0.31	0.0	1.3	0.0	0.32	—	—	—
17 (IV)	317	10–14	3 mo	1.3	1.6	40.0	0.7	50.0	1.0	102.0	10.6–987	***
18 (IV)	304	11–15	3 mo	1.0	4.3	7.7	0.7	33.3	4.0	11.9	1.0–140	*
19 (IV)	289	12–16	3 mo	0.4	1.8	0.0	0.4	0.0	1.8	—	—	—
20 (IIIR)	986	15	6 mo	4.8	6.6	—	—	—	—	4.5	2.1–9.6	*
21 (IIIR)	2762	8–16	3 mo	1.4	1.2	—	—	—	—	1.7	0.0–10.4	n.s.
a = ADHD, b = Anxiety												
1 (III)	792	11	1 yr	6.7	7.4	23.7	6.0	26.4	6.8	4.9	2.5–9.7	***
2 (III)	943	15	1 yr	2.1	10.7	4.0	1.9	20.0	10.5	2.1	0.7–6.5	n.s.
5 (III)	278	7–11	1 yr	2.3	15.4	5.5	1.8	36.4	14.9	3.3	1.0–11.7	n.s.
6 (IIIR)	278	12–18	6 mo	12.2	14.4	21.1	10.7	25.0	13.0	2.2	1.0–5.1	n.s.
11 (III)	222	9–16	6 mo	10.0	—	22.0	—	50.8	—	phi = .16	—	*
12 (IIIR)	1015	9–13	3 mo	1.9	5.5	4.3	1.7	12.8	5.3	2.6	1.0–6.7	*
13 (IV)	970	10–14	3 mo	1.02	3.7	4.7	0.9	17.2	3.6	5.6	1.9–16.2	**
14 (IV)	928	11–15	3 mo	0.9	2.8	5.3	0.7	17.2	2.7	7.4	1.7–33.3	**
15 (IV)	820	12–16	3 mo	0.6	1.0	0.0	0.6	0.0	1.0	—	—	—
16 (IIIR)	323	9–13	3 mo	1.3	5.3	0.0	1.3	0.0	5.4	—	—	—
17 (IV)	317	10–14	3 mo	1.3	3.8	0.0	1.3	0.0	3.9	—	—	—
18 (IV)	304	11–15	3 mo	1.0	2.0	16.7	0.7	33.3	1.7	29.2	2.3–377	**
19 (IV)	289	12–16	3 mo	0.4	3.9	0.0	0.4	0.0	3.9	—	—	—
20 (IIIR)	986	15	6 mo	4.8	12.8	—	—	—	—	1.0	0.4–2.5	n.s.
21 (IIIR)	2762	8–16	3 mo	1.4	4.4	—	—	—	—	2.6	0.5–8.6	n.s.
a = CD/ODD, b = Depression												
1 (III)	792	11	1 yr	9.1	1.8	78.6	8.7	15.3	0.47	38.3	10.4–141	***
2 (III)	943	15	1 yr	9.0	4.2	32.5	8.0	15.3	3.15	5.6	2.7–11.2	***
3 (IIIR)	930	18	1 yr	5.5	18.0	7.2	5.1	23.5	17.6	1.4	0.7–2.8	n.s.
4 (III)	150	14–16	1 yr	14.7	8.0	83.3	8.7	45.9	1.6	52.5	10.3–268	***
5 (III)	278	7–11	1 yr	9.8	1.6	13.5	9.7	2.2	1.5	1.5	0.2–14.3	n.s.
6 (IIIR)	278	12–18	6 mo	13.9	4.2	67.7	11.6	20.4	1.6	15.9	4.4–58.0	***
7 (IIIR)	776	9–18	1 yr	7.1	3.4	23.7	6.6	10.9	2.8	4.3	1.6–11.5	*
8 (IIIR)	776	11–20	1 yr	5.8	2.8	22.7	5.3	11.1	2.3	5.2	1.9–13.9	*
9 (IIIR)	1710	14–18	curr	1.8	2.9	8.0	1.6	12.9	2.7	5.3	1.8–15.7	**
11 (III)	222	9–16	6 mo	10.5	8.0	55.8	—	45.4	—	18.4	6.1–55.3	***
12 (IIIR)	1015	9–13	3 mo	5.2	1.5	28.9	4.8	8.4	1.1	8.0	2.8–22.6	***
13 (IV)	970	10–14	3 mo	4.9	3.1	25.7	4.3	16.0	2.4	7.8	2.6–23.1	***
14 (IV)	928	11–15	3 mo	3.4	3.2	42.9	2.0	41.4	1.9	36.2	11.1–118	***
15 (IV)	820	12–16	3 mo	2.9	2.7	4.4	2.9	4.0	2.6	1.6	0.4–6.5	n.s.
16 (IIIR)	323	9–13	3 mo	6.5	0.31	0.0	6.5	0.0	0.33	—	—	—
17 (IV)	317	10–14	3 mo	8.2	1.6	60.0	7.4	11.5	0.7	18.8	3.0–118	**

Table 3 (*cont.*)

Study (DSM)	*N*	Age	Time frame	Pop. rate of a (%)	Pop. rate of b (%)	Rate of a in b (%)	Rate of a in not b (%)	Rate of b in a (%)	Rate of b in not a (%)	OR	CI	*p*
18 (IV)	304	11–15	3 mo	5.3	4.3	38.5	3.8	31.3	2.8	15.9	4.5–56.6	***
19 (IV)	289	12–16	3 mo	4.2	1.7	0.0	4.2	0.0	1.8	—	—	—
20 (IIIR)	986	15	6 mo	10.8	6.6	—	—	—	—	3.4	1.9–6.3	*
21 (IIIR)	2762	8–16	3 mo	4.3	1.2	—	—	—	—	11.2	4.6–25.6	*
a = CD/ODD, b = Anxiety												
1 (III)	792	11	1 yr	9.1	7.4	32.2	8.1	26.4	6.3	5.4	2.9–9.9	***
2 (III)	943	15	1 yr	9.0	10.7	5.9	9.4	7.1	11.1	0.61	0.3–1.4	n.s.
3 (IIIR)	930	18	1 yr	5.5	19.7	7.1	5.1	25.5	19.3	1.4	0.7–2.7	n.s.
4 (III)	150	14–16	1 yr	14.7	8.7	69.2	9.5	40.9	3.1	21.5	5.8–79.5	***
5 (III)	278	7–11	1 yr	9.8	15.4	19.4	8.0	30.7	13.8	2.8	1.3–6.12	**
6 (IIIR)	278	12–18	6 mo	13.9	14.4	20.8	12.8	21.6	13.3	1.8	0.8–3.9	n.s.
11 (III)	222	9–16	1 yr	—	—	62.4	—	55.3	—	phi = .14	—	*
12 (IIIR)	1015	9–13	3 mo	5.2	5.5	18.3	4.4	19.2	4.7	4.81	2.1–10.9	***
13 (IV)	970	10–14	3 mo	4.9	3.8	13.0	4.6	9.9	3.4	3.1	1.4–6.9	**
14 (IV)	928	11–15	3 mo	3.4	2.8	7.9	3.2	6.6	2.7	2.6	0.9–7.7	n.s.
15 (IV)	820	12–16	3 mo	2.9	1.0	16.2	2.8	5.5	0.9	6.8	1.6–29.6	**
16 (IIIR)	323	9–13	3 mo	6.5	5.3	5.9	6.5	4.8	5.3	0.89	0.11–7.1	n.s.
17 (IV)	317	10–14	3 mo	8.2	3.8	33.3	7.2	15.4	2.8	6.4	1.8–23.0	**
18 (IV)	304	11–15	3 mo	5.3	2.0	33.3	4.7	12.5	1.4	10.1	1.7–60.2	*
19 (IV)	289	12–16	3 mo	4.2	3.8	27.3	3.2	25.0	2.9	11.2	2.5–49.4	**
20 (IIIR)	986	15	6 mo	10.8	12.8	—	—	—	—	3.2	1.8–5.5	*
21 (IIIR)	2762	8–16	3 mo	4.3	4.4	—	—	—	—	3.7	1.9–6.8	*
a = Depression, b = Anxiety												
1 (III)	792	11	1 yr	1.8	7.4	17.0	0.61	71.4	7.0	33.1	10.0–109	***
2 (III)	943	15	1 yr	4.2	10.7	12.9	3.2	32.5	9.8	4.5	2.2–9.0	***
3 (IIIR)	930	18	1 yr	18.0	19.7	45.9	11.1	50.3	13.0	6.8	4.7–9.8	***
4 (III)	150	14–16	1 yr	8.0	8.7	69.2	2.2	75.0	2.9	100.5	19.5–520	***
5 (III)	278	7–11	1 yr	1.6	15.4	4.4	1.1	43.3	15.0	4.3	0.6–31.0	n.s.
6 (IIIR)	278	12–18	6 mo	4.2	14.4	12.3	2.8	42.4	13.2	4.9	1.5–15.6	**
7 (IIIR)	776	9–18	1 yr	3.4	19.6	7.2	2.5	42.3	18.8	3.2	1.4–7.6	**
8 (IIIR)	776	11–20	1 yr	2.8	10.4	11.1	2.1	40.9	9.5	6.6	2.7–16.2	***
9 (IIIR)	1710	14–18	curr	2.9	3.2	16.7	18.0	18.0	2.7	7.9	3.6–17.2	***
10 (IIIR)	1170	15–18	life	20.4	8.8	48.7	17.6	21.0	5.7	4.4	3.1–6.3	***
11 (III)	222	9–16	6 mo	8.0	6.6	50.0	5.2	38.9	3.6	16.0	4.6–55.3	***
12 (IIIR)	1015	9–13	3 mo	1.5	5.5	8.01	1.1	28.6	5.09	7.5	2.6–21.7	***
13 (IV)	970	10–14	3 mo	3.1	3.8	17.0	2.5	20.9	3.2	7.9	2.2–28.5	**
14 (IV)	928	11–15	3 mo	3.2	2.8	23.7	2.6	20.7	2.2	11.5	3.2–40.6	***
15 (IV)	820	12–16	3 mo	2.7	1.0	58.5	2.1	21.5	0.42	65.2	12.5–341	***
16 (IIIR)	323	9–13	3 mo	0.31	5.3	0.0	0.33	0.0	5.3	—	—	—
17 (IV)	317	10–14	3 mo	1.6	3.8	16.7	1.0	40.0	3.2	20.1	3.0–134	**
18 (IV)	304	11–15	3 mo	4.3	2.0	33.3	3.7	15.4	1.4	13.0	2.2–79.0	**
19 (IV)	289	12–16	3 mo	1.7	3.8	18.2	1.1	40.0	3.2	20.4	3.0–137	**
20 (IIIR)	986	15	6 mo	6.6	12.8	—	—	—	—	4.6	2.6–8.0	*
21 (IIIR)	2762	8–16	3 mo	1.2	4.4	—	—	—	—	24.5	10.8–55.9	*

