

Vulnerability to Relapse in Schizophrenia

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The primary question we would like to consider is whether there is a special vulnerability among schizophrenic patients which distinguishes relapsers from non-relapsers. For our working definition, relapse occurs when a remitted patient – one who has been either entirely free of symptoms, or one who has shown only long-term residual symptoms – again develops sufficient symptoms to satisfy the criteria for an active episode of schizophrenia.

For investigating the nature of relapse, it would be most fortunate if we could find a group of first-episode patients, who do not seem easily distinguishable from each other in psychopathology, but who divide themselves on follow-up into relapsers and non-relapsers. Studies which yield such data are shown in Table 1.

Although these studies do not always meet the requirements demanded by Shepherd *et al* (1989) for a sound investigation, they provide a general idea of the variability to be expected in the proportion of non-relapsers within samples. It should be noted that the study by Shmaonova *et al* (1983) probably deviates in its definitions of schizophrenia and relapse because of potential differences in Russian

practice. Perhaps one common difficulty stems from the fact that even such well designed studies as that of Shepherd *et al* (1989) could not control for the type of treatment received, which probably accounts for the variability between studies. However, Shepherd *et al*'s study deserves special attention because it drew its patients from a specified catchment area and meticulously monitored them for five years following discharge. Data for the 49 first-admission patients were analysed separately from the total sample: 22% of these were found to be non-relapsers, having had only one episode with no subsequent impairment during the five-year follow-up.

Crow *et al* (1986) organised a controlled trial of prophylactic neuroleptic treatment in a multi-hospital follow-up study of first admissions. At discharge, 120 patients were randomly assigned to receive one of five neuroleptics or a placebo, and then followed-up for two years. In the medicated group, 54% did not relapse, while the proportion in the placebo group was 38%. The most important determinant of relapse was the duration of illness before the institution of initial neuroleptic medication. This finding may indicate that early treatment has a preventive effect on relapse, or merely that the duration of symptoms before initiating medication is a reflection of a more severe but insidiously developing disorder.

Rajkumar & Thara (1989) undertook one of the few prospective studies to focus on clinical and sociodemographic factors associated with relapse. Of the 64 first-episode patients, the 38 relapsers (59.4%) differed from the 26 non-relapsers (40.6%) at the time of their first admission on the following clinical variables: (a) presence of affective symptoms; (b) special features of depression (including self-depreciation, guilty ideas of reference, dulled perception, and lost affect); (c) self-neglect; (d) catatonic symptoms; and (e) neurotic symptoms during childhood. At the end of the three-year follow-up period, non-relapsers differed from relapsers in the following aspects: (a) fewer affective symptoms; (b) less dangerous behaviour; (c) less decline in religious activity; (d) a higher degree of social controls (social contacts); (e) fewer life events; and (f) greater regularity of attendance at the

Table 1
Proportion of Non-relapsers

Study	Non-relapsers %	Duration of follow-up: years	First admissions only
Bleuler, M. (1978)	30	23	-
Shmaonova <i>et al</i> (1983)	30	> 15	-
Crow <i>et al</i> (1986)			
medicated	54 (42) ¹	2	yes
placebo	38 (30) ¹	2	yes
Rajkumar <i>et al</i> (1988)	41	3	yes
Shepherd <i>et al</i> (1989)	22	5	yes
Ciampi (1990)	10	37 (mean)	-
(personal communication)			
World Health Organization (1990)			
(Susser, personal communication)			
developing countries	37	2	-
developed countries	15	2	-
Hogarty <i>et al</i> (1991)			
drugs + family treatment + social skills	75	2	-
drugs alone	38	2	-

