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Juarez-Reyes, Maria G.

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IMMUNOLOGICAL AND ENDOCRINE FUNCTION AMONG PSYCHIATRIC,
MEDICAL, AND HEALTHY SUBJECTS

by

MARIA GUADALUPE JUAREZ

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of
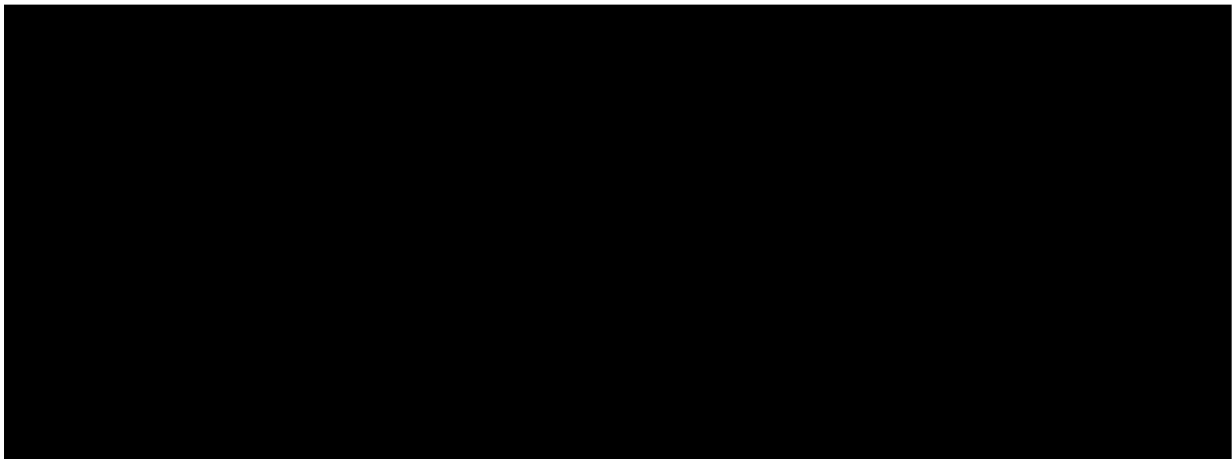
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To my parents Guadalupe and Alicia, and husband Joe, for their love and constant support, I dedicate this dissertation.

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technical supervision and consultation for this study.

ABSTRACT

IMMUNOLOGICAL AND ENDOCRINE FUNCTION IN PSYCHIATRIC, MEDICAL AND HEALTHY CONTROL SUBJECTS.

MARIA GUADALUPE JUAREZ

Evidence of immunological and endocrine abnormalities in schizophrenia may be due to factors other than the schizophrenic illness. Stress, chronic illness or demographic variables such as age, sex, and ethnicity may be more general explanatory factors. To explore the hypothesis that schizophrenic patients have significantly lower IgG, IgM, and T cell levels we compared immunological and endocrine parameters of DSM IIIR diagnosed schizophrenic patients to those of patients with major affective disorder and hypertension, and normal sex, age, and ethnically matched controls. IgG, IgM, and T suppressor/cytotoxic cell levels were chosen because of their anti-viral functions, and because there have been reports of abnormalities within these immune parameters among schizophrenic patients. Since cortisol is known to suppress some immunological responses, it was measured to determine whether any abnormalities can be correlated with high cortisol levels.

The study procedures included interviewing all subjects with a brief medical and psychiatric history form, and the BECK Depression Inventory and Recent Experience Survey. Demographic information including sex, age, ethnicity, and socio-economic status were also included in the medical and psychiatric history. The schizophrenic patients were also administered the Brief Psychiatric rating scale. A blood sample was then taken to measure IgG, IgM, Ts/c, and cortisol. Interviews and blood samples were taken before 12:00 noon. A subsample of schizophrenic patients also had a second blood sample taken during relapse.

The hypothesis that schizophrenic patients have significantly lower immune responses was not supported. Significant predictors of IgG were demographic and stress variables such as age, ethnicity, and cortisol levels. There were no group differences or significant predictors of IgM and Ts/c levels. Neuroleptic medication dose did not affect the immune responses. Relapse significantly decreased IgG response in the schizophrenic patients. Finally, cortisol was significantly predicted by sex, ethnicity, and depression level, and the affective disorder group only had significantly higher cortisol levels when compared to hypertensive patients.

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Introduction

Over the last 30 years there have been increasing reports of immunological abnormalities in schizophrenia. These abnormalities have ranged from antibrain antibodies (DeLisi, Weber, & Pert, 1985: Kagomi et al., 1987; Health & Krupp, 1967) to atypical (also referred to as P) lymphocytes (Habu et al., 1982). Unfortunately findings have not been consistent resulting in many speculations that the immunological abnormalities are not related to the disease etiology or process but are a result of the neuroleptic medications. However, reports of immunological abnormalities in schizophrenic patients who have never been medicated suggest that medication alone cannot explain these abnormalities.

An alternative explanation is that the immunological abnormalities are related to the disease process. For example, the disorder may cause immunological abnormalities or immunological agents such as viruses, which affect the immune system, may have caused the disorder. Therefore, studies on immunological abnormalities in schizophrenia are important because they will assist in the determination of a viral etiology to schizophrenia.

Studies thus far have been unable to suggest a relationship between viruses or immune responses and schizophrenia since consistent findings have been rare. The results of immunological studies in schizophrenia have been inconsistent for several reasons. Investigators have measured

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a variety of immunological responses, sometimes without a theoretical perspective, appropriate control groups have not always been used, and the effects of potential intervening variables such as gender, age, ethnicity, socio-economic status, medication dose, duration and severity of illness, and stress have not been examined or controlled.

The purpose of this study was to investigate whether immunological abnormalities in schizophrenic patients existed when proper control groups were used and when the effects of potential intervening variables were controlled. In this present study, the effects of intervening variables were determined as were any group differences. This study also determined whether any immunological abnormalities were specific to schizophrenia or whether they were common to other psychiatric or medical groups. Finally, the study determined whether any immunological abnormalities were state or trait markers (i.e. whether they were constant or whether they changed with changing stages of the schizophrenic disorder).

CHAPTER 1

VIRAL THEORIES AND IMMUNOLOGICAL ABNORMALITIES IN SCHIZOPHRENIA

Hypotheses that a viral agent may be involved in the etiology of schizophrenia have been postulated for at least sixty years (see DeLisi, 1987). These theories continue to be important since no etiology for schizophrenia has been established. Additionally, there have been several reports of immunological abnormalities in schizophrenia which have been argued as evidence supporting a viral origin to schizophrenia.

This important area of research is not without problems. For example, several viral theories have been proposed, but no mechanism of action for infection and illness have been agreed upon. Most theories have suggested an interaction between a virus and genetic predisposition to infection as the mechanism for infection and subsequent mental illness. However alternative hypotheses have proposed that viral infection alone can account for genetic predisposition to schizophrenia and subsequent mental illness. Additionally, while there have been several reports of immunological abnormalities, results have been conflicting and their implication to a viral etiology is not clear.

The purpose of this discussion was to review the various viral theories and immunological abnormality studies which might be used to support these theories of schizophrenia, and to establish what type of studies are still needed in the

field before a unified theory or mechanism of action can be proposed.

VIRAL THEORIES

A broad conceptualization of viral involvement in the etiology of schizophrenia was presented by Pert, Knight, Laing, and Markwell (1988). These authors suggested there may not be a single "schizophrenia virus", but there may be several viral infections which cause schizophrenia in genetically predisposed persons. The heritability factor or genetic predisposition to schizophrenia was conceptualized as the inability to mount a appropriate immune response to viral infections (Pert et al., 1988). Therefore schizophrenia is the result of an individual's inability to mount an adequate response to any number of common viral infections. Additionally, since viruses can cause autoimmune reactions, the authors suggested that an intermediate (but still insufficient) response to the viral infection may be an autoimmune reaction (Pert et al., 1988). The authors did not indicate whether this intermediate autoimmune response occurred immediately after infection or whether it was a reoccurring response.

This theory was difficult to test because it did not suggest the time of infection (i.e. pre-natal, post-natal, childhood, or puberty), or a specific mechanism of action. However, since the proposed genetic predisposition is a faulty immune response, then evidence of schizophrenic

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patients' inability to mount an appropriate immune response
(especially to viral infections) would support the theory.
Additionally, the authors suggested that determination of an
autoimmune response (immune response against one's own cells
or proteins) against neural tissue in schizophrenic
patients, would lend some support for the theory (Pert et
al., 1988). Autoimmune responses against neural tissue
would be a means to eliminate the virally damaged neural
tissue.

Torrey (1991) also presented genetic predisposition of
schizophrenia in terms of a susceptibility to a viral
infection. However in Torrey's viral theory, the
predisposition was anatomical and not immunological as Pert
and colleagues (1988) proposed. Torrey (1991) suggested
that a virus during infancy infects the brain through the
maxillary nerve and trigeminal ganglion. Thus genetic
predisposition may be explained by anatomical differences
which allow greater viral access through these pathways.
Furthermore, since the medial temporal cortex and
hippocampus are in close proximity to the trigeminal
ganglion, Torrey argued that abnormalities found in these
regions in schizophrenics can be explained by their close
proximity to the trigeminal ganglion (Torrey, 1991). These
regions would be most affected by a viral infection entering
the brain via the trigeminal ganglion. Finally, Torrey
argued that the virus remains latent until reactivated by

hormonal changes during puberty or by a reinfection in early adulthood.

While this theory described a specific mechanism for viral involvement in schizophrenia, it did not easily lend itself to testing. Torrey (1991) suggested that studies investigating the effects of viral infections on the trigeminal nerve and foramen rotundum would begin determining whether viruses can alter their function or structure. Additionally while a latent virus is proposed, identification of a non-specific virus in schizophrenic patients could prove very difficult. Post-mortem studies of maxillary nerve and trigeminal ganglion in schizophrenics could also determine whether any anatomical differences in these structures exist.

Conrad and Scheibel (1987) presented one of the better developed viral theories for schizophrenia. They argued that hippocampal cell disarray in schizophrenic patients can be explained by a pre-natal viral infection. Viruses which are dangerous during pregnancy all have neuroamindase, an enzyme which affects siliac acid, and siliac acid is related to cell binding properties of cell-adhesion molecules (Conrad & Scheibel, 1987). Abnormalities in this pathway would disturb proper migration of developing neurons. Therefore, maternal infection with viruses which contain neuraminidase may significantly affect migration of developing neurons into the hippocampus. The genetic factor

may be reduced immunocompetence in the mother, which allows the virus to infect the fetus (Conrad & Scheibel, 1987). The authors noted that the relationship between hippocampal cell disarray and clinical symptomatology still needed to be evaluated.

The most obvious method of testing this theory would be to infect animals with various viruses and note whether any neuronal migration patterns or hippocampal cell disarray occurs. This would not, however, establish any relationship between neuropathology and behavioral disorder. Further studies would be needed to determine whether the hippocampal cell disarray was simply a biological marker for schizophrenia or whether it was part of the etiology (Conrad & Scheibel, 1987).

A multifactor theory of schizophrenia was presented by Adler and Waldo (1991). This theory proposed that a "schizotaxic factor" is the primary factor for schizophrenia. The authors determined that the schizotaxic factor is a genetically determined deficit in auditory gating (Adler & Waldo, 1991). In the presence of a secondary deficit, the schizotaxic factor manifests itself into schizophrenia. Adler and Waldo proposed that the secondary deficit can be a variety of factors including a virus or birth complications. The authors favored Torrey's (Torrey, 1991) viral theory as an explanation for a secondary factor.

This theory would require the same types of studies as those suggested for Torrey's (1991) viral hypothesis. In addition, the authors suggested family studies of auditory gating deficits (Adler & Waldo, 1991), since family members without schizophrenia may demonstrate the auditory deficits alone.

Crow (1987) proposed a retrovirus/transposon theory for schizophrenia. According to this theory, schizophrenia is the result of a gene inherited from an affected or predisposed parent or an integration/transposition event early in development. The integration/transposition event causes the rearrangement of genes, which results in schizophrenia. Testing this theory would require the identification of an aberrant genetic sequence, which many investigators are attempting.

Finally, Crow, Taylor, and Tyrell (1986) discussed the possible role of the measles virus in the etiology of schizophrenia. They noted that measles can persist for long periods of time eventually leading to an excess of antibodies and neurological damage. Knight, Knight, and Pert (1987) commented that viruses such as mumps, measles, and echoviruses are known to have "encephalitogenic potential" which could lead to mental illness. Viruses could, therefore, influence the schizophrenia disease process especially in individuals whose immune responses have been altered by intrauterine infection (Knight et al.,

1987). The authors provided no further discussion of mechanisms or sites of action, which complicates validation of the theory. Studies of measles and other viral antibody titres may be helpful in developing the theory.

In summary, while several viral theories for schizophrenia have been proposed, most of them would be difficult to support because the proposed viral mechanisms do not easily lend themselves to testing. Most studies of immunological abnormalities in schizophrenia could help to support a general viral theory similar to the one proposed by Pert and colleagues (Pert et al., 1988). These studies include those on autoimmunity and cell mediated and humoral immunity. Studies on viral antibody titres could be used to further develop the theories proposed by Crow et al. (1986) and Knight et al. (1987).

IMMUNOLOGICAL ABNORMALITIES

Autoimmunity and Viral Antibody Titre Studies.
Autoimmunity is an immune reaction to the brain's (or other
tissue's) own proteins or cells (Stites et al., 1987). An
individual's immune system does not recognize other cells or
proteins as 'self', and an immune reaction is mounted
against them. This immune reaction is usually elicited by
autoantibodies. These antibodies (which are proteins)
attach themselves to "self" receptors instead of foreign
receptors of invading cells.

In one of the most controversial studies, Health and
colleagues (Heath & Krupp, 1967; Heath, Krupp, Byers, &
Liljekvist, 1967) reported finding a unique immunoglobulin
(Ig), "taraxein", in the blood of acute schizophrenics which
was not found in the blood of any of the control subjects.
When isolated and injected into monkeys and human
volunteers, behavioral changes lasting 1-2 hours were
reported. These changes included decreased flexibility of
limbs, thought disturbances, and auditory hallucinations in
the human subjects. Heath and colleagues also reported EEG
abnormalities in the septum and caudate nucleus of both
animal and human subjects after injections of taraxein.

After several attempted replications by independent
laboratories, Bergen, Grinspoon, Pyle, Martinez, and Pennell
(1980) isolated the taraxein protein and replicated Health's
EEG findings. However, Bergen and his colleagues found that

while there was more than a 25% positive reaction for taraxein in the schizophrenic patients' tested, approximately 8% of the control subjects also tested positive for the protein. Therefore, taraxein did seem to exist and have some EEG effects, but it did not seem to be specific to schizophrenia, and as a result, it alone could not cause the disorder.

There have also been several reports of autoantibodies in schizophrenics. DeLisi, et al. (1985) reported finding anti-brain autoantibodies in some hospitalized, DSM-III diagnosed schizophrenics. 18% of serum samples from hospitalized psychotic patients, including schizophrenics, affective disorder, and Huntington's Chorea patients, had IgG (an antibody class) binding to normal human brain membranes. Since the IgG was not specific to schizophrenics, the autoantibodies alone could not account for the disorder.

Kagomi, et al. (1987) found sera from chronic, hospitalized schizophrenics to be cytotoxic to normal human lymphocytes (white blood cells). The results were present in 8 of 13 male and 4 of 13 female schizophrenics. One female control showed the cytotoxic effect. Additionally, the anti-lymphocyte autoantibody was of the IgG class, and it was cross-reactive with brain tissue. Therefore these autoantibodies were not only toxic to lymphocytes but also brain tissue.

Baron, Stern, Anavi, and Witz (1977) reported a 43% positive reaction in schizophrenics compared to controls for antibrain antibodies to normal human septum tissue. Pandey, Gupta, and Chaturvedi, (1981) replicated Baron's findings using a less sensitive hemagglutin assay. However, since no other psychiatric groups were examined in these latter studies, it was not clear whether the antibodies were specific to schizophrenia.

Antibody titre tests determine the amount of antibodies available to bind with a specific antigen (a substance that elicits an immune response) (Kimball, 1986). These tests are very useful in determining a person's ability to mount an immune response against common viruses such as measles and mumps.