* $p < .05$; ** $p < .01$; *** $p < 001$.
Study 1. (Anderson et al., 1987).
Study 2. (McGee et al., 1990) A follow-up of Study 1.
Study 3. (Feehan, McGee, Raja, & Williams, 1994) A follow-up of Studies 1 and 2.
Study 4. (Kashani et al., 1987).
Study 5. (Costello et al., 1988).
Study 6. Costello, unpublished DISC DSM-IIIR diagnoses from a 5-year follow-up of Study 5.
Study 7. (Velez, Johnson, & Cohen, 1989).
Study 8. (Velez et al., 1989) A follow-up of Study 7.
Study 9. (Rohde et al., 1991).
Study 10. (Lewinsohn et al., 1993).
Study 11. (Bird, Gould, & Staghezza, 1993).
Study 12–15. (Angold, Costello, et al., 1998) Four annual waves of data collection.
Study 16–19. (Costello, Farmer, Angold, Burns, & Erkanli, 1997) Four annual waves of data collection.
Study 20. (Fergusson et al., 1993a). *p* values reported only as > or < .05.
Study 21. (Simonoff et al., 1997). *p* values reported only as > or < .05.

data necessary to reconstruct the multi-way contingency table that will allow others to compute any and all relevant correlational statistics. For studies that involved complex sampling designs requiring weighted analyses, the weighted percentages for the cells from each pairwise comparison are informative, as are the OR and 95% CI around the OR. Of course, other statistics may well be appropriate for particular purposes, but adoption of this basic set would greatly facilitate comparisons across studies in future.

A Meta-analysis of General Population Estimates of the Strengths of Associations between Disorders

One notable aspect of Table 3 is the wide CI around the estimates of the degree of association (OR) between disorders. Since instances of specific types of disorder are relatively uncommon in the general population, estimates of the probabilities of co-occurrences between disorders are based on small numbers of subjects in the comorbid cell, with the result that estimates based on any individual cross-sectional study or wave of a longitudinal study of the sizes found in child psychiatric epidemiology are of relatively low reliability (i.e. they have wide CI). Meta-analysis provides a means of combining information from multiple studies to produce an overall estimate of parameters of interest. Since a reasonable number of general population estimates of comorbidity rates were available in a form that allowed us to compute 95% CI around the OR for associations between disorders, we undertook the task of using all this information to come up with a single estimate of the strength of association between each pair of disorders.

Statistical Considerations

In combining results from several studies, an important issue is the assessment of variability between the study effects. If this variability is not large, then a weighted average of the individual study effects suffices to produce a reliable estimate of the overall effects, with the weights being equal to the reciprocals of the estimated variances of the individual study effects. If, however, there is evidence of heterogeneity among the individual study estimates, then failure to account for it will produce an estimate of the effect with a standard error substantially smaller than it should be.

We began, therefore, by performing chi-square tests of heterogeneity for each of the OR (using the log odds ratios) we planned to compute. The estimates for three of the comparisons (CD/ODD–depression, CD/ODD–anxiety, depression–anxiety) revealed heterogeneity, while those for the other three (ADHD–anxiety, ADHD–CD/ODD, and ADHD–depression) did not. To conduct meta-analyses for the three homogeneous pairs, we used the standard fixed effect model, which assumes that each study effect is estimating a common unknown study effect (i.e. the common mean). The resulting estimate of the common mean is the usual weighted (i.e. pooled) estimate with weights being equal to the inverse of the variances of the estimated log-odds ratios. For the heterogenous cases, we assumed that each study effect is estimating its own unknown effect, which, in turn, is assumed to be a random sample from the population of all study effects, having an unknown common mean and unknown variance. These parameters can be estimated using a hierarchical Bayesian approach. For the required computations, we used the BUGS package. We used empirical uniform prior distributions for the common mean and variance, with upper and lower bounds respectively taken to be slightly less than and greater than the values provided in each dataset. We also used other priors for sensitivity analyses, but the overall estimates were not very sensitive to variations in the priors.

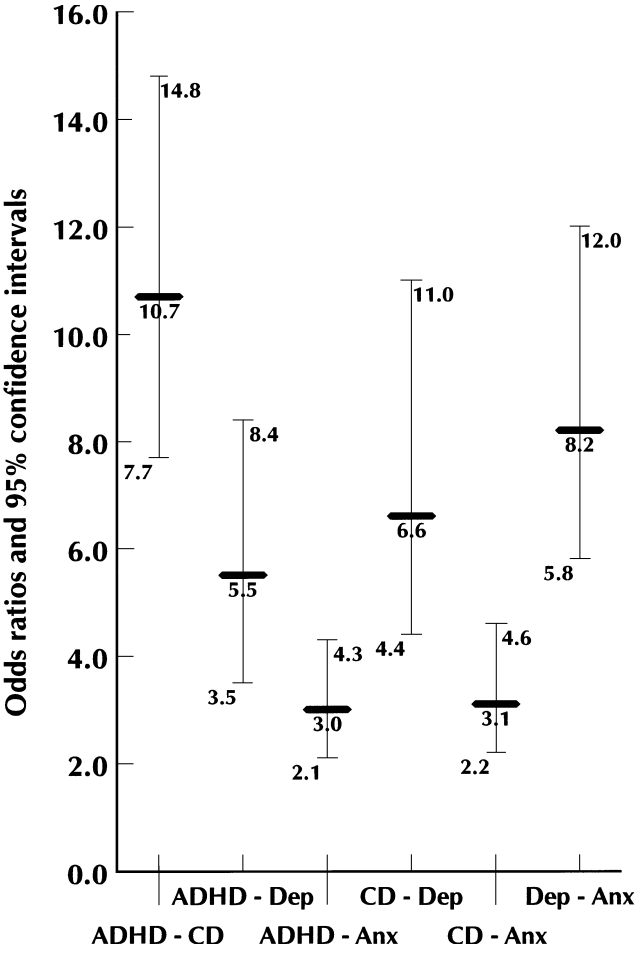

Figure 1. Median odds ratios and 95% confidence intervals from the meta-analysis of community sample based studies of comorbidity.

Results

The resulting median OR (thick central black bars), and their 95% CI (the thin lines extending above and below the black bars) are shown in Fig. 1. As expected, the 95% CI are now sufficiently narrow that we can be confident that all the OR are *not* the same, although there are highly significant associations between all pairs of disorders. When the OR for one pairing falls outside the 95% CI for another pairing we can say that the association between one pair and another pair is significantly different in strength (at the .05 level). The most obvious difference is that the association between CD/ODD and anxiety disorders is weaker than that between CD and depression. The relationship between ADHD and anxiety is also lower than that between ADHD and depression. This is important because it argues against the existence of a unitary association between "internalizing" and "externalizing" disorders. The other interesting point is that depression is almost as strongly related to CD/ODD as it is to anxiety.

Causes of Comorbidity

It is established that comorbidity is a real and unavoidable characteristic of the common childhood and adolescent psychiatric disorders, but how does this come about? What are the mechanisms that generate comorbidity? We should begin by saying that this question cannot be answered at present for any pair of disorders, but that there is a growing body of evidence relevant to understanding the causes of comorbidity. We have divided these contributions into four groups; (1) those that address the possibility that comorbidity may be the result of one or more methodological artefacts, (2) explanations in terms of problems with current official psychiatric nosologies, (3) evidence that certain diagnostic pairings are merely the statistical product of "real" relationships between both of that pair and a third disorder, and (4) explanations involving substantive causes for comorbidity. For each of the substantive explanations, we present a "case study" consisting of the evidence relating to that explanation for a particular type of comorbidity. Each of these "case studies" was selected either because the explanatory mechanism seemed particularly pertinent to that type of comorbidity, or because the literature relating to that type of comorbidity has tended to concentrate on that explanatory mechanism.

Is Comorbidity a Methodological Artefact?

Several authors have discussed the possibility that apparent comorbidity is simply an artefact, rather than a real psychopathological phenomenon (see, for instance, Angold & Costello, 1992, 1993; Caron & Rutter, 1991). The possibilities here include effects of referral bias, rater expectancy, or halo effects, and effects of current information collection strategies, such as the use of multiple informants.

Comorbidity in clinical samples is not just an effect of referral bias. The data we have presented establish beyond a reasonable doubt that the comorbidity seen in clinical samples is not simply the result of Berkson's or clinical referral biases, but represents a psychopathological phenomenon in relation to DSM-III, DSM-III-R, and DSM-IV diagnoses. The data from general population scale score studies discussed above also indicate that this relationship is present at all levels of severity of symptomatology.

Comorbidity is not just an effect of rater expectancies (halo effects) or information collection strategies. When clinicians conduct assessments unaided by structured procedures, it has been shown in many branches of medicine that they adopt idiosyncratic decision procedures and are subject to many information-collection and decision-making biases, some of which could result in the appearance of comorbidity. However, the use of structured assessments for research purposes, and the demonstration that comorbidity is seen with self-report questionnaires from children, parent-report questionnaires about children, respondent-based interviews, and interviewer-based interviews conducted with both parents and children, rule out clinician bias or interviewer expectancies as possible explanations of the observed rates of comorbidity.

