Depressed Adolescents Grown Up

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Context Major depressive disorder (MDD) that arises in adolescence impairs functioning and is associated with suicide risk, but little is known about its continuity into adulthood.

Objective To describe the clinical course of adolescent-onset MDD into adulthood.

Design and Participants Prospective case-control study. Seventy-three subjects had onset of MDD based on systematic clinical assessment during adolescence (Tanner stage III-V) and 37 controls had no evidence of past or current psychiatric disorders, and also were assessed in adolescence (assessment years: 1977-1985). Follow-up was conducted 10 to 15 years after the initial assessment by an independent team without knowledge of initial diagnosis (follow-up years: 1992-1996).

Setting Cases were identified at Columbia Presbyterian Hospital, New York City, NY; controls were recruited from the community.

Main Outcome Measures Suicide and suicide attempts, psychiatric diagnoses, treatment utilization, and social functioning.

Results Clinical outcomes of adolescent-onset MDD into adulthood compared with control subjects without psychiatric illness include a high rate of suicide (7.7%); a 5-fold increased risk for first suicide attempt; a 2-fold increased risk of MDD, but not other psychiatric disorders; an increased occurrence of psychiatric and medical hospitalization; and impaired functioning in work, social, and family life. Thirty-seven percent of those with adolescent MDD survived without an episode of MDD in adulthood vs 69% of the control participants (relative risk, 2.2 [95% confidence interval, 1.0-4.7; $P<.05$]).

Conclusion There is substantial continuity, specificity, morbidity, and potential mortality from suicide into adulthood in adolescent-onset MDD patients. Now that empirically based guides to their treatment are becoming available, early identification and treatment seems warranted.

JAMA. 1999;281:1707-1713 www.jama.com

IN CONTRAST TO DEBATES 2 DECADES ago, it is now clear that major depressive disorder (MDD) often has an onset in adolescence,[1-6] across diverse countries,[7,8] and is associated with substantial psychosocial impairment[6,9-15] and risk of suicide.[12,16] Despite the high prevalence and morbidity, it is not clear if adolescent-onset MDD predicts mood disorder and impairment in adult life. This information is clearly important in guiding early treatment.

While the available, well-designed, follow-up studies of depressed adolescents document the morbidity of youthful-onset MDD, most studies have not followed up the sample beyond adolescence, have had small samples, have not included control subjects, and/or have not made follow-up assessments blind to the initial diagnosis.[15,17-22]

Three studies[23-25] have the most relevant information. Harrington et al[23] used a catch-up longitudinal design to assess adult psychiatric status of 34 adolescent-onset MDD subjects, whom they compared with matched control subjects with other psychiatric disorders. Sixty percent of the depressed adolescent group when adults, compared with 27% of the control subjects, had 1 or more episode of MDD in adulthood. Pine et al[24] followed up 23 depressed adolescents from a community survey until the average age of 22 years and found a 4-fold increased risk of MDD. Both of these studies relied on retrospective reconstruction of the initial diagnosis of adolescent MDD from earlier clinical records or from symptom scales. Neither study used Tanner stages[26] to determine pubertal status at onset. Tanner staging has been shown to be more sensitive than chronological age to the emergence of MDD[1,27] and possibly a different course of MDD.[23] The study by Rao et al[25] used Tanner staging and had diagnostic assessment both in adolescence and adulthood but included only 28 adolescents followed up for 7 years to an average age of 22 years. They found

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a high adult recurrence rate as well as substantial psychosocial morbidity in adolescent-onset MDD compared with new cases of onset in 35 healthy subjects.

We report findings on the psychiatric status, treatment, and social functioning into adulthood of a sample of depressed patients fully assessed as adolescents. A sample of healthy subjects assessed in adolescence were also followed up. The purpose was to extend previous studies of adolescent-onset MDD by increasing the sample size, the period of follow-up, and the information collected to determine the outcomes of adolescent-onset MDD into adulthood.