King, et al. (1985) reported significantly lower cerebral spinal fluid (CSF) IgG and measles antibody titres in schizophrenics compared to controls. Additionally, CSF/serum ratios for measles, mumps, rubella, and IgG were significantly lower than controls. Mumps antibody titre was also significantly lower in hospitalized schizophrenics compared to controls. Males had an overall lower antibody titre compared to females across all groups. The authors suggested that these findings imply an impaired immune response, and that a perinatal or childhood viral infection of the CNS, particularly of mumps or measles, might contribute to the psychiatric outcome.

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In summary, there was evidence of autoimmune abnormalities in schizophrenics, especially antibrain autoantibodies, which may support a viral theory of schizophrenia. Schizophrenics also had lower antibody titres to some viral infections such as mumps and measles. However, these differences were only reported in a subgroup of the schizophrenic patients. Kagomi, et al. (1987), and Baron, et al. (1977) found less than 50% of their patients had autoantibodies. While King, et al. (1985) reported significant group differences between hospitalized patients and controls, there were some patients that did not differ from normal individuals in the measles antibody titre. Additionally, these results did not suggest whether the immunological differences were a result of the schizophrenia or related to the etiology.

Cell Mediated Immunity. Studies measuring T-cell function also have implications to a viral etiology of schizophrenia. One of the primary functions of T-cells, especially Tc (T-cytotoxic) is to eliminate viruses and virus infected cells (Bellanti, 1984). As a result, an alteration in the number or response of these cells could be indicative of a persistent viral infection, or could enable a virus to multiply unchecked. Additionally, T-suppressor cells (Ts) which suppress antibody synthesis by B cells or reactions of other T effector cells have been implicated in autoimmunity (Stites, Stobo, & Wells, 1987). Depletion of

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these cells results in a highly significant and spontaneous autoantibody (or autoimmune) response (Stites et al., 1987).

Vartanina, Kolyaskina, Lozovsky, Burbaeva, and Ignatov (1978) reported a significant increase in the proportion of B lymphocytes (cells which produce antibodies) for schizophrenics compared to normals. Additionally, the number of T lymphocytes capable for responding to foreign cells (sheep red blood cells) was significantly reduced in schizophrenics compared to controls. Vartanina and colleagues (1978) found a significantly higher level of antithymic antibodies in schizophrenics which may in part explain the low levels of T-cells since these cells originate from the thymus.

Decreased numbers of responding T lymphocytes were also reported by Kolyaskina (1983). The proliferative activity of T-cells in response to T-cell mitogens (substances, usually foreign, that induce activation of lymphocytes) was also significantly decreased in the schizophrenic group as was the proportion of T-cells responding to the mitogens. The author concluded that not only was the number of lymphocytes responding reduced in schizophrenics, but the response had unspecified "peculiarities" (Kolyaskina, 1983). Finally, T-suppressor cell subpopulations were reduced by approximately 40% when compared to healthy subjects.

Bessler, et al. (1987) found no differences in total

white blood cells (WBC) or T rosetting (T-cells which group or cluster around a foreign substance) cells in a group of medication free (2 weeks) hospitalized, DSM-III diagnosed schizophrenics. But like Kolyaskina (1983), they did find a significantly decreased number of Ts cells.

There have been a few studies of cell mediated immunity in schizophrenia that investigated the role of neuroleptics. Coffey, Sullivan, and Rice (1983) found no significant differences in the total number of lymphocytes between hospitalized, DSM-III and Research Diagnostic Criteria diagnosed schizophrenics and a control group, but they did find a significantly decreased percentage of T lymphocytes in schizophrenic patients with a prior history of neuroleptic treatment. Half of this group was on some type of neuroleptic medication and half was not; both groups had a low response. The percentage of T lymphocytes was also significantly decreased in a smaller group of drug free schizophrenics who had never been on any neuroleptic treatment. Therefore, the decreased number of T lymphocytes does not seem to be related to neuroleptic use.

DeLisi and Wyatt (1982) had contradictory results in cell mediated responses to those of Coffey and colleagues (Coffey et al., 1983). Chronic hospitalized schizophrenics (diagnosis based on Research Diagnostic Criteria) were used in their study; seven had been drug free for at least one month, and the remaining 31 were medicated on "stabilized"

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doses of neuroleptic medication. The schizophrenic patients

had significantly <u>higher</u> T and B cell percentages when

compared to controls, but there was still no significant

difference between the medicated and nonmedicated patients.

B-cell percentages were also significantly correlated with

IgG levels. DeLisi, Goodman, Neckers, & Wyatt (1982) also

reported an increase in B and T cell proportions as well as

an increased Ts ratios in hospitalized, DSM-III diagnosed

schizophrenics. There was no significant difference between

medicated and nonmedicated (for 1 month) patients. One

difference between this and the Coffey et al. (1983) study

is that the former study did not have a sample of

schizophrenics who had never been medicated.

Natural Killer cell (NK) activity also has implications

for the viral hypothesis since NK cells have some antiviral

function (Stites et al., 1987). DeLisi, Ortaldo, Maluish,

and Wyatt (1983) examined NK activity in 27 chronic,

hospitalized, DSM-III diagnosed schizophrenics. While they

did not report any significant mean differences between the

schizophrenics and the controls, they did find that 40% of

the patient group had some alteration of in vitro

mononuclear cell function (either decreased ability of NK to

lyse tumor cells or decreased ability of mononuclear cell

[usually a phagocytic cell] to lyse a virally induced

tumor). Six patients were medication free for at least one

month, and four patients were studied on and off

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medications. The authors state that different medications
may have different effects on immune response. They also
note that one month may not be a sufficient amount of time
to reverse the immunological effects of neuroleptics.

Urch, Muller, Aschauer, Resch, and Zielinksi (1988)
also examined differences in NK activity and antibody
dependent cytotoxicity (ADCC) in medicated and unmedicated
DSM-III diagnosed schizophrenics. The unmedicated patients
had significantly lower NK response compared to controls;
the medicated patients did not show this difference. The
dose of neuroleptics or the addition of antidepressants did
not influence immune response results. Schizophrenics on
combined neuroleptic and lithium treatments had NK and ADCC
results similar to the unmedicated group. The presence of
10% sera from unmedicated schizophrenics significantly
inhibited in vitro ADCC response. 20% sera significantly
inhibited both NK and ADCC in vitro responses. Both
concentrations of sera from treated schizophrenics inhibited
ADCC response. These results, like those of DeLisi, et al.
(1983), found decreased NK cell activity in schizophrenics.

Interestingly, the Urch, et al. (1988) study indicated
that never-medicated patients had the lower NK response, and
their sera, like some of treated patients, seems to have a
factor which inhibits ADCC and NK activity. Therefore, the
immunosuppression of cell mediated responses does not seem
to be entirely due to neuroleptics. The increased B and T

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cell proportions (DeLisi, Goodman, Neckers, & Wyatt 1982; DeLisi & Wyatt, 1982) may be due to an inhibition of this factor by the neuroleptics. As a result, medication use and duration since cessation are two additional factors which must be considered when evaluating the literature. Additionally, further studies attempting to identify this factor in the sera should be pursued.

These studies indicated there may be cell-mediated abnormalities which could suggest a viral involvement in schizophrenia. Schizophrenics as a group seem to have decreased numbers of Ts and Tc cells compared to normals. The decreased Tc may however be due to increased antithymic auto-antibodies. Also, Kolyaskina (1983) and Vartanina, et al. (1978) did not indicate whether patients were on medications and what type of diagnostic criteria was used. Therefore, conclusions drawn from these studies must be made with caution. The studies which did consider neuroleptic use found NK activity was decreased in patients who had never been medicated. Additionally there may be a factor in the schizophrenic's sera which inhibits some cell mediated immunity such as ADCC and NK activity, and neuroleptics may inhibit this factor. Also, measurements of total cell populations (i.e. total WBC or total T-cells) showed no differences between groups, while subtypes of WBC differed. Therefore, functional cell assays and/or cell subtype quantification is necessary to accurately determine

abnormalities.

Humoral Immunity. Humoral (pertaining to molecules in
solution) immunity is the immune response comprised
primarily of proteins, such as antibodies, which travel
through the circulatory system (Stites et al., 1987). There
are five types or classes of immunoglobulins. IgA is the
predominant class found in secretions. IgD is present on B
lymphocytes (cells that produce antibodies). IgE is
involved in immediate hypersensitivity reactions (such as
allergic reactions to a bee sting). IgG is the predominant
class present in human serum, and it can bind to macrophage
cells and function in a cytotoxic fashion (Stites et al.,
1987). Finally, IgM is the predominant class present in
early immune response. Humoral immunity is relevant to
supporting a viral theory for schizophrenia since low levels
of antibodies such as IgG and IgM may indicate a chronic
viral infection while high levels may indicate an acute
infection (DeLisi, 1987).

Several studies have reported elevations in
immunoglobulin levels. Legros, Mendlewicz, and Wybran
(1985) reported significantly higher serum IgM levels in a
hospitalized psychiatric group (schizophrenics, unipolar
depression, and bipolar depression) compared to normal
controls. However, the bipolar group had higher IgM levels
compared to the schizophrenic and unipolar depressive
groups. Torrey, et al. (1978) reported elevations in IgG

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and measles antibody for 6 of 17 multiple admission hospitalized schizophrenics (diagnosis followed Research Diagnostic Criteria), but no overall significant differences between schizophrenics and controls on IgG, IgA, or IgM were detected. Amkraut, Solomon, Allansmith, McClellan, and Rappaport (1973) reported significantly increased levels of IgG, IgA, and IgM in hospitalized schizophrenics. Patients had not been on phenothiazines for one month or given electric convulsive shock treatment for six months. Solomon, Allansmith, McClellan, and Amkraut (1969) found significantly higher IgG, IgA, and IgM levels in a group of hospitalized psychiatric patients (schizophrenia, depression, character disorders, neurosis, alcoholism and migraine) compared to normal controls. However, schizophrenics alone did not have significantly different Ig (immunoglobulin) levels compared to the non-schizophrenic patients. Also, no standardized diagnostic criteria was used, all diagnosis were made by an "experienced psychiatrist" (p. 274).

Amkraut, et al. (1973) reported a significant relationship between IgG and IgA and improvement in newly admitted, acutely ill schizophrenics. Patients with immunoglobulin (Ig) levels below the median were more likely to show improvement during hospitalization than those with Ig levels above the median. Pulkkinen (1980) found that IgM was significantly correlated with psychopathology.

Withdrawn patients had the highest IgM levels.
Additionally, IgM was positively correlated with withdrawal
symptoms on first admission and with the mean of these
symptoms during the entire hospitalization period. IgA and
IgM significantly decreased with an increased length of
hospitalization. Ig values were highest in patients with
short hospitalization periods, and infectious diseases
increased with the duration of illness.

Therefore while Amkraut, et al. (1973) reported low IgG
and IgA levels related to improvement during
hospitalization, Pulkkinen (1980) showed increased IgA and
IgM levels at the beginning of treatment correlated with
short hospitalization periods.

Strahilevitz, Fleischman, Fischer, Harris, and
Narasimhachari (1976) reported the effects of sex and race
on Ig levels in schizophrenics. They found significantly
higher IgA levels in DSM-III diagnosed schizophrenic women
compared to control women and in schizophrenic blacks
compared to both schizophrenic whites and control blacks.
IgD was higher in schizophrenic blacks compared to
schizophrenic whites. IgG was higher in schizophrenics with
a positive phenothiazine response in the urine compared to
schizophrenics with a negative response. Fourteen patients
were negative for phenothiazines using a urine analysis.
Three patients were positive, and 1 showed only trace
amounts. The authors suggested that since there was no

significant difference between black and white controls for
IgA or IgD, the differences between black and white patients
may be due to a "constitutional factor and/or environmental
factors between black and white schizophrenics" (p. 774).

Overall, these studies found increased IgM, IgA, and
IgG levels in schizophrenics. There was also differences
between black and white schizophrenic patients. Whether
these increased Ig levels are related to better prognosis or
shorter hospitalization is, however, not clear. The other
problem with these studies (except Legros et al., 1985 and
Strahilevitz, 1976) is that they did not use standardized
diagnostic criteria. As a result, homogeneity of the groups
may have been poor. Additionally, several studies seem to
indicate that the elevated Ig levels are not unique to
schizophrenics.

Bock (1978) compared Ig levels among schizophrenic,
endogenous depressed, demented, and control subjects. The
diagnostic criteria was not referenced, and there was no
mention of medications. The results indicated a
significantly decreased IgM level in the schizophrenics
compared to controls. No other groups showed this
difference. Using DSM-III diagnostic criteria, DeLisi,
King, and Targum (1984) compared Ig levels in hospitalized
depressives, schizophrenics, substance abusers, and
"miscellaneous" diagnosed patients. They found a
significant number of patients fell two standard deviations

below the normal levels of IgM. This was however not specific to schizophrenics. The results were not associated with medications or length of illness prior to admission. DeLisi, et al. (1981) again found significantly lower IgM as well as IgG and IgA in the CSF and sera of hospitalized, chronic schizophrenics when compared to controls (diagnosis based on Research Diagnostic Criteria). Additionally, CSF and plasma IgA and IgM levels were positively correlated in the schizophrenics. The patients had been off medications for approximately 3 weeks, but all had a history of neuroleptic treatment. Bock, Weeke, and Rafaelsen (1970) also reported a low IgM level and a normal IgA level compared to controls. All patients had been unmedicated for one month, and samples were drawn two weeks after hospitalization.

Zarrabi, et al. (1979) found significant correlations between neuroleptic use and immunological abnormalities in chronic hospitalized schizophrenics (diagnostic criteria not given). Additionally, serum IgM levels in schizophrenics who had been on chlorpromazine (CPZ) or CPZ plus another drug for more than 2 1/2 years (Groups A and B) were significantly higher than both patients treated for less than 2 1/2 years on CPZ or another drug and controls. Approximately 40% of the patients in the longer treated groups also had antibody titres to native DNA (autoantibodies).

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Goldstein, et al. (1980) reported several immunological effects of neuroleptics both in rodent cells and in schizophrenic patients. CPZ inhibited the production of IgM in murine (rodent) cells reacting to sheep red blood cells (SRBC). Additionally, secondary antibody response (24-48 hours after challenge) seems to be less sensitive to CPZ than the primary response (0-24 hours). Therefore, it seems that once cells have reached a critical point they are no longer sensitive to CPZ. Goldstein et al. (1980) also found antibody formation to SRBC was 95% inhibited in the cells of CPZ (10 mg/kg daily for 21 days) treated animals.

Immunological response of 26 schizophrenics on a 28-day CPZ treatment (400-1200 mg/day) revealed an increase in all mitogen (Con-A, Pokeweed mitogen [PWM], and PHA) responses on day 14 (Goldstein et al., 1980). Schizophrenics also had a mean anti-thymocyte cytotoxicity (autoantibody response for self T-cells) of 45.5% (controls had a surprising high 30.4%). This value dropped to 37.2% after 28 days of CPZ treatment. While the authors could not explain the increased mitogen responses, they did note that the other immunosuppressive effects of CPZ both in rodent cells and in schizophrenics was consistent with other reported data.

In summary, earlier humoral immunity studies which did not consider medication status found consistently higher Ig levels while later studies which did consider medication status reported decreases. However the role of medications

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in immunological responses of schizophrenic patients is not clear since some studies reported decreased Ig responses in patients with a history of neuroleptic use but currently off medications (Bock et al., 1970; DeLisi et al., 1981), and other studies (Zarrabi et al., 1979) reported increases in Ig levels with neuroleptic use. Additionally, one study (DeLisi et al., 1984) reported no association between immune response and neuroleptic use.

The effects of medication may be more complicated than simply medicated versus non-medicated. Type of medication alone, as well as in conjunction with duration of illness and duration of use may effect immunological responses. Nevertheless, it does seem clear that neuroleptics do effect some immunological measures (Goldstein et al., 1980), and some measures are depressed in schizophrenics despite neuroleptic use. What is not clear, is how many of the immunological abnormalities reported in schizophrenics were due to confounding factors such as neuroleptic treatment.

IMPLICATIONS FOR FUTURE STUDIES

This review clearly indicated that immunological abnormalities in some schizophrenic patients do exist. Furthermore, some responses were depressed in never medicated patients (such as T cell level). However, to accurately assess the role of immunological abnormalities in schizophrenia and to test any of the viral hypotheses presented, stringent methodological procedures in well

designed studies will be required to control for the effects of potential confounding variables.