1. Actuarial % of relapse-free patients

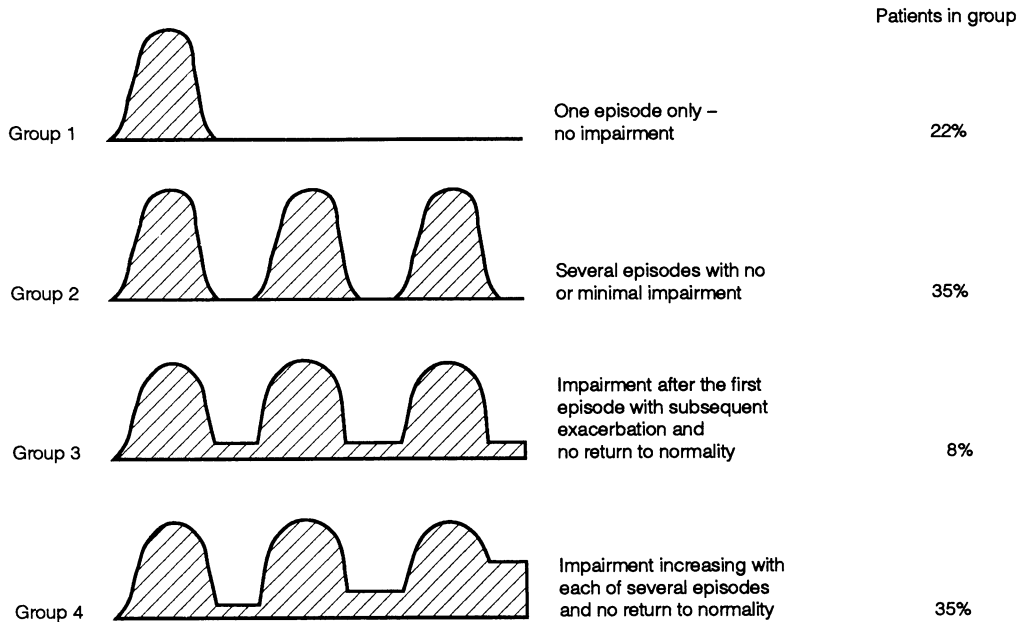


Fig. 1 The natural history of schizophrenia: a five-year follow-up (from Shepherd *et al*, 1989)

out-patient clinic. However, a regression analysis indicated that only 3 out of 12 measured variables had significant loadings: (a) self-neglect; (b) social contacts; and (c) regularity of clinic attendance. Since the treatment consisted of oral neuroleptics, the authors noted the uncertainty of compliance with it.

Thus, there are at least three well designed studies of first admissions which indicate that between 22% and 54% of patients did not relapse within the two- to five-year periods examined. Non-relapsers within this time frame are apparently not uncommon.

Hogarty *et al* (1991) examined relapse as a function of treatment strategy that was randomly assigned to consecutively admitted in-patients, rather than to first admissions. The most effective treatment involved a programme that combined family treatment, social skills training, and drug regimen, which resulted in 75% not relapsing during two-year follow-up. In contrast, only 38% of the drug-only control group did not relapse. Thus, the combined treatment approach doubled the proportion of non-relapsers, when compared with the drug-only group.

These data raise several fundamental questions. What are the characteristics of patients who do not relapse? What strategies may they have developed for prevention? If we could discover what these effective strategies are, the need for treatment would

be drastically reduced, and work could be focused on preventing even the first episode for individuals who are at risk of developing schizophrenia.

Possible causes of relapse

What causes relapse, and how could one identify vulnerability to its occurrence? We suggest the following general hypotheses.

- (a) Relapse is an indigenous characteristic of a subtype of schizophrenia which occurs in some patients regardless of treatment, i.e. they possess a special vulnerability which is not present in non-relapsers.
- (b) Relapse occurs only as a result of a life-event stressor.
- (c) Relapse occurs because of a disruption of physiological homeostasis. This might become manifest, as Manfred Bleuler has informally suggested, as a mood swing.
- (d) Relapse occurs when the individual's coping ability (with or without the assistance of therapeutic intervention) no longer serves to screen out the impinging stressors, which formerly could be contained.
- (e) Some combination of the above mechanisms may interact to increase the likelihood of relapse.

Triggers of relapse

The prediction of relapse is a desirable goal; it would enable us to foresee the event and so improve the possibility of its prevention. However, the literature on prediction is somewhat limited. Several examples of such attempts will be presented below, including the role of mood changes, the use of biochemical assays (with norepinephrine serving as an example), and psychophysiological responses as predictors.