METHODS

The overall design was a clinical follow-up conducted approximately 10 to 15 years after the initial assessment. One hundred thirty-four subjects with an original diagnosis of adolescent-onset MDD (n = 91) or nonpsychiatrically ill control subjects (n = 43) were in the potential sample eligible for follow-up. The initial evaluation was described previously.[14,28-30]

Selection of Depressed Probands

The depressed adolescents were identified at Columbia Presbyterian Hospital from 1977-1985 and were initially accepted for screening if they were younger than 18 years and reported to be sad or "blue." Each case was screened for inclusion during a 2-week diagnostic evaluation that included the Schedule for Affective Disorders and Schizophrenia for School-age Children administered by a psychiatrist.[29] A pediatric examination was also performed that included Tanner staging to determine adolescence (Tanner stage III, IV, and V)[26] and intelligence testing. A second Schedule for Affective Disorder for School-age children was conducted 2 weeks later to ensure the stability of the initial diagnosis. These dual assessments were carried out blindly, and the examiners reached independent diagnoses using the Schedule for Affective Disorder for School-age children. Interrater reliability and test-retest results based on the original study have been reported previously.[29]

Subjects medically cleared by the pediatrician were accepted into the original research protocol only if they met the research diagnostic criteria for MDD[31] in both evaluations. They were excluded from the original sample if they had been taking medication that could produce depressive-like symptoms (eg, amphetamines, phenothiazines) or other medication that could interfere with brain hypothalamic or pituitary function. In such a case, a 2-week washout period determined if the affective symptoms were primary or secondary to drug intake. Other exclusion criteria included (1) severe medical illness (especially endocrinopathies or heart disease), (2) obesity (weight-height ratio greater than the 95th percentile), (3) height or weight under the third percentile, (4) clinical seizures or other major neurological illness, (5) IQ lower than 70, or (6) a diagnosis of anorexia nervosa, autism, or schizophrenia. Diagnostic information on adolescents was obtained first from parents and then the adolescents.

Selection of Control Subjects

The healthy subjects were recruited at the same time by newspaper advertising and word of mouth, contact with schools and counselors, and meetings with parent and teacher organizations.[14,30] Only adolescents who fit none of the psychiatric disorder (current or past) and other exclusion criteria, using the same diagnostic procedures used for the depressed group, were accepted as healthy subjects. To avoid selective sampling of children from families with mood disorders, the study was described as an overall mental health survey and questions on a variety of psychiatric disorders were asked. Informed consent was obtained from parents or legal guardians and from the adolescents.

Follow-up Procedures

Subjects had to be 18 years or older at follow-up. To ensure accurate estimates of rates, extensive efforts were made to locate the original sample. Once the subjects were located, interviews were conducted, and informed consent was obtained. All data from the proband and informant were collected by clinical interviewers blind to original diagnosis and without access to the original clinical records.

At follow-up, diagnostic information was collected from the subject and from an informant separately, usually a parent, about the subject. When a parent was not available, another adult with knowledge of the subject's functioning over the follow-up period was the informant. This study was approved by the combined institutional review boards of the New York State Psychiatric Institute and the Columbia University Department of Psychiatry.

Detailed information on sociodemographic status and hospitalizations using standard questions was obtained. All original case records of adolescent-onset MDD were reviewed by a child psychiatrist for evidence of a first-onset MDD earlier than adolescence. This occurred in 5 of the original adolescent-onset cases. They were removed from these analyses.

Lifetime psychiatric status from each proband and separately from 1 parent (or other informant) was asked via direct interview using a revised Schedule for Affective Disorders and Schizophrenia for Lifetime Disorders.[32,33] Information covering the past 2 months of functioning was obtained by interview using the Social Adjustment Scale interview scored on a 5-point scale with higher scores indicating more impairment.[34] Copies of medical records were obtained and used to supplement the interview data with the exception that initial medical records were not used in making the follow-up diagnosis to preserve blindness. Follow-up assessments were completed by 18 clinically trained and experienced interviewers who underwent a 5-day training program followed up by 2 supervised interviews. Interviewers were assigned to cases only after completing both supervised interviews and reaching reliabil-

ity with the clinical supervisor. Every 2 months, each interviewer administered the Schedule for Affective Disorders and Schizophrenia for Lifetime Disorders with a second interviewer present for independent scoring.[35]

Final follow-up psychiatric diagnoses are based on the best estimate procedure.[36] To derive best estimate diagnoses, an experienced psychiatrist or psychologist who was not involved in interviewing reviewed all available information, but was kept blind to the initial diagnostic status and assigned lifetime *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* diagnoses. Eight clinicians completed the best estimate diagnosis procedure.[35]

