Negative Association Between Schizophrenia and Rheumatoid Arthritis

by Sophia Vinogradov, Irving I. Gottesman, Hans W. Moises, and Susan Nicol

Abstract

Persuasive evidence has accumulated demonstrating a strong negative association between rheumatoid arthritis and schizophrenia at the population level. Explanations for this phenomenon have taken into consideration immunological, biochemical, and genetic factors. In this article, we examine these and other factors in closer detail. We then propose hypotheses at the molecular level that might account for the negative association between the two diseases. These hypotheses may provide clues for our colleagues in molecular biology as they search for candidate genes, “anti-genes,” and molecular mechanisms relevant to schizophrenia.

Over the past 50 years, an impressive amount of evidence has accumulated demonstrating a negative correlation between the coexistence of schizophrenia and rheumatoid arthritis in patient populations (Nissen and Spencer 1936; Gregg 1939; Ross et al. 1950; Trevathan and Tatum 1954; Pilkington 1956; Rothermich and Philips 1963; Mellsop et al. 1974; Osterberg 1978; Baldwin 1979, 1980; Mohamed et al. 1982; Allebeck et al. 1985). This negative association appears specific to schizophrenia; Baldwin (1979, 1980), using a record-linkage approach, found only one case of schizophrenia among 2,122 patients with rheumatoid arthritis (relative risk of 0.15%), whereas nonpsychotic depression and affective psychosis carried relative risks of 0.94 percent and 1.38 percent, respectively, among these patients with rheumatoid arthritis. Allebeck and colleagues, in an attempt to reproduce these findings, found no substantial difference between observed and expected numbers of rheumatoid arthritis in 3,978 cases of “neurosis,” whereas they found that the incidence of rheumatoid arthritis was half the expected value in 1,190 cases of schizophrenia. The incidence of rheumatoid arthritis was also surprisingly low in 621 patients with affective psychosis; this sample was relatively small, not well defined, and results were not statistically significant (Allebeck et al. 1985). It is important to note that these population studies have not, as a rule, been well controlled, nor have they been based on carefully gathered, operationalized diagnostic criteria such as

These earlier studies were based on record review and often had flaws in their design and methodology; however, over the years, many other investigators using increasingly sophisticated methodology have continued to report a similar negative association between the two diseases (Pilkington 1956; Rothermich and Philips 1963; Mellsop et al. 1974; Osterberg 1978; Baldwin 1979, 1980; Mohamed et al. 1982; Allebeck et al. 1985). This negative association appears specific to schizophrenia; Baldwin (1979, 1980), using a record-linkage approach, found only one case of schizophrenia among 2,122 patients with rheumatoid arthritis (relative risk of 0.15%), whereas nonpsychotic depression and affective psychosis carried relative risks of 0.94 percent and 1.38 percent, respectively, among these patients with rheumatoid arthritis. Allebeck and colleagues, in an attempt to reproduce these findings, found no substantial difference between observed and expected numbers of rheumatoid arthritis in 3,978 cases of “neurosis,” whereas they found that the incidence of rheumatoid arthritis was half the expected value in 1,190 cases of schizophrenia. The incidence of rheumatoid arthritis was also surprisingly low in 621 patients with affective psychosis; this sample was relatively small, not well defined, and results were not statistically significant (Allebeck et al. 1985). It is important to note that these population studies have not, as a rule, been well controlled, nor have they been based on carefully gathered, operationalized diagnostic criteria such as

Reprint requests should be sent to Dr. S. Vinogradov, Dept. of Psychiatry, Pacific Presbyterian Medical Center, San Francisco, CA 94115.
Schizophrenia and Rheumatoid Arthritis: Anything in Common?

How might one explain such hypothetical "genetic differences" between subjects with schizophrenia and those with rheumatoid arthritis? Is there any possible overlap in etiology or pathophysiology between the two diseases that could account for their negative association at a population level? And if so, does this provide some useful directions for future research in schizophrenia? (Of course, we well recognize that schizophrenia is probably not a single disease entity, but that instead it most likely represents a syndrome or final common pathway caused by several different etiopathogenetic processes. In the following discussion, we will consider only the "form" of schizophrenia that shares some processes with rheumatoid arthritis.)

