Overall Design and Methodology of the Israeli High-Risk Study

by Shmuel Nagler

Abstract

The unique contribution of the Israeli high-risk study is the comparison of children at risk for schizophrenia with matched controls in two settings: those raised in nuclear families in towns, and those raised in children's houses on kibbutzim. Such a design makes possible direct comparison of genetic and environmental effects on the psychosocial functioning of a group of high-risk children, over time. In this article we describe methods of collecting and examining the sample, provide an overview of the examination procedures, and describe the basic principles of data analysis.

The Israeli high-risk schizophrenia study is an ongoing investigation comprising data collected periodically over the past 15 years from a sample of children at risk for development of schizophrenia and a matched control group. In the articles that follow, we report on results of the initial investigation of these subjects, performed when the majority of the group was in the preadolescent age range. Selected reports of the first followup study, performed when subjects were in their late teens, are also included in this issue, as is one followup report conducted when the subjects were in their mid-twenties. The present article deals with characteristics of the subject population, sampling methods, brief descriptions of the studies currently reported, and general organization of the project. Rationales for inclusion of each of the individual protocols will be discussed in more detail in subsequent sections.

The Sample

Our sample consists of 100 subjects: 46 boys and 54 girls. We planned to limit the sample as much as possible to children who were preadolescents at the time of the initial investigation. The age range of the subjects in 1967 (when they were first studied) was 8.1 to 14.8 years; the mean age of boys was 11.3, and that of girls was 11.4. The whole sample is divided into two subgroups: 50 children at high risk for schizophrenia, defined as offspring of a schizophrenic parent, who will be referred to as the index (I) subjects; and 50 children at low risk for schizophrenia, whose parents showed no symptoms of psychiatric pathology, who compose the control (C) group. The group of 50 high-risk children is again divided into two subgroups: 25 children born in a kibbutz to a schizophrenic parent, and raised from birth in a kibbutz children's home, hereafter called "IK" or index-kibbutz, and 25 children born to a schizophrenic parent in town, and raised in the usual family setting, the "IT" or index-town group. The 50 low-risk children are also divided into two subgroups, 25 "CK" or control-kibbutz children and 25 "CT" or control-town children. From a different point of view, the sample can be divided into 50 pairs; 25 kibbutz pairs and 25 town pairs, each consisting of an index and a control subject. Within each pair, the control was matched to the index (in pair matching) for the following variables in order of preference: (1) Both had to be classmates; (2) of the same sex; (3) about the same age (in a few instances an age gap of up to 1½ years was unavoidable); (4) the same ethnic origin; (5) born to a middle-class family; (6) same size of family; (7) similar parental
educational level; and (8) similar cultural level of the parents.

Having matched control to index within each pair, we tried to match each town pair to a kibbutz pair (interpair matching), according to the aforementioned variables, so that the 100 subjects were finally divided into 25 "quadrons," each consisting of one kibbutz pair and one town pair. In interpair matching, we had to compromise because of the small size of some of the kibbutz school classes, even regarding the sex variable, and to combine five kibbutz pairs of girls with five town pairs of boys. From among the 50 schizophrenic index-parents, we had 38 mothers and 12 fathers; 6 boys had a schizophrenic father, 17 boys had a schizophrenic mother; 6 girls had a schizophrenic father, 21 girls had a schizophrenic mother. Ninety-six percent of control families and 80 percent of index families were intact up to the time of the first examination; in the remainder, the parents were either separated or divorced. However, in 36 percent of the index cases, one parent was temporarily absent from the home due to hospitalization or for some other reason at the time of initial testing.

In one case, the spouse of the identified schizophrenic parent also proved to be schizophrenic. Global estimates of psychopathology were made for 46 index spouses seen by the social worker at the time of the parental interview (see below). Ratings were made on a 1 to 4 scale, in order of increasing psychopathology. Of the index spouses seen, 59 percent were rated "1," 14 percent rated "2," 23 percent rated "3," and 4 percent rated "4" on this scale.

The Sampling Method

The logistical problems we had to face in setting up our sample were difficult because of the ethical considerations intrinsic to clinical research in general and in the kibbutz setting in particular.