Data Analysis

Group differences between subjects with and without MDD were determined as follows. When the risk of the outcome considered did not vary with age and was dichotomous, χ^2 analyses[37] were used for direct comparisons, and logistic regression was used when controlling for potential confounders.[38] Continuous outcomes that are normally distributed were tested using *t* tests and analysis of variance. When continuous outcomes were not normally distributed, the Mann-Whitney and Kruskal-Wallis nonparametric procedures were used.[37]

For outcomes for which the risk was believed to vary with age, differences between groups were examined using survival analysis techniques. Specifically, the proportional hazards model[39] was used to determine the relative risk of the outcome under consideration between the 2 groups controlling for the effects of confounding variables. Plots comparing the cumulative probability of remaining free from depression after the age of 18 years between the 2 groups were made using the Kaplan-Meier method.[40] For all of the analyses, the follow-up period used was 1 year since the time of ascertainment (time 1) to ensure that the episodes when the disorder occurred in the follow-up period were new episodes and not a continuation of the index episode. All analyses were conducted using SAS software.[41]

RESULTS

Follow-up Rates

The original samples of depressed and healthy subjects included 134 adolescents. Of those 134 subjects, 121 (90%) were located, 110 (82%) were assessed, 13 (10%) were not located, and 11 (8%) refused assessment. The group with MDD had a potential sample of 91 subjects: 81 were located, 73 were assessed, 10 were not located, and 8 refused assessment. The group with healthy subjects had a potential sample of 43 subjects: 40 were located, 37 were assessed, 3 were not located, and 3 refused assessment. Two subjects with adolescent-onset MDD, who received only a brief interview consisting of demographics and diagnostics because of refusal to continue with the complete interview, as well as 7 subjects, all adolescent-onset MDD, committed suicide in the follow-up period. A psychological autopsy was completed on the subjects who committed suicide[16] and their clinical diagnoses have been added to subsequent results. Follow-up response rates did not significantly dif-

Table 1. Demographics at Follow-up by Adolescent-Onset Diagnosis*

	Adolescent-Onset Diagnosis		
	Major Depressive Disorder (n = 73)	Healthy (n = 37)	*P* Value†
Women, %	50.7	35.1	.12
Age at follow-up, mean (SD), y	26.1 (2.5)	26.0 (2.2)	.67
Follow-up interval, mean (SD), y	10.7 (1.7)	9.6 (1.5)	.001
Race, %			
White	58.9	59.4	.18
Black	9.6	21.6	
Hispanic	27.1	18.9	
Other	4.1	0.0	
Current religion, %			
Protestant	21.2	19.4	.01
Catholic	38.5	32.3	
Jewish	19.2	0.0	
Other	21.2	48.4	
Highest education, %			
>College	43.8	70.5	.04
High school graduate	60.0	21.6	
<High school	6.3	8.1	
Current employment, %			
Full-time	45.9	68.6	.06
Part-time	13.1	17.1	
Unemployed	41.0	14.3	
Income for past year, mean (median) [SD], $	16 423 (14 995) [12 421]	18 934 (14 995) [10 588]	.17
Social class of household, mean (SD)‡	46.0 (20.1)	35.1 (16.5)	.01
Time out of work due to psychopathology, %			
None	62.3	85.7	.05
<1 y	26.2	11.4	
≥1 y	11.5	2.9	
Marital status, %			
Single	81.0	75.0	.49
Married	11.1	19.4	
Separated, divorced, or widowed	7.9	5.6	

*Seven probands who committed suicide were removed from the calculation of age and follow-up interval.
†χ^2 Comparisons used for discrete outcomes and Mann-Whitney comparisons for continuous outcomes.
‡Social class derived from Hollingshead.[42] A lower score denotes higher social status.