The role of depression and/or change of mood in relapse

In a recent letter, Manfred Bleuler suggested to us that a disposition to manic-depressive disorder is present in the family background of schizophrenic individuals who relapse. In his personal experience, schizophrenic patients who show an intermittent course, presumably with numerous relapses, are frequently found to have manic-depressive parents. Furthermore, he suggested that as patients with typical schizophrenic psychoses and frequent relapses become older, they exhibit typical manic-depressive episodes. In addition, lithium, which serves as a prophylactic for manic-depressive episodes, has some preventative value against relapse in schizophrenia. Bleuler further suggested that even mild mood swings, which he described as 'manic or depressive *attitudes*', might be a trigger for developing a subsequent schizophrenic episode.

Green *et al* (1990) have lent some credence to Bleuler's suggestions by finding independently that the simultaneous onset of depressive periods and of psychotic symptoms occurred with high frequency in 27 recent-onset schizophrenic and schizoaffective (mainly schizophrenic) patients. The period in which the onset of the psychotic episode occurred was preceded by a prodromal phase, and succeeded by four other well demarcated periods. Of these six epochs, the one in which the psychotic episode occurred had the highest frequency of mood changes. Although Green *et al* did not find the mood change to be an immediate trigger (i.e. occurring just before the onset of psychosis), it is possible that a prospective study pinpointing the time period immediately before the onset of psychotic symptoms might identify a subtype in which the mood swing does serve as a trigger.

Experimental prediction of relapse

One of the most closely controlled approaches to studying relapse after withdrawal of medication is being used at the Veterans Affairs Medical Center

in Pittsburgh, on the Schizophrenia Research Unit, a programme conducted by Daniel van Kammen and his colleagues. Most of the participating chronically ill patients have shown repeated episodes over long periods. All patients are stabilised on haloperidol, which is later withdrawn through double-blind placebo replacement. Patients receive daily and weekly clinical evaluations throughout treatment and drug-free periods; a variety of biochemical, physiological, and psychological measures are obtained during all phases of participation. Special emphasis is given to the data collected during the treatment phase, which are used to determine the factors predictive of relapse after withdrawal of medication.

In addition to the likely involvement of dopaminergic activity in schizophrenia, evidence has also accumulated for a role of noradrenergic systems. For example, van Kammen *et al* (1990) have reported that of 32 patients studied, the 14 who relapsed within six weeks of withdrawal of medication showed significantly higher cerebrospinal norepinephrine (NE) levels, both before and after cessation of medication. This suggests that relapse might be associated with an increased NE level, even during treatment periods. Furthermore, after drug withdrawal, the relapsers showed significant positive correlations of NE levels with psychosis ratings and with the clinical assessment of negative symptoms. In contrast, the patients who remained stable showed non-significant, negative correlations between NE levels and symptoms.

Behavioural and psychophysiological measures may also be used to investigate the prediction of relapse. For example, previous work has demonstrated the relevance of the pupillary light reaction for schizophrenia (Hakerem *et al*, 1964). Specifically, Hakerem *et al* (1964) found that acute patients were characterised by an earlier termination of pupillary constriction compared with normals. In collaboration with van Kammen, we monitored weekly the pupillary light reaction in the schizophrenic in-patients from the relapse prediction protocol (Steinhauer *et al*, 1992). Latency of the pupillary light reaction was compared in 9 non-relapsers and 10 relapsers for the final week of their neuroleptic treatment just before double-blind placebo replacement. A significantly earlier termination of pupillary constriction was observed in those patients who ultimately relapsed. Thus, the eventual relapsers in our protocol, when studied before drug withdrawal and relapse, were more like the acute patients of the Hakerem *et al* study, while those patients who remained stable were more similar to the normals of that earlier study. These findings

suggest that psychophysiological measures, such as the pupillary light reaction, could serve as a clinical adjunct in the prediction of whether individual patients are likely to relapse within a few weeks after withdrawal of medication.