At the time we began our project, no general register of psychiatric patients was in existence in Israel. If there had been such an arrangement, the act of conveying the registered information to a research team would have been looked at as a violation of medical ethics. Most of the psychiatrists we approached refused to cooperate with us on the basis of their obligation to observe without compromise the rule of confidentiality. In addition, since at that time (1965), clinical research could still be considered a pioneering undertaking in Israel, we were also unable to elicit cooperation from the heads of the psychiatric institutions where we hoped to find most of the patients according to our selection criteria for index-parents (see below).

We decided to appeal to the Ministry of Health for a general permit for access to the card index of every psychiatric hospital and/or outpatient clinic. This request was also denied. The reason given was that such an act could be considered an unwise interference with the autonomy of the respective institutions. Thus, we had to find our own ways to locate our 50 index parents, and at the same time, observe the legitimate right of the patients for anonymity. To guarantee this, we made it a rule that no member of our research team should contact any of the would-be index parents, whether they were at that time hospitalized or not, unless the doctor in charge had previously explained to the patient or to the patient's spouse what the project was all about. Then he could obtain their consent to cooperate with us. Thus, all index-parents were fully informed about the reason their child was included in our sample. We were aware that under such circumstances it was possible that only less-afflicted patients would be ready to give their consent. This could lead to a biased formation of the sample, but in fact, there were very few refusals. Such rare cases of refusal were expressed more often by the patient's spouse than by the patient.

We worked out a standard procedure that was followed step by step (with only a few exceptions, due to special conditions in one or the other kibbutz). On the basis of the author's personal relationships with the more research-minded and interested psychiatrists at hospitals, we approached these psychiatrists, and with their cooperation, administrative personnel at their respective institutions were given the task of examining hundreds of hospital registration cards. The kibbutz population in Israel was never more than 4 percent, which means that in the kibbutz sector, there is a much smaller selection pool than in town. Therefore, we were first and foremost trying to locate suitable kibbutz-cases, and only after that, did we look for matching town-cases. We, therefore, looked for (1) all kibbutz patients diagnosed as schizophrenics with children of preadolescent latency age, born and raised in the kibbutz; and (2) middle-class town patients with children suitable for matching with these kibbutz families with respect to sex, age, ethnic origin, family size, and educational level of the parents.

The search through registration cards was usually not very effective because there was not enough adequate information concerning some of our criteria, such as ethnic origin, socioeconomic level, children's ages, and other essential data. Therefore, we came to the conclusion that in most institutions it
would be less time-consuming and more effective to discuss with the therapeutic personnel (doctors, psychologists, social workers, and nurses), individually or in groups, the objectives of our project. We described our sampling principles and tried to motivate them to recall patients, past or present, who might meet our criteria. Often memory proved more reliable than stacks of illegible reports in files, written in various languages, according to the psychiatrists’ origins.

After this first screening, each of the chosen index-parents and his or her spouse were invited to meet with one of the professional hospital staff members (preferably one who had established some therapeutic contact with the patient). The objective of our project was explained in general terms, in order to obtain consent for cooperation. However, each patient had to be told the truth; that his or her child was chosen because of the parent’s disease, and without any preconception on our or the hospital’s part as to the child’s state of health.

Parents were assured that all measures would be taken to counteract such suspicion by teachers or peers. It was emphasized that their child would always be paired with another child (of healthy parents) of the same group. Both of them would always be invited together to meetings with the research team. Everyone (except the patients and their spouses) was told that the children were selected at random, sometimes according to the A-B-C of family names, so that our real selection principles were well camouflaged. It was further stressed that nobody outside our team would ever have access to any individual material concerning our subjects. Each subject automatically became a number, and appeared as such in our files, index cards, and other records. It was also made clear that all expenses would be our obligation, including possible work-day compensations for accompanying adults.

We had some cases at that time, not hospitalized, who lived and worked in a kibbutz. In such instances, the motivating talk was carried out by the local medical nurse, with the psychiatrist’s consent. Our endeavors were fruitless in two town-cases and in one kibbutz-case, due to the spouse’s opposition.