Table 2. Completed Suicides and Suicide Attempts During Follow-up*

	No./Total (%) Adolescent-Onset Diagnosis		Relative Risk, Major Depressive Disorder vs Healthy (95% Confidence Interval)	*P* Value
	Major Depressive Disorder (n = 73)	Healthy (n = 37)		
Completed suicides†	7/91 (7.7)	0/43 (0)	. . .	.06
Attempts reported by time 1	25/73 (34.2)	. . .	. . .	. . .
First attempt, postascertainment‡	12/46 (26.1)	2/37 (5.4)	5.6 (1.2-25.2)	.03
Attempts during lifetime§	37/73 (50.7)	2/37 (5.4)	14.3 (3.1-65.4)	<.001
None	49.3	94.6	1.0	. . .
1	27.4	2.7	13.9 (1.7-122)	.001
≥2	23.3	2.7	14.6 (1.8-121)	.01

*Ellipses indicate unable to statistically calculate data.
†Completed suicide rate is based on the potential sample of 91 subjects. The rate for the located sample of 81 subjects is 8.6%. $P = .05$ if calculated on the located sample. *P* value based on χ^2 statistic.
‡Risk ratio derived from proportional hazards model to control for unequal follow-up time adjusted by educational level and social class. Persons with a reported suicide attempt by time 1 were removed from these analyses.
§Odds ratio for group comparison derived from logistic regression and adjusted by education level and social class.

Table 3. Rates of Psychiatric Disorders Through Follow-up*

	Rates per 100 Subjects of Adolescent-Onset Diagnosis		Relative Risk, Major Depressive Disorder vs Healthy (95% Confidence Interval)†	*P* Value
	Major Depressive Disorder (n = 73)	Healthy (n = 37)		
Major depression	49.3	27.0	2.6 (1.2-5.3)	.01
Dysthymia	5.5	2.7	1.0 (0.1-9.3)	.95
Bipolar 1	4.1	0.0	. . .	.55‡
Bipolar 2	1.4	2.7	0.6 (0.03-11.5)	.72
Any anxiety disorder	19.2	10.8	2.1 (0.6-6.6)	.17
Alcohol abuse	4.1	8.1	0.4 (0.1-2.4)	.34
Alcohol dependence	27.4	21.6	1.5 (0.6-3.6)	.36
Drug abuse	12.3	10.8	1.5 (0.3-4.6)	.95
Drug dependence	17.8	8.1	2.1 (0.6-7.6)	.27
Schizophrenia	1.4	0.0	. . .	.66‡
Eating disorder	9.6	0.0	. . .	.09‡
Conduct disorder	1.4	0.0	. . .	.66‡
Antisocial personality	6.8	0.0	. . .	.16‡

*Refers to the period from 1 year after ascertainment to follow-up interview. Probable or definite psychiatric diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Ellipses indicate unable to statistically calculate data.
†Risk ratio derived from proportional hazards model to control for unequal follow-up time, adjusted by education and social class.
‡Fisher exact probability value.

fer between groups. The assessed and nonassessed sample also did not differ significantly within groups on initial age, sex, and race with the exception of the healthy subjects. More white (83.3%) than nonwhite (40.5%) healthy subjects were followed up ($P = .04$) (data available on request).

Demographic Characteristics of the Follow-up Sample

The healthy subjects were 1 year younger than the depressed probands at time 1 (15.4 vs 14.4 years, $P = .01$). However, at follow-up there were no significant differences between depressed and healthy subjects by sex, age, race, current employment, income, or marital status (TABLE 1). The depressed subjects were followed up about 1 year after the healthy subjects probably because of greater difficulty in locating them. They had lower educational achievement, lower social class, and more time out of work due to psychopathology. There were no significant differences in number of offspring, miscarriages or abortions (which was low in all groups), or in age of first pregnancy (data not shown). One child in the MDD group was given up for adoption.

Suicide Attempts and Completions

Seven suicides (7.7%) occurred in the adolescent-onset depressed subjects (TABLE 2) documented elsewhere.[16] This figure is a conservative estimate since it includes the full potential sample in the denominator. Excluding any persons with a history of suicide attempts by time 1, 26.1% of the adolescent-onset MDD and 5.4% of healthy subjects made their first attempt during the follow-up. Thus, more than half (50.6%) of the adolescent-onset MDD subjects made a suicide attempt over their lifetime to follow-up and 22% had made multiple attempts. Adolescent-onset MDD probands compared with healthy subjects had more than a 5-fold increased risk for first suicide attempts in the follow-up period and a 14-fold increased risk over their lifetime.

Rates of Psychiatric Disorders 1 Year After Ascertainment

The rate of psychiatric disorders was calculated 1 year after the initial ascertainment to the time of follow-up to avoid including the index episode. Similar analyses were done for 2 years after ascertainment and since the results were generally similar, only analyses for 1 year after ascertainment are included (TABLE 3). Adolescent-onset MDD subjects compared with healthy subjects had a significant increased risk of MDD (>2-fold) but not a significant increased risk of other psychiatric disorders. There were no sex differences in survival rates of MDD in either group (data not shown).

