Discussion of Epidemiology of Schizophrenia
Session II in the Symposium on
"Search for the cause of Schizophrenia"

Joseph Zubin, Ph.D.
VA Medical Center, Highland Drive
Pittsburgh, PA 15206
and
Department of Psychiatry
University of Pittsburgh School of Medicine

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Both Professor Hafner and Dr. Sartorius, the initial
and final contributors to this symposium point out the
tremendous progress that has occurred in the field of
schizophrenia. From my own vantage point, since the 1930's,
I agree heartily. I am however, reminded of what Szent
Gyorgyi once said regarding the science of biochemistry.
When he entered the field as a young man, there were few
facts but many theories; now we have a plethora of facts but
meaning still escapes us. The same seems to apply to
psychopathology. However, the search for truth seems to be
the shifting residue of competition in ideas as Justice
Oliver Wendell Holmes Jr. once said, and it is in this
spirit that I propose to present my remarks.

Perhaps the most exciting finding reported in Professor
Hafner's paper is the constancy of the rate of incidence of
schizophrenia across the 10 different countries and
cultures, and the most challenging conclusion is that this
constancy may be interpreted as signaling the absence of causality in the social cultural forces as factors in producing schizophrenia.

The claims for the constancy of the incidence rate reputed to be about 1% of the general population have been heralded ever since I can remember. Furthermore, while many of us have for a long time leaned in the direction of believing that internal factors seem to be more important in the causation of schizophrenia than external factors, this is the first time that I have heard this claim to be based on such reliable epidemiological evidence. For this reason it behooves us to examine carefully both the evidence as well as the cogency of the conclusion.

Let us first lay aside the question of whether the S+ category really represents echte schizophrenia.

Are there any other ways of interpreting the data? I believe that at this time any other plausible, even though unproven, interpretation, can not be dismissed.

First, there is no other disorder to my knowledge which has a constant incidence rate across the world. This would put schizophrenia into a class all by itself and raise the question whether indeed it is a disorder. We would have to add the incidence of schizophrenia to such other natural constants as the speed of light.

Second, the incidence rate of schizophrenia represents the phenotypic expression of an underlying causal agent. For example, under the genetic hypothesis of causality, and
under a monogenic hypothesis it can be demonstrated that the
degree of penetrance is about .26 and a similar figure can
be calculated under certain assumptions for polygenic
causation. Let us assume that the genetic hypothesis is
tenable and analyze the various possibilities that might
give rise to a constant incidence rate.

One possible alternative explanation is that though the
phenotypic rate is constant, the genotypic rate is not
constant but that the degree of penetrance, which is
postulated to explain the discrepancy between phenotype and
genotype varies inversely with the genotypic rate. That is,
if \( r \) is the phenotypic incidence rate, \( r = pg \) where \( p \) is the
degree of penetrance and \( g \) is the genotypic rate. As the
genotypic rate rises, the penetrance drops correspondingly
so as to keep the incidence rate constant and vice versa
when the genotypic rate drops. Is there a rationale for
this assumption? The appeal can be made here to a
perceptual threshold for the conspicuousness of symptoms.
The assumption is that the community has a threshold for the
perception of deviance. If the frequency of deviance rises
above a certain level of tolerance, only the most
conspicuous are categorized as truly deviant and milder
deviance is ignored. On the other hand, as the frequency of
deviance falls below a certain level, even the milder
deviances become conspicuous. In this way, the incidence
rate may remain constant even though the genotypic rate
varies. Is this explanation plausible?
A careful reading of the original report on the WHO study supplied by Dr. Sartorius indicates that the source of the patients was not a survey of the total population in a given catchment area, but of those who "had made a first, contact with any 'helping' agency because of problems suggesting the presence of a psychotic illness." The authors admit that patients "who never contact any agency would still be missed." Whether these missing cases reflect the tolerance threshold for deviancy which I suggested, remains an open question and can be answered only by a complete sampling survey of the populations discussed. But even such a survey may not entirely remove the effect of community tolerance for deviancy. In other words, as long as the incidence rate is phenotypic, there is always a possibility that culture gets its licks in somehow.

I wonder whether mortality plays a part in incidence rates? Would the more severe cases tend to die off in all cultures and in this way make the rate more constant, if the severity is proportional to the basic rate? i.e. if the basic rate is low there would be fewer deaths of severe cases and mutatis mutandis when the basic rate is high.

Only when we develop objective markers for the presence of vulnerability for schizophrenia can this question be finally settled. The markers must be either the genetic alleles themselves or linkage markers but not pathophysiologial markers since the latter may already represent the emergence of the phenotype.
Whether the same argument will hold true for other etiological models beside the genetic seems highly plausible, but needs further elaboration. The parallel that Hafner draws between mental retardation and schizophrenia may also reflect ceiling and floor effects with regard to tolerance of deviant behavior in the community. As the author points out, perhaps the perceived threshold for tolerance may vary with incidence.

Regarding differences between males and females in age of onset one wonders whether the closer ties of the female to the family in most cultures prevents the perception on the part of the family of the deviant behavior in the daughter as compared to the son. Perhaps protective attitudes toward the female and the warmth of her social network postpones the emergence of the psychosis.