Comorbidity is not a result of the use of multiple informants. Imagine a child who cried every day on leaving for school, and reported that this was because she was afraid of leaving the house. A parent could misinterpret this symptom of separation anxiety as being a manifestation of depressed mood and report it as such. Using the usual multiple-reporter combinatorial rule (that a symptom counts as being present if reported by either the parent or the child), a situation like this could result in the same symptom appearing as both separation anxiety and depressed mood. Although this may sometimes occur, it cannot be the explanation for most comorbidity, for four reasons. First, adult studies, which usually employ only a single informant, find high rates of comorbidity—rates that are similar to those described in childhood. Second, Lewinsohn's study of adolescents, which employed only self-reports, documents rates of comorbidity that are similar to those derived from multi-reporter studies (Lewinsohn, Klein, et al., 1995; Lewinsohn, Rohde, Seeley, & Hops, 1991; Rohde et al., 1991; Rohde, Lewinsohn, & Seeley, 1996). Third, Jensen et al.'s (1995) work on children of the military found, using only parent reports, that the mean number of diagnoses per child in those with a diagnosis was 1.3, compared with 1.4 for child-only reports, and 1.4 for combined reports. Fourth, the parent-report scale score literature discussed above shows that there are correlations between factors, and the content of the factors is such as to indicate that there are links between what diagnosticians call "different disorders".

Comorbidity is not the result of single behaviors resulting in the coding of multiple symptoms. Another possible cause of comorbidity is that different aspects of a single behavioral or emotional state may result in coding as multiple symptoms given the definitions incorporated into current interview schedules and questionnaires. For instance, if a child "often leaves seat in classroom or in other situations in which remaining seated is expected", that symptom counts towards the diagnosis of ADHD. However, if the child is told to sit still and fails to do so, it would not be unnatural for a parent or teacher to report that the child "often actively defies or refuses to comply with adults' requests or rules", thus the single behavioral problem also serves as the basis for a positive coding on a symptom of ODD. It is also easy to see how the frustration felt in the face of the frequent repetition of such a scenario between an adult and a child could lead to arguments resulting in the child being described as "often losing temper", "often arguing with adults", "often touchy or easily annoyed by others", and "often angry and resentful". Now the child has sufficient symptoms to meet criteria for ODD provided that he or she is also impaired. Is it helpful to classify the child as suffering from two disorders—ADHD and ODD—or would it be better to regard that individual as having ADHD with resultant impairment of relationships with adults? Clearly, the latter makes more sense in relation to this example, but our technology for discriminating between "independent" ODD and "dependent" ODD is not well advanced. At least the designation of comorbidity signals that not all ADHD children have major problems of the ODD sort, and provides an index of when such additional problems are present. It may well be that in time we will

find that it is better to regard some of what we now call "symptoms of a second disorder" as impairments resulting from an underlying disorder, with the result, perhaps, that ODD in those with ADHD would be seen as a "complication" rather than a separate diagnosis. On the other hand, this mechanism could not explain comorbidity between CD and depression, or CD and ADHD, or anxiety and depression, so this methodological problem also fails to offer a possible general explanation for comorbidity.

In summary, comorbidity is not the product of any likely methodological problem or bias.

Is Comorbidity an Artefact of Current Diagnostic Systems?

Having rejected the possibility that comorbidity is solely the spurious product of methodological problems, we turn our attention to the possibility that the diagnostic systems we use might result in comorbidity between supposed "disorders", when the underlying disorders themselves are unrelated. Here we consider possible effects of the inclusion of nonspecific symptoms in the definitions of multiple diagnostic categories, and then go on to discuss the idea that our whole categorical diagnostic system may be fundamentally flawed.

"*Nonspecific symptoms*" *as an explanation for heterotypic comorbidity*. Several authors have pointed out that comorbidity could be generated by the fact that individual "nonspecific" symptoms are shared by disparate diagnoses (e.g. Caron & Rutter, 1991), with the result that a certain amount of overlap is built into the diagnostic system. This raises the question of the degree to which the current DSM and ICD nosologies really suffer from this problem. All that needs to be done to examine this possibility is to look at the criteria for different disorders to determine the degree of overlap. When one does so, this possibility fades for some pairs of diagnoses. The criteria for CD do not overlap at all with those for depressive disorders, anxiety disorders, or ADHD, but there is no doubt that CD is often comorbid with all three, so overlapping symptom lists cannot be the explanation in this case. On the other hand, irritability is common in depressive episodes and several symptoms of ODD could result from irritability (e.g. often loses temper). The DSM-III-R and DSM-IV criteria require that the ODD symptoms should not occur exclusively during a mood disorder, but this sort of criterion is very difficult to implement in practice, especially with disorders of long duration, when it may be difficult to remember what the child's behavior was like before the mood disorder arose. This difficulty is exacerbated by the fact that it may not be clear just when the mood disorder should be regarded as having begun or ended. Sleep disturbances are included in the criteria both for depressive disorders and anxiety disorders, as are concentration difficulties and fatigue. Thus, a child who had had these three symptoms for a year, and who also manifested both depressed mood and anxiety or worry, would thereby meet DSM-IV criteria for both dysthymic disorder and generalized anxiety disorder. Indeed, after only 2 weeks of symptoms such a child could also meet criteria for the new DSM-IV experimental category of minor depression. Three diagnoses from a total of five symptoms! Before we conclude that this explains comorbidity, we should remember that such work as has been done on this question indicates that there is also comorbidity between the non-overlapping symptoms of such syndromes, again suggesting that comorbidity is not just an artefact of our flawed diagnostic system. Two studies have looked at whether comorbidity remains when overlapping symptoms are removed from the criteria for the diagnosis for two disorders. Milberger and colleagues (Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995) examined comorbidity with ADHD by removing symptoms that overlapped with the criteria for depression or generalized anxiety and reallocating diagnoses according to two different methods. The great majority of individuals maintained their comorbid diagnoses even when the overlapping symptoms were taken out of consideration. Biederman and colleagues (Biederman, Faraone, Mick, & Lelon, 1995), using the same approach, found that eliminating overlapping symptoms failed to eliminate comorbidity between depression and ADHD or ODD. It seems safe to conclude, therefore, that comorbidity is not *just* an artefact of overlapping diagnostic criteria.

One reaction to this might be to suggest that we should remove the offending criteria in order to produce better demarcated categories. However, this solution will result in *atypical* symptoms becoming the diagnostic criteria for the major disorders. Both depressed and anxious individuals really do suffer from sleep disturbances and fatigue, and they have difficulty in concentrating. If we consider only the criteria not shared between disorders we will end up ignoring many key symptoms. Neither is this how we would behave in any other branch of medicine. We would hardly deny the right of the symptoms of chest pain, breathlessness, and cough to be considered in the diagnosis of both myocardial infarction and pneumonia. To ignore them and rely on nonshared symptoms would be a disaster. This example, of course, points to where the real problem lies. The issue is not the inclusion of similar symptoms in different diagnoses, but the paucity of research on the *differential characteristics* of those symptoms in different disorders. When the patient describes crushing central chest pain, radiating down the left arm to the elbow, with breathlessness and cough exacerbated by lying flat, we can be pretty sure that pneumonia is not the problem. But we know very little abut the specifics of the "nonspecific" symptoms in psychiatry. There are now many studies large enough to allow examination of the ways in which, for example, the sleep disturbances of anxious and depressed patients differ. For instance, Angold found that mild insomnia (occurring on fewer than 12 nights in 3 months) was strongly associated with anxiety disorders, and less strongly associated with depression, but that severe insomnia (most nights over 3 months) was significantly associated only with depression. Thus, severe insomnia was evidence of depression, but not of anxiety (Angold, 1996). There is a real need for more work detailing the qualitative and quantitative aspects of individual symptoms in relation to different diagnoses, and we believe that such an approach could go a long way toward cleaning up the boundaries between diagnoses. However,

there is no reason to suppose that it will make comorbidity go away.

Comorbidity as evidence that the official diagnostic system is fundamentally flawed at the conceptual level. Some of the most radical critiques of diagnostic "medical" models of psychopathology have used the fact of comorbidity as a plank in the argument that diagnostic approaches simply impose arbitrary cutpoints on a series of dimensional phenomena. Comorbidity arises because diagnosticians insist on assigning naturally linked sets of phenomena to different classes of disorder. For instance, the "depression" dimension that repeatedly emerges from general population questionnaire studies of psychopathology always contains a mixture of what, from a diagnostic perspective, would be called depressive and anxiety symptoms (Achenbach et al., 1989). The problem became acute with DSM-III, when diagnostic criteria were developed for a much greater number of "specific" diagnoses for children and adolescents than had previously existed. Indeed, whole new disorders were invented: for instance, conduct disorder was split into oppositional defiant disorder and conduct disorder (it remains a single category in ICD-10). Doubts about whether this proliferation of categories in DSM-III was going to be helpful were expressed by some proponents of the diagnostic approach at the time (Rutter & Shaffer, 1980), and there is surely no doubt that the criteria for individual diagnoses ran far ahead of the research supporting them—witness the very substantial changes that have continued to appear with each revision of the DSM. In spite of all these problems, however, the recent diagnostic literature has been helpful in two ways. First, it has shown that associations between symptoms of different types occur at the extremes of the distributions of psychopathology, and not just at the level of factor scores in relation to mild symptomatology, which could be interpreted as not being measures of serious clinical disorders. In other words, we can be sure that what the diagnostically inclined call comorbidity is a feature of behavioral and emotional problems across the entire range of severity. This is important because many severe manifestations of disturbance are not included in the scales upon which "empirical" syndromes have been based, as a result of the fact that they occur too rarely in the general population to be suitable for inclusion in classical factor analyses. The clinical literature on comorbidity has also indicated that comorbidity is an issue for a range of relatively uncommon syndromes, such as post-traumatic stress disorder, eating disorders, or bipolar disorders, which are not identified in generic general population questionnaire studies.