It seems imperative that studies use a standardized diagnostic criteria such as DSM-IIIR, Research Diagnostic Criteria, or the International Diagnostic Criteria (ICD). Studies using these diagnostic criteria will significantly reduce the chance of confounding results because of mixed diagnostic groups.

Since some studies found no differences between medicated and non-medicated patients while other studies reported differences with respect to duration of CPZ use, the type of medication and dose should be considered and examined for any effects on immunological responses.

Duration of illness may be confounded by age. Also since there have been reports of age effects on immune responses in non-psychiatric (Oyeyinka, 1984; Weksler, 1983) and psychiatric populations (Scheifer et al., 1989), age may be a more appropriate variable to examine.

The studies reviewed above did not consider the possibility that immunological abnormalities in schizophrenia may be related to severity of illness. This would be possible for two reasons. First, the more severely ill patients may also be more stressed, and since stress can effect immune response (see below), severely ill patients may have lower immune responses compared to less symptomatic or ill patients. Second, immunological abnormalities may

not necessarily be trait markers. They may change with changing phases of the illness. For example, if immunological abnormalities are state markers, they may change during decompensation. For both these reasons, severity of illness is an important variable to examine in these types of studies.

Gender and ethnicity must also be investigated. It is clear from the Strahilevitz, et al. (1976) study that there may be distinct ethnic and gender differences for immunological responses in schizophrenics. However, socio-economic status of the patients should also be examined since studies have indicated that racial differences in the occurrence of mental illness can be eliminated by controlling for socio-economic status (for review see Williams, 1986). Therefore, ethnic differences in immunological responses in schizophrenics may also be explained by socio-economic status. This will require further investigation.

There also seem to be differences based on the type of immunological parameters being measured. Schizophrenics do not have overwhelming immunological abnormalities; they are subtle. For example, total WBC and T-cell levels may not be different, but subpopulation and functional responses may. Therefore immunological measures should focus on immunoglobulin and T-cell subpopulations, and on functional assays.

An important consideration the reviewed studies did not consider was the role of stress on patients' immunological response. Stress has been shown to decrease both specific immune responses and health status in animals (Monjan, 1981) and humans (Palmblad, 1981) (also see Ader, 1981 for a complete review). Cortisol is secreted heavily during periods of stress (Guyton, 1986), and cortisol can depress certain immune functions (see Ader, 1981 for review). Therefore measures of stress and cortisol should also be examined in studies of immune response in schizophrenia.

The specificity of immunological abnormalities in schizophrenic patients also needs to be addressed. There have been reports of increased cortisol levels (Asnis & Lemus, 1987) and immunological abnormalities (Stein, Miller, & Trestman, 1991) in affective disorder patients when compared to controls and other psychiatric groups. However, Stein and colleagues note that many immunological studies are flawed by poor methodology (Stein et al., 1991). Therefore it would be interesting to compare immunological and cortisol responses of schizophrenic and affective disorder patients. If they are similar, then the viral hypothesis specifically and uniquely for schizophrenia would not be supported. Additionally, comparisons between a schizophrenic group and a group of chronically medically ill patients would determine whether immunological abnormalities are specific to psychiatric patients or whether they are

common to groups of chronically ill patients, whether psychiatric or medical.

Similar immunological responses between the schizophrenic, affective disorder, and medically ill groups would indicate a common process, perhaps stress associated with having a chronic illness.

In summary, it is apparent that conclusions regarding the role of immunological abnormalities in the etiology of schizophrenia will be determined only after more methodologically stringent studies are conducted.

CHAPTER 2

STUDY METHODS

PURPOSE

The purpose of this study was to replicate and extend previously reported findings of immunological abnormalities in schizophrenia using proper control groups and examining the effects of possible confounding variables. Immunological responses of a carefully diagnosed group of schizophrenic patients were compared to those of another psychiatrically ill group (affective disorder patients), a chronic medically ill group (hypertensive patients), and a healthy age, sex, and ethnically matched control group. The affective disorder group was selected because immunological abnormalities have been reported in these patients (see Chapter 1) and comparisons between the two psychiatric groups would determine whether any immunological differences in the schizophrenic group are specific to schizophrenia or are present in one or more other serious psychiatric illnesses.

A chronic medically ill group was also used as a comparison group for the schizophrenic patients. This comparison would determine whether any immunological abnormalities were specific to psychiatric patients or whether they also occurred in chronically ill medical patients. Hypertensive patients were chosen because they had the least chance of immunologic aetiology or involvement (compared to other chronically ill patients such as asthmatics.

Finally, the healthy control group was matched to the schizophrenic group by gender, age, and ethnicity. This group would allow comparisons between the schizophrenic group's immune function and normal immune status. The control group was matched on gender, age, and ethnicity since these variables had been shown to affect immune responses (see Chapter 1).

The study also investigated the effects of socio-economic status (income and type of medical insurance type), recent stress (change in life events, cortisol level, and level of depression), neuroleptic medication dose, and severity of illness on immunological measures because they may also influence immune response in schizophrenics (see Chapter 1). While socio-economic status (SES) is often defined by education and income, Liberatos, Link & Kelsey (1988) suggested using multiple SES indicators which are appropriate to the specific study question. Therefore, the current study included income and insurance type as the SES variables. Income alone is not a good measure of SES (Liberatos, Link, & Kelsey, 1988), however income is a good SES variable in predicting health status (House, Kessler & Herzog, 1990). The author believed that the additional variable to accompany income should be one which best predicted health behaviors. Therefore type of medical insurance was used since the author believed that people with insurance would be more likely to seek out medical help than people without medical insurance.

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The effects of medication dose and severity of illness were examined in the schizophrenic group alone since they were the primary group of interest. Severity of illness was examined in two ways. First, baseline severity of all schizophrenic patients was examined for its effects on the immune parameters. Second, immune response changes with relapse or decompensation were examined.

HYPOTHESES

Based on findings from previous studies, the schizophrenic patients were hypothesized to have significantly lower levels of T cells, IgM and IgG compared to the control group (Hypothesis 1). Previous studies suggested that neuroleptic medication dose did not significantly effect immunological levels of the schizophrenic patients, therefore this variable was hypothesized not to have any effect on the immunological responses of this group (Hypothesis 2). There were no directional hypotheses for age, gender, and ethnicity since part of the purpose of this study was to explore their effects on the immunological responses of schizophrenics. Finally, the immune responses of the schizophrenic patients were expected to decrease with increased severity of illness since the stress level might increase as the severity of illness increases. Therefore, the immune responses were hypothesized to decrease with increased baseline level of severity (Hypothesis 3) and with relapse (Hypothesis 4). The effects of relapse on cortisol were also examined to determine

whether any changes in immune response were associated with changes in cortisol.

The affective disorder group was hypothesized to have higher cortisol levels and therefore potentially lower immune measures (because of the effects of cortisol on immune response, see Chapter 1) than the healthy control group (Hypothesis 5).

STUDY DESIGN

T suppressor/cytotoxic cell (Ts/c), immunoglobulin G (IgG), immunoglobulin M (IgM), and cortisol levels among four groups were analyzed. Ts/c cell levels were measured because T-cytotoxic and T-suppressor cells both have the same CD8+ receptor for identification and quantification, and both are indicative of cellular immune function (Stites et al., 1987). IgG and IgM were the antibodies measured since abnormal levels may indicate a viral infection (DeLisi, 1987). Gender, age, ethnicity, socioeconomic status, stress, and duration and severity of illness were also examined to determine any association they may have with immune status.

SAMPLE SIZE

Sample size was based on a power analysis. The effect sizes (Cohen & Cohen, 1983) in similar studies examining T-suppressor cell, total T-cell, and IgM levels were surprisingly high, ranging from 2.78 (Coffey et al., 1983) to .365 (DeLisi et al., 1984). This was predominately due to small variance within the groups. Based on these results, a

conservative power analysis was conducted using an effect size which was considerably smaller than the .365 found in the DeLisi study (DeLisi, et al., 1984). This conservative effect size of .25 was used with an alpha = .05, power = .75, and k_b = 4 (groups) to determine that 40 subjects per group would be required. However, only 115 subjects agreed to participate in the study. With this sample size, the power to detect the small, conservative effect size of .25 is approximately .60. However our ability to detect the smallest observed effect size from previous studies (.365) is still high at approximately .85.

SUBJECTS AND ELIGIBILITY CRITERIA

The schizophrenic patients were recruited from the Treatment Strategies in Schizophrenia (TSS) study clinic at San Francisco General Hospital and the Sunset Day Treatment Center in San Francisco.

There were several inclusion criteria for this group. Patients were required to have a DSM-IIIR diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder. No patients with a dual diagnosis of serious mental illness and substance abuse were eligible. The effects of various medications on immune response were controlled for by only using patients taking Fluphenazine or no neuroleptic medication for at least 2 weeks. Patients who had any recent (1 week) casual use of street drugs (cocaine, marijuana, or others) or recent heavy substance abuse (addiction to drugs or

alcohol) in the last 6 months were excluded, since drug use might affect health status and immune response. The study did not control for the potential effects of tobacco or nicotine. Drug use information was based solely on self and staff reports. Patients with a major medical illness or injury (asthma, major surgery, blood transfusions) in the last 6 months were also excluded since these conditions could also affect the immune response. The majority of schizophrenic patients were on anti-parkinsonian medication such as benzotropine mesylate (Cogentin) or trihexyphenidyl HCL (Artane), benzodiazapines such as lorazepam (Ativan), or anti-histamines such as diphenhydramine hydrochloride (Benadryl). Therefore use of these medications could not be an exclusion criterion.

The affective disorder group was comprised of patients with a DSM-IIIR diagnosis of major depression or bipolar affective disorder taking only lithium or no medications for at least 2 weeks. The same drug and medical history criteria used for the schizophrenic patients were applied to this group. These patients were recruited from various sources including inpatients of the Behavioral Neuroscience Unit at the Langley Porter Psychiatric Institute, University of California San Francisco, and the San Francisco Manic Depressive Association.

Among the hypertensive patients, only non-medicated patients or those on diuretics and/or Angiotensin enzyme

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inhibitors were included in the study because these
medications are not known have major effects on the
sympathetic nervous system. Persons on other hypertensive
medications such as beta blockers or calcium channel blockers
were excluded because these medications could influence the
immune system (Hall & Goldstein, 1981). Hypertensive patients
with a history of psychiatric illness or current substance
abuse were excluded. This information was obtained from
medical staff, chart, and patient self reports. Patients were
recruited from the Hypertension Clinic at San Francisco
General Hospital.

Persons with a history of psychiatric disorders and those
taking prescription medications were excluded from
participating as control subjects, as were persons with any
current illness such as asthma, and hypertension. Control
subjects were recruited among staff members at SFGH and U.C.
San Francisco, via bulletin board notices and personal
contacts.

BEHAVIORAL MEASURES (See Appendix 1)

Medical History Form. This is a standard history form
used by clinics at San Francisco General Hospital. It
includes educational and occupational sections which were
supplemented by questions on medical insurance and average
monthly income. This additional information was used to
determine socioeconomic status (SES). Items in the additional
illnesses or problems section, the major hospitalization

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section, the test and immunization section, and the medication section were used to determine whether participants had any existing or recent medical condition which would exclude them from the study, such as recent injury, illness or substance abuse.

Life Experiences Survey. This is a modified version of the Sarason, Johnson, & Siegel (1978) Life Experiences Survey which asks subjects to determine whether any of 60 life events have occurred to them in the last 3 months. Subjects are asked to determine whether each event was positive or negative and how much of an effect the event had on their life (rated from 1 to 7). This modified version also has a section for subjects to add any conditions they considered stressful in the last 6 months. Ratings by the subjects from 1 to 7 are also made on these situations. This survey was used because life experiences are an established methodological tool for measuring psychological stress (Dohrenwend et al., 1982). Total Life Event Survey Scale score was used in the analyses.

Beck Depression Inventory. This version of the Beck Depression Inventory (BDI) (Beck, Rush, Shaw, & Emery, 1979) is a 21 item scale developed to determine the severity of depressive symptoms in adults and adolescents. The scale was chosen because it is a standard, reliable instrument for measuring clinical depression. Total BDI score was entered into the analyses.

Brief Psychiatric Rating Scale. The Brief Psychiatric

Rating Scale (BPRS), which incorporates the Clinical Global Impressions (CGI) scale, is an extensively used measure of psychiatric symptoms with well established psychometric properties (Woerner, Mannuzza, & Kane, 1988). It consists of 18 symptom ratings and two global ratings of severity of illness and improvement (Overall & Gorham, 1962). Ratings on a seven point scale from not present to very severe are made on each item. The anchored version of the BPRS was used since it improves reliability (Woerner et al., 1988). This version of the BPRS provides brief definitions of each scale point response for each item.

All measures except the Brief Psychiatric Rating Scale (BPRS) were administered by the author. The BPRS was administered either by the author or a faculty psychiatrist, Mary Susan Hansen, M.D., University of California, San Francisco. When administered by the author a series of standard prompt questions developed for the multisite collaborative Treatment Strategies in Schizophrenia study (unpublished) were used (see appendix 1). Results obtained by the author were reviewed with Dr. Hansen for corroboration.

BIOLOGICAL MEASURES

T suppressor/cytotoxic cell. Analyses of Ts/c cells were performed by the U.C. San Francisco Immunology Laboratories. The cell levels were phenotyped using a monoclonal antibody (Becton Dickinson) which fluorescently tags the CD8+ antigens (receptors) on cells which are then sorted using fluorescent

activated cell sorting procedures. This analysis yields the percent of lymphocytes which are Ts/c cells.

Immunoglobulin G and Immunoglobulin M. IgG and IgM levels were determined using a radial immunodiffusion kit (Kallestad Diagnostics). 5 μl of subject's serum and laboratory standards were pipetted into wells surrounded by agarose gel containing a monospecific antiserum (to either IgG or IgM). The sample diffuses radially through the gel forming a precipitin ring (the area where the antigen-antibody complexing was at equivalence) with the antiserum. After 72 hours, ring diameters were measured in mm. Subject samples were assayed along with 3 control standards and 1 serum control. Kallestad Diagnostics reported intra-assay precision (percent coefficients of variation) for high, medium, and low samples as 4%, 5.2%, and 6.8% respectively for IgG, and 3.4%, 2.5%, and 4.2% for IgM. Interassay precision was 3.7%, 5.5%, and 7.5% respectively for IgG and, 4%, 5.9%, and 5.1% for IgM. The lowest detectable levels were reported as 4.6 and 4.5 mg/dl for IgG and IgM respectively. Average adult concentrations for IgG and IgM were reported as 1200 mg/dl and 100 mg/dl respectively (Kallestad Diagnostics).

Cortisol. Serum cortisol levels were measured using a radioimmunoassay kit (Kallestad Diagnostics). 20 μl samples were pipetted into tubes coated with cortisol antibody and incubated with an ^{125}I labelled cortisol derivative. The unlabelled cortisol then competes with the ^{125}I labelled

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cortisol for antibody binding sites. After aspiration, a gamma counter measured radioactivity remaining in the test tubes. The amount of radioactivity is inversely proportional to the amount of unlabelled cortisol in the sample. Subject samples were assayed with seven control standards and three serum controls. Serum controls for this assay are only stable for seven days in their liquid form (they are stable for several months in their lyophilized form). Therefore serum control samples were reconstituted and separated into many individual aliquots and frozen. Approximately one hour before assaying, a frozen aliquot was thawed for the procedure. When frozen, the serum controls are stable for several months. Kallestad Diagnostics reported intra-assay and interassay variability as between 3.9-7.1% and 2.9-7.1% respectively. The lowest detectable cortisol level with 95% confidence was 0.5 μg/dl. The average adult level for morning serum cortisol levels was 5-28 μg/dl (Kallestad Diagnostics).

PROCEDURES

When potential subjects were identified, the purpose and procedures of the study were explained to them by their primary clinician. Those interested in participating scheduled an intake appointment with the author. At this appointment, signed informed consent (see Appendix II) was obtained, and the medical history, Beck Depression Inventory, and Life Experience Survey were administered. The BPRS was also completed on schizophrenic subjects. Participants were

encouraged to respond accurately by emphasizing that any information given was strictly confidential. If subjects acknowledged use of any drugs, they were asked to quantify their consumption. If subjects reported a history of substance abuse or were current substance abusers they were excluded from the study. It is likely that self reported substance use resulted in underestimation of true incidence. However, self and staff reports were the only means of determining substance abuse since there were not sufficient funds available to conduct toxicology screening tests on all of the subjects.