To summarize, the author maintains that both transculturally and transtemporally, the constancy of the incidence rate would suggest that incidence of schizophrenia, like Avogadro's number, is a natural constant independent of time and place. This would put schizophrenia in a class by itself, a maverick among all the other disorders of mankind.

Dr. Strauss's paper came as a surprise in this session since it deals primarily with the course of illness in individual cases - a far cry from the usual epidemiological concerns. Strauss wishes to discover the particular mechanism which determines the circuitous path that recovery
takes in the single individual although he probably hopes to find groups of like-minded individuals that cohere in these paths. The latter might bring him into the epidemiological fold. The most striking factor he focuses on is the person himself as a controlling agent, a factor which epidemiologists often lose sight of. Rene Dubos has called attention to this neglect in a dramatic way. According to Rene Dubos, the biological approach assumes that "all the constituents and processes found in living things including man, obey the laws of inanimate matter", Something which the early Freud, before he became involved in psychoanalysis, also believed.

Dubos goes on to explain: "We know a great deal concerning the physiochemical phenomena that make life possible, and we can formulate reasonable hypotheses concerning their origin and evolution. We can imagine, even though we do not completely understand, how each particular living thing is shaped by genetic constitution, experiences and environment...the physiochemical forces provide (however) only the props and stage machinery." (Dubos, 1971)

The etiologic models are described by Dubos as blind forces which control man's destiny and to some extent, given the current scene, this is a true picture. For the ecological niche in which man finds himself does determine his well-being, his genetic make-up does limit his potential, his internal environment and neuropsychologic make-up control his behavior. In fact, we might agree with
Dubos, that all of these forces are merely the stage props for the drama that man is to enact on the stage of life. However, we have omitted perhaps the most important determinant of man's stage behavior—his ability to be a self-starter, to alter developmental trends, to modify the internal environment as well as his neurophysiologic equipment. Unlike other organisms which are shaped by their environment through eons of gradual evolutionary developments, man can shape his own environment if he chooses to do so and has developed the know-how to apply changes not only to the exogenous but also to the endogenous environment. It is in these directions that the future of man's normal development, as well as the containment and improvement of abnormal development, lies.

I have been impressed with Dr. Strauss' appeal to the process of healing in his title. I may be putting words in his mouth but it strikes me that we have forgotten that man is not only a self determiner but that he is also a self-healer. Much of what therapists do may be regarded as removing the obstacle from the path of natural healing which nature provides us with. It is often said that in order to prove the efficacy of a treatment we must beat the spontaneous improvement rate. But what is spontaneous improvement if not natural self-healing? Perhaps Dr. Strauss should concentrate on finding his mechanisms in spontaneous recoveries and find out how nature brings them about. For this, of course, he would have to conduct an
epidemiological experiment by monitoring a catchment area for cases of individuals who develop episodes that spontaneously heal and discover what were the mechanisms involved in such healing.

Tsuang and Fleming have presented another study in the famous series of Iowa studies and this time devoted themselves to the problem of atypical schizophrenia.

Four outcome variables were considered: (1) marital status (2) residential status (3) occupational status and (4) psychopathological status.

One wonders whether marital status can really be regarded as an outcome variable, but it seems to serve as a differentiator between atypical schizophrenia and the comparison groups. In general, establishing the authenticity of a diagnostic category on the basis of the variables chosen reminds me of Squires attempt after World War II to classify patients on the basis of treatment outcome which in those days consisted of insulin, ECT and psychosurgery. The classification system did not outlast the therapies!

I also wonder whether the isolated treatment of the four outcome variables is a satisfactory procedure. The authors indicate that they are planning a multivariate attack and maybe that will help us understand the results better. In the proposed analysis linear relationships of the regression variety are contemplated. I wonder whether a pattern analysis by means of a clustering procedure might be
helpful. Thus, a divorced man, not working and living alone with little or no psychopathology present may represent an outcome which is quite different in quality of life from the same individual living with his family. In other words, the regression analysis may crush all the possible non-linear relationships out of existence.

All in all, the authors have made a valiant effort to establish the category of atypical schizophrenia on a more certain footing, and if the proposed multivariate analysis they promise bears out their previous conclusions, they will have made a considerable contribution to the category of atypical schizophrenia.

This paper seems to present the very antithesis of the Strauss paper since it deals with specifically identifiable factors like marital, occupational, residential and psychopathological status in relation to outcome on follow up of a specifically delimited group of patients. The individual's course of outcome with regard to these variables is completely ignored and the statistical product of an equation is used to indicate whether the outcome was good or poor in each factor. This study fits well into the epidemiological mold.

In contrasting the epidemiological approach as represented by the team of Tsuang and Fleming with the individual approach of Strauss, we might note that both these approaches have led to well known fallacies. The epidemiological-statistical approach has sometimes suffered
from the ecological fallacy while the individual approach has sometimes given rise to the clinical fallacy. The ecological fallacy has been illustrated by the Faris and Dunham claim that low socioeconomic level as measured by average rental in an area is negatively related to rate of schizophrenia. A more individual analysis by Edward Hare in Bristol found that living alone was the differential factor regardless of socioeconomic status.