Whether one sees comorbidity as diagnostic misrepresentation of naturally linked phenomena, or overlap between more-or-less well-defined natural categories, the issue for future research is the same: to explore why symptoms group together in the ways that they do, and why there is overlap between syndromes, whether defined by diagnostic criteria or factor scores. In phenomenological terms, for instance, depressed mood and anxiety are not the same thing; why then do they so often occur together? On the other hand, why is it that some individuals with depressed mood are not anxious? These questions can be cast in factor terms by asking why some individuals with a high depression factor have mostly "depressive" symptoms, while others have mostly "anxiety" symptoms, and still others have a mixture of both? On the other hand, we can ask why do some individuals who meet diagnostic criteria for a depressive disorder also meet criteria for an anxiety disorder, while others do not? One possible answer to both questions is that "depression" and "anxiety" are simply alternative manifestations of the same underlying diathesis and that the diagnostic criteria are carving nature anywhere but at the joints. However, it is also possible that the links are due to correlations between separate sets of causes for anxiety and depressive disorders. Some genetic studies of adults suggest that depression and anxiety have a similar genetic basis, but that environmental factors determine whether this is expressed as depression or anxiety (Kendler, Heath, Martin, & Eaves, 1987), whereas other studies have indicated that different sorts of life events are related to depression and anxiety (Brown, Harris, & Eales, 1993).

It would not be surprising if some aspects of comorbidity do arise because our diagnostic criteria have not drawn the appropriate boundaries between disorders (see the discussion of examples of the causes of homotypic comorbidity below). That is one reason for doing research on comorbidity. As Achenbach (1990) has pointed out, both categorical and quantitative models offer complementary approaches to the issue of nosology.

"*Epiphenomenal*" *Comorbidity*

The standard approach to quantifying comorbidity has been to look at the pairwise concordances among diagnoses. As we have seen, there is no doubt that this approach has shown that the common conditions occur together much more frequently than can be explained by chance associations. When three conditions are all associated with one another, it is possible that one of the pairwise associations is nothing other than the mathematical product of the other two. We will refer to this possibility as *epiphenomenal comorbidity* (Angold, Erkanli, Egger, & Costello, 1998). To present a concrete example, we have shown that there are significant associations between depressive and anxiety disorders, depressive and conduct disorders, and anxiety and conduct disorders (see Fig. 1). Perhaps the last of these associations could be explained simply by the second—anxiety disorders are only seen more often in those with CD because people with CD are more likely to be depressed, and this depressed group includes a substantial number of individuals who also have an anxiety disorder. The Great Smoky Mountains Study provided a large enough sample to test for this possibility, by controlling each pairwise comparison for the effects of other comorbidities. The results support this epiphenomenal explanation for the relationship between depression and ADHD (via anxiety and CD), and for the relationship between CD and anxiety (via depression) and ODD and anxiety (via ADHD). For instance, the OR for the association between anxiety and ODD fell from 3.0 to a nonsignificant 0.56 when other comorbidities were con-

trolled for. In other words, there was no independent relationship between ODD and anxiety disorders. On the other hand, there were independent associations of CD with ODD, CD and ODD with depression and ADHD, and ADHD and depression with anxiety. The apparent pairwise covariation of ADHD with depression, and CD and ODD with anxiety, was explained by comorbidity between other pairs of disorders; it was an epiphenomenon of the relationships between other pairs of disorders. These results need to be replicated, but they do suggest that some simplification of the problem of comorbidity may be at hand—we may have to explain only a subset of the possible pairings of disorders. We should note that this does not mean that those who *do* have both depression and ADHD do not have "real" depression or ADHD (see, e.g., Biederman, Mick, & Faraone, 1998). It simply means that, in the absence of comorbid anxiety, CD, or ODD, depressed individuals are no more likely to have ADHD than children who are psychiatrically well.

This review of methodological and nosological explanations for comorbidity leads us to the conclusion that one of the major achievements of research on comorbidity over the last decade has been its demonstration that we are dealing with a real phenomenon. We still cannot be sure to what extent comorbidity implies that we should change our diagnostic categories, but it has certainly led to much more work being done to examine the psychometric properties of those categories and to modify them on the basis of information generated by research than has been the case in the past. The challenge now lies in explaining how comorbidity comes to be so common. So we turn our attention to what is known about the substantive causes of comorbidity. Among the many possible causes of comorbidity (Angold & Costello, 1993; Caron & Rutter, 1991; D. N. Klein & Riso, 1993), the type of explanation most commonly investigated has varied according to the group of diagnoses being studied. We have, therefore, presented research on the causes of comorbidity between or within groups of diagnoses as case studies of particular explanatory possibilities. We do not imply that for each pair only the explanations discussed in relation to that pair are relevant; clearly, each possible explanation could be examined in every case.

Causes of Homotypic Comorbidity

Homotypic comorbidity has been most studied in relation to the anxiety disorders, CD/ODD, and the depressive disorders (particularly unipolar depression and dysthymia). We examine three key potential causes of homotypic comorbidity; (1) invalidity of individual diagnostic categories (anxiety disorders), (2) that current diagnostic boundaries may obscure developmental continuities at the symptom level (CD/ODD), and (3) that homotypic comorbidity over time may be a marker for underlying homotypic *continuity* of a single disease process (dysthymia/depression). It will be seen that (2) and (3) are restatements of the same idea in slightly different terms, reflecting differences in the ways in which comorbidity has been approached in these two diagnostic areas.

Homotypic comorbidity in anxiety disorders—evidence for the invalidity of current diagnostic categories? Of the common disorders, anxiety disorders have received much less research attention than the disruptive behavior disorders and depression, and uncertainties about the classification of these disorders is probably greater than in relation to any other major category of child and adolescent disorder. DSM-III introduced three "new" diagnoses for children: separation anxiety disorder (SAD), overanxious disorder (OAD), and avoidant disorder. These have no parallel in the classification of adult disorders. Only SAD has survived into DSM-IV, and that survival can be attributed to the fact that the category was solidly based on longstanding clinical research on "school phobia" (e.g. Hersov, 1960a, b) and a vast literature on separation responses in children. Avoidant disorder was little more than a category for shyness, and has now been folded back into social phobia. OAD was an attempt to provide a category for the commonly seen generally worried or anxious child, at a time when no-one knew whether such children would or would not meet adult criteria for generalized anxiety disorder. DSM-III-R specified the criteria for OAD in greater detail (although there had been little research on the topic), but again produced a category that drew substantial criticism. R. G. Klein, Tancer, and Werry (1994) in their report to the DSM-IV work group on anxiety disorders, noted that what little research had been done on the phenomenology of OAD pointed to "a lack of syndromal specificity for several items in the criteria and to their limited face validity because of their overlap with the clinical criteria of other anxiety disorders". Their recommendation was that OAD be retained, but "modified to remove the considerable clinical overlap with the other anxiety disorders".

These conclusions appear to be well supported by the research evidence. Kashani and Orvaschel's general population study found that of children with OAD, 55% met criteria for a second anxiety diagnosis, compared with 42% of children with SAD (Kashani & Orvaschel, 1990), whereas in the Dunedin Longitudinal Study, only 15% of those with an anxiety diagnosis met criteria for two or more anxiety diagnoses (McGee et al., 1990). Last, Strauss, and Francis (1987) found that 45% of children with OAD had no other anxiety diagnosis in an anxiety clinic sample, compared with 56% of children with SAD—hardly a significant difference given the small numbers involved. In an earlier paper, which appears to have been based on a substantially overlapping sample, this group reported that OAD was associated with much greater comorbidity with other anxiety disorders than was SAD, but even here only "more than half" of the OAD group had a second anxiety disorder diagnosis (Last, Hersen, Kazdin, Finkelstein, & Strauss, 1987). It has also been found that children with OAD and SAD can be discriminated in terms of the types of worries they report (Last, Hersen, Kazdin, Finkelstein, et al., 1987), that children presenting to clinics with OAD are older, but of higher socioeconomic status than those presenting with SAD (Last, Hersen, Kazdin, Finkelstein, et al., 1987; Last, Perrin, Hersen, & Kazdin, 1992), and that panic disorder is more common in the families of OAD children than it is in the families of children with SAD

(Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991). In other words, there is evidence that OAD and other anxiety diagnoses are not just measures of a single unitary construct. We do not mean to suggest that homotypic comorbidity amongst the anxiety disorders is not a significant issue; there is no doubt that it is, both cross-sectionally and even more so when lifetime diagnosis is considered (Beidel, Fink, & Turner, 1996; Biederman et al., 1997; Bradley & Hood, 1993; Clark, Smith, Neighbors, Skerlec, & Randall, 1994; Francis, Last, & Strauss, 1992; Hirshfeld et al., 1992; Keller, Lavori, Wunder, et al., 1992; Last et al., 1992). The question is what to do about such issues.

The DSM-IV solution was to abolish OAD and substitute a special subset of generalized anxiety disorder (GAD) for children and adolescents, requiring only one symptom apart from worrying or anxiety from a list that overlaps greatly with the symptoms of depression or dysthymia (restlessness, fatigability, difficulty concentrating, irritability, and sleep disturbance). It is hard to see how this will reduce homotypic comorbidity among the anxiety disorders, and it could actually increase heterotypic comorbidity. Indeed, the reported levels of comorbidity amongst all the anxiety diagnoses could equally have been used as evidence for the abolition of each individual disorder, and all the current categories would have ended up collapsed into one. Even more damagingly, if the level of homotypic comorbidity displayed by OAD is sufficient for it to be removed as a diagnosis, then all of the diagnostic distinctions currently made in child and adolescent psychiatry would be liable to abolition because, as we have seen, rates of some types of heterotypic comorbidity are as high as those associated with the homotypic comorbidity of OAD. Lest this seem to be an argument in favor of abolishing diagnosis and adopting a purely dimensional approach to psychopathology, we must remember that the effort to define syndromes using factor analysis, or to base typologies of children on cluster analyses of factor scores, would be equally undermined by the correlations between factors (see e.g. McConaughy & Achenbach, 1994; Verhulst & van der Ende, 1993). We would end up where we were 30 years ago, with nothing but generic measures of "disturbance". A start had been made on differentiating OAD from the generic mass of anxiety symptoms, but given the fact that the "replacement" diagnosis of a special childhood form of GAD is defined quite differently from OAD, that task will now have to begin again with GAD. As the two following examples will demonstrate, research in this area would likely benefit from a more developmental approach than has hitherto usually been adopted.

