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EFFECTS OF INFORMED CONSENT ON RESEARCH PATIENTS AND STUDY RESULTS

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Recent rulings by the National Institutes of Health about research grant applications require a detailed description of the manner in which informed consent of research subjects is obtained. Many researchers have been alarmed by the possibility that informing patients of the research nature of their treatment will severely limit the validity of results. Negative effects of informed consent in patients would include: resentment about being used as research subjects or about being given supposedly inactive treatments (for instance, placebo); anxiety resulting from knowledge that treatments are assigned arbitrarily; poor response to treatments which might be effective in a positively oriented nonresearch atmosphere. Another issue would be the researcher's anxiety and guilt about "using" patients, which might be alleviated by the patient's ignorance of research goals.

With regard to the patient's resentment of inactive treatments, Liberman stated, "If subjects were forewarned of placebo administration, many would not cooperate with the experimenter—such candid statements of placebo use early in the experiment would engender suspicion and perhaps hostility in subjects, making them undesirable if not unwilling candidates for placebo research" (18, p. 236). However, he did note that when the use of placebo was revealed to patients at the end of his experiment, "Almost all the subjects reacted to the disclosure in a relaxed fashion. Some expressed surprise but most were unruffled and left the room without any sign of resentment or dismay" (18, p. 238). Bukantz stated, "Indeed, I have been told by some highly qualified investigators that their patients are increasingly reluctant to sign the required consent form, particularly if the use of placebo is involved. It is very difficult to explain to a patient why he should be the one to voluntarily agree to receive no medication if the luck of the draw runs that way. His concern, quite justifiably, is with his own health, not with the advancement of medical knowledge" (5, p. 25). Similarly, Lasagna stated, "This business of consent has already deterred some investigators from doing research" (16, p. 1). He reported that a recently proposed study was dropped because less than 20 per cent of the informed patients agreed to sign the consent form and he questioned whether valid results could be obtained from such a selective population.

With regard to the possibility that premature disclosures might bring about faulty study findings, Liberman wrote, "To bring greater understanding into the dynamics of placebo reactivity, placebo research must be carried out under conditions as nearly similar to those occurring

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in *real* drug experiments as possible" (18, p. 236). Fisher, Cole, Rickels and Uhlenhuth stated: "Patients more often see themselves as being 'treated' rather than 'researched,' and this may provide a highly favorable setting for drug action. In many controlled experiments, the patients become definitely aware that they are participating in a research project (implying 'Let's see if the drugs will help you'), and such a perception could tend to inhibit drug action" (7, p. 151).

With such an atmosphere of negative expectations, there have been few attempts to evaluate objectively the pros and cons of these issues.

Over the last few years, we have participated in a number of clinical psychopharmacological studies in which careful concern was given to patients' attitudes and concerns about research procedures, although at the time it was still considered necessary for valid findings that patients be kept unaware of key facts indicating the research nature of their treatment. In this paper, we present material from some of our studies in which patients have been given information and instructions not usually given in such research and have nevertheless consented to participate. In addition, we discuss the findings of a survey in which patients were asked about their perceptions of the research procedures and goals in a drug study just completed.

METHOD AND RESULTS

In an 8-week double-blind, cross-over study of the effectiveness of imipramine and placebo on neurotic depressed outpatients, carried out in 1959–1960, Uhlenhuth and Park formulated the following statement for the patients: "The kind of trouble you have been telling me about often responds quite well to medicine. We now have two different medicines available that we know help many people with difficulties like yours. However, some people do better with one and other people do better with the other medicine. The best way to find out which of the two medicines is best for you personally is to try them both. So we have set up a treatment program which will give you the opportunity to do just that. You will be able to take each medicine for 4 weeks. At the end of the 8 weeks, if necessary, you may continue to take whichever medicine works best for you" (31, p. 103). This was presented to the patients as treatment rather than as research, although such a presentation of alternative treatments is not made in the usual treatment setting. Rather, patients are usually given one medicine and advised it will help them; then, if the medicine doesn't work, the doctor subsequently may switch to another medicine.