The next step was the study of each individual case history. At the time the sample was gathered, there were no widely accepted inclusion criteria, such as the Research Diagnostic Criteria or DSM-III, for schizophrenia or its subtypes. Diagnostic labels such as process schizophrenia, pseudoneurotic schizophrenia, and borderline schizophrenia reflected the psychiatrist’s “Weltanschauung” rather than the psychic condition of the patients. The idea of reexamining our index-parents according to a unified diagnostic scheme had to be relinquished, if only for technical and financial reasons. We, therefore, used a checklist of symptoms that, by consensus of the research team, were felt to be closely related to the diagnosis of schizophrenia (table 1). We then selected patients whose records showed (1) a diagnosis of schizophrenia or any subgroup of schizophrenia; (2) several rehospitalizations because of the aforementioned disease; and (3) at least three of the symptoms appearing in the aforementioned checklist.

In cases where the diagnostic information in hospital records was

<table>
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<tr>
<th>Table 1. Symptom checklist: Criteria for selection of schizophrenic parent</th>
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<tr>
<td><strong>Severe autism</strong></td>
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<tr>
<td><strong>Neologisms</strong></td>
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<tr>
<td><strong>Markedly incoherent thought</strong></td>
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<tr>
<td><strong>Concretization</strong></td>
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<tr>
<td><strong>Autistic logic</strong></td>
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<tr>
<td><strong>Marked ideas of reference and/or influence phenomenon</strong></td>
</tr>
<tr>
<td><strong>Many hallucinations</strong></td>
</tr>
<tr>
<td><strong>Marked over-aggressiveness</strong></td>
</tr>
<tr>
<td><strong>Continuous or very frequent catatonic behavior</strong></td>
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<tr>
<td><strong>Continuous bizarre behavior</strong></td>
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<tr>
<td><strong>Markedly dull, flat, or poor affect</strong></td>
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<tr>
<td><strong>Marked apathy or indifference</strong></td>
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<tr>
<td><strong>Marked negativism</strong></td>
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<tr>
<td><strong>Marked hypobulia</strong></td>
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<tr>
<td><strong>Mutism</strong></td>
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<tr>
<td><strong>Absorbed by own psychotic thought content</strong></td>
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<tr>
<td><strong>Continuous lack of interest in own appearance</strong></td>
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<tr>
<td><strong>Continuous lack of interest in other patients</strong></td>
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<tr>
<td><strong>Marked mannerisms</strong></td>
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<tr>
<td><strong>Continuous ideas of persecution</strong></td>
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<tr>
<td><strong>Megalomania</strong></td>
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<td><strong>No participation in occupational therapy</strong></td>
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incomplete, hospital doctors were approached by Professor S. Kugelmass to clarify the diagnosis and decide about the patient's suitability. He was in a position to do so, because he had no direct contact with subjects and no individual evaluation tasks in the project; i.e., he had no reasons to be kept "blind." Table 2 lists the distribution of symptoms in the final sample of 50 index cases as abstracted from hospital records.

As soon as an index case was considered suitable, a corresponding control subject had to be located. Ways and means by which we selected controls differed in the town and kibbutz. In the kibbutz, the medical nurses had all the members' medical records and helped us find a suitable control. They also contacted the child's parents and educators for cooperation, all the while keeping our real research goal a secret. Our "official" goal was "the comparison of behavior and development of children born and reared in the kibbutz vs. town." The nurse was instructed to stress the fact that the research project was being sponsored by the educational authorities of the kibbutz movement, headed by Dr. Shmuel Nagler of "Oranim," and carried out at the Kibbutz Research Institute.

Whereas all subjects of our kibbutz sample, studying in the same school class, had the same past regarding their educational settings during all developmental stages, we could not make this a condition in our town sampling. We, therefore, emphasized only the present-day school setting (besides all other criteria) for index and control. Up to the point of searching for a matchable control child in town, all the information we had at our disposal concerned the child's age, school, classroom, neighborhood, size of family, ethnic origin, and parent's educational level. In order to search for subjects in individual school classrooms, permission had to be obtained from the Ministry of Education, regional school inspectors, and finally, classroom teachers.