Homotypic comorbidity in conduct and oppositional defiant disorders—does diagnosis obscure developmental progressions at the symptom level? The diagnostic criteria for antisocial personality disorder require that conduct problems should have been present in adolescence, and the DSM-IV diagnosis of CD precludes that of ODD, whereas in ICD-10 the two diagnoses are treated as a single category. All of these diagnostic rules recognize the well-established fact that there is a developmental pathway from oppositional problems in childhood through adolescent conduct disorder to antisocial personality disorder (Fergusson, Lynskey, & Horwood, 1996a; Loeber, Green, Keenan, & Lahey, 1995; Loeber, Green, Lahey, Christ, & Frick, 1992; L. N. Robins, 1974). It is also well established that this pathway grows narrower with time—there are more oppositional children than there are CD adolescents than there are adults with antisocial personality disorder. Here is an unusual situation in which "comorbidity" is either *required* (the relationship between CD and antisocial personality disorder) or *forbidden* (the relationship between CD and ODD) at different points in the developmental trajectory of the disorder. If we confine ourselves to childhood and adolescence, and thereby to the relationship between ODD and CD, we find that the small literature comparing the correlates of these two disorders finds them to be similar in terms of socioeconomic status, family history, and impairment, but that the relationships of these factors with CD are stronger (Faraone, Biederman, Keenan, & Tsuang, 1991; Frick et al., 1992; Rey, Bashir, & Schwartz, 1988). There seems to be good evidence then that ODD is often a developmental precursor of CD, which could be regarded as being a later and more severe manifestation of a process that earlier appeared as oppositionality. Under this assumption, it is a serious problem that the organization of the diagnostic criteria for ODD and CD creates a disjunction between the two. Many ODD behaviors become less common between childhood and adolescence (Campbell, 1990; Loeber, Lahey, & Thomas, 1991), whereas many CD behaviors (especially covert behaviors) become more common (Farrington, 1986; Farrington, Loeber, & Elliott, 1990; Le Blanc & Fréchette, 1989; Loeber, 1988). Given that the criteria for ODD and CD do not overlap in content, this means that it is possible for an individual who has previously met criteria for ODD, and who will later meet criteria for CD, to meet criteria for neither at an intermediate stage, despite having, say, three ODD symptoms and two CD symptoms at that point—a total of five relevant symptoms when ODD requires only four symptoms and CD only three. Considerations of this sort, combined with work on symptom aggregation and a willingness to consider symptoms that are not included in the DSM definitions of ODD and CD, led Loeber and his colleagues (Loeber, Keenan, Lahey, Green, & Thomas, 1993; Russo, Loeber, Lahey, & Keenan, 1994) to suggest that these diagnoses be replaced by three categories ordered both in time and severity, which they called "modified oppositional disorder", "intermediate CD", and "advanced CD".

In many ways it would be attractive to accept this position, or something very like it, but we also have to remember that questionnaire studies consistently find that oppositional-type behaviors and CD-type behaviors load on different factors (Achenbach, Connors, Quay, Verhulst, & Howell, 1989; Frick et al., in press); that a number of individuals begin to manifest notable CD behaviors in adolescence, without a previous history of antisocial behavior (Loeber, 1988; Moffitt, 1990; Moffitt, Caspi, Dickson, Silva, & Stanton, 1996); and that this group probably has better adult outcomes than the early-onset group. There is also evidence that the transition from having ODD plus fewer than three CD symptoms to having at least three symptoms of CD is associated with

a sharp increase in police contacts and school suspensions (Lahey et al., 1990), which suggests that it may be more useful to regard ODD and CD as being different conditions. Our aim here is not to take a stand on what the answer should be, but rather to point out some features of the work done in this regard that could serve as a model for other areas. First, the notion of development has been taken seriously, and a good deal of attention has been paid to the relative timing of onsets and offsets of *individual symptoms*. Second, the diagnostic categories have been subjected to serious scrutiny, and various alternatives *based on empirical research* have been experimented with. Third, methods usually associated with the questionnaire approach to psychopathology, like factor analysis of individual items, have sometimes been applied to the distinction between ODD and CD, with interesting results. For instance, Frick et al. (1991) found that bullying (a symptom of CD) consistently loaded on an ODD factor, whereas fighting and lying (again both CD symptoms) loaded equally on both the ODD and CD factors. Another report from the same study (Loeber et al., 1995) found that physical fighting was the single symptom of all the symptoms of CD that best predicted the onset of full CD. This suggests that bullying may be misplaced in the diagnostic criteria, whereas fighting and lying may belong in *both* sets of criteria, if they are to be kept separate. Overall, the work in this area can be seen as having treated the diagnostic criteria as "hypotheses" to be examined and tested. In our present state of knowledge this would appear to be the right attitude to take to all diagnoses in child and adolescent psychiatry.

Homotypic comorbidity between major depression and dysthymia—a marker of homotypic continuity? A second area in which the study of homotypic comorbidity has moved beyond rates of comorbidity to studying comorbidity longitudinally concerns the affective disorders. Some adult studies have suggested that major depression, dysthymia, and the simultaneous comorbidity of the two represent either nothing more than separate phases or manifestations of the same disorder (e.g. Keller, Lavori, Mueller, et al., 1992; Keller, Shapiro, Lavori, & Wolfe, 1982a, b; D. F. Klein, 1990), or points on a continuum of severity of depressive conditions (Angst & Dobler-Mikola, 1984; Angst, Dobler-Mikola, & Binder, 1984). Several studies have identified differences between children with dysthymia, major depression, and double depression in symptomatology, impairment, heterotypic comorbidity, and rates of suicidality (Asarnow & Ben-Meir, 1994; Ferro, Carlson, Grayson, & Klein, 1994; Fine, Moretti, Haley, & Marriage, 1985; Ryan et al., 1987; Shain, King, Naylor, & Alessi, 1991), but even these can be interpreted as indicating that "major depression may be the driving force behind the expression of depressive symptomatology, regardless of whether the child is acutely or chronically depressed" (Ferro et al., 1994).

Longitudinal studies of children have, on the whole, given a similar impression (see e.g. Kovacs et al., 1984), but Kovacs' 12-year clinical follow-up of children with major depressive episodes and dysthymia resulted in a rather more differentiated conclusion. By the 12-year follow-up (Kovacs, 1996), no less than 76% of children whose first depression was dysthymic disorder had a subsequent major depressive disorder and 13% had a bipolar disorder. Of those whose first episode was a major depressive episode, 48% later met criteria for dysthymia and 15% had bipolar disorders. These writers go on to emphasize that childhood dysthymia in their sample *did not* persist into adulthood itself, but exerted its influence on later risk for affective disorder through major depressive episodes. They now regard childhood-onset dysthymic disorder as an "early marker of recurrent affective illness". Here we see the fruits of careful long-term follow-up of diagnostically well-characterized samples for clarifying comorbidity issues. However, Kovacs and her colleagues suggest that we should maintain the distinction between early-onset dysthymic disorder (with somewhat modified diagnostic criteria) and major depressive disorder (MDD), because the former had an earlier age of onset (see also Ferro et al., 1994), a subset of early dysthymics did not develop MDD, dysthymia was associated with shorter disorder-free periods than MDD without dysthymia, and first-episode dysthymia and MDD carried different levels of risk for later affective and substance use disorders. There are interesting parallels here with Lewinsohn and colleagues' work on older adolescents (Lewinsohn et al., 1991). They found that lifetime comorbidity between MDD and dysthymia was twice as high in their adolescent general population sample as in an adult sample, and that dysthymia nearly always preceded MDD when both occurred. However, MDD was vastly more common than dysthymia in adolescents.

Here again, we see that attention to timing yields important findings. We also see that research under the heading of "comorbidity" has stimulated exploration of the *development of patterns of symptomatology*. At present there seems to be more to be gained, as Kovacs and her colleagues have indicated, by exploring the implications of the "separate" diagnoses of dysthymia and major depression, and their co-occurrence, than in collapsing them into a single diagnosis. Such studies could lead eventually to the lumping together of dysthymia and major depression, or to further splitting of these diagnostic categories (perhaps "double depression", as comorbidity between MDD and dysthymia is sometimes called, should be a separate diagnosis). Ignoring these indications that there are developmental differences between depression and dysthymia, however, would be counterproductive. We need longitudinal, general population samples of sufficient size to allow comparisons among individuals with MDD, dysthymia, and both disorders.

Causes of Heterotypic Comorbidity

Heterotypic comorbidity involves comorbidity of diagnoses from different diagnostic groupings (for instance depression and CD). Here we consider the following possible causes for comorbidity; (1) that it is nothing more than a marker for the severity of a relatively undifferentiated mass of symptoms upon which arbitrary diagnostic cutpoints have been imposed; (2) that one disorder may be nothing more than a particular mani-

festation of another disorder; (3) that it may be caused by the other disorder; (4) that the two disorders may share certain causes, while differing etiologically in some other ways; and (5) that comorbidity may be a marker for specific subtypes of disorder. We then go on to emphasize the importance of timing in the study of comorbidity.

Heterotypic comorbidity as a marker of severity. Comorbidity has often been associated with increased levels of symptomatology within each of the disorders making up the comorbid group, and with increased levels of impairment in functioning. Comorbid conditions have also been associated with higher levels of psychosocial adversity. For instance, individuals with both ADHD and ODD or CD have higher levels of CD/ODD symptoms than children with "pure" CD (Hinshaw et al., 1993; Kuhne, Schachar, & Tannock, 1997; Offord, Sullivan, Allen, & Abrams, 1979; Walker, Lahey, Hynd, & Frame, 1987), greater levels of parental psychopathology, conflictual interactions with parents, peer rejection, school problems, and psychosocial adversity (Abikoff & Klein, 1992; C. L. Carlson, Tamm, & Gaub, 1997; Fletcher, Fisher, Barkley, & Smallish, 1996; C. Johnston & Pelham, 1986; Kuhne et al., 1997; Lahey et al., 1988; Milich & Dodge, 1984; Reeves, Werry, Elkind, & Zametkin,1987; Schachar & Wachsmuth, 1990), and worse outcomes than those with either ADHD or conduct problems alone (see Barkley, 1990; Lyons, Serbin, & Marchessault, 1988; Satterfield & Schell, 1997; Taylor, Chadwick, Heptinstall, & Danckaerts, 1996, for a review).