Nevertheless, neither the 42 patients who completed the treatment nor the 8 patients who dropped out indicated any particular interest or concern about this manner of presentation. On follow-up, it was determined that 2 patients were dropped because they were hospitalized, 2 obtained jobs which interfered with appointments, 1 complained that the medicine wasn't helping, 1 complained of side effects, and 1 was ill with a medical condition. There is inadequate information on the other patient. There is some evidence of possible factors influencing drop-outs. For instance, 4 of the 8 drop-outs were patients of one of the seven treating doctors. Thus, informing patients of an experimental manipulation of medicine—in their own interests—did not appear to result in drop-outs, and, in fact, the study doctors reported that patients appeared to accept the rehearsed speech without reservation. Similarly, subsequent to a 6-week double-blind controlled study of the effectiveness of meprobamate, phenobarbital and placebo, given in green, pink and yellow capsules of identical size and shape (30), patients generally did not exhibit inquisitiveness or reaction

when asked to take the three kinds of capsules in succession and then to rank capsule colors for effectiveness.

In the imipramine study, as well as in subsequent studies (19, 25, 32), patients were asked to participate in an apparently obvious research procedure: at each interview patients were given a surplus of pills and asked to cooperate by returning the remaining pills at the next scheduled interview. In the following interview, patients were asked whether they had taken the prescribed number of pills and, if a deviation was reported, the patient was asked to estimate the number of pills missed. The reason for this was not explained, and the patients did not ask for an explanation. Nevertheless, at least 70 per cent of the patient population (23) returned their bottles with the unused medication. It was also noted that in all our studies patients filled out forms, accepted use of tape recorders and were interviewed in rooms with obvious one-way screens but seldom commented and almost never complained about such procedures. We became increasingly interested in patient perceptions of research and research procedures but realized that we would learn little about this through their spontaneous comments.

To explore patient perceptions, it seemed necessary either to conduct exploratory interviews with patients who had completed a controlled study or to break with traditional taboos about informing patients of critical research aspects of their ongoing treatment. Following the former plan, a post-study survey was conducted, reported by Park, Slaughter, Covi and Kniffin (27), in which 72 anxious neurotic outpatients were carefully interviewed concerning their perceptions and opinions immediately following completion of a 1-week controlled drug study (19). Patients were reassured that their opinions were confidential and that constructive criticism was encouraged to improve administrative planning of clinic services. These patients had been subjected to multiple research procedures, including double-blind drug-placebo prescription, pill counts, evaluation by several interviewers, role playing by treating doctors, brief interviews, unexpected change of treating doctor after two interviews, completion of multiple forms, and one-way screen observation and tape recording of interviews. No statement was made to patients as to whether research was or was not involved.

Only 3 of the 72 patients were positive that any research was involved and only 17 would even consider this possibility. Of these 17 patients, only 2 were strongly negative about the possibility of having been research subjects. The patients tended to have only vague or mistaken ideas as to why different procedures were employed and missed the point that the treatments were not specifically administered for their own benefit but also—and primarily—for learning about how to help patients in general (2).

When asked to indicate on a five-point scale their expectations when coming into treatment, 31 of the 72 patients had expected "a complete cure," and 33 expected to be "a good deal better." Forty-six patients indicated that they were enthusiastic about the "treatment" they had received. Patients indicated more concern with the doctor-patient relationship than with research procedures. Thus, when each patient was asked to state his chief complaint about the program, 28 patients (39 per cent) had chief complaints specifically involving the treating doctor: 14 persons wanted more time to talk with the doctor, 5 wanted more advice from him and 9 patients stated that they were chiefly bothered by the change of treating doctor. Eighteen patients complained about degree of improvement, 7 had other miscellaneous complaints and 19 patients stated they had no complaints. No patient stated as

chief complaint their dissatisfaction with research procedures or research in general.

Patients were also specifically asked about responses to doctor change, one-way screen, tape recorder, forms and administrative procedures. They were asked to indicate positive, neutral or negative feeling about these items on a five-point scale. Negative reactions were significantly preponderant regarding doctor change and one-way screen, with relatively neutral reactions to the other items. Interestingly, of the tape recorder, forms and one-way screen, only the screen had not been explicitly identified for the patients. With regard to the recorder, patients were told the doctor was using it so that he could be relieved of taking notes. Although 39 patients (54 per cent) had noticed the screen, only 2 commented on it during the course of the drug study.