The nature and process of relapse

Little is known about the process of natural relapse because most of the data come from treatment programmes which involve intervention. Since it is no longer possible in industrialised countries to study a truly natural course of illness without the presence of some type of treatment intervention, we shall consider natural relapse as a process that occurs in patients undergoing standard treatment, and contrast it to the relapse associated with a treatment-free process (e.g. withdrawal of treatment to achieve a treatment-free state).

The term 'natural relapse' parallels the older concept of 'natural course of illness', which in earlier times referred to a condition in which nature takes its course untrammelled by human intervention, or at least by only accidental human intervention. Today, the 'natural' course of illness is a misnomer, since only in developing countries can it take place, and, even there, as soon as it comes under any observation, it is no longer natural.

Our definition of natural relapse is similar to that of Shepherd *et al* (1989), who defined the natural history of schizophrenia as follows: "it occurs under contemporary conditions, subject to the cultural, social and medical influences and interventions that prevail; more particularly, subject to the contingencies of passing through the psychiatric system as it now exists". Thus, under these conditions natural relapse signifies a patient who relapses despite receiving standard treatment. In contrast, a second type of relapse occurs when a major component of the patient's treatment is discontinued during investigatory research, as described earlier.

Since the cause of 'natural relapse', as well as that of 'natural recovery', is still unknown, we need to develop theoretical models for these phenomena and to provide hypotheses for testing their tenability through empirical observations. The tendency to relapse and the contrary tendency to recover could be incorporated into a single model, in which they might vie with each other and thus reveal their underpinnings.

Let us postulate that there is a set of factors (stressors, physiological dysregulation, excessive or deficient neurotransmitters, etc.) continuously bombarding the vulnerable, although stabilised

patient, while he/she is undergoing standard treatment. Let us also assume that there is another set of factors (the tendency to natural self-healing, or activity of the protective immune and other systems) impinging on the patient who is undergoing a psychotic episode, and which serve to energise coping efforts toward recovery. We might then raise the following question regarding relapse. What could have brought about the failure to prevent relapse under standard treatment? Unless relapse is a built-in cyclical phenomenon, it is possible that the effectiveness of continuous treatment may have 'worn off' despite the clinician's best efforts; analogous to the repeated stimulation that leads to physiological habituation.

Similarly, it is worth considering the processes leading to remission. Perhaps the natural tendency towards self-healing energised the patient's coping ability, and facilitated the effectiveness of the therapeutic regime.

Depending upon the assumptions underlying a model for relapse, it may become possible to conceive of a 'safe-point' – a time-interval before which relapse is probable and beyond which it is improbable. Such a 'safe point' has been reported for smoking abstinence (Brownell *et al*, 1986). The point at which a stable proportion no longer smoke is four months, at which time 21% remain abstinent after quitting; the same holds true at eight months – 21%. However, these data are for groups, so that not all the same individuals are involved in subsequent comparisons. We formerly regarded the 'safe point' for permanent chronicity in schizophrenia as two years of continuous in-patient treatment, since after that period recovery was a rarity. The data of Bleuler's (1978) long-term follow-up, however, indicate a different fate for these patients. The 'end state', as he defines it, is given by the proportion of patients "whose condition has remained constant for at least five years" – that is, they do not relapse or exhibit exacerbation of symptoms. This proportion (30% in Bleuler's cohort of the 1940s) is subsequently maintained for the entire cohort, with similar numbers of patients moving between states of illness and remission, much like the equilibrium of ions in solution.

What explanation can we offer for the constancy of the 'safe point'? The following hypothesis was formulated for schizophrenia. We assumed that relapse occurs because the vulnerable individual, even when he/she is not in an episode, is being bombarded continually by stressors from a variety of sources both external and internal, just as normals are. We also assumed that vulnerable individuals who are in the midst of an episode continually struggle to free

themselves from their state by various coping strategies. There seems to be an equilibrium between the tendency to relapse into a new episode from a recovered or remitted state, and the reverse tendency to emerge from an episode into a recovered or remitted state. Vulnerable individuals whose tolerance for stress is exceeded by the continuous bombardment to which they are exposed will be catapulted into a new episode. Others, who are still in their episode, may succeed in their spontaneous struggle against their illness by coping efforts, and improve or recover.

