The Volunteer Subject in Research

Louis Lasagna and John M. von Felsinger

Anesthesia Laboratory, Harvard Medical School, Massachusetts General Hospital, Boston

CLINICAL research frequently depends, for its existence, on the cooperation of volunteer subjects, paid or unpaid. Such volunteers are often utilized to provide data to serve as a "normal" baseline, or a standard of reference, against which data from "abnormal" subjects (for example, patients) may be measured. This article deals with certain aspects of a study (*1*) of drug responses in a specific "normal" volunteer population: (i) the psychological make-up of the volunteers, (ii) the reasons involved in volunteering, and (iii) the interaction between these first two factors and "primary" drug effects in determining the total drug responses. Finally, the problem of using the results obtained in such volunteer groups for generalizations to the population at large are discussed.

In the course of certain pharmacological studies on healthy young male volunteers, routine Rorschach tests and psychological interviews were obtained on 56 subjects. These young men were from 21 to 28 years of age and (with a few exceptions) were college students. All of them received one or more drugs as a part of experiments for which they received a fixed hourly stipend.

An examination of the Rorschach data and interview material revealed what seemed to be an unusually high incidence of severe psychological maladjustment (Table 1). The nosological classification is an arbitrary one, chosen to simplify the presentation of data. The "pigeonholing" of individuals into neat psychiatric categories is admittedly an oversimplification that is intended here only to indicate, in a rough way, the magnitude or nature of the psychological disturbance. There is little question that most of the subjects listed in Table 1 would qualify as deviant, regardless of the diagnostic label affixed to them by examining psychiatrists or clinical psychologists. Of the three psychotics described, for example, two were hospitalized for psychiatric treatment either before or after the studies in our laboratory. One of the subjects listed as neurotic suffered from increasingly severe anxiety, for which he ultimately sought treatment in a psychiatric outpatient department. There the majority of staff members considered him to be schizophrenic. The incidence of homosexuality refers only to those volunteers freely describing overt and continuing homosexual activities and excludes any volunteers for whom evidence of homosexuality was only presumptive (for example, Rorschach responses or behavior under drugs). In all cases, *both* the Rorschach data *and* the interview material had to show significant deviation of personality structure and defense mechanisms from a broadly defined norm to warrant inclusion of a volunteer in the seriously maladjusted group.

Table 1. Incidence of psychological maladjustment in 56 volunteers.

Psychosis	3
Psychoneurosis:	
Under treatment	1
Seeking treatment	6
Others	5
Psychopathic personality	3
Alcoholism	1
Overt homosexuality	6*
Peptic ulcer, severe	1
Stutter, severe	1

* Two of these are also represented in psychotic group above.

The findings described thus raised the question of whether our "normal" sample was representative even of the special population subgroup from which it was drawn—that is, college students. Since our subjects differed from other students by reason of the very fact of volunteering for participation in experiments, it seemed reasonable to examine the literature for evidence of the importance of the "volunteer factor" in the accumulation of data.

Brower (*2*) studied the psychomotor performance of 59 volunteer psychology students and compared it with the performance of 149 students who were required to participate in the same experiments as part of their course. For five of the six measurements made, significant differences were demonstrated between these groups. Brower attributed these differences to variations in "incentive." Maslow (*3*) found considerable "volunteer-error" in a study of sexual habits of women. The volunteers in his study rated higher in both "self-esteem" and the incidence of "unconventional" sexual behavior than did his nonvolunteers. In another study, Maslow and Sakoda (*4*) studied the volunteer problem in conjunction with the acquisition of data from a college group by Kinsey and Pomeroy. Again, the volunteers rated higher in "self-esteem" than did the nonvolunteers.

Data from two college guidance clinics tend to confirm the suspicion that our volunteer group is indeed an abnormal sample in regard to personality problems. Fry (*5*) states that 16 to 20 percent of undergraduate students are seen in the guidance clinic at some time during their college career, usually with problems related to performance in the academic sphere. McArthur (*6*) estimates that up to 20 percent of college

students have serious adjustment problems, "usually neurotic but sometimes prepsychotic." In an essentially unselected sample of two college classes, Funkenstein and King (*7*) found that only 9 percent of 125 students were seriously maladjusted. Although it is difficult to be sure of the comparability of definitions of "serious maladjustment" when different observers are concerned, our group *seems* to show approximately an incidence of serious psychological difficulties that is twice as high as would be expected in an unselected college population.