A 15 cc blood sample was taken, with equal amounts drawn into heparinized and non-heparinized tubes. Blood samples were collected between 9:00 a.m. and noon to reduce fluctuations in cortisol levels due to circadian rhythms (Guyton, 1986). The blood sample in the non-heparinized tube was allowed to clot for no less than 30 minutes and no more than 60 minutes. The sample was then centrifuged at 4750 $\pm$ 50 RPM for 15 minutes. After centrifugation, the serum was removed and stored in four aliquots. The aliquots were placed in small plastic tubes (Sardstat Inc.) and frozen at $-20°C$. The samples were thawed and analyzed later for IgG, IgM, and cortisol. The sample in the heparinized tube was delivered to the U.C. San Francisco Immunology Laboratory for Ts/c cell analysis. These analyses were performed within 24 hours of drawing the blood sample.

Two blood samples were taken from a subsample of the schizophrenic patients. The first sample was taken when the schizophrenic patient was "stable" as defined by a score of 4 or less on five key items of the Brief Psychiatric Rating Scale (Unusual Thought Content, Hallucinatory Behavior, Grandiosity, Conceptual Disorganization, and Suspiciousness). The second blood sample was taken during a state of "Exacerbation" as defined by an increase of one scale point or more on any of the above scales.

The entire procedure took approximately 1 hour for ill subjects and 20-30 minutes for control subjects.

ANALYSES

Previous studies examining immunological abnormalities in schizophrenia primarily used t-tests or analysis of variance (ANOVA) to compare immunological measures among psychiatric groups and controls. This study employed these analyses but also compared them with more comprehensive multiple regression analyses which control the effects of confounding variables such as gender, age, ethnicity, and severity of illness on group differences in immunological measures. Therefore ANOVA and multiple regression analyses were conducted for each dependent measure (Ts/c, IgG, IgM, and cortisol). Results were presented in multiple regression format. Readers unfamiliar with this format should refer to footnote 1 in the Results Section.

Hypothesis 1. This hypothesis stated that schizophrenic

patients had significantly lower Ts/c, IgG, and IgM levels compared to the normal controls. The analyses included three one-way between groups ANOVAs with Ts/c, IgG, and IgM as dependent variables. The planned comparisons for the ANOVAs were coded such that the schizophrenic group was compared to the affective disorder, hypertensive, and control groups, respectively.

Three multiple regression models, one for Tc/s, IgG, and IgM, were also used to test the hypothesis that schizophrenic patients have significantly lower immune responses compared to control subjects. In addition these analyses determined whether any of the potential confounding variables such as gender, ethnicity, age, SES, and stress affected immune response in the various groups. The regression analysis (along with the ANOVA) would also determine whether any immunological differences were specific to schizophrenic patients or whether they occurred in other psychiatric and medically ill patients.

Hierarchical multiple regression analysis (Cohen & Cohen, 1983) were used , i.e sets of variables were entered into the regression in a predetermined logical order and tested for significance. Variables which temporally precede other variables were entered first; therefore demographic variables such as gender, ethnicity and age were entered before the SES and stress variables. The model I error term (Cohen & Cohen, 1983), which excludes from the error variance only the

variance associated with the variables already entered into the model, was used to test the significance of variables at each step.

Demographic variables such as sex, ethnicity, and age would determine whether immune function changes were accounted for by differences between males and females, whites versus non-whites, and younger versus older subjects. The SES (income and insurance) and stress (cortisol level, Life Experience Survey, and BECK score) variables tested for the main effects of these variables on immune status.

The group variables were entered after the stress variables. To determine whether schizophrenic patients had significantly lower immune responses, the schizophrenic group was compared to the other three groups in this regression model.

The interaction variables, Sex x Group, Ethnicity x Group and Age x Group, followed the group variables. The interactions revealed whether these variables affected immune responses differently for the schizophrenic groups compared to the other three groups.

Finally, the Cortisol x Group interactions were entered into the regression model. The set indicated whether any group differences in cortisol affected the immune responses.

Hypothesis 2 and 3. This analysis tested the hypotheses that the schizophrenic group's neuroleptic medication dose would not affect immune response, and immune response decreased with increased baseline severity of illness. A

hierarchical multiple regression analysis with model I error was also used to examine the effects of medication dose, and baseline severity and duration of illness on the immune measures within the schizophrenic group.

Hypothesis 4. This hypothesis stated that the immune responses of the schizophrenic patients decreased with relapse. A repeated measures ANOVA was performed to test the hypothesis. This analysis included patients immune response variables measured during stabilization and an exacerbation of symptoms (clinical decompensation). Therefore, the results of this analysis would determine whether any differences in immune response should be considered state or trait markers. Additionally, a repeated ANOVA for cortisol was conducted to determine whether any decreased immune responses with relapse were accompanied by increased cortisol levels. There was a small sample size (N = 10) since only 10 second blood samples were obtainable from decompensated schizophrenic patients.

Hypothesis 5. Hypothesis 5 stated that the cortisol levels of the affective disorder group were significantly higher compared to the other three groups. Since elevated cortisol levels decrease some immune responses (see Chapter 1), the immune responses of the affective disorder group were also compared to the other three groups.

One-way ANOVAs were conducted comparing the affective disorder group to the schizophrenic, hypertensive and control groups on cortisol, IgG, IgM, and Ts/c. Additionally,

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multiple regression analyses similar to those used for Hypothesis 1 were conducted for the dependent variables. However, for these regression analyses, the affective disorder group was compared to the other three groups (instead of having the schizophrenics compared to the other groups as with Hypothesis 1).

VARIABLE CODING

Many variables had to be recoded for the regression analyses. Ethnicity was coded so all groups were compared to a reference group (Dummy Coding). Two new variables were created for Black and "Other minority" such that the subject was coded "1" if in the ethnic subgroup and zero otherwise. Since White subjects were coded zero on both new variables, White became the reference group. When such a set of dummy variables is entered into a regression, the test of each variable is a test of whether the subgroup coded "1" on that variable (Black or Other, in this case) is different from the reference group (White). Sex and medical insurance were dichotomously coded because there were only two categories to compare: Female = 0 and Male = 1; Medicaid, Medicare, or private = 1 and none = 0. Thus the females were compared to the males, and the subjects with some type of medical insurance were compared to those who had none.

For the regression models, group was also dummy coded. For Hypothesis 1, group was coded so the schizophrenics (the reference group) were compared to the other groups. For

Hypothesis 5, the affective disorder group was the reference group, and the other three groups were compared to it.

REGRESSION MODEL SETS

Eight sets of variables were created for the hierarchical regression models for Tc/s, IgG, and IgM. **Set 1** included the demographic variables Sex, Age, Black, and Other Minority. **Set 2** represented SES and included Income and Insurance. **Set 3** included the stress variables: Beck Depression Inventory score, Life Experience Survey total score, and serum cortisol levels.

Set 4 included the group variables. For the regression models testing Hypothesis 1, group included the dummy coded variables representing schizophrenia versus affective disorder, schizophrenia versus hypertensive, and schizophrenia versus control. For the regression models testing Hypothesis 5, group included the dummy coded variables contrasting the affective disorder and other groups: affective versus schizophrenic, affective versus hypertensive, and affective versus control groups. **Set 5, 6, 7 and 8** were the interaction sets Sex x Group, Ethnicity x Group, Age x Group, and Cortisol x Group, respectively.

The sets for the cortisol regression analysis, testing Hypothesis 5, were the same as those for the immune response regression models. However, cortisol was not entered in the stress set (Set 3). Additionally Set 8, the Cortisol x Group interaction variables, was not entered into the regression

model.

The sets for the regression analyses testing Hypotheses
2 and 3 for the schizophrenic group alone were different from
the other regression models. **Set 1** for this analysis included
the demographic variables Sex, Age, Black and Other. **Set 2**
included the variable Duration (years since first
hospitalization). **Set 3** represented baseline severity of
illness and included baseline BPRS and Beck total scores. **Set
4** was fluphenazine dose (RX1).

CHAPTER 3

RESULTS

Results from the ANOVAs and multiple regression analyses were all presented in multiple regression format. Therefore the amount of variance accounted for by a set of variables (R^2) was presented, along with the degrees of freedom and F value for the significance test.[1] The squared semipartial correlations, sr^2, were presented for the ANOVA planned comparison results since they reflect the amount of variance accounted for by the individual variable, controlling for the other variables in the set.[2]

PRELIMINARY RESULTS

Correlational Analyses. Preliminary analyses were conducted among the independent variables to better understand their relationship. The results of these analyses indicated that age and sex were significantly related ($r = -0.32$, $p < .001$) indicating that female subjects tended to be older.

Other correlations revealed that total score on the Life

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[1] The sums of squares given in the ANOVAs were converted to R^2 using the formula given in Cohen & Cohen (p. 197, 1983). The formula for converting sums of squares into R^2 is as follows: $R^2 = $ Between SS/Total SS. The F ratio is the same regardless of whether results are presented in ANOVA or multiple regression format.

[2] The sr^2 was computed as follows (Cohen & Cohen, 1983, pp. 107):

$$sr^2 = \frac{t^2(1-R^2)}{n-k-1}$$

For software that reports F test of single-degree-of freedom variables, this is equivalent to the t^2 value.

Experience Survey increased when scores on the BPRS and Beck Depression Inventory increased ($r = .69$, $p < .0001$ and $r = .97$, $p < .0001$, respectively). Thus as psychological stress levels increased, psychotic (for the schizophrenic group) and depressive symptoms (for all subjects) increased. Additionally, a significant correlation ($r = .70$, $p < .0001$) between the Beck Depression Inventory Scale and the BPRS indicated that as schizophrenic psychotic symptoms increased, so did level of depression. The latter correlation may also have been due to the fact that the BPRS has a category for depressive symptomatology. Therefore depressive symptoms could have also increased total BPRS score.

The lack of correlation between the Life Experience Survey and serum cortisol levels ($r = -0.01$, $p = .89$) was unexpected since both were considered stress measures. This lack of correlation may be due to the fact that the Life Experience Survey measures stress which occurred during the last 3 months while cortisol secretion in response to stress is usually an immediate and acute response (Guyton, 1986). Therefore serum cortisol levels may have normalized by the time the Life Experience Survey was administered.

Demographic and Ethnic Distributions. The demographic distribution for the various groups (see Table 1) showed differences in age between the hypertensive patients and the other three groups. The hypertensive group was approximately 20 years older, on the average, than the schizophrenic,

affective disorder, and control groups.

Gender distributions were also different for the schizophrenic and control groups compared to the affective disorder and hypertensive groups (see Table 1). The latter two groups had an approximate 50-50 distribution of males to females. However the schizophrenic and control groups had approximately 80% males and 20 % females.

The ethnic distribution between the schizophrenic and control groups was approximately equal as anticipated. There were however differences in ethnic distribution among the affective disorder and hypertensive groups. The affective disorder group was predominately white (81%), with only 4 (19%) non-black ethnic patients. There were no black subjects in this group. Conversely, the hypertensive group was predominately black (50%) and other ethnicities (45%). Only two subjects (5%) were white.

Diagnostic Distribution for the Schizophrenic Group. The majority of patients in this group had a diagnosis of schizophrenia (N = 28). Only 1 subject had a diagnosis of schizoaffective disorder and 2 subjects had a diagnosis of schizophreniform disorder.

Immune and Cortisol Levels for the Groups. Figures 1 to 4 illustrate the mean immune and cortisol levels and standard errors for the four groups. The hypertensive group had the highest level of IgG (1691.21 mg/dl) compared to the schizophrenic (1411.83 mg/dl), affective disorder (1122.98

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mg/dl), and control groups (1270.94 mg/dl). The hypertensive group had a slightly higher IgM level compared to the schizophrenic, affective disorder, and control groups (214.64 versus 194.17, 188.86, and 194.40, respectively). The Ts/c cell levels were practically identical among the four group (see Figure 3). Finally, the affective disorder group had higher cortisol levels (15.36) compared to the schizophrenic (14.24), hypertensive (11.28), and control groups (12.88).

Cortisol Analyses. Cortisol was an important variable to examine since it influences immune response (see Chapter 1). The regression analyses testing Hypothesis 1 examined any main effects cortisol had on the immune responses, and differences in immune responses due to varying cortisol levels for the various groups. However to better understand relationships between cortisol and the independent variables, and group differences in cortisol, a one-way ANOVA and hierarchical regression model were conducted with cortisol as the dependent variable. These analyses had group represented as schizophrenic versus the other groups.

For the cortisol analyses, there was one extreme outlier in the affective disorder group. This outlier was especially troublesome since these data were also used to test Hypothesis 5. Therefore, the outlier was winsorized (Winer, 1972). This extremely high value (49.96 μg/dl) was given the next highest cortisol value of 30.99 μg/dl.

The ANOVA for cortisol with comparisons for schizophrenic

versus the other groups (see Table 3) revealed a significant group difference (R^2 = .087, F = 3.51, p < .05, df = 3, 111). Planned comparisons indicated the schizophrenic group had significantly higher cortisol levels than the hypertensive group (sr_2 = .047, F = 5.74, p < .05, df = 1, 111). No other comparisons reached significance.

The multiple regression analysis for cortisol revealed main effects for the demographic and stress sets (see Table 4). The significance of the demographic set (R^2 = .145, F = 4.55, p < .01, df = 4, 107) was due to the significant effects of sex and the black versus white ethnic variable. Males had 2.41 μg/dl more cortisol than females (B = 2.41, sr^2 = .043, F = 5.36, p < .05, df = 1, 107). The black subjects had 3.27 μg/dl less cortisol than the white subjects (B = -3.27, sr^2 = .063, F = 7.90, p < .01, df = 1, 107).

The significant stress set (R^2 = .060, F = 3.93, p < .05, df = 2, 103) was predominantly due to the significant contribution of the Beck Depression Inventory (B = .159, sr^2 =.06, p < .01, df = 1, 103). With every point increase in the BDI, there was a .159 μg/dl increase in cortisol levels. Since there was no significant group set effect, the schizophrenic group did not differ in cortisol levels from the affective disorder, hypertensive, or control groups.

TESTS OF THE HYPOTHESES

Hypothesis 1. These analyses tested the hypothesis that schizophrenic patients have significantly lower Ts/c cell,

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IgG, and IgM levels compared to the control group. These analyses also determined whether any immunological differences were specific to the schizophrenic group or whether they occurred in other psychiatric and medically ill patients.

The one-way ANOVA for IgG (see Table 5) indicated a significant group difference (R^2 = .37, F = 21.78, p < .0005, df = 3, 111). Therefore 37% of the total variance in the IgG analyses was associated with group. In planned comparisons contrasting the schizophrenic group to the affective disorder, hypertensive and control groups, the schizophrenic group IgG levels were significantly higher than the affective disorder group (sr^2 = .079, F = 13.11, p < .0005, df = 1, 111) and significantly lower than the hypertensive group (sr^2 = .10, F = 16.73, p < .0005, df = 1, 111), but not different from controls.

The regression analysis for IgG (see Table 6) revealed a significant main effect for the demographic set (R^2 = .371, F = 15.78, p < .0005, df = 4, 107). Age accounted for 13.5% of the variance (B = 9.42, sr^2 = .135, F = 22.97, p < .0005, df = 1, 107). Thus for every one year increase in age, the IgG level increased 9.42 mg/dl. There were also significant effects for ethnicity. The black subjects had 377 mg/dl more IgG than the white subjects (B = 377.28, sr^2 = .187, F = 31.81, p < .0005, df = 1, 107). Similarly, the other ethnic groups had 333 mg/dl more IgG compared to the white subjects (B = 333.27, sr^2 = .146, F = 24.83, p < .0005, df = 1, 107).

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Thus older, black, and other ethnic subjects had higher levels of IgG compared to white and younger subjects.

The main effect for group and the stress set were not significant. However, within the stress set, there was a significant main effect for cortisol (B = 12.50, sr^2 = .027, F = 4.77, p < .05, df = 1, 102). Therefore for every unit increase in cortisol, there was a 12.5 mg/dl increase in IgG. Similarly, the Age x Group set was not significant, but the Age x Control and Age x Hypertensive interactions were significant (B = -28.78, sr^2 = .035, F = 6.42, p < .05, df = 1, 88 and B = -18.12, sr^2 = .022, F = 4.0, p < .05, df = 1, 88 respectively). The control and hypertensive groups had a 28.78 and 18.12 mg/dl decrease in IgG for every year increase in age compared to the schizophrenic group.