To explore further the possibility of breaking with the traditional taboo of informing patients of the research nature of treatment, Park and Covi in 1963 carried out a brief (1-week) non-blind treatment of 15 anxious patients with placebo. Each patient was told, "Mr. Doe, at the intake conference we discussed your problems and your condition, and it was decided to consider further the possibility and the need of treatment for you before we make a final recommendation next week. Meanwhile, we have a week between now and your next appointment, and we would like to do something to give you some relief from your symptoms. Many different kinds of tranquilizers and similar pills have been used for conditions such as yours, and many of them have helped. Many people with your kind of condition have also been helped by what are sometimes called 'Sugar Pills' and we feel that a so-called sugar pill may help you, too. Do you know what a sugar pill is? A sugar pill is a pill with no medicine in it at all. I think this pill will help you as it has helped so many others. Are you willing to try this pill?" (25, p. 337).

Surprisingly, 14 patients completed the treatment and showed symptomatic improvement as a group, on a 65-item symptom checklist, to a greater degree than patients in our double-blind studies of drugs and placebos. In this study, in which patients were asked to participate for only 1 week, no patients showed the expected resentment, although some were skeptical, and some showed friendly amusement, accompanied in at least 1 patient by a report of symptomatic improvement even before the "treatment" began. Furthermore, the social worker who interviewed some of the patients after the study reported that they were very different from patients seen after other drug studies: they appeared much more verbal, comfortable, inquisitive and free with comments.[2]

In spite of the fact that each patient was told the pills were placebos, only three patients were certain of this after the week of treatment. Five additional patients thought the pills probably were placebos. On the other hand, two patients thought the pills definitely contained drugs and four thought they probably contained drugs. Thus, there appeared to be limits in the capability of the experimenter to influence established concepts in the patients.

The five patients who were certain the pills contained either placebo or drugs showed more symptomatic improvement on the symptom checklist than the other nine patients, significant by the Mann-Whitney U-Test ($p < 0.05$). These five patients also tended to have a higher initial distress.

DISCUSSION

Our experiences in clinical psychopharmacological studies have led us away from an initial "black box" approach to patients as being like nonhuman subjects. In the traditional psychological approach,

[2] Unpublished material. Post-treatment interviews were conducted by Regina Slaughter, MSSW.

one feeds a variable into the "box" containing the subject and reads what comes out the other side but does not open the "box" to look inside to see what the experimental subject thinks of all this (10). It has often been assumed that the human subject could not contribute and would only become upset at being informed he was actually participating in research or being included as part of the research team. There has been concern that patients would respond poorly (5, 7, 18) and also the contrasting concern that giving a subject too much information would allow him to please the researcher by helping him find the result desired (21).

We learned that clinic outpatients come into our studies with deep feelings of trust and expectations of marked improvement, and they often do not believe they are subjected to research or are given inert medication, even when research paraphernalia are obvious or they are informed of the nature of the treatment. They will obediently perform "unusual" tasks in "unusual" settings without question. In some of our research, patients were given information usually withheld because such knowledge might have a detrimental effect on patients and study results. We found no evidence that this information had negative effects on either patients or findings.[3]

In fact, in the non-blind placebo trial (25), the patients showed more symptomatic improvement than patients who participated in our double-blind drug studies. Various factors might have accounted for this, but we will here consider only those factors which might account for patients showing positive responses as a *result* of being informed. First of all, the refreshing openness, uniqueness and yet harmless nature of our non-blind placebo treatment plan, along with a requirement that the patient be willing to participate, may have had a positive effect on patients similar to that noticed when a novel program was introduced in an industrial work environment ("Hawthorne effect") (12). The amusement and willingness to cooperate in the non-blind placebo trial may also have reflected for some patients the relief that their conditions were not considered so serious as to require drastic treatment but were mild enough for inclusion in an optional and novel research project, with decrease of "dread" (33) that they could become incapacitated and/or "crazy." (As an example of individual meaning, the knowledge the pills contained no medicine was of considerable positive significance for one patient because she was relieved of the fear of a suicidal attempt with them.)