Similar indications of the malignancy of comorbidity have been reported for the associations of ADHD with depression or anxiety disorders (Jensen, Shervette, Xenakis, & Richters, 1993), though other data suggest that comorbidity between ADHD and internalizing disorders may not necessarily be indicative of more severe ADHD (August, Realmuto, MacDonald, Nugent, & Crosby, 1996; Pliszka, 1992). The indications are that depression has little effect on the course of CD (Capaldi, 1992; Zoccolillo, 1992), though there are suggestions that CD may be associated with more severe concurrent depressions (Marriage, Fine, Moretti, & Haley, 1986; Noam, Paget, Valiant, Borst, & Bartok, 1994; Rudolph, Hammen, & Burge, 1994), but perhaps with less risk that depression will continue into adulthood (Harrington, Fudge, Rutter, Pickles, & Hill, 1991). On the other hand, the combination of CD and depression is strongly associated with suicide, especially when combined with alcohol use (Andrews & Lewinsohn, 1992; Brent, Kolko, Allan, & Brown, 1990; Brent, Kolko, et al., 1993; Brent et al., 1988; Brent, Perper, et al., 1993; Lewinsohn, Rohde, & Seeley, 1994; Martunnen, Aro, Henriksson, & Lönnqvist, 1991; Rohde et al., 1991; Shaffer, 1993; Shaffer & Fisher, 1981).

CD with an anxiety disorder has been associated with less impairment (Walker et al., 1991), and perhaps lower rates of aggression and violent crime (Hinshaw et al., 1993), at least in younger children, and with higher levels of evening salivary cortisol than those found in either CD or anxiety alone (McBurnett et al., 1991). On the other hand, several studies of shyness and social withdrawal indicate that these features have negative implications for children with conduct problems (see Loeber & Keenan, 1994, for a review). Both anxiety and depression may also be more severe when they occur together (Last, Perrin, Hersen, & Kazdin, 1996).

It is hard to draw any hard and fast conclusions from this confusing literature, but it cannot be said to support the notion that comorbidity is simply a marker for overall severity of the component disorders. Rather it points to complex relationships among disorders over time, and in the case of suicide, to the particularly negative effects of depression and conduct disorder.

Comorbidity between conduct disorders and depressive disorders—are the latter simply part of the former, does CD cause depression, or do CD and depression have common or correlated causes? Zoccolillo's (1992) thoughtful review of the relationships between conduct disorder and depressive and emotional disorders across the life span concluded that, in our present state of knowledge, separate disorders should be diagnosed when conditions comorbid with CD are observed, and it firmly rejected the ICD-10 category of depressive conduct disorder. In considering the very limited evidence on a variety of explanations for CD comorbidity, he concluded that the best solution might be to regard CD as a "disorder of multiple dysfunction", with depression or anxiety representing dysfunctions in affect regulation and CD presumably being a form of social dysregulation. Given the evidence cited, it seems that this conclusion is only meant to apply to life-course persistent conduct problems. His key lines of evidence were: (1) the more severe the antisocial behavior, the greater the likelihood of comorbidity with non-antisocial disorders; (2) CD only predicts *adult* affective disturbance in individuals who have persistent antisocial behavior in adulthood; and (3) CD is associated with earlier onset of affective disturbances, at around the same time as the first CD symptoms appear. A good deal of additional work is needed to provide convincing evidence on each of these topics, but they also admit an alternative explanation—that CD causes affective disorders. Aggressive and CD children often interpret the social actions of others as being hostile (Quiggle, Garber, Panak, & Dodge, 1992), have problems in all sorts of social relationships, do poorly at school, get into serious trouble with the authorities, and are often told that they are bad. The literatures on life events, chronic difficulties and hassles, and cognitive styles in depression suggest that these correlates of CD could cause depression (see Capaldi, 1992, for a version of this model). This suggests the hypothesis that individuals with CD who had lower rates of difficulties arising from their CD behavior would manifest less depression. If specific predictors of the appearance of depression in CD (other than just the severity of CD itself) could be identified, and some or all of those predictors were effects of CD, then it would be reasonable to regard CD as causing depression. If depression were simply a manifestation of the diathesis underlying CD, no such specific risk factors should be identified because CD itself is the risk. An alternative approach was employed by Fergusson and his colleagues (Fergusson, Lynskey, & Horwood, 1996b). They fit structural equation models to their general population data to test the contrasting hypotheses that the relationship between CD and depression was either the result of

correlations among the risk factors for the two disorders or the result of reciprocal causation. They found no support for the idea that either disorder caused the other, but noted that a substantial amount of the covariation between them could be explained by their having common or correlated risk factors. This elegant study underscores the usefulness of having measures of comorbidity on individuals at more than one point in time, and suggests an analytic approach that could be replicated with data from several of the general population studies listed in Table 3.

The work of Cohen and her colleagues (Cohen, Brook, Cohen, Velez, & Garcia, 1990) illustrates an alternative approach involving direct statistical comparisons among the relationships of risk factors measured in childhood with internalizing, externalizing, and substance abuse problems measured 8 years later. This study found that certain risk factors were "common" to more than one problem outcome. For instance, parental mental illness and remarriage were associated with both internalizing and externalizing problems. Other factors appeared to be relatively "specific" to only one sort of problem. For instance, residential instability was protective against substance abuse, but had no significant effect on either internalizing or externalizing problems. Family social isolation was related only to internalizing problems. The key strengths of this study are that it involves simultaneous examination of the effects of multiple risk factors on multiple outcomes measured at multiple points in time. Many statistical approaches to complex longitudinal data are now available, and, although it is often difficult to decide exactly how to implement the effects of comorbidity in such models, this general approach is one that deserves to be much more widely implemented.

Heterotypic comorbidity as a means of subtyping disorders—the case of ADHD. It has often been suggested that comorbidity may provide a means of subtyping disorders, and this possibility has been taken up in ICD-10 by the inclusion of diagnoses like hyperkinetic conduct disorder. The process began with clinical studies documenting high rates of comorbidity in clinical populations of children with ADHD, which led investigators to suggest that there might be meaningful differences in the nature of comorbid and non-comorbid disorders (e.g. Biederman, Newcorn, & Sprich, 1991; Jensen, Martin, & Cantwell, 1997; Munir, Biederman, & Knee, 1987; Schachar & Logan, 1990). The evidence discussed above, that ADHD comorbid with conduct problems had particularly malignant outcomes, strengthened the case (Taylor, 1994). More recently, family studies have lent further weight to the argument. These provide strong evidence that antisocial, substance abuse, and depressive disorders are more common in the parents of children with combined ADHD and CD/ODD than in parents of children with "pure" ADHD, but not unassailable evidence that hyperkinetic conduct disorder is a familially distinct subtype (see Faraone, Biederman, Jetton, & Tsuang, 1997). Results from the Virginia Twin Study of Adolescent Behavioral Development also suggest a common genetic component underlying hyperkinetic disorder and CD in younger boys (Silberg, Meyer, et al., 1996; Silberg, Rutter, et al., 1996), but weaker genetic liability for non-comorbid antisocial behavior. On the other hand, some longitudinal data have not supported the subtype hypothesis (e.g. Taylor et al., 1996), and the literatures on pharmacotherapy and neuropsychological tests in ADHD indicate that the presence of conduct problems has little effect on the response of ADHD symptoms to medications or neuropsychological performance (Abikoff & Klein, 1992; Schachar & Rannock, 1995; Seidman et al., 1995). At least some of the data can also be seen to support the idea that ADHD and antisocial behavior reflect "different phases of the manifestation of the same underlying liability" (Rutter, 1997); in other words, heterotypic continuity in a unitary underlying disease.

This chain of work from cross-sectional observations of high rates of comorbidity to longitudinal outcome studies and family genetic approaches provides a good model of how progress can be made in understanding the implications of comorbidity. For instance, there is evidence that rates of both depressive and anxiety disorders are higher in the relatives of children with ADHD (Biederman et al., 1990; Biederman, Faraone, Keenan, & Tsuang, 1991; Perrin & Last, 1996). We can also expect ever-finer tuning of questions concerning comorbidity, since there is already evidence that the different subtypes of ADHD are associated with different patterns of comorbidity; in particular, that emotional disorders may be more strongly associated with non-hyperactive attention deficit disorders, whereas the combined subtype is more strongly associated with CD (see Eiraldi, Power, & Nezu, 1997, for a discussion of these findings and comments on the possible effects of changes in the subtyping of ADHD introduced in DSM-IV). Some are already moving towards subtyping the comorbid subtypes; witness Biederman and colleagues' (Biederman, Faraone, Milberger, et al., 1996) work suggesting that in ADHD there are two subtypes of ODD comorbidity with different correlates, course, and outcomes—one that is prodromal to CD and one that rarely progresses to CD. In contrast, we also have to remember that it may be relatively hard to find "pure" disorders, so we can also interpret the relationship between ADHD and ODD as failing to support the existence of meaningful distinctions between them (Paternite, Loney, & Roberts, 1995). However, the use of clinical samples to determine whether there are "pure" types of frequently comorbid disorders is particular problematic, because clinical presentation is associated with comorbidity (Angold, Messer, et al., 1998).