The analyses of IgG indicated that the group differences seen in the one-way ANOVA could actually be explained by confounding variables such as age, ethnicity, and cortisol levels. Additionally, the interaction effects for Age x Group should be interpreted with caution since the overall set was not significant.

The ANOVA and regression analyses for IgM and Ts/c revealed no group differences or significant contributions by any of the sets (see Tables 7, 8, 9 & 10). Therefore, the hypothesis that schizophrenic patients have significantly lower Ts/c, IgG, and IgM levels compared to other groups was not supported by these results. The relevant variables in

predicting IgG levels were not group membership but age, ethnicity and cortisol levels.

Hypotheses 2 and 3. This analysis with the schizophrenic group alone tested the hypothesis that medication dose did not affect immune response and immune response decreased with increased severity of illness. Severity of illness was represented by experimental baseline levels of severity of illness on the BPRS.

For IgG (Table 11), the demographic set predicted a significant amount of variance (R^2 = .30, F = 2.69, p < .05, df = 4, 25). The significant effects of Age and Black (B = 21.87, sr^2 = .214, F = 7.64, p = .01, df = 1, 25 and B = 406.09 sr^2 = .20, F = 7.14, p = .01, df = 1, 25, respectively) indicated that for every yearly increase in age the schizophrenic group there is a 21.87 mg/dl increase in IgG. Additionally black schizophrenic patients had 406.09 mg/dl more IgG than white patients. None of the other sets in this regression model were significant.

With IgM (Table 12), Duration (years since first hospitalization) accounted for a significant amount of the variance (B = -7.19, R^2 = .13, F = 4.60, p < .05, df = 1, 24). For every year patients had a diagnosis of schizophrenia, schizo-affective disorder, or schizophreniform disorder, there was a decrease in IgM levels by 7.19 mg/dl. However no other variables influenced levels of IgM. The regression model for Ts/c (Table 13) revealed no significant predictors for the

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schizophrenic group. Therefore the hypothesis that medication dose did not effect Ts/c, IgG, or IgM was supported. Duration of illness significantly predicted IgM while age and ethnicity predicted IgG. The hypothesis that differences in baseline level of severity of illness affected immune response was not supported by these results.

Hypothesis 4. To determine whether immunological levels of the schizophrenic group decreased with relapse, a within-subjects repeated measures analysis of variance was conducted on a small sample (N = 10) of schizophrenic patients who had two blood samples taken. Only IgG significantly decreased during the decompensated state (R^2 = .53, F = 10.26, p = .01, df = 1, 9). Over half (53%) of the within subjects variance is associated with relapse.

The repeated measures analyses for IgM and Ts/c indicated no change with decompensation (R^2 = .225, F = 2.61, p > .05, df = 1, 9 and R^2 = .218, F = 1.95, p > .05, df = 1, 8, respectively). Thus the hypothesis that relapse affected immunological responses was partially supported; IgG significantly decreased with decompensation.

Hypothesis 5. The affective disorder group was hypothesized to have significantly higher cortisol levels compared to the schizophrenic, hypertensive and control groups. These analyses also determined whether elevated cortisol levels were associated with decreased immune response. The ANOVA (see Table 14) for cortisol with the

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group comparisons was significant (R^2 = .087, F = 3.51, p < .05, df = 3, 111). The affective disorder versus hypertensive group comparison was significant (sr^2 = .069, F = 8.66, p < .005, df = 1, 111). Therefore, while the affective disorder group had the highest cortisol levels, this difference was only significant when compared to the hypertensive group.

When the effects of confounding variables were accounted for, there was no main effect for group with the cortisol regression analyses (Table 15). As with the preliminary cortisol regression analysis (see Table 4), sex, black, and Beck score significantly affected cortisol level. Therefore the hypothesis that affective disorder patients had significantly higher cortisol levels compared to the other groups was not supported.

While there were no group differences for cortisol, the IgG ANOVA and regression analysis indicated differences between the affective disorder and other groups. The ANOVA for IgG (Table 16) indicated a significant main effect for group (R^2 = .371, F = 21.78, p < .005, df = 3, 111). The planned comparisons revealed the affective disorder group had significantly lower IgG compared to the schizophrenic and hypertensive groups (sr^2 = .079, F = 13.11, p < .005, df = 1, 111 and sr^2 = .329, F = 54.82, p < .005, df = 1, 111, respectively). The regression analysis indicated that when the confounding variables were analyzed, only the difference between the affective disorder and hypertensive groups

remained significant (B = 250.31, sr^2 = .023, F = 4.14, p < .05, df = 1, 99) (Table 17). The hypertensive group has an average 250.31 mg/dl more IgG than the affective disorder group.

The ANOVAs and regression analyses for IgM and Ts/c (see Tables 18 and 19 for regression analyses) showed no significant differences between the affective disorder and other groups on these variables.

Therefore, hypothesis 5 was not entirely supported. The affective disorder group did not have significantly higher cortisol levels compared to the other groups. However, the affective disorder group did have significantly lower IgG compared to the hypertensive group.

Summary of Results. The hypothesis that schizophrenic patients had significantly lower levels of Ts/c cells, IgG, and IgM was not supported in this study. Significant predictors of IgG were demographic and stress variables such as age, ethnicity, and cortisol level. The hypothesis that medication dose would not affect immunological response in schizophrenic patients was supported. Baseline level of severity for the schizophrenic group did not affect immune response. Relapse did decrease IgG response, therefore Hypothesis 4 was partially supported.

Finally, cortisol was significantly predicted by sex, ethnicity and depression level. However there were no significant group differences for cortisol when the effects of

confounding variables were controlled. Therefore the
hypothesis that affective disorder patients have significantly
higher cortisol levels was not supported. While the
differences in cortisol levels were not significant, the
affective disorder group did have significantly lower levels
of IgG compared to the hypertensive group.

CHAPTER 4

DISCUSSION

This study did not support previous reports of immunological abnormalities in schizophrenic patients. While the ANOVA analyses indicated some group differences, these differences were eliminated when the effects of variables such as age, ethnicity and cortisol levels were controlled. For example, with every yearly increase in age, there was an increase in IgG. Additionally, black subjects had more IgG than white subjects. The other ethnic groups (hispanics, filipinos, asians, and others) also had higher IgG levels than the white subjects. Increased cortisol was associated with an increase in IgG levels.

Immunoglobulin levels in humans are very low during infancy, but they increase and stabilize at adulthood (Bellanti, 1985). Additionally, while the total number of lymphocytes does not change with aging, the subclasses of immunoglobulins change. Levels of IgG (and IgA) increase in older humans both in serum and in cerebral spinal fluid while IgM levels decrease (Weksler, 1983). Therefore, since IgG levels for the groups in the present study were within normal ranges, the increasing IgG with age was probably normal and not due to disease or infection.

The ethnic differences in IgG were not as easily explained. Strahilevitz and colleagues (Strahilevitz et al., 1976) reported immunoglobulin differences between black and

white schizophrenic patients, but not between black and white controls. Additionally, it was suggested that environmental differences may account for their findings. However the present study showed ethnic differences even after the effects of SES were controlled. Therefore, SES differences could not explain the racial differences in IgG levels. However, the hypertensive group with the majority of black and other ethnic subjects was also the group which had the oldest subjects. Therefore, the elevated IgG levels in the black and other ethnic subjects was likely due to the fact that these were also the older subjects in the study.

The positive relationship between cortisol and IgG was unexpected since acute increases in cortisol lead to decreased immune responses (Jemmott & Lock, 1984). Cell mediated immune responses have been reported to rebound after initial suppression due to stress or dexamethasone (synthetic cortisol) injections (Borysenko & Borysenko, 1982). This cell mediated rebound has been suggested to be the result of elevated somatotropin and thyroid hormones during the immunosuppression (Riley, 1981). Therefore, it is possible that a rebound also occurs with humoral immunity, accounting for the elevated IgG and cortisol levels.

This study also found that baseline level of severity of illness for the schizophrenic group did not affect immune response. However relapse did decrease IgG levels. Together these findings suggest that immunological abnormalities in

schizophrenic patients are not trait but state markers. Had immunological differences been trait markers, they would have helped support a viral theory for schizophrenia (see Chapter 1). However, since immunological changes were only found with relapse, the changes are probably secondary effects of the disease process rather than an aspect of etiology.

A potential explanation for state changes in immune response is related to the neuropathology found in schizophrenics. Schizophrenic patients have cortical and hypothalamic abnormalities such as prefrontal and frontal cortical structural differences (Benes, Davidson, & Bird, 1986) and hypothalamic gliosis (Stevens, 1982). Additionally, frontal (Renoux, 1988) and hypothalamic (Cross, Markesbery, Brooks, & Roszman, 1984; Jankovick & Isakovic, 1973) control of immune responses have been demonstrated. Therefore, the activation of these damaged or altered cortical and hypothalamic areas during an exacerbation of symptoms or decompensation may also cause a faulty activation of the immune responses modulated by these neural regions. This would account for changes in immune responses during relapse or decompensation.

Baseline levels of psychotic symptoms, measured by BPRS, for the schizophrenic group were not affected by fluphenazine medication dose. However, the present study did not examine the effects of different types of neuroleptics at different doses. Therefore, future studies in the area should continue

to explore the potential effects of various neuroleptics on immune response in schizophrenic patients.

Duration of illness for the schizophrenic patients did effect IgM response. The longer the patients had been ill, the lower the IgM level. Since sex, age, and ethnicity did not significantly affect IgM response of the schizophrenic subjects, it is unlikely that the effects of duration of illness are due to age (i.e. the older patients are also those with the longer duration of illness). Additionally, while decreased IgM levels were not associated with current neuroleptic dose, they may be due to long term medication use (the longer the duration of illness, the longer the duration of neuroleptic treatment).

Several studies have reported elevated cortisol levels in affective disorder patients, and the present study did find significantly higher cortisol levels in the affective disorder group compared to the hypertensive group. However, when the effects of sex, ethnicity, and depression level were controlled, these differences were no longer significant. Therefore, it is important for future studies to analyze the effects of these variables before interpreting group differences in cortisol.

Another potential reason for the lack of significant cortisol results with the affective disorder group was that most studies reporting elevated cortisol levels in affective disorder patients have done so in acutely ill major depressive

patients (Asnis & Lemus, 1987). Major depressive patients in acute episodes may be the only group of affective disorder patients which experience elevated cortisol levels. The current study included patients with a diagnosis of Major and Manic Depression, who were both acute and stable. Since elevated cortisol levels were not found with all affective disorder patients, elevated cortisol levels are probably trait markers specific to major depressive patients not state markers for affective disorder patients.

Finally, the affective disorder group had significantly lower IgG compared to the hypertensive group. This was likely due to the correspondingly, but not significantly, higher cortisol levels in the affective disorder group compared to the hypertensive group.

It was clear from the present study that immunological abnormalities in IgG, IgM, and Ts/c cell did not exist among schizophrenic patients when variables such as age, ethnicity, and cortisol level were controlled. Age was an especially important variable to consider since there have been several reports of autoantibodies in schizophrenic patients (see Chapter 1), and autoantibodies increase with age in normal subjects (Oyeyinka, 1984; Weksler, 1983). Thus reports of increased autoantibodies in schizophrenic patients may simply have been due to differences in ages between the schizophrenic and control subjects. There may be similar relationships between gender and ethnicity and other immune responses which

may in part account for some of the conflicting reports in the area.

Additionally, immunological differences in antibody levels such as IgG were state and not trait markers of the disorder. Therefore, immunological differences may not be related to the etiology of schizophrenia, and suggestions that antibody differences in schizophrenia support a viral theory should be made with caution. Immunological abnormalities in schizophrenia may be due to factors such as neuropathology commonly reported in schizophrenic patients.

Finally, elevated cortisol levels are not generally found in affective disorder patients. This finding supported previous reports that elevated cortisol levels were specific state marker for major depression.

Future studies using methodological procedures like those employed in the present study will be necessary to determine whether other reported immunological abnormalities in schizophrenia can be accounted for by age, ethnicity, and cortisol levels. Additionally, these same studies will be required to determine exactly which immunological abnormalities are trait markers not related to the etiology of the disorder.

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Table 1

Demographics

Group	N	Age (mean +/- s.d.)	Sex M	F
Schizophrenic	31	31.94 +/- 9.07	26	5
Affective Disorder	21	35.33 +/- 12.27	11	10
Hypertensive	38	53.18 +/- 10.85	18	20
Controls	25	31.12 +/- 10.00	21	4

Table 2

Ethnic Distribution

	White	Black	Other*
Schizophrenic	7	13	11
Affective Disorder	17	0	4
Hypertensive	2	19	17
Controls	7	9	9