Rheumatoid arthritis is considered, first and foremost, to be an autoimmune illness that is prostaglandin-dependent. There are various well-established human leukocyte antigen (HLA) associations in rheumatoid arthritis and related diseases, including a strongly positive association between rheumatoid arthritis and HLA-DRw4, and a negative association with HLA-A1 and HLA-A1/B8 (Gilliland and Mannik 1983; Grennan et al. 1986; McDermott et al. 1986; Ollier et al. 1986; Spector and Silman 1987).

Based on research evidence from various sources, several investigators have suggested that a primary or secondary immune-related process may be taking place in some schizophrenic patients as well (e.g., Goldstein et al. 1980; Mendlewicz et al. 1981; DeLisi 1984; Pert et al. 1980; Stevens 1988; Henneberg and coworkers 1990). McAllister et al. (1989) recently demonstrated increased numbers of CD5+ B-lymphocytes in schizophrenic patients, while Henneberg and coworkers (1990) found significant increases in the numbers of Pan T and T-helper cells in schizophrenic patients compared with numbers of these cells in control subjects. Spivak et al. (1991) have reported a high frequency of cold agglutinin titers in schizophrenic patients, compared with titers found in patients with bipolar or unipolar affective disorder or in normal controls.

A small group of studies also has shown that schizophrenic patients may have abnormal arachidonic acid or prostaglandin metabolism (Horrobin et al. 1978, 1989; Mathe et al. 1980; Horrobin and Huang 1983; Demisch et al. 1987). See figure 1 for a schematic outline of those aspects of lipid metabolism that might be pertinent to this discussion. In addition, there are many reports of associations between certain HLA haplotypes and certain subtypes of schizophrenia, and genetic linkage studies between the HLA locus and schizophrenia have been carried out in several pedigrees (Eberhard et al. 1975; Smeraldi et al. 1976; Julien et al. 1977; Ivanj et al. 1978; McGuffin et al. 1978, 1981, 1983; Asaka et al. 1981; Gattaz et al. 1981; Mendlewicz et al. 1981; Sturt and McGuffin 1985; McGuffin and Sturt 1986). Unlike the case for rheumatoid arthritis, however, the association between schizophrenia and HLA haplotypes is controversial and far from clear-cut; major linkage studies have shown no linkage between the HLA locus and schizophrenia (e.g., Goldin et al. 1987).

In addition to the immune system findings, rheumatoid arthritis shows a strong genetic component inferable from twin and family studies just as schizophrenia does. Severe rheumatoid arthritis is found at four times the expected rate in first-degree relatives of probands with the illness, and twin studies demonstrate a monozygotic concordance rate of 25 to 40 percent (Lawrence 1970). Rheumatoid arthritis also shows a variable age of onset and a widely varying clinical presentation. This, in combination with a number of genetic and family studies, has led researchers to conclude that rheuma-
Figure 1. Schematic representation of certain aspects of lipid metabolism that may be pertinent to the negative association between rheumatoid arthritis and schizophrenia

Dietary lipids, including essential fatty acids: linolenic acid + linoleic acid

Some amino acids

Palmitoyl CoA ←— palmitic acid

+ serine

Some amino acids

Sphingomyelins

Glycosphingolipids

Phosphoglycerides: e.g., phosphatidylcholine, phosphatidylserine

Phospholipids important in cell membrane structure/function

Myelin sheath components: specialized membrane receptors

Phospholipases:

Phospholipase A2

Arachidonic acid

Cyclooxygenase

Prostaglandins, prostacyclins (prostanoids)

Phospholipase C

Components of intracellular second messenger systems

Lipoxygenase

Leukotrienes (eicosanoids)

Arachidonic acid metabolites important in inflammatory response, immune response, and neurotransmission
toid arthritis is subject to multifactorial influences, including genetic and environmental factors. If a single gene is involved, such as an autosomal dominant gene, it most likely shows incomplete penetrance; polygenes and genetic heterogeneity also may be part of the etiologic picture (Grennan et al. 1986; Payami et al. 1986). Such a complex picture is nearly identical to one that many investigators paint for the genetics of schizophrenia (Baron 1986; Gottesman et al. 1987; Gottesman and Bertelson 1989; McGue and Gottesman 1989).