Combined Subtypes—Implications for Research on "Criteria Sets and Axes Provided for Further Study"

The two "combined" conditions for which there is most research support in child and adolescent psychiatry are hyperkinetic CD and depressive CD. However, it is interesting to note that the data typically adduced in favor of these two categories differ. Depressive CD is supported by arguments that the psychosocial and genetic correlates and outcomes of the combined category are more like those of CD than they are like those of depression—hence depressive CD is basically a form of CD. In essence, the combined form is *not* distinct from

CD (Esser et al., 1990; Harrington et al., 1991; Renouf, Kovacs, & Mukerji, 1997; Steinhausen & Reitzle, 1996). Coupled with this is evidence that the depressions in depressive CD *are* distinct from other depressions, though there is also evidence that they may not be so distinct as all that (J. E. Fleming, Boyle, & Offord, 1993; Kovacs, Paulauskas, Gatsonis, & Richards, 1988). On the other hand the evidence in favor of considering a separate subtype of hyperkinetic CD (or perhaps it would be better called conduct disordered ADHD) is that this condition is distinct *both* from other forms of ADHD *and* from other forms of CD.

In this field, we have a fairly noncontroversial approach to deciding whether conditions are separate, which relies on demonstrating *differences* between putative disorders at multiple levels (Cantwell, 1995; E. Robins & Guze, 1970; Rutter, 1978). According to this approach, lack of differentiation between pure CD and depressive CD is evidence that depressive CD is not a separate condition from CD, as Steinhausen and Reitzle (1996) have pointed out. But in the case of hyperkinetic CD, the argument is that both the ADHD and the CD components are different in the combined disorder. By the logic that allows a new subcategory to be created when only one of the components is different in the combined form compared with the pure form, a situation in which both components are different should surely be regarded as having identified a separate disorder. The danger here is that we could end up with an even greater proliferation of disorders than we already have, let alone of subcategories. If only one component of the combined disorder needs to be different from its uncombined form, we also face a possible proliferation of subcategories, because there are so many possible combinations of even a few disorders—and they all occur. One wonders, for instance, whether individuals with CD and ADHD and depression are not dissimilar in some ways from "pure" hyperkinetic CD. If any one of the three components were to be shown to have different correlates, then we would have a new subtype, presumably called "depressive hyperkinetic conduct disorder". Now such subtypes may exist, but with comorbidity being such a ubiquitous and poorly understood phenomenon, we imagine few would want to take this route. Similarly, psychometric evidence that the relationship between aggression and depression is a specific case of a broad-band association between internalizing and externalizing disorders (Weiss & Catron, 1994) leads us to expect that we would have to produce a similar group of subtypes for those with disruptive disorders and anxiety.

We suggest that *disorders* defined by comorbidity should be different from the pure forms of *both* their components. By this rule, the data on comorbid ADHD and CD is evidence for establishing a separate *diagnosis* based on comorbidity. This working hypothesis would be consistent with Zoccolillo's "disorder of multiple dysfunction" (Zoccolillo, 1992).

What about situations where one subcomponent only has been shown to differ from its "pure" form? There we have a valid *subtype* of *that* individual disorder. At first sight it may seem that this will create a confusing number of subcategories, but there are some important advantages to this solution. Let us suppose for a moment that further research reveals that most depressions associated with CD were nonfamilial disorders that did not continue into adulthood, as current evidence suggests may be the case (Harrington et al., 1991). Let us also suppose (although the evidence is not yet available on this) that these did not respond to medications known to work in non-comorbid depressions. Let us also suppose that the typical non-comorbid depression was a highly familial disorder with a higher probability of continuation into adulthood and a good response to medication. In this hypothetical scenario we have good evidence that these two sorts of depression are meaningfully different. Let us also suppose that, say, pathological guilt and feelings of worthlessness are uncommon in the comorbid subtype compared with the non-comorbid subtype. We know that depression is relatively common in the general population, so some individuals with CD would actually be expected to have depressions of the *non*-comorbid type. If one were to see a child with CD who had a strong family history of depression, in a depressive episode involving pathological guilt and feelings of worthlessness, it would be appropriate to offer antidepressant medication, because that individual had a form of depression that resembled non-CD depression. This approach focuses attention on the place where the differences between the comorbid and the non-comorbid forms lie, whereas subtyping the CD focuses attention on the place where there are no differences. It may also avoid the possibility that we will need to create subcategories of depressive ODD and depressive ADHD, since if it were found that individuals with these disorders had depressions that were like those in CD, it would be necessary only to rename the comorbid depressive subtype to reflect its relations with all of the disruptive behavior disorders. The third potential advantage of subtyping the disorder where the differences lie stems from the fact that *most* depressions are comorbid with another disorder or disorders. If we find that the manifestations and correlates of depression are typically somewhat different in relation to each of the different disorders with which it co-occurs, we could end up effectively abolishing the diagnosis of depression if we treated each of these as a subtype of another disorder. In fact we would be back to the situation that pertained before the 1970s, when everyone recognized that depressive symptoms occurred in children, but no-one was given the diagnosis because these symptoms were seen as "reactions" to other underlying processes. In the face of growing evidence that there are effective treatments for depression, even when it is comorbid with other disorders, this would seem to be a serious mistake. If, on the other hand, we recognized subtypes of depression that differed in some, or all, of their correlates and outcomes, we would, at least, have a coherent description of depressive conditions available from the nosology.

An example for the future: Mixed anxiety-depressive disorder. Having set out this position, let us now turn to what is likely to emerge as a new line of comorbidity research over the next few years. Mixed anxiety-depressive disorder, one of the criteria sets "provided for further study" by DSM-IV, can be expected to spawn some work on this topic, if only because any study that

included assessments of the regular DSM-III-R or DSM-IV anxiety and depressive disorders is likely to be able to generate diagnoses according to these experimental criteria. In the absence of any published research to date, we can nonetheless predict some findings from what we already know about the relationship between depression and anxiety. There is bound to be a big overlap between this disorder and GAD because so many of the symptoms overlap, and GAD requires only one symptom in addition to anxiety or worrying. Second, we can expect it to be quite common, so long as the exclusion criteria are ignored, as they usually have been in comorbidity research. But can we expect it to be differentiable from other depression or anxiety categories? First, it seems likely to be potentially useful as a residual category for individuals who are impaired but do not meet criteria for another diagnosis. The problem in this situation is that research algorithms do not diagnose the various not otherwise specified (NOS) categories provided by DSM-IV for these individuals (Angold, Costello, Farmer, Burns, & Erkanli, in press), so having a residual diagnosis with a specified set of criteria may be a help. On the other hand, we already have multiple overlapping diagnoses in the anxiety disorders, so do we really need another one? As we have already indicated, the answer to this lies in being able to differentiate between individuals with mixed symptoms and those with "pure" symptoms, and there are some indications in the current literature that there are differences between mixed and "pure" anxiety and depressive disorders. For instance, Kelvin, Goodyer, and Altham (1996) found that high emotionality on a temperament measure was associated with comorbidity between depression and anxiety, and particularly with the association between separation anxiety and dysthymia. Goodyer, Herbert, Secher, and Pearson (1997) found that depression at 36-week follow-up was predicted by severity of depression at presentation and comorbidity with obsessive-compulsive disorder. In another study, he and his colleagues (Herbert et al., 1996) found that comorbid panic or phobic disorders were associated with the *absence* of high evening cortisol in MDD. Lewinsohn, Rohde, et al. (1995) found that comorbidity with depression had a very substantial negative impact on the outcome of anxiety disorders. Williamson et al. (1995) found that comorbid anxiety *reduced* the rate of nonaffective diagnoses in relatives of depressed adolescents. On the other hand, Kovacs et al. (1989) and Alpert, Maddocks, Rosenbaum, and Fava (1994) reported that anxiety preceded depression in about two thirds of cases where they occurred together (see also Giaconia et al., 1994) and often persisted after the depression had remitted, but had no effect on the course of either MDD or dysthymia. Stark, Kaslow, and Laurent (1993) could not distinguish between anxious, depressed, and anxious-depressed individuals on the basis of several scale scores (but their samples were small). There seems to be enough evidence here to suggest that mixed disorders may constitute either a subtype of depression or anxiety or even perhaps a separate diagnosis. We suggest that the decision depends upon which comorbid components differ from their "pure" counterparts.

The Importance of Timing in Comorbidity Research: Substance Abuse—Timing of Onset or Comorbidity as Predictors of Adult Outcomes?

Another area where a key issue in the relationship between disorders turns on developmental timing concerns substance abuse and other psychiatric disorders. Many retrospective studies have noted the link between reported early onset of drug use and later persistence or problem use (Andreasson, Allebeck, Brandt, & Romelsjo, 1992; Kandel, Davies, Karus, & Yamaguchi, 1986; Kaplan, Martin, Johnson, & Robbins, 1986; Mills & Noyes, 1984; L. N. Robins & Murphy, 1967; L. N. Robins & Przybeck, 1985; L. N. Robins & Ratcliff, 1980; Welte & Barnes, 1985; Yamaguchi & Kandel, 1984). Anthony and Petronis (1995), for example, made elegant use of the Epidemiologic Catchment Area Study (ECA) data to show that risk of adult drug problems was linearly related to age at onset, being twice as high in adults reporting first use before age 13 as in those with first use after age 17. The time from first use to problem use was around 4 years, irrespective of age at first use. Although prospective data are generally to be preferred, there is a shortage of prospective studies with a sufficiently long timespan to compare adult outcomes of early vs. late onset of use in adolescence (Kandel, 1978). Remarkably, we could find no prospective study testing Anthony and Petronis's retrospective finding of a linear relationship between age at onset and probability of adult problem drug use. Most of the prospective studies simply compare later drug use of early users with early nonusers, but still point to the negative impact of early use for later problem use (Anderson, Bergman, & Magnusson, 1989; Boyle et al., 1992; Stein, Newcomb, & Bentler, 1987; Van Kammen, Loeber, & Stouthamer-Loeber, 1991; Windle, 1990; Zucker & Gomberg, 1986). Fleming and colleagues (J. P. Fleming, Kellam, & Brown, 1982) found that early-onset drug use predicted intensity of use at age 16–17; "The strongest contrast in frequency of use is between those teenagers who first used the substances after age 15 and those who initiated use prior to age 15". The small but intensive New York Longitudinal Study (Tubman, Vicary, von Eye, & Lerner, 1990) suggested that early-onset drug use (13–15 years) carried a worse adult prognosis than later-onset drug use (16–19). Overall, there is a strong support for the idea that early onset of substance use is associated with a worse substance abuse prognosis in adulthood.