*Others: Hispanics, Filipinos and Asians

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FIGURE 1
IgG LEVELS FOR EXPERIMENTAL GROUPS
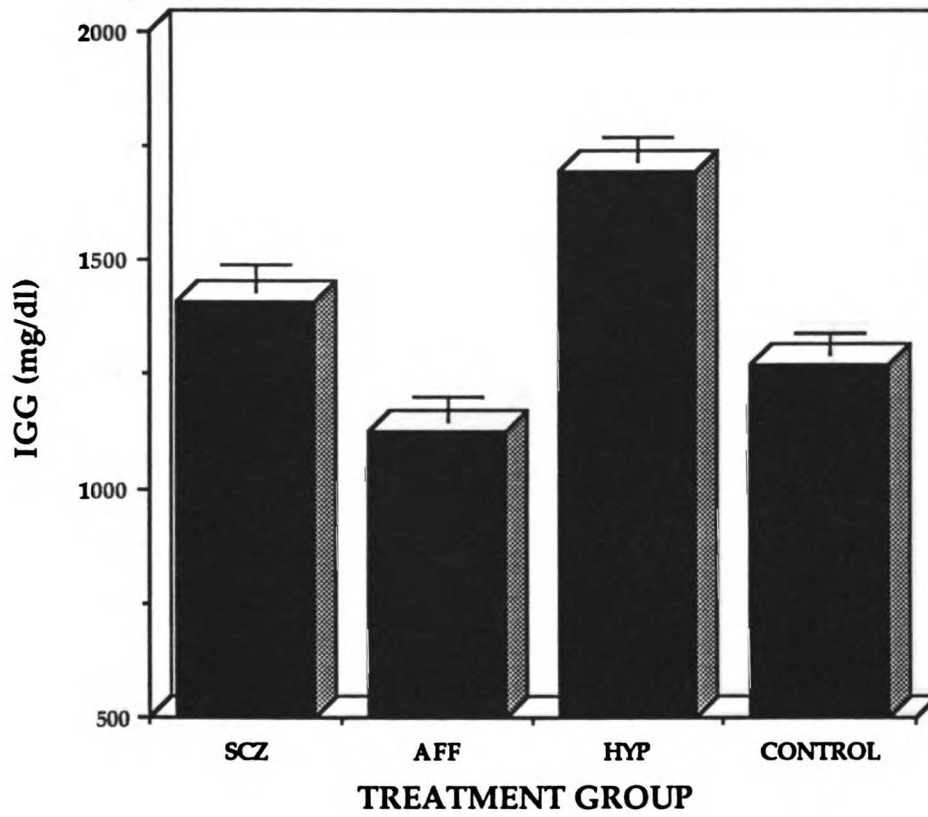
FIGURE 2
IgM LEVELS FOR EXPERIMENTAL GROUPS
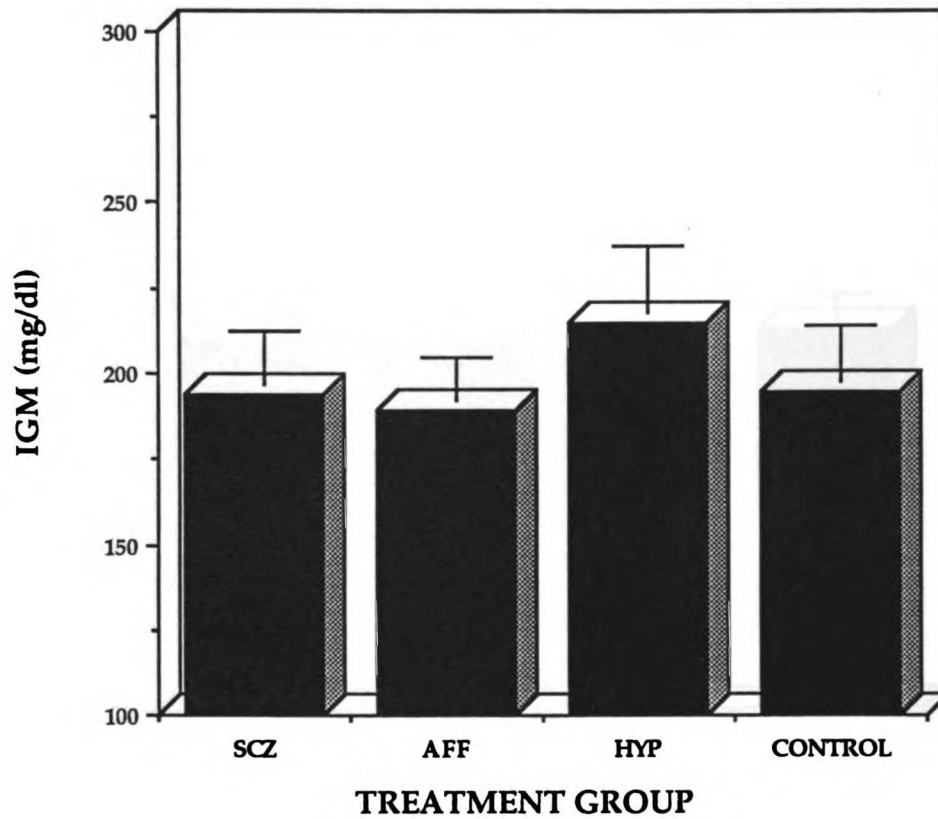
FIGURE 3
Ts/c LEVELS FOR EXPERIMENTAL GROUPS
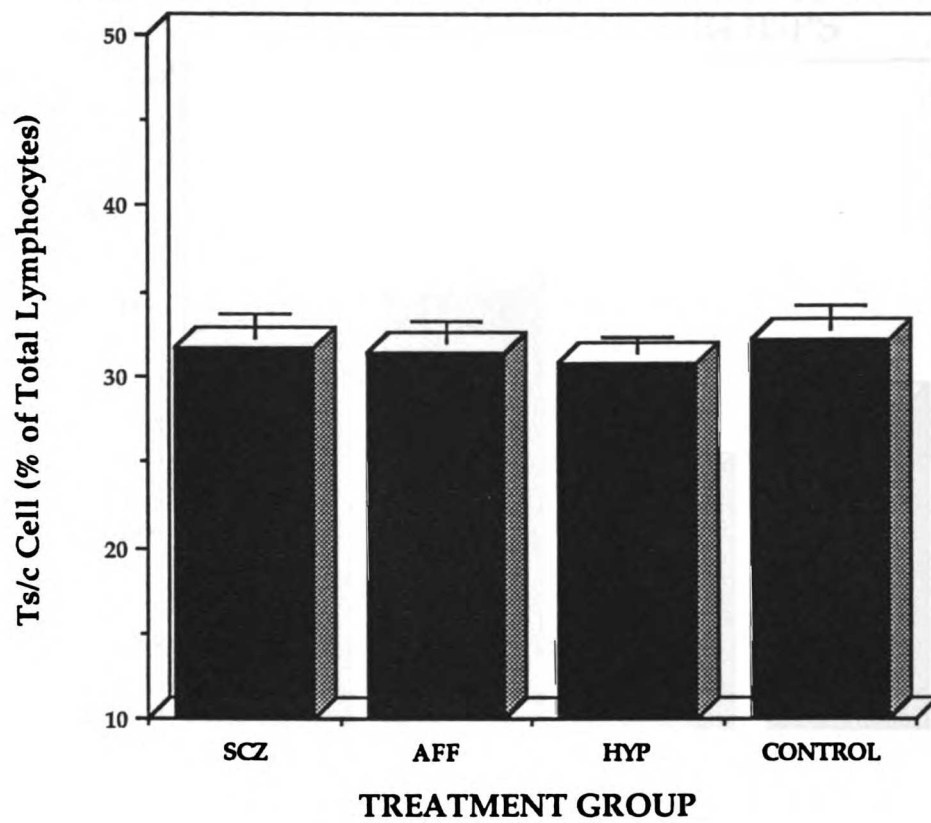
FIGURE 4
CORTISOL LEVELS
FOR EXPERIMENTAL GROUPS

Table 3

Summary Table for Cortisol Anova

Source	Amount of Variance accounted for by set (R² Change)	df	F	Amount of Variance accounted for by I.V. (sr²)	df	F
Group	.087	3,111	3.51*			
Schiz vs Affect				.005	1,111	.607
Schiz vs Hyper				.047	1,111	5.74*
Schiz vs Control				.008	1,111	.974

*p<.05

Table 4

Regression Summary for Cortisol

Source	Variance accounted for by Set (R² change)	df+	F ratio R²	Variance accounted for by I.V. (sr²)	df+	F ratio sr2	Raw Score Regression Coefficient
Demographics	.145	4,107	4.55**				
Sex				.043	1,107	5.36*	2.41
Age				.015	1,107	1.82	-.046
Black				.063	1,107	7.90**	-3.27
Other Ethnicities				.018	1,107	2.27	-1.75
Socio-economic							
Status	.007	2,105	.411				
Stress	.060	2,103	3.93*				
Beck				.06	1,103	7.81**	.159
Life Events				.006	1,103	.785	-.018
Group (Schiz vs Others)	.011	3,100	.463				
Sex x Group	.006	3,97	.233				
Ethnic x Group	.033	5,92	.819				
Age x Group	.014	3,89	.583				

+ "Model I" error terms used throughout (Cohen & Cohen, 1983); * p<.05; ** p<.01

Table 5

Summary Table for IgG Anova

Source	Amount of Variance accounted for by set (R^2 Change)	df	F	Amount of Variance accounted for by I.V. (sr^2)	df	F
Group	.37	3,111	21.78***			
Schiz vs Affect				.079	1,111	13.11***
Schiz vs Hyper				.10	1,111	16.73***
Schiz vs Control				.021	1,111	3.45

*** p<.0005

Table 6

Regression Summary for IgG

Source	Variance accounted for by Set (R² change)	df+	F ratio R²	Variance accounted for by I.V. (sr²)	df+	F ratio sr²	Raw Score Regression Coefficient
Demographics	.371	4,107	15.78***				
Sex				.002	1,107	0.362	36.02
Age				.135	1,107	22.97***	9.42
Black				.187	1,107	31.81**	377.28
Other				.146	1,107	24.83***	333.27
Socio-economic							
Status	.017	2,105	1.49				
Stress	.028	3,102	1.60				
Cortisol				.027	1,102	4.77*	12.50
Beck				.001	1,102	0.189	-1.49
Life Events				.000	1,102	0.008	.10
Group (Schiz. vs Others)	.032	3,99	1.93				
Sex x Group	.006	3,96	.377				
Ethnic x Group	.026	5,91	.914				
Age x Group	.037	3,88	2.25				
Age x Control				.035	1,88	6.42*	-28.78
Age x Affective				.016	1,88	2.87	-17.18
Age x Hypertensive				.022	1,88	4.00*	-18.12
Cortisol x Group	.025	3,88	1.55				

+ "Model I" error terms used throughout (Cohen & Cohen, 1983); * $p < .05$; *** $p < .0005$

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Table 7

Summary Table for IgM Anova

Source	Amount of Variance accounted for by set (R² Change)	df	F	Amount of Variance accounted for by I.V. (sr²)	df	F
Group	.013	3,111	.488			
Schiz vs Affect				.0004	1,111	.041
Schiz vs Hyper				.007	1,111	.833
Schiz vs Control				0	1,111	0

Table 8

Regression Summary for IgM

Source	Variance accounted for by set (R^2 change)	df[+]	F ratio for R^2
Demographics	.035	4,107	.961
Socio-economic Status	.010	2,105	.529
Stress	.003	3,102	.116
Group (Schiz. vs Others)	.016	3,99	.579
Sex x Group	.016	3,96	.640
Ethnic x Group	.028	5,91	.574
Age x Group	.028	3,88	.963
Cortisol x Group	.059	3,85	2.09

+ "Model I" error terms used throughout (Cohen & Cohen, 1983).
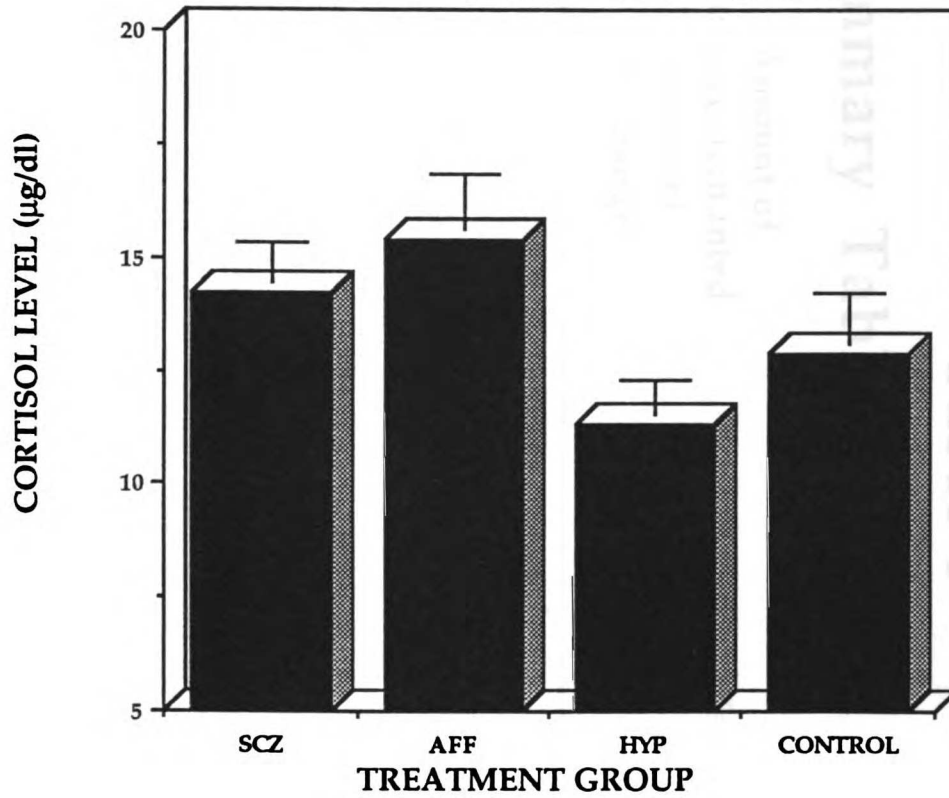
Table 9

Summary Table for Ts/c Anova

Source	Amount of Variance accounted for by set (R² Change)	df	F	Amount of Variance accounted for by I.V. (sr²)	df	F
Group	.007	3,111	.247			
Schiz vs Affect				.0003	1,111	.033
Schiz vs Hyper				.004	1,111	.403
Schiz vs Control				.0003	1,111	.036

Table 10

Regression Summary for Ts/c

Variable	Variance accounted for by set (R^2 change)	df^+	F ratio for R^2
Demographics	.025	4,107	.689
Socio-economic Status	.001	2,105	.049
Stress	.020	3,102	.711
Group (Schiz. vs Others)	.004	3,99	.144
Sex x Group	.033	3,96	1.16
Ethnic x Group	.095	5,91	2.11
Age x Group	.028	3,88	1.04
Cortisol x Group	.024	3,85	.886

+ "Model I" error terms used throughout (Cohen & Cohen, 1983).

Table 11

Summary of IgG Regression Model for Schizophrenic Group

Source	Variance accounted for by Set (R² change)	df+	F ratio R²	Variance accounted for by I.V. (sr²)	df+	F ratio sr²	Raw Score Regression Coefficient
Demographics	.30	4,25	2.69*				
Sex				.063	1,25	2.24	236.50
Age				.214	1,25	7.64**	21.87
Black				.200	1,25	7.14**	406.09
Other				.106	1,25	3.78	361.56
Duration	.063	1,24	2.38				
Severity of Illness	.002	2,22	.041				
Medication	.017	1,21	.583				

+ "Model I" error terms used throughout (Cohen & Cohen, 1983)

* $p < .05$; ** $p = .01$

Table 12

Summary of IgM Regression Model for Schizophrenic Group

Source	Variance accounted for by Set (R^2 change)	df[+]	F ratio R^2	Raw Score Regression Coefficient
Demographics	.176	4,25	1.34	
Duration	.133	1,24	4.60[*]	-7.19
Severity of Illness	.057	2,22	.990	
Medication	.057	1,21	2.06	

[+] " Model I" error terms used throughout (Cohen & Cohen, 1983)

[*] $p < .05$

Table 13

Summary of Ts/c Regression Model for Schizophrenic Group

Source	Variance accounted for by set (R^2 change)	df[+]	F ratio for R^2
Demographics	.136	4,25	.981
Duration	.027	1,24	.765
Severity of Illness	.135	2,22	2.11
Medication	.014	1,21	.431

+ "Model I" error terms used throughout (Cohen & Cohen, 1983).

Table 14

Summary Table for Cortisol Anova
Affective Disorder vs Other Groups

Source	Amount of Variance accounted for by set (R² Change)	df	F	Amount of Variance accounted for by I.V. (sr²)	df	F
Group	.087	3,111	3.51*			
Affect vs. Schiz				.005	1,111	.607
Affect vs. Hyper				.069	1,111	8.66***
Affect vs. Control				.022	1,111	2.69

*   p<.05;   ***   p<.005

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Table 15

Summary of Cortisol Regression Model
Affective Disorder vs. Other Groups

Source	Variance accounted for by Set (R² change)	df+	F ratio R²	Variance accounted for by I.V. (sr²)	df+	F ratio sr²	Raw Score Regression Coefficient
Demographics	.145	4,107	4.55***				
Sex				.043	1,107	5.36*	2.41
Age				.015	1,107	1.82	-.046
Black				.063	1,107	7.90**	-3.27
Other				.018	1,107	2.27	-1.75
Socio-economic Status	.007	2,105	.411				
Stress	.060	2,103	3.93*				
Beck				.06	1,103	7.81**	.159
Life Events				.006	1,103	.785	-.018
Group (Affect vs Others)	.011	3,100	.463				
Sex x Group	.006	3,97	.233				
Ethnic x Group	.033	5,92	.819				
Age x Group	.014	3,89	.583				

+ " Model I" error terms used throughout (Cohen & Cohen, 1983)

* p<.05; ** p<.01; *** p<.0005

Table 16

Summary Table for IgG Anova
Affective Disorder vs Other Groups

Source	Amount of Variance accounted for by set (R^2 Change)	df	F	Amount of Variance accounted for by I.V. (sr^2)	df	F
Group	.371	3,111	21.78***			
Affect vs. Schiz				.079	1,111	13.11***
Affect vs. Hyper				.329	1,111	54.82***
Affect vs. Control				.019	1,111	3,14

*** p<.005

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Table 17

Summary of IgG Regression Model
Affective Disorder vs. Other Groups

Source	Variance accounted for by Set (R^2 change)	df+	F ratio R^2	Variance accounted for by I.V. (sr^2)	df+	F ratio sr^2	Raw Score Regression Coefficient
Demographics	.371	4,107	15.78***				
Sex				.002	1,107	0.362	36.02
Age				.135	1,107	22.97***	9.42
Black				.187	1,107	31.81***	377.28
Other				.146	1,107	24.83***	333.27
Socio-economic Status	.017	2,105	1.49				
Stress	.028	3,102	1.60				
Group	.032	3,99	1.93				
Affect vs. Schiz				.007	1,99	1.19	108.51
Affect vs. Hyper				.023	1,99	4.14*	250.31
Affect vs. Control				.000	1,99	0.011	10.98
Sex x Group	.006	3,96	.377				
Ethnic x Group	.026	5,91	.914				
Age x Group	.037	3,88	2.25				
Cortisol x Group	.026	3,85	1.62				

+   "Model I" error terms used throughout (Cohen & Cohen, 1983)

* $p<.05$;   *** $p<.0005$

Table 18

Regression Summary for IgM
Affective Disorder vs. Other Groups

Source	Variance accounted for by set (R^2 change)	df[+]	F ratio for R^2
Demographics	.035	4,107	.961
Socio-economic Status	.010	2,105	.529
Stress	.003	3,102	.116
Group (Affect. vs Others)	.016	3,99	.579
Sex x Group	.016	3,96	.564
Ethnic x Group	.028	5,91	.574
Age x Group	.028	3,88	.963
Cortisol x Group	.059	3,85	2.09

+ "Model I" error terms used throughout (Cohen & Cohen, 1983).