An examination of the reasons for volunteering in our group is also of interest. A number of volunteers undertook to participate in experiments primarily for the monetary rewards. Many others, however, volunteered for other reasons. Some hoped to find professional advice and help or a drug that might prove "the golden key" to their personality problems. Some volunteered in a search for new experiences, much as a potential drug addict experiments with a variety of agents in a search for "thrills" or "kicks." Finally, there were certain volunteers whose primary reason for volunteering was a search for escape or release from personal problems and drives. This latter category included (among others) those who desired temporary relief from the boredom or pressure of everyday life, those who sought sexual gratification in a relatively guilt-free environment, and those who sought to satisfy self-destructive urges.

An interaction between "primary" drug effects and a psychological interpretation of, or reaction to, such effects, was reflected rather clearly in some of the subjective responses elicited from our volunteers. At times these "secondary" reactions were more marked than the "primary" drug effects. In these interactions, the basic personality of the subject and the reasons for volunteering seemed to modify the total response to a varying extent.

Certain subjects, for example, found that drug reactions which decreased reality contact were unpleasant. One subject described pentobarbital as unpleasant because "I was victimized by the drug. I dislike feeling sleepy when it's not produced by lack of sleep." Another subject found three different drugs (all of which produced a dulling of senses) extremely unpleasant because he feared that further dulling of his senses might occur without his knowledge or that he might not regain control of his senses. Both of these subjects had volunteered primarily for financial compensation, a fact that was not infrequently associated with a certain degree of apprehension and anxiety over the effects of the experiments.

The relationship of content of response to personality is demonstrated by the reaction of a homosexual volunteer to a dose of mescaline. Reduplication of visual images is a well-known occurrence after ingestion of this drug, but the fact that this subject described an infinite series of erect phalluses seems best interpreted as an idiosyncratic determination of content.

The presence of considerable chronic anxiety also appeared to affect responses to drugs, by providing, as it were, a certain psychological "substrate." Thus one volunteer with severe anxiety neurosis had as a prominent part of his reaction to a series of sedative drugs the "release of tension." The three psychopathic personalities included in our volunteer group were characterized by a poverty of responses to a series of five drugs. Whether this was due to greater "inertia" of affect in these people, or to purposeful understatement of their reactions, or to other factors is impossible to say. Certain subjects who volunteered mainly in a search for new experiences described their reactions to placebos as "disappointing" or "depressing," since they looked forward to drug-induced mood changes.

It must be emphasized that most of the responses described were in no sense "placebo-reactions." Our volunteers were usually able to recognize an inactive medication on days when such was given.

What conclusions may be drawn from these data in regard to the use of volunteers? (i) Volunteers may differ quite markedly from nonvolunteers in a number of important respects. (ii) Regardless of whether *specific* volunteers can be categorized as "normal," the personality of such subjects or their reasons for volunteering, or both, may be important determinants of their responses in an experimental situation (*8–10*). (iii) Perhaps, especially in the area of subjective reactions, a careful eliciting of responses may permit the dissection of "primary" drug effects from "secondary" psychological reworking of such effects. (iv) Placebo controls, although important, are not adequate safeguards in this area. (v) Generalizations from data based on "volunteers" should be cautiously made. This is only an exaggeration of a general problem in investigation. For example, it is well-known that certain effects of morphine in a patient with severe pulmonary disease or of digitalis in a patient with congestive heart failure may differ strikingly from those seen in healthy male volunteers. Less well appreciated at times is the fact that even with two groups of healthy males, the incidence of certain "drug effects" may differ markedly. An interesting example is the fivefold increase in the gastrointestinal toxicity of quinacrine in Ohio State medical students when compared with Sing Sing prisoners (*11*). There is thus ample reason for wariness in making generalizations regarding drug effects from a study, no matter how careful, of any *single* group of individuals, be they sick or healthy, volunteer or nonvolunteer.

In view of the abundant evidence for the remarkable effects of feeling states on a large variety of physiological and psychological functions, and the nature of many volunteer groups (prisoners, conscientious objectors, students, and so forth), generalizations and predictions deserve to be exceptionally reserved when *volunteers* are the sole source of data. The recent excursion by Huxley (*12*) into the pharmacology of the subjective response is a reminder that much of the literature on marihuana, morphine, heroin, and similar drugs is derived from the experiences of "volunteers"

with unusual psychological orientation and imaginative, romantic proclivities. Without denying the "reality" of responses in such people, it has proved scientifically unwise to assume that such responses are typical of those experienced by all individuals under all circumstances.