During the process of obtaining the necessary permission, we stuck strictly to our "official" research goal: "to compare behavior and development of children reared in the kibbutz vs. children reared in the nuclear family in town." We gave the teacher a questionnaire, asking for a list of all girls (or boys, according to the index's sex) whose family names started with a range of five letters, including the already selected index subject. She usually obtained an average of about 15 names. The questionnaire required information on each child listed, covering most of our matching criteria. This enabled her to pick the most suitable control child in class. Since these elementary schools were neighborhood schools, most of the criteria (especially those concerning socioeconomic and cultural levels) were matchable.

When compromises had to be made, we always adhered to our order of preference. Teachers were asked to elicit the cooperation of the selected child, emphasizing that the school authorities were most interested in the research project and that they appreciated the parents' cooperation.

The final stage in the selection of control children actually took place at the time the family was interviewed by the social worker. At this point, there was a chance to assess serious psychopathology in either parent that had not previously come to light. In 12 instances, children had to be disqualified and replaced in the control group because such parental pathology was discovered.

Having described our sampling in kibbutz and town, we would like to mention some of the difficulties we had to overcome in both settings. There were kibbutzim where the population was very small, with very few children. This meant that school classes were not quite homogeneous regarding pupils' ages. In such instances, we were forced to accept age differences between index and control up to 1½ years. However, in the majority of cases, we tried to keep the age difference as low as possible—usually not exceeding 5 months. We also encountered difficulties in judging the comparability of the socioeconomic and educational

Table 2. Distribution of symptoms in schizophrenic parents

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent of sample</th>
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<tr>
<td>Delusions</td>
<td>80</td>
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<tr>
<td>Suicidal ideation, tearfulness, or mention of depression</td>
<td>70</td>
</tr>
<tr>
<td>Over-aggressiveness, hyperactivity, grandiosity, or mention of mania</td>
<td>70</td>
</tr>
<tr>
<td>Other miscellaneous symptoms</td>
<td>68</td>
</tr>
<tr>
<td>Thought disorder</td>
<td>64</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>60</td>
</tr>
<tr>
<td>Bizarre behavior</td>
<td>48</td>
</tr>
<tr>
<td>Inappropriate affect</td>
<td>36</td>
</tr>
<tr>
<td>Catatonia</td>
<td>26</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>22</td>
</tr>
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level of parents. Whereas in town, the present occupation and living standard of oldtimers in Israel usually reflect their economic and educational level, this is not applicable in the kibbutz. For instance, in the kibbutz, the director of a large technological plant enjoys the same living standard as one of his manual workers, and the manual worker may be a university graduate, but living this kind of life for ideological reasons. So we decided to put more weight on the original educational level of parents, rather than their present occupation. In some cases in building our "quadrons," the education of parents of the town subjects was slightly lower than that of kibbutz subjects. The economic level of our town population is middle class.

Since we had to match town-index cases to the available kibbutz index cases, we had some difficulty finding the town counterparts to highly educated kibbutz members. In town, such persons seem to do everything to avoid hospitalization, preferring private treatment. Consequently, it took a long time to discover the few suitable cases. We wanted to adhere as much as possible to our selection criteria; therefore, each of the above-mentioned steps, particularly the location of the right index cases, was very time-consuming. Thus, there was some overlap in sampling and examination activities.

**Statistical Analysis**

Statistical analysis took into consideration the particular strategy of careful matching of the subjects in quadrons. Each of the subgroups actually contained a relatively small number of subjects (n = 25) with variance in important related variables. This seemed particularly striking in regard to the variance of age (8–14 years). It was felt that it was most appropriate to use matching to neutralize the effects of these variables and thus permit any effects of the main research variables of interest to be more clearly evaluated. The decision was made to use the $t$ test for matched pairs adapted to a condition of matching in groups of four (matching of the city and kibbutz indexes with their specific controls).