Numerous questionnaire and diagnostic studies have demonstrated associations between adolescent drug and alcohol use and various forms of psychopathology, including low self-esteem, depression scale scores, antisocial behavior, rebelliousness, aggressiveness, crime, delinquency, truancy and poor school performance, CD, anxiety disorders, depressive disorders, suicide, and ADHD (see, e.g., Beals et al., 1997; Brent et al., 1986; Bukstein, Glancy, & Kaminer, 1992; Clayton, 1989; Deykin, Buka, & Zeena, 1992; Deykin, Levy, & Wells, 1987; Fergusson et al., 1993a; Greenbaum, Prange, Friedman, & Silver, 1991; Hovens, Cantwell, & Kiriakos, 1994; Jessor & Jessor, 1977; L. D. Johnston, O'Malley, & Eveland, 1978a; Kaminer, Tarter, Bukstein, & Kabene, 1992; Kandel et al., 1986; Kandel, Kessler, & Margulies,

1978; Kandel, Single, & Kessler, 1976; Kaplan, 1980; King et al., 1996; Kleinman, Wish, Deren, & Rainone, 1986; Neighbors, Kempton, & Forehand, 1992; Paton & Kandel, 1978; Paton, Kessler, & Kandel, 1977; Smith & Fogg, 1979; Stowell & Estroff, 1992; Wingard, Huba, & Bentler, 1979). In fact, many studies of antisocial behavior still include early drug use as one among a range of possible symptoms (e.g. Elliott, Huizinga, & Ageton, 1984; Farrell & Taylor, 1994; Farrington, 1983; Hammersley, Forsyth, & Lavelle, 1990; Moffitt, 1993), although it is treated in DSM-IV as an *associated* symptom. Children who *later* become problem drinkers or drug users have been found to have high rates of school dropout and poor achievement, rebelliousness, antisocial behavior, aggressive behavior, delinquency, and family problems (Anderson et al., 1989; Barnes, 1984; Barnes & Welte, 1986; Boyle & Offord, 1991; Cairns & Cairns, 1994; G. A. Carlson, Bromet, & Jandorf, 1998; Chilcoat & Anthony, 1996; Fergusson et al., 1993a; Greenbaum et al., 1991; Jessor et al., 1980; Jessor, Graves, Hanson, & Jessor, 1968; L. D. Johnston et al., 1978b; Jones, 1968; Kandel et al., 1978; Kaplan, 1980; Kleinman et al., 1986; Kleinman, Wish, Deren, Rainone, & Morehouse, 1988; Knop, Goodwin, Teasdale, Mikkelsen, & Schulsinger, 1984; Knop, Teasdale, Schulsinger, & Goodwin, 1985; J. McCord, McCord, & Thurber, 1962; W. McCord & McCord, 1960; Monnelly, Hartl, & Elderkin, 1983; Orive & Gerard, 1980; Ricks & Berry, 1970; L. N. Robins, 1974; L. N. Robins & Murphy, 1967; L. N. Robins & Wish, 1977; Rydelius, 1981; Santo, Hooper, Friedman, & Conner, 1980; Schuckit, 1982; Vaillant & Milofsky, 1982; Windle & Barnes, 1988; Zucker & Barron, 1973; Zucker & DeVoe, 1975).

Studies of temporal ordering have generally found that onset of other psychiatric disorders precedes that of problem alcohol and drug use (Boyle et al., 1992; Ellickson & Hays, 1991; Elliott, Huizinga, & Menard, 1988; Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Rohde et al., 1996; Van Kammen & Loeber, 1994), but this may be because it takes longer to reach DSM-level drug abuse or dependence than to manifest other disorders. Loeber (1988, pp. 94–95) summarizes the evidence in relation to delinquency thus: "Across different delinquent types of offenders, about twice as many initiate drug use after their delinquent involvement compared with initiating delinquency after drug use." However, one would expect that the trajectory of antisocial behavior would be interwoven with the trajectory of drug involvement (A. S. Friedman, Utada, Glickman, & Morrissey, 1987). Brook, Cohen, and Brook's (1998) work provides a nice example here. Across the period from middle adolescence to early adulthood, they found no evidence that depressive disorders, anxiety disorders, or CD had any influence on later drug use once adolescents had started to use drugs. On the other hand, drug use was related to the development of later depressive disorders. As the authors of this study pointed out, their findings do not contradict the idea that *earlier* psychiatric problems (such as CD in late childhood or early adolescence) are associated with later substance abuse. Indeed, their own earlier work showed pathways from various childhood personality characteristics and aggression to later substance use, mediated by depressive symptoms and unconventionality (Brook, Whiteman, Balka, & Cohen, 1997; Brook, Whiteman, Cohen, Shapiro, & Balka, 1995; Brook, Whiteman, Finch, & Cohen, 1995; Brook, Whiteman, Finch, & Cohen, 1996). General developmental principles (Costello & Angold, 1996) teach us that relationships among disorders may change over time as patterns of reciprocal influence between the causes and effects of different forms of psychopathology become established.

Almost all this research has been on boys only, and we need more work on girls, especially since what has been done suggests that drug use may follow depression or anxiety in girls, but that this order is reversed in boys (Rohde et al., 1996). In passing, we should also note that studies showing that ADHD is probably associated with an increased risk of substance abuse have also found this association to be mediated through the high rates of CD that occur in ADHD, rather than being a direct effect of ADHD itself (Fergusson, Lynskey, & Horwood, 1993b; Gittelman et al., 1985; Loney, 1988). Here we see that it is sometimes necessary to consider three-way comorbidities over time.

Robins, using data from two follow-up studies and from the ECA, states (L. N. Robins & McEvoy, 1990, p. 196),

> Abuse is extremely rare for those free of (early) conduct problems, no matter how early substance use began. At every other level of conduct problems, however, the earlier that use begins, the greater is the likelihood of substance abuse…. For those first using substances before age 20, the number of conduct problems was an even better predictor of substance abuse than was age of onset (before or after age 15). Among those beginning substance use before age 15 with seven or more conduct problems, more than half developed substance abuse; with only one conduct problem, only 5% did so. When first use occurred between ages 15 and 19, there is still a large effect from number of conduct problems, but the control for age of first use somewhat reduced their impact.

Despite the mass of literature reviewed above, we can find no direct, prospective test of this important conclusion. Also, the implications for intervention drawn by Robins are open to question when she argues that her findings support a "Just say later" prevention strategy, to delay onset of drug use to beyond age 15 or 19 (Robins & McEvoy, 1990, p. 203). The data we have presented could also be seen as indicating that it is conduct problem comorbidity that predicts later drug abuse, not age of initiation of use itself, and that the apparent effect of age at initiation results from earlier initiation of substance use by individuals with conduct problems (and perhaps other psychiatric disorders). These contrasting hypotheses are directly testable, though we are aware of no prospective study that has tested them.

Conclusions

The last 10 years have seen comorbidity established as unquestionably "real", and attitudes have swung towards regarding comorbidity as an opportunity for

better understanding of the development of psychopathology. The result has been a good deal of research aimed at improving diagnostic boundaries, and describing the course and correlates of comorbid and "pure" disorders.

As we have already said, in no case can we be sure that we understand the substantive causes of comorbidity between any pair of diagnoses. However, we can be sure that substantive causes need to be sought, because none of the possible methodological explanations for comorbidity holds water for all pairs of diagnoses. We can also reject the notion that all child psychopathology constitutes an undifferentiated mass upon which diagnostic conventions impose meaningless categorical boundaries, though the various individual anxiety diagnoses are so poorly validated in childhood that homotypic comorbidity amongst them is probably partly explained by inappropriate diagnostic boundary placement. On the other hand, nonspecific symptoms in the criterion sets for disorders do not explain comorbidity between disorders sharing those symptoms. Even if we reject categorical diagnosis, we still have to explain why there are correlations among different dimensions of psychopathology derived from factor analysis, while a single factor does not suffice to explain covariation among symptoms. There is little evidence that any one disorder directly causes any other disorder, but it is likely that some homotypic comorbid patterns (depression with dysthymia and ODD with CD) represent developmental sequences of unitary underlying developmental psychopathologic processes (at least in some individuals). There is enough evidence to support continuing research on the idea that certain patterns of heterotypic comorbidity (particulary hyperkinetic CD, depressive CD, and anxious depression) represent separate subtypes or even diagnoses from their component diagnoses (though this is by no means proven). On the other hand, comorbidity of CD or ODD with anxiety, and ADHD with depression, may simply be epiphenomenal. Different disorders appear to share some risk factors in common, but there are also risk factors that are specific to particular disorders, so the presence of shared risk factors is likely to be an important component in the causation of comorbidity.

At many points in our discussion, the topic of timing has come up, and we need to remember that this is a key component for understanding comorbidity. Most studies of the subject in both childhood and adulthood have relied either on a single wave of cross-sectional data, or relied on recall of disorders over the whole life course. Both of these approaches involve a "snapshot" at a particular point in time, and are incapable of providing descriptions of the interplay of shared and specific risk factors over time and their effects on diagnostic status, again over time. Now there is a need to shift beyond documenting rates of comorbidity to studying correlates and implications of comorbidity over time in the hope of identifying likely etiological mechanisms. One obvious conclusion is that community-based longitudinal diagnostic studies will be needed. These studies will have to be large enough to separate out the specific and nonspecific effects of a range of risk factors across a range of diagnoses. A start has been made in this area, but we have a long way to go. Family genetic approaches are already making a big contribution, and twin studies that focus on comorbidity will also be productive (Rutter, 1997). Very little attention has yet been paid to age or gender effects on comorbidity, and the psychobiology of "pure" and comorbid conditions has hardly begun to be addressed. There are still a lot of conceptual confusions and conflicts to be sorted out if we are to have a set of coherent explanations of comorbidity and nosological responses to them, but there is also a much better appreciation of what the problems are, and of the need to use multiple approaches to overcoming them. If things move as fast over the next 10 years as they have over the last 10, comorbidity may have ceased to be a problem by the time this journal commissions another research review.

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