Secondly, results of the non-blind placebo trial indicated that patients with clear ideas about the nature of treatment showed more improvement. Perhaps attempts to keep secrets from patients, such as the research nature of a treatment, in conjunction with obvious clues that the treatment is research, can leave patients uneasy and unclear about what is really going on. Kelman stated that the use of deception "may actually produce an unspecifiable mixture of intended and unintended stimuli that makes it difficult to know just what the subject is responding to" (13, p. 14). Should we not explore ways of controlling patient positive or negative bias other than by ambiguous deception? Parallels in purely clinical situations offer some clues. Ford (8) has discussed the importance of an appropriate straightforward explanation to a patient when he is referred by a physician for psychiatric evaluation. Informing a patient he has a fatal disease is a special consideration because the patient's wish to know and ability to handle an inexorable process must be taken into account.

Thirdly, probably anyone who has par-

[3] Our findings, of course, may have been biased by patients' high expectations about Johns Hopkins Hospital as a prominent medical center. Perhaps patients would be less willing to participate as informed research subjects in a small or less known clinic (5).

ticipated in clinical research has wrestled with the problem of medical ethics and has experienced at least a vague discomfort about concealing information from patients. Meyer pointed out that in our attempts to deal with such feelings and still carry through our research, "It may be that we tend to show less confidence and trust in patients subjected to experimental studies because of our own guilt. This tends in some measure to dehumanize our patients in such experimental projects." [4] Spiegel stated that "patients who respond favorably to treatment by ready acceptance of such intervention or even by the placebo effect are the very ones who may retain their symptoms in response to the physician's covert communication of anxiety and despair" (29, p. 1279). The patient, in conforming to his role in this quasi-psychodrama, must expend psychic energy on denial so that he doesn't trespass on the investigator's taboos about what he should know. This may explain why only 2 of 39 patients commented on the one-way screen during one study (27). Subsequently, it was learned that patients were particularly unhappy with this piece of equipment, and it is hypothesized they might have been more comfortable about it if it had been specifically identified for them.

Our personal experience suggests that patients' acceptance of procedures formerly concealed from them alleviates the investigator's possible guilt and makes the doctor-patient relationship more comfortable. We have evidence that even in a short term drug evaluation the doctor-patient relationship was more important to the patient than the various research procedures (27).

The practice of deception has generated its own problems in research. It is becoming common knowledge that deception is a frequent factor in experimentation (13), as exemplified by one research subject who said, "Psychologists always lie" (21, p. 779). These problems are in addition to the ethical issues, which have been strongly voiced recently (3, 14, 15, 22, 34).

A basic purpose of this paper is to suggest that the present anxiety about informed consent may be based partly on preconceived bias and that the process of informing patients is worthy of research in itself. Orne pointed out, "If one were to employ any form of deception, it is crucial to find out whether it is the subject or experimenter who is deceived." [5] We make assumptions that some information may have negative effects and even that some may have positive effects, but there has been little objective experimentation to test these assumptions with distressed patients as opposed to volunteer subjects. The issues of the patient's welfare and informed consent have become so prominent in clinical research that perhaps very few clinical psychiatric studies should be performed in the future in which critical information is withheld or false information is given, unless there is a control group in which the correct information is furnished to patients. This might extend and complicate a study, but it would prevent the continued use of grossly deceptive studies in a particular area of research unless the informed group furnished significantly different and inadequate results.

In some studies, relationship of the amount of information given to the degree of improvement is the primary focus of the research. Such a study was carried out by Hoehn-Saric, Frank, Imber, Nash, Stone and Battle (11), in which one group of patients was given a role induction interview preparing them for psychotherapy and one group was given no such preparatory information. The group prepared for psychotherapy showed significantly more improvement.

There are fascinating possibilities for studying the effects of giving and withholding information as related to the at-

[4] Meyer, E.: Personal communication, 1965.