Whereas the previous analysis considered the full age range, the FIGURE shows the proportion of subjects surviving without MDD in young adulthood after age 18 years. Adolescents who were depressed during the index assessment were at high risk for an episode of MDD during adult life. After age 18 years until the end of the observa-

tion period, only 37% of the adolescent-onset MDD subjects survived without an episode of MDD, whereas 69% of the control subjects survived without an episode in the same period (relative risk, 2.2; 95% confidence interval, 1.0-4.7; $P<.05$).

Treatment and Social Adjustment

Both psychiatric and medical hospitalization were increased in the MDD subjects compared with control subjects over the follow-up (TABLE 4). Taking the 2 months prior to last interview as a time frame, the adolescent-onset MDD subjects, compared with control subjects, reported significantly more social impairment in most areas of functioning (work, social, and family) (Table 4).

COMMENT

This study was designed to determine the continuity between adolescent and adult MDD in adolescents being treated. The major findings are a poor outcome of adolescent-onset MDD and the continuity and specificity of MDD arising in adolescence and continuing into adulthood. The course includes a high rate of suicide and suicide attempts; recurrence of MDD but not other psychiatric disorders into young adulthood; increased rates of psychiatric and medical hospitalizations; psychosocial impairment, including extended time out of work due to psychopathology; and lower educational achievement.

Comparison With Other Studies

It is difficult to directly compare results with the data in the study by Pine et al[24] because of the different diagnostic technique used in a community survey. They found increased risk of MDD as well as an increase in phobias in adulthood but not other anxiety disorders and did not report on substance abuse, suicide, or psychosis.

The high suicide attempt rate we report is consistent with findings from the study by Kovacs et al[12] in which 38% of the 142 children with various types of depression had made an attempt by age 17 years. The suicide attempt rate we report should also be considered in the context of the completed suicide rate, which was higher than 7%, highlighting the serious outcome of adolescent-onset MDD. The increased rates of medical hospitalization in the depressed subjects have been found by others[43,44] and may reflect the consequences of poor self-care, trauma, or self-injury. We could not find any particular pattern for the medical hospitalizations.

We also found that a substantial number of healthy subjects had first onsets of MDD in the follow-up period.[25] Epidemiologic studies show that the rates of MDD are high in youthful samples.[2,5,6,45] Also, the healthy subjects were not screened for family history of depression in either study, when they were initially assessed. The lifetime suicide attempt rate (5.4/100) in the healthy subjects is close to the rate (7%) reported by Andrews and Lewinsohn[46] based on a survey of a representative sample of 1710 high school students (mean age, 16 years). The lack of sex differences in rates of recurrence of MDD is consistent with numerous clinical studies and a recent longitudinal study of a birth cohort followed up to age 21 years.[47]

Generalizability and Limitations

These results can be safely generalized only to adolescents being brought to treatment in the early 1980s when the new and more effective treatments were not available. They also may not extend to depressed adolescents who are less severely depressed. It should be noted that both Pine et al[24] in a community sample and 2 of us (M.M.W. and P.W.)[48] in a 10-year follow-up study of offspring of depressed parents, including largely untreated offspring, had parallel findings. Other study limitations include our sample size. While this is by far the largest sample followed up into adulthood, it is still small for more fine analysis of potential subgroups. Follow-up covered a long time span possibly leading to retrospective recall bias. We tried to compensate by using multiple sources of information

Figure. Survival Free From Major Depression After Age 18 Years by Adolescent-Onset Diagnosis