Three different sets of difference scores were thus calculated and served as the basis for their respective $t$ tests of significance. The first set of 25 difference scores (D1) was calculated so as to evaluate the possible significance of differences between index and control cases in the two different environments: $D1 = (IK + IT) - (CK + CT)$. The second set of difference scores (D2) was calculated to evaluate the possibility of differences between town and kibbutz environments: $D2 = (IK + CK) - (IT + CT)$. The third set of difference scores (D3) gives us the basis for an evaluation of an interaction between the index-control variable and the town-kibbutz variable: $D3 = (IK - CK) - (IT - CT)$. Following the calculation of these difference scores, it was possible to test for the significance of these three influences using $t$ tests of the form:

$$t = \frac{(\text{mean } D - \text{error (mean } D))}{\text{(estimated variance (mean } D))} \text{ where error (mean } D) \text{ is assumed to be zero.}$$

Quadron analysis was the basic univariate statistic used to test group differences and interactions in both clinical and objective evaluations. However, quadron analysis was supplemented by more standard procedures, such as analysis of variance, when deemed appropriate.

**Procedures**

Below is an outline of the overall organization of subject examinations and testing procedures as they were used during the initial (1967) examination period. While the articles that follow also deal with several of the procedures that were repeated during the first followup period (1973), results of procedures that were performed only during the followup investigation will be reported in subsequent publications. Two series of examinations on 2 different days were carried out: the first at the Child Guidance Clinic at Oranim Teachers' College, and the second, usually 1 week later, at the Department of Psychology, Hebrew University, Jerusalem.

**Examination Day at Oranim.** Those subjects who came from a long distance were accommodated the day before the examinations, together with their parents or other adults accompanying them, at a small boardinghouse in Tivon (a small garden-city near Oranim). Children who did not have to travel so far arrived the same morning, either accompanied by some adults or by our secretary, who on this day served as their hostess. We helped parents and other guardians plan their activities so that they were away from Oranim for the whole day in order to avoid any contact between subjects and their parents or child-care workers, and particularly between our research personnel and these adults. Activities began between 8:30 and 9:00 a.m. Children were given refreshments and introduced to the author for a short warm-up talk. The subjects' reactions, their questions during and after my explanations, their answers, and last but not least, their nonverbal communication gave me
an impression of their motivation to cooperate. Sometimes anxieties were noticeable, especially with children who were reminded of “school exams.” I always made a point of stressing that we were not at all interested in individual achievements and did not give any marks as they do in school. I think, in most cases, I did succeed in creating a warm, relaxed atmosphere from the beginning, to counteract the possible arousal of anxiety. Finally, I described the day’s program, expressing my hope that they would enjoy being our guests and suggesting that they turn with every possible request or problem that might arise, to our hostess. After that, the day’s schedule was as follows:

1. First part of the clinical interview performed by Shmuel Nagler, Ph.D. (clinical psychologist). Time: 40–50 minutes.

2. A set of experiments performed by Michaela Lifshitz, Ph.D. (clinical psychologist), consisting of (a) individual rhythm experiment, (b) mirror drawing experiment, (c) distractibility experiment, (d) learning experiment, (e) digit span experiment, and (f) decision-making experiment. Time: 50–60 minutes.

3. First half of psychometric test battery administered by Shaul Sohlberg, Ph.D. (clinical psychologist), including (a) figure drawing test, (b) Bender-Gestalt test, (c) Wechsler Intelligence Scale for Children (four verbal subtests), (d) Taylor closure test. Time: 60–90 minutes.

4. Second half of psychometric battery administered by Shaul Sohlberg, Ph.D. (clinical psychologist), including (a) Rorschach, (b) specially designed sentence completion test, (c) thematic apperception test, (d) Sarason anxiety scale. Time: Approximately 60 minutes.

5. Second part of the clinical interview performed by Shmuel Nagler, Ph.D. (clinical psychologist). Time: approximately 50 minutes.

After each set of experiments mentioned above, subjects returned to the playroom where they had 10–15 minutes of free time, with refreshments, sweets, toys, and our hostess at their disposal. She saw to it that they enjoyed these intermissions and were kept in good spirits. The hostess observed unobtrusively and informally the subjects’ behavior during these breaks, and anything that seemed interesting to her was recorded afterwards.