More than a century ago, Sir Gilbert Blaine contrasted two enduring attitudes toward treatment: the emphasis on the natural self-healing tendencies in man, as promulgated by Hippocrates in the treatment of the ill *person*, and the more aggressive approach of the ancient ontologists in their attack on the *disease*. Blaine succinctly argued that “the benefit derivable to mankind at large, from artificial remedies, is so limited, that if a spontaneous principle of restoration had not existed, the human species would long ago have been extinct” (Blaine, cited by Bigelow, 1972). Although we have transcended the ‘artificial remedies’ of the last century by our present-day medical sophistication, we should not forget that without the spontaneous principle of self-restoration through self-initiated coping efforts, even the most sophisticated medication might not succeed. While it is somewhat disappointing to realise that the ‘safe points’ reflecting a non-relapsed state are not permanent individual characteristics, but merely group characteristics, it is possible that there is a stable proportion of the patient cohort that remains steadfastly in the non-relapsed state (and a corresponding stable proportion in the chronically ill state). Moreover, there is likely to be a varying group that moves back and forth. This question remains to be investigated.

The question of whether the rates of relapse are paralleled by the rates of recovery can be investigated more fully by studying a representative population epidemiologically. Furthermore, we might question whether the constancy is a reflection of some threshold value in the community based on its degree of tolerance for deviance. These are problems to be considered in the future.

Conclusions

Our hypotheses for the occurrence of relapse may be summarised as outlined below.

(a) A vulnerability to relapse can be investigated by comparing relapsers with non-relapsers, using the various indicators that have been suggested as predictors of clinical change.

(b) That relapse occurs as a result of or as an accompaniment to a life event stressor has already been established for schizophrenic patients in general (Day *et al*, 1985). It may also be possible that the life-event stressors may serve as prodromal events preceding full relapse, and not as independent causal agents. These, however, may lead to stress-producing responses from the environment, which serve as circular feedback for the development of a full-blown episode. How to render the life-event interviews more reliable is still a problem. Perhaps a monitoring of the immune system’s response may serve to indicate current levels of stress. For the control of relapse, expressed emotion studies indicate a much higher rate of relapse for high expressed emotion families (Leff *et al*, 1982).

(c) Whether or not relapse occurs because of an internal disturbance in homeostasis can be examined by the challenge involving withdrawal of medication. The biochemical changes accompanying challenged relapse should be revealed in this process; if spontaneous natural relapse also shows these biochemical changes, their importance will be better established.

(d) Relapse due to the loss of the protective value of therapeutic intervention (neuroleptic or other therapeutic treatment) should also be revealed by the investigation of patients who relapse despite the neuroleptic shield of depot treatment.

Additional considerations include:

(e) a comparison of the personalities of probands with those of their unaffected siblings might yield discriminators for relapse proneness

(f) the World Health Organization’s (1978) study has indicated that in developing countries, cultural factors may contribute to lowering the rate of relapse (Ezra Susser, personal communication).

The biological challenge posed by the current *Zeitgeist*, views schizophrenia as something one *has*, not what one *is*, and that what one *has* is a biological disease. However, unlike some physical disorders, which are confined to specific organs, schizophrenia permeates the entire personality. From a basic conceptual standpoint, targeting only the biological focus and ignoring the psychosocial penumbra will not be an adequate solution. The biological factors, important as they are, may merely be the plumbing and wiring of the organism. Hence, the current tendency towards curtailing psychosocial research is tantamount to cutting off the roots of even biological progress, and can prevent the progression of scientific enterprise.

For these reasons, our classification systems should not be limited to clinical diagnoses which include only symptoms, but should be supplemented

by a consideration of the assets of the individual. For example, the available coping skills, and the strength of the social network and family support, are important characteristics which may guide the types of therapeutic strategies best suited to the patient. By exploiting these assets, we may attempt to instill coping and hopefulness, so that their presence might prevent relapse. The fact that these assets (or disabilities) cannot yet be located in the brain should not lessen their pursuit.

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