Explanations for the Negative Association

A number of suggestions at the metabolic and biochemical level have been proposed to explain the negative association between rheumatoid arthritis and some possible forms of schizophrenia (Malek-Ahmadi 1985; Spector and Silman 1987). Fields of inquiry have included the following:

1. The role of prostaglandins and related precursors (arachidonic acid and essential fatty acids; see figure 1). Increased prostaglandins have been found in the synovial fluid of patients with rheumatoid arthritis, and anti-inflammatory agents with prostaglandin-synthetase-inhibiting activity are an effective form of treatment for this illness (Gilliland and Mannik 1983). Both increased prostaglandins (Horrobin et al. 1978; Horrobin and Huang 1983) and decreased prostaglandins (Feldberg 1976) have been proposed to play a role in schizophrenia, although cerebrospinal fluid findings have been inconsistent (Mathe et al. 1980; Mathe and Sedvall 1986). More recently, Horrobin et al. (1989) found a significant reduction in n-3 essential fatty acids (those derived from linoleic acid) and a significant elevation in n-6 essential fatty acids (derived from alpha-linolenic acid) in the plasma of three different groups of schizophrenic patients when compared with plasma levels in controls.

2. Histocompatibility factors and other immune system-related factors. Gattaz and coworkers (1980, 1981) have hypothesized that the presence of HLA-B27 antigen serves as a protective factor in both schizophrenia and arthropathy: they found no cases of arthopathy in a sample of schizophrenic subjects with HLA-B27, and likewise found no schizophrenia in a sample of arthritic patients with HLA-B27. Mell sop and co-workers (1973) specifically searched for but were unable to demonstrate the presence of significant autoimmune serological reactions in schizophrenic subjects. It also has been suggested that other HLA factors and other immune system modulators may play a role in the negative association between the two diseases (Spector and Silman 1987; McAllister et al. 1989).

3. The role of serum beta-endorphin. Decreased levels of serum beta-endorphin have been reported in rheumatoid arthritis (Denko et al. 1982), whereas both increased and normal levels have been found in some schizophrenic patients (Ross et al. 1979; Brambilla et al. 1984).

4. The metabolism of tryptophan and serotonin. Taylor (1978) has concluded that there is an increased binding of tryptophan to serum proteins—and thus a decreased bioavailability—in rheumatoid arthritis, while there may be an excessive intracellular uptake in some forms of schizophrenia. He has suggested that this inverse metabolic relationship may explain the negative association between the two illnesses. Serotonin is increasingly being recognized as a neurotransmitter that may play an important role in some forms of schizophrenia (Csernansky et al. 1990).

In addition to these fields of inquiry, we suggest a fifth possible area: the role of prolactin—and hence dopamine—in immunomodulation. Prolactin has important immunoregulatory properties. Human lymphocytes have prolactin receptors, and prolactin appears to play a role in the development and maintenance of normal lymphocyte function (Russell et al. 1988). Prolactin restores immunocompetence in immunocompromised mice (Russell 1989), while hypoprolactinemia impairs lymphocyte responses to antigenic stimuli in experimental animals (Bernton et al. 1988). The dopamine agonist bromocriptine, through inhibition of prolactin, suppresses various immune reactions, including adjuvant arthritis and experimental allergic encephalitis (Nagy et al. 1983; Bernton et al. 1988); administration of prolactin reverses some of these effects.

One could thus hypothesize that the state of dopaminergic hyperactivity, which has been proposed to occur in some forms of schizophrenia, could result in a state of relative hypoprolactinemia. This state would result in a suppression of various lymphocyte-modulated immune reactions, including the autoimmune reactions that give rise to rheumatoid arthritis. A model for this hypothetical mechanism was recently suggested by a report in which several patients with a longstanding autoimmune iridocyclitis underwent complete remission after incidental treatment with bromocriptine for unrelated conditions (Hedner and Bynke 1985).
Recommendations for Future Research

Whatever the exact model for the etiologic and pathophysiologic relationship between some forms of schizophrenia and some forms of rheumatoid arthritis, the negative association between the two diseases appears robust. In fact, "some of the strongest and most consistent evidence of a relationship between a form of mental illness and physical disease exists for schizophrenia and rheumatoid arthritis" (Harris 1988, p. 90). Given this negative association, there are several fruitful areas for future research in the molecular biology of schizophrenia. These include consideration of gene products and regions in the genome that could be "protective" in either schizophrenia or rheumatoid arthritis and might best be conceptualized as candidate "anti-genes" (Gurling 1986).