That generalizations from volunteer groups are *necessarily* invalid, however, is a nihilistic and pessimistic view as untenable as claiming that volunteer data are infallibly transferable to all other situations. For example, the results obtained in a study of drug-induced mood changes in young healthy male volunteers in our laboratory were quite comparable with those obtained in a similar study in elderly patients hospitalized for chronic disease (*13*). In addition, distinct and reproducible patterns of response could be discerned in the volunteer group (*14*). This apparent predominance of drug effects, cutting across personality differences, suggests that the modifying effects of personality and motivation may be relatively minor at times or may affect details without obscuring larger patterns of response. *How* important the modifying nondrug factors are needs to be determined, if possible, in each specific situation. It is obvious that an awareness of the problems involved and care in eliciting and describing data will help in avoiding error and improving precision.

A final word should be said about the possibility of using to good purpose the very characteristics of certain volunteers that render them different from their fellows. As previously pointed out, the total spectrum of a drug's effects is often apparent only when "abnormal," as well as "normal," states are studied. Purposeful focusing on subjects with "addict potential," or anxiety, or depression should render more easily detectable the effects of drugs on such parameters.

References and Notes

1. This work was supported by a grant from the Medical Research and Development Board of the U.S. Army, contract No. DA-49-007-MD-92 (made to Henry K. Beecher).
2. D. Brower, *J. Gen. Psychol.* **39**, 145 (1948).
3. A. H. Maslow, *J. Soc. Psychol.* **16**, 259 (1942).
4. ——— and J. M. Sakoda, *J. Abnormal and Social Psychol.* **47**, 259 (1952).
5. C. C. Fry, personal communication.
6. C. C. McArthur, personal communication.
7. D. Funkenstein and S. King, personal communication.
8. The entire problem of the operationist approach in pharmacology and psychiatry has been ably discussed by Wikler (*9, 10*).
9. A. Wikler, *Am. J. Psychiat.* **108**, 590 (1952).
10. A. Wikler, *Neuropsychiatry* **2**, 87 (1952).
11. E. K. Marshall, Jr., personal communication.
12. A. Huxley, *The Doors of Perception* (Harper, New York, 1954).
13. L. Lasagna, J. M. von Felsinger, and H. K. Beecher, unpublished data.
14. It is of interest, however, that those subjects in the study who gave "atypical" response to drugs were, in general, the more "abnormal" members of the group. (For example, the number of "anxiety-hostility" responses of the "atypical" reactor was likely to be higher than the median group score.) In this sense, therefore, the more "abnormal" volunteers increased the difficulty of observing distinct patterns of response within the group.

Toxicity of Cations toward Living Systems

William H. R. Shaw

Department of Chemistry, The University of Texas, Austin

THE correlation of metal-ion toxicity with some physical or chemical property of the metals presents a challenging problem. Biologists, physiologists, and toxicologists have expressed widely divergent opinions (*1, 2*) concerning the possibility of such a correlation. Some have argued that the complexity of the living organism precludes any simple relationship. Others have pointed out that complexity has been encountered in other fields of science and explained.

In an important paper, A. P. Mathews (*3*), basing his arguments on data obtained for the eggs of the fish *Fundulus,* demonstrated a significant relationship between metal-ion toxicity and "electrolytic solution tension" (standard electrode potential). J. R. Erickson Jones subsequently made careful measurements with the planarian (*4*) *Polycelis nigra* and the stickleback (*5*) (a fish). He again observed a rough correlation with standard electrode potential. W. Seifriz (*2*) presented an excellent discussion of the problem with particular reference to the slime mold.

The purpose of this investigation (*6*) is to describe a simple physiochemical model of the toxicological process and attempt to correlate the available data in terms of this model.

Consider an enzyme E_1 at a total molar concentration e_1 confined in a living cell. The enzyme finds itself in an environment containing its substrate s_1 with which it reacts at a rate V_1[a] to form a product s_2. Assuming that the enzyme obeys Michaelis-Menten kinetics, the following mechanism pertains:

$$E_1 + s_1 \underset{r_1}{\overset{f_1}{\rightleftharpoons}} \sigma_1 \xrightarrow{d_1} E_1 + s_2, \qquad (1)$$

where σ_1 is the enzyme-substrate complex, f_1 the rate-constant for the forward reaction, r_1 the rate-constant for the reverse reaction, and d_1 the rate-constant for the decomposition reaction.