Table 19

Regression Summary for Ts/c
Affective Disorder vs Other Groups

Variable	Variance accounted for by set (R^2 change)	df[+]	F ratio for R^2
Demographics	.025	4,107	.689
Socio-economic Status	.001	2,105	.049
Stress	.020	3,102	.711
Group (Schiz. vs Others)	.004	3,99	.144
Sex x Group	.033	3,96	1.16
Ethnic x Group	.095	5,91	2.11
Age x Group	.028	3,88	1.04
Cortisol x Group	.024	3,85	.886

+ "Model I" error terms used throughout (Cohen & Cohen, 1983).

_____

University of California, San Francisco

Consent to Participate in a Research Study on Immune Response

A. PURPOSE AND BACKGROUND:

Dr. William Hargreaves, Dr. Marc Jacobs, and Ms. Maria Juarez-Reyes are conducting a study to learn more about immune response in different types of patients at SFGH and UCSF. These immune responses will then be compared to those of a non-patient control group. The immune response is the measure of the body's ability to fight off infection, and it is measured by taking a blood sample. You have been asked to participate in this study because you meet the criteria for one of the four groups which will be studied.

B. PROCEDURES:

If I agree to participate in the study, the following will happen:

1. I will have one sample of blood taken between 9:00 a.m and noon by a nurse or lab technician at San Francisco General Hospital or UCSF. One group of patients will have two blood samples taken, both between 9:00 a.m and noon on two separate days.

2. I will also fill out 2 questionnaires on how I am feeling and on any recent life changes. I will also have a brief medical history taken to check for any recent illness, allergies, activity level, and social economic status. The entire process will take no longer than 1 hour.

All procedures will be done at the San Francisco General Hospital or at the Medical Center at U.C. San Francisco.

C. RISKS/DISCOMFORTS:

1. Confidentiality: Participation in research may involve some loss of confidentiality. My records will be handled as confidentially as is possible within the law. All data will be number coded so that no names appear. This form and the medical history form will be kept in a locked file until the end of the study when they will be destroyed. Only the investigators will have access to them. No individual identities will be used in any reports or publications resulting from this study.

2. Venipuncture: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and rarely, infection. All needles will be new, sterile, and used only once.

Treatment and Compensation for Injury:

If I am injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, I may call the office of the Committee on Human Research at (415) 476-1814.

                                                        12-18-89

Approval # H599-05101

D. BENEFITS:

I will not directly benefit from personally participating in this study. However, the investigators hope to learn more about the immune response of different types of patients which will help many other people in the future.

E. ALTERNATIVE:

I do not have to participate in this study. I can withdraw from the study at any time and not hurt my chances of receiving treatment from any of the clinics at San Francisco General Hospital or the Medical Center at U.C. San Francisco. Additionally, non-participation will not affect my employment status at either San Francisco General Hospital or the Medical Center at U.C. ·San Francisco.

F. COSTS:

I will not be charged for any of the study procedures. All costs will be covered by the study.

G. REIMBURSEMENT:

I will be reimbursed $10 for my time and participation in this study. If I have two blood samples taken, I will receive $10 per trial. A check will be mailed to me approximately 2 weeks after my participation in the study.

H. QUESTIONS:

This study has been explained to me by Ms. Maria G. Juarez-Reyes, and I have had the opportunity to ask questions. If I have any further questions, I may call and speak with Dr. Hargreaves or Ms. Juarez-Reyes at (415) 821-5211.

I. CONSENT:

I have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. I have the right to decline to participate or to withdraw at any point in this study without jeopardy (to my medical care/employment/student status).

I AGREE TO PARTICIPATE IN THIS STUDY.

---------------------------------   ----------------------
Signature of Patient   Date

---------------------------------   ----------------------
Person Obtaining Consent   Date
                                                                12-18-89

IDENTIFICATION DATA Please print the following information.

Date _____ File no. _____

Name _____

Address _____

_____ (zip code)

Home telephone _____
(area code)

Business telephone _____
(area code)

___ Male ___ Female   Race _____   Date of birth ___/___/___

___ Married ___Separated ___ Divorced ___ Widowed ___ Single

Education: _____ years Elementary _____ years High School

_____ years College. Technical. Business. etc.

Occupation _____

FAMILY HISTORY: For each family member below. follow the line across the page and mark an X in those boxes which indicate their present state of health (good). (poor). or their death (write in the cause). and any of the illnesses that they have ever had.

If married, print the names of your spouse and children in the spaces below.

	Health			If deceased. note age at death and cause of death (include fatal accidents and suicides)	Allergies or asthma	Anemia	Bleed easily	Diabetes	Cancer or tumor	Epilepsy	Glaucoma	Genetic disease	Alcoholism	Kidney or bladder trouble	Stomach / duodenal ulcer	Nervous breakdown	Rheumatism or arthritis	High blood pressure	Heart trouble	Gout
	Good	Poor	Deceased																	
Father:																				
Mother:																				
Brothers or Sisters:																				
Spouse:																				
Child:																				
Child:																				
Child:																				
Child:																				
Child:																				
Paternal relatives (write how many affected in each box) ———→																				
Maternal relatives (write how many affected in each box) ———→																				

YOUR HEALTH HISTORY (begin here with illnesses) ———→

Additional Illnesses or Problems: Mark an X in the box next to any of the following that you have now or have ever had.

☐ eye infections ☐ pneumonia ☐ neuralgia or neuritis ☐ scarlet fever ☐ mononucleosis
☐ thyroid disease ☐ pancreatitis ☐ tension/anxiety ☐ measles ☐ venereal disease
☐ eczema ☐ liver disease ☐ depression ☐ mumps ☐ yellow jaundice
☐ hives or rashes ☐ diverticulosis ☐ childhood hyperactivity ☐ polio ☐ other
☐ bronchitis ☐ hernia ☐ chicken pox ☐ rheumatic fever ☐ _____
☐ emphysema ☐ hemorrhoids ☐ German measles ☐ malaria ☐ _____

Have you ever been turned down for life insurance, military service or employment because of health problems?.............. _____ Yes _____ No

---

Major Hospitalizations: If you have ever been hospitalized for any serious medical illness or operation. write in your most recent hospitalizations below. Check this box ☐ if you have had more than three such hospitalizations. (Do not include normal pregnancies)

	Year	Operation or Illness	Name of Hospital	City and State
1st hospitalization				
2nd hospitalization				
3rd hospitalization				

Tests and Immunizations: Mark an X next to those that you have had. Enter the year when you last were given the test or "shots."

Year	Year
☐ 19___chest x-ray	☐ 19___smallpox "shots"
☐ 19___kidney x-ray	☐ 19___tetanus "shots"
☐ 19___G.I. series	☐ 19___polio series
☐ 19___colon x-ray	☐ 19___typhoid "shots"
☐ 19___gallbladder x-ray	☐ 19___flu injections
☐ 19___electrocardiogram	☐ 19___mumps "shots"
☐ 19___TB test	☐ 19___measles "shots"
☐ 19___sigmoidoscopy	☐ 19___other _____

Medicines: Mark an X in the box next to any medicines that you are now taking. or that you are sensitive or allergic to:

taking	allergic to:		taking	allergic to:	
☐	☐	antibiotics	☐	☐	aspirin
☐	☐	penicillin	☐	☐	diet pills
☐	☐	sulfa	☐	☐	antacids
☐	☐	opiates/codeine	☐	☐	laxatives
☐	☐	diuretics/water pills	☐	☐	cold tablets
☐	☐	sedatives	☐	☐	_____
☐	☐	stimulants/caffeine	☐	☐	_____
☐	☐	Demerol	☐	☐	_____
☐	☐	blood pressure medicine	☐	☐	_____

Signature (if filled out by other than patient): _____

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Instructions: Listed below are a number of events which may bring about changes in the lives of those who experience them. Rate each event that occurred in your life during the past 3 months as GOOD or BAD (circle which one applies). Show how much the event affected your life by circling the appropriate number from "1" to "7", with "1" indicating no effect at all on your life and "7" indicating an extreme effect on your life.

If you have not experienced a particular event in the past 3 months, leave it blank.

If a specific event happened more than once, please make a note of it.

Event	Type of Event		Effect of Event on Your Life						
			not at all						extremely
1. Marriage	good	bad	1	2	3	4	5	6	7
2. Detention in jail or comparable institution	good	bad	1	2	3	4	5	6	7
3. Death of spouse	good	bad	1	2	3	4	5	6	7
4. Major change in sleeping habits (much more or much less sleep)	good	bad	1	2	3	4	5	6	7
5. Death of close family member									
a. mother	good	bad	1	2	3	4	5	6	7
b. father	good	bad	1	2	3	4	5	6	7
c. brother	good	bad	1	2	3	4	5	6	7
d. sister	good	bad	1	2	3	4	5	6	7
e. grandmother	good	bad	1	2	3	4	5	6	7
f. grandfather	good	bad	1	2	3	4	5	6	7
g. other _____	good	bad	1	2	3	4	5	6	7
6. Major change in eating habits (much more or much less food intake)	good	bad	1	2	3	4	5	6	7
7. Foreclosure on mortgage or loan	good	bad	1	2	3	4	5	6	7
8. Death of close friend	good	bad	1	2	3	4	5	6	7
9. Outstanding personal achievement	good	bad	1	2	3	4	5	6	7

Event	Type of Event	Effect of Event on Your Life						
		not at all						extreme!

10. Minor law violations (traffic tickets, disturbing the peace, etc.)   good bad   1   2   3   4   5   6   7

11. **Male:** Wife's/Girlfriend's pregnancy   good bad   1   2   3   4   5   6   7

12. **Female:** Pregnancy   good bad   1   2   3   4   5   6   7

13. Change in work situation (different work responsibility, major change in working conditions, working hours, etc.)   good bad   1   2   3   4   5   6   7

14. New job   good bad   1   2   3   4   5   6   7

15. Serious illness or injury of close family member:

    a. mother   good bad   1   2   3   4   5   6   7

    b. father   good bad   1   2   3   4   5   6   7

    c. brother   good bad   1   2   3   4   5   6   7

    d. sister   good bad   1   2   3   4   5   6   7

    e. grandmother   good bad   1   2   3   4   5   6   7

    f. grandfather   good bad   1   2   3   4   5   6   7

    g. other _____   good bad   1   2   3   4   5   6   7

16. Sexual difficulties   good bad   1   2   3   4   5   6   7

17. Trouble with employer (in danger of losing job, being suspended, demoted, etc.)   good bad   1   2   3   4   5   6   7

18. Trouble with in-laws   good bad   1   2   3   4   5   6   7

19. Major change in financial status (a lot better off or a lot worse off)   good bad   1   2   3   4   5   6   7

20. Major change in closeness of family members (increase or decrease in closeness)   good bad   1   2   3   4   5   6   7

21. Gaining a new family member (through birth, adoption, family member moving in, etc.)   good bad   1   2   3   4   5   6   7

22. Change of residence   good bad   1   2   3   4   5   6   7

	Event	Type of Event	Effect of Event on Your Life

not at all   extreme

#	Event	Type of Event		not at all						extreme
23.	Marital separation from mate (due to conflict)	good bad		1	2	3	4	5	6	7
24.	Major change in church activities (increased or decreased attendance)	good bad		1	2	3	4	5	6	7
25.	Marital reconciliation with mate	good bad		1	2	3	4	5	6	7
25.	Major change in number of arguments with spouse (a lot more or a lot less)	good bad		1	2	3	4	5	6	7
27.	Married male: Change in wife's work outside the home (beginning work, ceasing work, changing to a new job, etc.)	good bad		1	2	3	4	5	6	7
28.	Married female: Change in husband's work (loss of job, beginning new job, retirement, etc.)	good bad		1	2	3	4	5	6	7
29.	Major change in usual type and/or amount of recreation	good bad		1	2	3	4	5	6	7
30.	Borrowing more than $10,000 (buying home, business, etc.)	good bad		1	2	3	4	5	6	7
31.	Borrowing less than $10,000 (buying car, TV, getting school loan, etc.)	good bad		1	2	3	4	5	6	7
32.	Fired from job	good bad		1	2	3	4	5	6	7
33.	Male: Wife/Girlfriend having abortion	good bad		1	2	3	4	5	6	7
34.	Female: Having abortion	good bad		1	2	3	4	5	6	7
35.	Major personal illness or injury	good bad		1	2	3	4	5	6	7
36.	Major change in social activities (e.g., parties, movies, visiting)	good bad		1	2	3	4	5	6	7
37.	Major change in living conditions of family (building new home; remodeling; deterioration of home, neighborhood, etc.)	good bad		1	2	3	4	5	6	7
38.	Divorce	good bad		1	2	3	4	5	6	7
39.	Serious injury or illness of close friend	good bad		1	2	3	4	5	6	7

Event	Type of Event	Effect of Event on Your Life
		not at all extremely
40. Retirement from work	good bad	1 2 3 4 5 6 7
41. Son or daughter leaving home (due to marriage, college, etc.)	good bad	1 2 3 4 5 6 7
42. Ending of formal schooling	good bad	1 2 3 4 5 6 7
43. Separation from spouse (due to work, travel, etc.)	good bad	1 2 3 4 5 6 7
44. Engagement	good bad	1 2 3 4 5 6 7
45. Breaking up with boyfriend/girlfriend	good bad	1 2 3 4 5 6 7
46. Leaving home for the first time	good bad	1 2 3 4 5 6 7
47. Reconciliation with boyfriend/girlfriend	good bad	1 2 3 4 5 6 7
48. Beginning a new schooling experience at a higher academic level (college, graduate school, professional school, etc.)	good bad	1 2 3 4 5 6 7
49. Changing to a new school at same academic level (undergraduate, graduate, etc.)	good bad	1 2 3 4 5 6 7
50. Academic probation	good bad	1 2 3 4 5 6 7
51. Being dismissed from dormitory or other residence	good bad	1 2 3 4 5 6 7
52. Failing an important exam	good bad	1 2 3 4 5 6 7
53. Changing a major	good bad	1 2 3 4 5 6 7
54. Failing a course	good bad	1 2 3 4 5 6 7
55. Dropping a course	good bad	1 2 3 4 5 6 7
56. Joining a fraternity/sorority	good bad	1 2 3 4 5 6 7
57. Financial problems concerning school (in danger of not having sufficient money to continue)	good bad	1 2 3 4 5 6 7

103

Other recent experiences (in the last 3 months) which have had an impact on your life. Please list and rate:

	Event	Type of Event	Effect of Event on Your Life

			not at all					extreme

58.   good bad   1 2 3 4 5 6 7

59.   good bad   1 2 3 4 5 6 7

60.   good bad   1 2 3 4 5 6 7

Some problems are chronic ongoing problems that may not have been listed above (for example, ongoing problems with your boss, relationship problems). Please think about any chronic ongoing problems you might have and write below a phrase which describes each.

Ongoing stressful situations	For how long has this been happening?	How stressful is it for you?
		not at all extremely

1.   _____   1 2 3 4 5 6 7

2.   _____   1 - 2 3 4 5 6 7

3.   _____   1 2 3 4 5 6 7

4.   _____   1 2 3 4 5 6 7

BDI

Date: _____

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2 or 3) next to the one statement in each group which best describes the way you have been feeling the past week, including today. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1
0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2
0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3
0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4
0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5
0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7
0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8
0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11
0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

_____ Subtotal Page 1   CONTINUED ON BACK

9-018359

14
0   I don't feel I look any worse than I used to.
1   I am worried that I am looking old or unattractive.
2   I feel that there are permanent changes in my appearance that make me look unattractive.
3   I believe that I look ugly.

15
0   I can work about as well as before.
1   It takes an extra effort to get started at doing something.
2   I have to push myself very hard to do anything.
3   I can't do any work at all.

16
0   I can sleep as well as usual.
1   I don't sleep as well as I used to.
2   I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3   I wake up several hours earlier than I used to and cannot get back to sleep.

17
0   I don't get more tired than usual.
1   I get tired more easily than I used to.
2   I get tired from doing almost anything.
3   I am too tired to do anything.

18
0   My appetite is no worse than usual.
1   My appetite is not as good as it used to be.
2   My appetite is much worse now.
3   I have no appetite at all anymore.