One such area is the fatty-acid desaturase systems (enzymes involved in essential fatty acid interconversion and metabolism). Both the n-3 and the n-6 series of essential fatty acids are basic precursors for the prostaglandins via phospholipid and arachidonic acid metabolism (see figure 1) and both serve a structural role in all cell membranes. The n-6 essential fatty acids have been shown to influence the amount of dopamine released from the caudate nucleus in response to electrical stimulation. It also has been suggested that both series influence normal presynaptic control of dopamine release (Davidson et al. 1988). Horrobin and Huang (1983) have proposed that a defective desaturase enzyme could lower levels of n-6 fatty-acid metabolites; this scenario could predispose an individual to schizophrenia and also lead to an underproduction of prostaglandins. It is this same underproduction of prostaglandins that protects the individual from the myriad environmental and multifactorial insults that otherwise would lead to rheumatoid arthritis (Horrobin and Huang 1983).

The phospholipase systems, including phospholipase-A2 inhibiting proteins, represent another area of potentially fruitful research. These metabolic systems are involved in the synthetic pathway from phospholipids to arachidonic acid, as well as in the metabolism of arachidonic acid into prostanoids and eicosanoids (see Rotrosen and Wolkin 1987). Horrobin and coworkers (1989) have recently suggested that "The basic physiology and biochemistry of . . . eicosanoids, and their effects on neural function, mean that they are just as likely as neurotransmitters to contribute to abnormal psychiatric states" (p. 567). Associations among membrane phospholipids, neurotransmitters, and schizophrenia have been reported by various investigators over the years (Stevens 1972; Feldberg 1976; Hirata and Axelrod 1980; Rotrosen et al. 1980; Henn and Henn 1982; Hitzemann and Gaver 1982). Membrane fluidity, which is in turn influenced by phospholipid composition and methylation, affects binding affinities for dopamine, noradrenaline, serotonin, and endogenous opiates (Heron et al. 1980; Hirata and Axelrod 1980; Cimino et al. 1984).

In two separate studies, Gattaz et al. (1987, 1990) demonstrated increased serum phospholipase-A2 activity in schizophrenia and discussed the metabolic implications. They also noted that some of the phospholipase-A2-inhibiting proteins may be under the influence of the HLA locus. Hibbeln and coworkers (1989) proposed that disturbances in lipid-protein interactions by phospholipase-A2 may be a predisposing factor to serious affective illness; they described in detail the many known influences of phospholipase-A2 on systems important in neuronal function. Human phospholipase-A2 has been mapped to chromosome 12 and shares a marked homology with snake-venom phospholipase (McKusick 1988).

Alternatively, a more parsimonious research strategy might first consist of definitive identification of pathophysiological similarities or interactions between the two diseases, which could then be followed by more targeted genetics studies. For example, the phenomenon of chronic psychosis itself may somehow secondarily produce a protective effect against developing rheumatoid arthritis in at-risk individuals, perhaps through an increase in circulating corticosteroids.

The Lewis rat model suggests a mechanism by which a defective hypothalamic-pituitary-adrenal axis response to inflammatory and immune mediators (related to a specific genetic defect at the level of gene expression for cortisol-releasing factor in the hypothalamus) results in an increased liability to environmentally induced arthritis (Sternberg et al. 1990). This theory raises at least two provocative questions: Do other inflammatory and autoimmune disorders also show a negative correlation with schizophrenia? And are there familial or population differences in these associations?

Increasing knowledge of the effects of dopamine and prolactin on immunomodulation suggests yet another avenue of exploration. Since pharmacologic agents with dopaminergic properties (amphetamines, bromocriptine, cocaine) alter plasma prolactin levels, it would be important
to determine the incidence of rheumatoid arthritis in populations chronically exposed to these agents. In a subgroup of chronic cocaine abusers, hyperprolactinemia has been found, a condition possibly related to dopamine receptor down-regulation (Mendelson et al. 1989); this finding underscores the complexity of the relationship between dopamine-receptor activity and prolactin release.