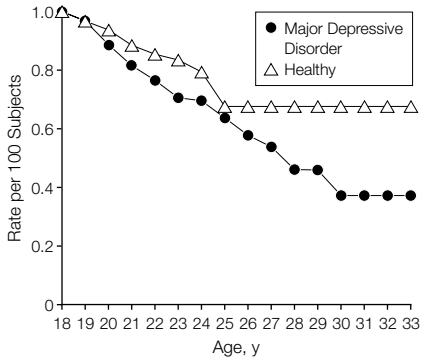

Table 4. Treatment and Social Adjustment at Follow-up

Variable	Adolescent-Onset Diagnosis: Major Depressive Disorder	Adolescent-Onset Diagnosis: Healthy	*P* Value*
Psychiatric hospitalizations, mean (SD), [%]	2.0 (2.4) [55.1]	0.2 (0.4) [5.4]	.001
Any medical hospitalization, %	44.9	18.9	.008
Area in life that was affected by impairment in past 2 mo, mean (SD)†			
Work	2.4 (1.4)	1.5 (0.7)	<.001
Social/leisure	2.7 (1.3)	1.7 (0.6)	<.001
Extended family	2.7 (1.2)	1.7 (0.6)	<.001
Marital relations	2.2 (0.9)	2.0 (1.5)	.20
Parental role	1.9 (0.5)	1.2 (0.4)	.01
Overall	2.8 (1.2)	1.7 (0.7)	<.001

*χ^2 of Fisher exact comparisons for bivariate outcomes and Mann-Whitney comparisons for continuous outcomes.
†A higher value signifies greater impairment. The number of subjects assessed for major depressive disorder were as follows: work, 58; social/leisure, 64; extended family, 62; marital relations, 18; parental role, 14; and overall, 64. For healthy subjects the number assessed was 29, 31, 31,11, 5, and 32 for the same categories. The number of subjects assessed varied based on whether the category applied to their lives (ie, marital status, whether they had children).

and best-estimate procedures, which combine all sources. There may be questions about the use of Tanner stage III as the lower boundary for adolescence and age 18 years as the upper boundary in the original study. These seemed like reasonable choices at the time and more recent work suggests that Tanner staging may be better than chronological age as an indicator of vulnerability to onset of MDD.[1] Finally, we did not have a comparison group of adolescents with other psychiatric disorders.

In the 1980s, when this sample was first ascertained, there was no empirical research to guide the clinical management of depressed adolescents. Even among depressed adults for whom there was evidence for efficacy of pharmacologic agents and some specific psychotherapies, many did not receive these treatments.[49] Depressed adolescents were even less likely to be diagnosed and treated. This was largely because depression was seen as a disorder of the middle aged and elderly. Following this thinking, adolescents were excluded from psychopharmacologic trials, and clinical trials confirming the efficacy of psychotherapy had not yet been conducted. The adolescents in this study provide some of the first systematic data on the diagnosis and course of adolescent MDD.

The treatment received by these depressed adolescents when first identified was state of the art for the time. This included individual or group counseling or psychotherapy and/or tricyclic antidepressants. Over the course of the 10- to 15- year follow-up, they were unlikely to obtain sustained, or as we know now from clinical trials, effective treatments in the community. The clinical trials conducted in the 1980s and early 1990s failed to demonstrate the efficacy of tricyclic antidepressants in depressed adolescents. The first positive clinical trial including depressed adolescents using a selective serotonin reuptake inhibitor was only published in 1997.[50] Trials of time-limited psychotherapies, which were developed specifically for depressed adolescents, have also only recently been completed and have been shown to be efficacious.[51-55] Recognizing the early age of onset of MDD and the fact that psychotropic drugs are used in this population, the US Food and Drug Administration has recently required that adolescents be included in clinical trials. The National Institute of Mental Health is sponsoring multicentered clinical trials of selective serotonin reuptake inhibitors and psychotherapy for depressed youth. Thus, evidence-based guides to treatment that were not available when these adolescents were first identified are becoming available now. Since treatments are now available, our findings argue for the early identification of depressed adolescents by physicians in primary care, pediatric, obstetrics and gynecology, and school-based or mental health clinics. Any debate about whether society can afford the cost of their psychiatric treatment or the cost of the research to develop the evidence needs to take the consequences of adolescent MDD into consideration.

Funding/Support: This research was supported by National Institute of Mental Health grant MH50666, and in its initiation by the National Alliance for Research on Schizophrenia and Depression Senior Investigator's Award (Dr Weissman).

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On every scientist's desk there is a drawer labeled UNKNOWN in which he files what are at the moment unsolved questions, lest through guesswork or impatient speculation he come upon incorrect answers that will do him more harm than good. Man's worst fault is opening the drawer too soon. His task is not to discover final answers but to win the best partial answers that he can, from which others may move confidently against the unknown, to win better ones.
—Homer W. Smith (1895-1962)