19
0   I haven't lost much weight, if any, lately.
1   I have lost more than 5 pounds.
2   I have lost more than 10 pounds.
3   I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____ No _____

20
0   I am no more worried about my health than usual.
1   I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2   I am very worried about physical problems and it's hard to think of much else.
3   I am so worried about my physical problems that I cannot think about anything else.

21
0   I have not noticed any recent change in my interest in sex.
1   I am less interested in sex than I used to be.
2   I am much less interested in sex now.
3   I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

TPC 0528-000   6 7 8 9 10 11 12 A B C D E

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE Alcohol, Drug Abuse, and Mental Health Administration NIMH Treatment Strategies in Schizophrenia Study	PATIENT NUMBER ____ ____ ____ ____	DATA GROUP **lbprs**	EVALUATION DATE __ __ . __ __ . __ __ M M D D Y Y
	PATIENT NAME		
BRIEF PSYCHIATRIC RATING SCALE - Anchored **Overall and Gorham**	RATER NAME		

RATER NUMBER ____ ____ ____	EVALUATION TYPE *(Circle)*		
	LITHIUM—DOUBLE BLIND		LITHIUM—OPEN TREATMENT
	80 Baseline 83 8-Week study completion 81 1-Week rating 84 Early termination 82 2-Week rating 85 Other		90 Baseline 93 8-Week study completion 91 1-Week rating 94 Early termination 92 2-Week rating 95 Other

·Introduce all questions with "During the past week, have you . . ."

* **1. SOMATIC CONCERN:** Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not. Do not rate mere report-ing of somatic symptoms. Rate only concern for (or worrying about) physical problems (real or imagined). **Rate on the basis of reported (i.e., subjective) information pertaining to the past week.**

    1   =   Not reported

    2   =   Very Mild: occasionally is somewhat concerned about body, symptoms, or physical illness

    3   =   Mild: occasionally is moderately concerned, or often is somewhat concerned

    4   =   Moderate: occasionally is very concerned, or often is moderately concerned

    5   =   Moderately Severe: often is very concerned

    6   =   Severe: is very concerned most of the time

    7   =   Very Severe: is very concerned nearly all of the time

    9   =   Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

* **2. ANXIETY:** Worry, fear, or overconcern for present or future. **Rate solely on the basis of verbal report of patient's own subjective experiences pertaining to the past week.** Do not infer anxiety from physical signs or from neurotic defense mechanisms. Do not rate if restricted to somatic concern.

    1   · =   Not reported

    2   =   Very Mild: occasionally feels somewhat anxious

    3   =   Mild: occasionally feels moderately anxious, or often feels somewhat anxious

    4   =   Moderate: occasionally feels very anxious, or often feels moderately anxious

    5   =   Moderately Severe: often feels very anxious

    6   =   Severe: feels very anxious most of the time

    7   =   Very Severe: feels very anxious nearly all of the time

    9   =   Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

* Ratings based primarily upon verbal report

3. **EMOTIONAL WITHDRAWAL:** Deficiency in relating to the interviewer and to the interview situation. Overt manifestations of this deficiency include poor/absence of eye contact, failure to orient oneself physically toward the interviewer, and a general lack of involvement or engagement in the interview. Distinguish from BLUNTED AFFECT, in which deficits in facial expression, body gesture, and voice pattern are scored. **Rate on the basis of observations made during the interview.**

1 = Not observed

2 = Very Mild: e.g., occasionally exhibits poor eye contact

3 = Mild: e.g., as above, but more frequent

4 = Moderate: e.g., exhibits little eye contact, but still seems engaged in the interview and is appropriately responsive to all questions

5 = Moderately Severe: e.g., stares at floor or orients self away from interviewer, but still seems moderately engaged

6 = Severe: e.g., as above, but more persistent or pervasive

7 = Very Severe: e.g., appears "spacey" or "out of it" (total absence of emotional relatedness), and is disproportionately uninvolved or unengaged in the interview. (DO NOT SCORE IF EXPLAINED BY DISORIENTATION.)

4. **CONCEPTUAL DISORGANIZATION:** Degree of speech incomprehensibility. Include any type of formal thought disorder (e.g., loose associations, incoherence, flight of ideas, neologisms). DO NOT include mere circumstantiality or pressured speech, even if marked. DO NOT rate on the basis of the patient's subjective impressions (e.g., "my thoughts are racing. I can't hold a thought," "my thinking gets all mixed up"). **Rate ONLY on the basis of observations made during the interview.**

1 = Not observed

2 = Very Mild: e.g., somewhat vague, but of doubtful clinical significance

3 = Mild: e.g.. frequently vague, but the interview is able to progress smoothly; occasional loosening of associations

4 = Moderate: e.g., occasional irrelevant statements, infrequent use of neologisms, or moderate loosening of associations

5 = Moderately Severe: as above, but more frequent

6 = Severe: formal thought disorder is present for most of the interview. and the interview is severely strained

7 = Very Severe: very little coherent information can be obtained

*5. GUILT FEELINGS: Overconcern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report pertaining to the past week. Do not infer guilt feelings from depression, anxiety or neurotic defenses.

    1 = Not reported

    2 = Very Mild: occasionally feels somewhat guilty

    3 = Mild: occasionally feels moderately guilty, or often feels somewhat guilty

    4 = Moderate: occasionally feels very guilty, or often feels moderately guilty

    5 = Moderately Severe: often feels very guilty

    6 = Severe: feels very guilty most of the time, or encapsulated delusion of guilt

    7 = Very Severe: agonizing constant feelings of guilt, or pervasive delusion(s) of guilt

    9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

6. TENSION: Rate motor restlessness (agitation) observed during the interview. DO NOT rate on the basis of subjective experiences reported by the patient. Disregard suspected pathogenesis (e.g., tardive dyskinesia).

    1 = Not observed

    2 = Very Mild: e.g., occasionally fidgets

    3 = Mild: e.g., frequently fidgets

    4 = Moderate: e.g., constantly fidgets, or frequently fidgets, wrings hands and pulls clothing

    5 = Moderately Severe: e.g., constantly fidgets, wrings hands and pulls clothing

    6 = Severe: e.g., cannot remain seated (i.e., must pace)

    7 = Very Severe: e.g., paces in a frantic manner

*Ratings based primarily upon verbal report

7. MANNERISMS AND POSTURING: Unusual and unnatural motor behavior. **Rate only abnormality of movements. Do not rate simple heightened motor activity here. Consider frequency, duration, and degree of bizarreness. Disregard suspected pathogenesis.**

1 = Not observed

2 = Very Mild: odd behavior but of doubtful clinical significance, e.g., occasional unprompted smiling, infrequent lip movements

3 = Mild: strange behavior but not obviously bizarre, e.g., infrequent head-tilting (side to side) in a rhythmic fashion, intermittent abnormal finger movements

4 = Moderate: e.g., assumes unnatural position for a brief period of time, infrequent tongue protrusions, rocking, facial grimacing

5 = Moderately Severe: e.g., assumes and maintains unnatural position throughout interview, unusual movements in several body areas

6 = Severe: as above, but more frequent, intense, or pervasive

7 = Very Severe: e.g., bizarre posturing throughout most of the interview, continuous abnormal movements in several body areas

*8. **GRANDIOSITY:** Inflated self-esteem (self-confidence), or inflated appraisal of one's talents, powers, abilities, accomplishments, knowledge, importance, or identity. Do not score mere grandiose quality of claims (e.g., "I'm the worst sinner in the world," "The entire country is trying to kill me") unless the guilt/persecution is related to some special, exaggerated attributes of the individual. Also, the patient must claim exaggerated attributes: e.g., if patient denies talents, powers, etc., even if he or she states that others indicate that he/she has these attributes, this item should not be scored. **Rate on the basis of reported (i.e., subjective) information pertaining to the past week.**

1 = Not reported

2 = Very Mild: e.g., is more confident than most people, but of only possible clinical significance

3 = Mild: e.g., definitely inflated self-esteem or exaggerates talents somewhat out of proportion to the circumstances

4 = Moderate: e.g., inflated self-esteem clearly out of proportion to the circumstances, or suspected grandiose delusion(s)

5 = Moderately Severe: e.g., a single (definite) encapsulated grandiose delusion, or multiple (definite) fragmentary grandiose delusions

6 = Severe: e.g., a single (definite) grandiose delusion/delusional system, or multiple (definite) grandiose delusions that the patient seems preoccupied with

7 = Very Severe: e.g., as above, but nearly all conversation is directed towards the patient's grandiose delusion(s)

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*Ratings based primarily upon verbal report

*9. DEPRESSIVE MOOD: Subjective report of feeling depressed, blue, "down in the dumps," etc. Rate only degree of reported depression. Do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints. Rate on the basis of reported (i.e., subjective) information pertaining to the past week.

1   =   Not reported

2   =   Very Mild: occasionally feels somewhat depressed

3   =   Mild: occasionally feels moderately depressed, or often feels somewhat depressed

4   =   Moderate: occasionally feels very depressed, or often feels moderately depressed

5   =   Moderately Severe: often feels very depressed

6   =   Severe: feels very depressed most of the time

7   =   Very Severe: feels very depressed nearly all of the time

9   =   Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*10. HOSTILITY: Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others during the past week. Do not infer hostility from neurotic defenses, anxiety or somatic complaints.

1   =   Not reported

2   =   Very Mild: occasionally feels somewhat angry

3   =   Mild: often feels somewhat angry, or occasionally feels moderately angry

4   =   Moderate: occasionally feels very angry, or often feels moderately angry

5   =   Moderately Severe: often feels very angry

6   =   Severe: has acted on his anger by becoming verbally or physically abusive on one or two occasions

7   =   Very Severe: has acted on his anger on several occasions

9 · =   Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*Ratings based primarily upon verbal report

*11. **SUSPICIOUSNESS:** Belief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances. Rate on the basis of reported (i.e., subjective) information pertaining to the past week.

1 = Not reported

2 = Very Mild: rare instances of distrustfulness which may or may not be warranted by the situation

3 = Mild: occasional instances of suspiciousness that are definitely not warranted by the situation

4 = Moderate: more frequent suspiciousness, or transient ideas of reference

5 = Moderately Severe: pervasive suspiciousness, frequent ideas of reference, or an encapsulated delusion

6 = Severe: definite, delusion(s) of reference or persecution that is (are) not wholly pervasive (e.g., an encapsulated delusion)

7 = Very Severe: as above, but more widespread, frequent, or intense

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*12. **HALLUCINATORY BEHAVIOR:** Perceptions (in any sensory modality) in the absence of an identifiable external stimulus. Rate only those experiences that have occurred during the last week. DO NOT rate "voices in my head", or "visions in my mind" unless the patient can differentiate between these experiences and his or her thoughts.

1 = Not reported

2 = Very Mild: suspected hallucinations only

3 = Mild: definite hallucinations, but insignificant, infrequent, or transient (e.g., occasional formless visual hallucinations, a voice calling the patient's name)

4 = Moderate: as above, but more frequent or extensive (e.g., frequently sees the devil's face, two voices carry on lengthy conversations)

5 = Moderately Severe: hallucinations are experienced nearly every day, or are a source of extreme distress

6 = Severe: as above, and has had a moderate impact on the patient's behavior (e.g., concentration difficulties leading to impaired work functioning)

7 = Very Severe: as above, and has had a severe impact (e.g., attempts suicide in response to command hallucinations)

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*Ratings based primarily upon verbal report

13. **MOTOR RETARDATION:** Reduction in energy level evidenced in slowed movements. **Rate on the basis of observed behavior of the patient only.** Do not rate on the basis of the patient's subjective impression of his or her own energy level.

   1 = Not observed

   2 = Very Mild and of doubtful clinical significance

   3 = Mild: e.g., conversation is somewhat retarded, movements somewhat slowed

   4 = Moderate: e.g., conversation is noticeably retarded but not strained

   5 = Moderately Severe: e.g., conversation is strained, moves very slowly

   6 = Severe: e.g., conversation is difficult to maintain, hardly moves at all

   7 = Very Severe: e.g., conversation is almost impossible. does not move at all throughout the interview

14. **UNCOOPERATIVENESSS:** Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. **Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation.** Do not rate on the basis of reported resentment or uncooperativeness outside the interview situation.

   1 = Not observed

   2 = Very Mild: e.g., does not seem motivated

   3 = Mild: e.g., seems evasive in certain areas

   4 = Moderate: e.g., monosyllabic, fails to elaborate spontaneously. somewhat unfriendly

   5 = Moderately Severe: e.g., expresses resentment and is unfriendly throughout the interview

   6 = Severe: e.g., refuses to answer a number of questions

   7 = Very Severe: e.g.. refuses to answer most questions

*15. UNUSUAL THOUGHT CONTENT: Severity of delusions of any type - consider conviction, and effect on actions. Assume full conviction if patient has acted on his or her beliefs. **Rate on the basis of reported (i.e., subjective) information pertaining to past week.**

    1 = Not reported

    2 = Very Mild: delusion(s) suspected or likely

    3 = Mild: at times, patient questions his or her belief(s) (partial delusion)

    4 = Moderate: full delusional conviction, but delusion(s) has little or no influence on behavior

    5 = Moderately Severe: full delusional conviction, but delusion(s) has only occasional impact on behavior

    6 = Severe: delusion(s) has significant effect, e.g., neglects responsibilities because of preoccupation with belief that he/she is God

    7 = Very Severe: delusion(s) has major impact, e.g., stops eating because believes food is poisoned

    9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

16. BLUNTED AFFECT: Diminished affective responsivity, as characterized by deficits in facial expression, body gesture, and voice pattern. Distinguish from EMOTIONAL WITHDRAWAL, in which the focus is on interpersonal impairment rather than affect. Consider degree and consistency of impairment. **Rate based on observations made during interview.**

    1 = Not observed

    2 = Very Mild: e.g., occasionally seems indifferent to material that is usually accompanied by some show of emotion

    3 = Mild: e.g., somewhat diminished facial expression. or somewhat monotonous voice or somewhat restricted gestures

    4 = Moderate: e.g., as above, but more intense, prolonged, or frequent

    5 = Moderately Severe: e.g., flattening of affect, including at least two of the three features: severe lack of facial expression, monotonous voice, or restricted body gestures

    6 = Severe: e.g., profound flattening of affect

    7 = Very Severe: e.g., totally monotonous voice, and total lack of expressive gestures throughout the evaluation

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*Ratings based primarily upon verbal report

17. EXCITEMENT: Heightened emotional tone, including irritability and expansiveness (hypomanic affect). Do not infer affect from statements of grandiose delusions. **Rate based on observations made during interview.**

    1 = Not observed

    2 = Very Mild and of doubtful clinical significance

    3 = Mild: e.g., irritable or expansive at times

    4 = Moderate: e.g., frequently irritable or expansive

    5 = Moderately Severe: e.g., constantly irritable or expansive; or, at times, enraged or euphoric

    6 = Severe: e.g., enraged or euphoric throughout most of the interview

    7 = Very Severe: e.g., as above. but to such a degree that the interview must be terminated prematurely

18. DISORIENTATION: Confusion or lack of proper association for person, place or time. **Rate based on observations made during interview.**

    1 = Not observed

    2 = Very Mild: e.g.. seems somewhat confused

    3 = Mild: e.g., indicated 1982 when, in fact, it is 1983

    4 = Moderate: e.g., indicates 1978

    5 = Moderately Severe: e.g., is unsure where he/she is

    6 = Severe: e.g., has no idea where he/she is

    7 = Very Severe: e.g., does not know who he/she is

    9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

GLOBAL RATINGS

19. SEVERITY OF ILLNESS: Considering your total clinical experience with this patient population, how mentally ill is the patient at this time?

    1 = Normal, not at all ill

    2 = Borderlilne mentally ill

    3 = Mildly ill

    4 = Moderately ill

    5 = Markedly ill

    6 = Severely ill

    7 = Among the most severely ill patients

20. GLOBAL IMPROVEMENT: Rate total improvement whether or not, in your judgment, it is due to treatment.

  — At *lithium-double blind* baseline, circle "Not assessed."

  — For all other *lithium-double blind* ratings, rate Global Improvement as compared to *lithium double-blind* baselilne

  — At *lithium-open treatment* baseline, circle "Not assessed."

  — For all other *lithium-open treatment* ratings, rate as compared to *lithium-open treatment* baseline.

    1 = Very much improved

    2 = Much improved

    3 = Minimally improved

    4 = No change

    5 = Minimally worse

    6 = Much worse

    7 = Very much worse

    9 = Not assessed