The sequence of procedures was exactly the same for both subjects (A and B). However, while subject A began with the activities, i.e., the first half of the clinical interview, subject B had time at his disposal, which he spent in the playroom with our hostess, waiting until subject A finished that procedure. Then subject A went on to Dr. Lifshitz’s experimental battery, while subject B began his clinical interview with Dr. Nagler. Thus, subject A was always (until they met during lunchtime) ahead of subject B. By the end of the experimental day, subject A had to wait for subject B to complete his part. That meant that one of them had about an hour’s waiting time in the morning and the other one had about an hour’s waiting time in the evening. Our hostess had extracted from subject A a promise not to tell subject B what was ahead of him, so as not to spoil the “surprise” that was waiting for him. It usually worked out that way. The examination day ended by about 6:00 p.m. when the subjects were brought to their guardians or their destinations, according to individual arrangements.

Examination Day in Jerusalem. Again, children who came from a distance arrived the evening before the examination day and spent the night together with the accompanying adults in a private flat at their disposal, which was in walking distance of the university. Children from Jerusalem and vicinity came directly to the examination the same morning.

The examinations took place in the morning hours only, and were scheduled as follows:

1. Electrophysiological examinations, planned by Sol Kugelmass, Ph.D., and carried out by Joseph Marcus, M.D., and Joseph Shmueli.

2. Neurological examination: This examination was planned and carried out by Joseph Marcus, M.D.

Behavioral Observations. All team members who had direct contact with subjects during interviews and testings (Nagler, Lifshitz, Sohlberg, and Marcus) were requested to observe subjects’ behavior during these activities and (in addition to test-specific behavior scores built into their respective test score sheets) to fill out a uniform observation score sheet.

Observations and Group Tests in Classrooms. We decided that it was of importance to observe our subjects, not only in laboratories, but in their routine school environments as well. Shoshana Yaniv (educational psychologist) was given the task of visiting each class where our subjects (always a pair of index and control) were in school at that time—50 classes all over the country. Her duties consisted of (1) observation of each subject during a lesson, using a time sample method, with special attention given to automatic movements and recorded on specif-
ically prepared score sheets; and
(2) administration of a sociometric
test that was given to the class to
add more objective information
concerning subjects' social standing.
These classroom activities lasted
about 1½ hours.

Parental Interview. Through this
semistructured interview, we aimed
to obtain information (1) on present
behavior of our subjects arranged
according to specific behavioral-
dimensions; and (2) on develop-
mental phases which, according to
experience and research, could have
bearings on the etiology of schizo-
phrenia. This interview, which took
place whenever possible at subjects'
homes, was carried out by Judith
Heller Shotten (psychiatric social
worker).

Teachers' Interview. Since some
degree of distortion of parents’
descriptions of their children's
behavior and development could be
expected, and in order to obtain
information from other than their
home environment, interviews with
teachers in city schools, and with
teachers and child-care workers in
kibbutzim, were also carried out.
This interview was structured by
Moshe Ayalon (clinical psychologist),
and performed by him until he
became ill. The work was continued
by Hanna Merom (psychologist).

Anti-Bias Measures and
Insurance of Discretion

All team members who came into
direct contact with subjects for
assessment procedures had to be kept
unaware of the subjects' genetic
background. However, the
environment from which they came
(kibbutz or town) was too easily
recognizable to be kept a secret.
Children were approached by their
first names only, and all written
material was filed according to first
names and subjects' numbers. Three
team members who were involved in
preparation work and sampling
activities were, of course, informed
about subjects' identity. They were
our secretary and hostess, Loni
Bonwitt; our psychiatric social
worker who did the parental inter-
views, Judith Heller Shotten; and
Professor Shlomo Kugelmass, who
was in charge of affirming the sick
parents' diagnosis of schizophrenia.
All team members were expressly
asked not to exchange thoughts and
opinions about subjects examined by
them.

Order of examination of index and
control subjects on a given day
followed a prearranged sequence.
The sequence repeated every 16 test
days until completion of all exami-
nations. Subjects were told that the
arrangement as to who of the two
was first to enter examinations was
made according to the alphabetical
order of their names. Our hostess
then told subjects that the order was
either alphabetical, or reverse alpha-
betical, in order to conform to the
prearranged examination schedule.

The Author

Shmuel Nagler, Ph.D., now retired,
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