Chronic exposure to dopamine-blocking agents, such as neuroleptics, may result in dopamine receptor up-regulation and a relative hyperprolactinemia that blunts lymphocyte responses to antigenic stimuli. Thus, we would hypothesize that individuals treated with neuroleptics will be "protected" from autoimmune inflammatory responses, such as those which occur in rheumatoid arthritis. Chronic cocaine users, on the other hand, may be prone to such reactions. Further population studies are clearly warranted.

Conclusions

In sum, we suggest that the negative association between rheumatoid arthritis and schizophrenia represents a tantalizing clue for future research in the molecular biology of these diseases and deserves further study. The factors we have proposed as possibly playing a role in both schizophrenia and rheumatoid arthritis will most likely represent genes or gene products that contribute to a liability to schizophrenia, as opposed to factors that are actually causative. Such "liability genes" could determine an idiosyncratic immune response to a viral infection (see Pert et al. 1988), leaving an individual prone to interference with normal brain functioning in some cases (schizophrenia) or to an autoimmune arthropathic condition in others (rheumatoid arthritis). The implications of a possible etiologic relationship between the two diseases must be carefully distinguished from those of a possible pathophysiologic relationship.

Future researchers will find it useful to seek out pedigrees containing both schizophrenia and rheumatoid arthritis in order to examine genotypic and environmental differences within families. "Further use of family studies should also be made to determine whether unaffected relatives are also 'protected' from either schizophrenia or rheumatoid arthritis" (Spector and Silman 1987, p. 309). We have already observed a monozygotic adult twin pair discordant for schizophrenia in which only the nonschizophrenic twin has rheumatoid arthritis. We also have begun studying a large multiplex schizophrenia pedigree, which includes an "obligate female carrier" of the hypothetical schizophrenia gene(s) who is the sister of a schizophrenic patient and the mother of four schizophrenic adults. The "obligate carrier" herself has no major psychiatric illness but suffers from severe rheumatoid arthritis. McAllister et al. (1989), who demonstrated an increase in CD5 + B cells in schizophrenic patients similar to that reported for patients with rheumatoid arthritis, have suggested that "genetic and/or environmental factors may cause the selection of a putative idiotype that contributes to the development of either disorder in certain patients" (p. 894).

Although the negative association between the two diseases offers fascinating avenues for further probes into the molecular biology of some forms of schizophrenia, we do not mean to suggest that any easy breakthroughs lie just around the bend. The real nature of the relationship between rheumatoid arthritis and schizophrenia will undoubtedly turn out to be subtle and complex, and probably multifactorial. We must be prepared, in the words of Alfred North Whitehead (1971), to "seek simplicity and distrust it" (p. 49).

References


Mendelson, J.H.; Mello, N.K.; Teoh, S.K.; Ellingboe, J.; and Cochin, J.


**Acknowledgments**

The authors thank Dr. L.L. Cavalli-Sforza for reviewing the manuscript and Ms. Victoria Jensen for her help in preparing the figure for the manuscript.

**The Authors**

Sophia Vinogradov, M.D., is Medical Director, Outpatient Psychiatry Clinic, Pacific Presbyterian Medical Center, San Francisco, CA; Irving I. Gottesman, Ph.D., F.R.C.Psych. (Hon.), is Commonwealth Professor of Psychology, University of Virginia, Charlottesville, VA; Hans W. Moises, M.D., is Assistant Professor, Department of Psychiatry, Kiehl University Hospital, Kiehl, Germany; and Susan Nicol, Ph.D., is Senior Clinical Psychologist, Department of Psychiatry, Hennepin County Medical Center, Minneapolis, MN.

**Announcement**

The Seventh Annual Pennsylvania Conference on Schizophrenia entitled "Accentuating the Positive" will be held March 12-13, 1992, at the Adam's Mark Hotel in Philadelphia, Pennsylvania. The purpose of the Conference is to increase awareness and public concern about schizophrenia and to serve as a forum for the dissemination and exchange of information on recent advances in the understanding and treatment of this mental illness. The program is designed to encourage the training of mental health professionals, consumers, family members, and program administrators and to promote schizophrenia research. Conference lectures, workshops, panel discussions, and question and answer sessions with recognized experts will provide a rewarding learning experience. In addition, the Arthur P. Noyes reception and award ceremonies will be held to provide a rich social experience for those working in the field of schizophrenia.

For a complete brochure about the Conference, please contact:

**Foli & Company**
137 Woodview Lane
North Wales, PA 19454
Telephone: 215-542-9210