[5] Orne, M. T.: Personal communication, 1967.

titudes and behavior of patients *and* researchers. An obvious project would be a controlled drug study in which half the patients were told everything the researchers knew about the study and half the patients were handled in the usual manner for such studies. However, it should be pointed out that the bias of the researcher about positive or negative effects of informed consent (28) and the patient's attitude about a particular clinic would *not* be controlled. Therefore, a collaborative project would be indicated, with the same study performed at different clinics with investigators holding different attitudes concerning patient responses. Post-study interviews by investigators not involved in the main study (27) could aid in obtaining relatively unbiased reports of patient perceptions. Our experience indicates that many patients who are informed that they are research subjects may have rather unique interpretations of what that means (25).

Special variables to be considered in results would be the patient's feelings about being used or the patient's desire to please the doctor. Possible benefits for the study arising from the patient's opportunity to furnish more information when given more information also should be considered. We feel that in appropriate settings patients can function as reliable members of a research group (26), although such an approach to a patient as a relative peer can be threatening to the doctor's need for the more formal psychological distance which preserves his traditional status. We have found several times that the tradition of keeping patients ignorant of our aims and goals has inhibited us from explaining certain procedures to patients and has prevented subsequent inquiry which might bring an explanation for unexpected results. For instance, in a study evaluating a positively interpreted side effect (dry mouth), patients experiencing dry mouth under the positive approach unexpectedly improved less than patients not given the positive interpretation (19). Since patients were given no indication that this was research, it became awkward to make follow-up inquiries of their subjective experiences. In a study of withdrawal symptoms after replacement of active tranquilizers with placebo in identical capsules (6), it became too conflicting to inquire later how patients felt when they were switched from their medicine to something else, since they were not forewarned of such a possibility. This lack of subjective reports is a problem in many areas of clinical research. For example, Bowers and Freedman (4) recently pointed out the difficulty of comparing subjective experiences in psychedelic states with those in acute psychoses because of the paucity of adequate subjective reports of the latter (9, 20, 24).

Informing patients might be especially helpful in long term studies and follow-up studies in which patient cooperation would be facilitated by the patient's awareness of the significance of his participation not only for himself but for patients in the future. This kind of doctor-patient collaborative atmosphere would be conducive to the acceptance of arrangements in which patients could be called back or visited at home at predefined intervals. This would be necessary for certain studies, such as evaluation of periodic oscillations of distress (17). There is a growing interest in such longitudinal studies, as opposed to brief cross-sectional evaluations which do not take into account long term factors such as periodicity.

Such doctor-patient collaboration could operate in a positive manner, with certain studies requiring dummy treatments or other alternative treatments to control for this positive atmosphere, with the patient aware that there are alternative treatments, some better than others, but agreeing to participate under "blind" conditions (1, 2). Our data (27) suggest that a patient will be more likely to ac-

cept such apparently undesirable research procedures if a doctor-patient relationship is first established which the patient can count on as the study is carried out and if the explanatory statements to the patient are carefully formulated. Furthermore, it appears that the more uncomfortable, disabling and/or life-threatening the patient's condition, the more likely patients will be to accept appropriately uncomfortable and/or dangerous experimental procedures (1). For instance, 14 out of 15 patients were willing to participate in our non-blind placebo trial. At the other end of the spectrum, dying patients agree to experimentation with a mechanical heart. On the other hand, neurotic patients generally would not and should not agree to dangerous experiments. Thus, the patient may actually be a good monitor for the appropriateness of a study.

SUMMARY

Many researchers have been concerned that adherence to rulings about informed consent in clinical research will severely limit patient cooperation and validity of results. We have presented evidence from our psychopharmacological studies which suggest that in the setting of the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital 1) the welfare of the patient and the doctor-patient rapport will be better protected in the long run if it is a matter of routine to inform the patient of key aspects of the research, 2) the patient's preconceived notions and prior experiences determine his expectations to a degree that they are not easily shaken by whatever information is given to him, 3) patients will be likely to accept unusual or even unpleasant research procedures when they are explained with care in the setting of a good doctor-patient relationship and 4) informed consent often does not limit studies and actually can be a valuable asset to research design.

Preconceived biases should be avoided concerning this issue. Further objective experimental exploration is suggested concerning the effects on both subjects and researchers of furnishing information usually withheld in clinical psychiatric experimentation.

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