On the other hand, the clinical fallacy is well illustrated by the claim that Buergher's disease was a Jewish disease until the King of England developed it.

The essential problem of these two fallacies inheres in the fact that the total covariance between factors x and y is divisible into two portions, the covariance between the means of the subgroups in the population and the covariance within the subgroup $r_{xy} = r_{xy} + r_{x} y$. The ecological fallacy results when only the covariance between the means is attended to, while the clinical fallacy results when only the covariance within the group is considered. By harnessing a keen individual clinician like Strauss with ingenious epidemiologists like Tsuang and Fleming we might be able to avoid both types of fallacies.

The study by Schubart, Krum, Berland, and Maurer is an investigation of a prospective five year follow-up study of schizophrenic patients with recent onset of illness based on the WHO-Collaborative Study on the "Assessment and Reduction of Psychiatric Disability". The focus of this paper is on
the influence of risk factors on the course and outcome of symptomatology (psychopathology) and Social Adjustment in long-term follow up.

I must admit that either because I am unacquainted with their work, or because of language difficulty in the presentation, my comments may be beside the point.

The outcome variables were:

1) Disability at time of final assessment on 5 year follow-up.
2) Time in psychotic episodes during follow up.
3) Acute psychotic symptoms (positive symptoms) at time of follow up.
4) Negative symptoms at time of follow up.

The predictors of outcome were (1) sociodemographic variables (2) symptomatology at initial assessment (3) negative symptoms, positive symptoms and the disability score 6 months after initial assessment and (4) variables concerning EE of the key figure (most important relative?) at initial assessment. (note that predictors are earlier estimates of outcome variables)

The results indicated that the one year outcome can be predicted best. The five year outcome can not be predicted.

Proximity in time between the measures which are used initially as predictors and later as criteria of outcome, may explain the results. For example, correlation between initial symptomatology (the predictor) with symptomatology at 6 months (outcome) may reflect the effect of self-
correlation. That is why the correlation is high when the 6 month outcome is predicted, but quite low when the 5 year outcome is predicted.

I hope that the final version of the paper may clarify these issues.

Norman Sartorius had not let me have the benefit of previewing his paper but he did send me two of his recent papers on which he built his presentation here. The magnificent scope of the systematic studies of WHO into the problems of schizophrenia which he describes cannot help but arouse our admiration. He focused on the advances in this field stemming from the WHO effort to the exclusion of some of the other contributions to the common goal. One of the predecessors of the WHO effort in which he himself participated, to my great satisfaction, was the US-UK Project which laid the foundation for cross-national if not cross-cultural studies.

The three most striking results which he reported are first, the constancy of the incidence rate of the S+ category, second, the better outcome of the developing countries and third, the replication of the Brown & Birley findings on the importance of life events in the three weeks preceding an episode as triggers of episodes on a cross-cultural basis. Regarding the constancy of the incidence rate for nuclear schizophrenia (S+), I have already discussed some of the possible interpretations in the discussion of Professor Hafner's paper. It should be noted
that in a forthcoming paper Sartorious regards the "first contact" incidence rate as only an approximation to the "true" rate and in need of replication.

Here all I would like to point out is that because of the importance of that finding, the exact method for computing the $X^2$'s should be described for the uninitiated. Would it have clarified matters if a multiple contingency analysis including the sex differences were undertaken and the total $X^2$ decomposed into the sex differential component and the center differential component. Freed from the sex component, which is not really germane here, the constancy of the rate could be more purely examined. The value of the first rank symptoms as measures of severity is a noteworthy added feature, since there is such a strong demand for overall measures of severity. Perhaps also the speculation regarding the effect of the drop in size of the sample has on the outcome when the restricted $S+$ category is used, could be resolved simply by computing the coefficient of variation for the total group and the restricted group.

There are three findings that seem to need further explanation - the better outcome for developing countries, the delay in onset in females and the better outcome for females. Is there a common link here? Is it possible that the social network and family relations in developing countries and similarly the social network and family relations of the females serve as buffers to ameliorate
outcome and by the same token delay the onset of episodes in females.

There seems to be a tendency for the developing countries to show a higher frequency of positive symptoms. Is there a corresponding gain for negative symptoms in developed countries? If so, is this balancing of symptoms partly responsible for the constancy in the apparent incidence.

Regarding the replication of the Brown & Birley findings of the relation between life events during the 3 weeks preceding an episode and the occurrence of the episode, it should be pointed out, that though Brown and Birley did not regard life events as important in the triggering of an episode, the cross-cultural replication seems to enhance the value of the finding. Furthermore, though life events seem to have come into prominence only since the work of Holmes & Rahe, it should be pointed out that precipitating events have a long history in schizophrenia. Furthermore, the importance of the concept dates back to Burton in his Anatomy of Melancholy who listed a series of life events in the "causes" of mental disorders.

In general, the evidence presented in this paper does not give any weight to causality for the psychosocial variable of culture, season of birth, and age of onset (delayed in females) but it does lend support to the possibility that psychosocial factors may be important in
determining time of onset, maintenance of the episode, relapse and recovery.