

Exhibit P-73

ETHNIC VARIATIONS IN DRUG RESPONSE

Results of an International Survey

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The possibility that the cultural background of patients might influence the effectiveness of psychotherapy is today quite widely recognized, and has been extensively explored by such workers as Caudill (1959) and Sanua (1966). On the other hand, the possibility that this same background might influence the effectiveness of drug therapy has hardly been explored at all. Recently the editors of *Transcultural Psychiatric Research* carried out a small international enquiry on the subject, with interesting if inconclusive results. The present paper will review the background of the question and the results which the international enquiry provided.

BACKGROUND

There have been three main lines of development pointing to the possibility that culture might affect drug response. At the most theoretical level such a possibility came into view as soon as it was realized that culture did affect symptomatology, and that most psychotropic drugs attacked specific groups of symptoms rather than the basic psychopathological processes themselves. More concretely, however, there was the impression that North American psychiatry had to use higher doses of such drugs as chlorpromazine in order to obtain results which European psychiatry was apparently getting with lower doses. This impression crystallized in the work of Denber and his colleagues in Manhattan and Europe and is now, for certain drugs, a proven fact. Finally, the psychodynamic formulations of Sarwer-Foner and Azima provided a second theoretical basis from which to expect cultural influences on drug response through the medium of modal personality traits, and these formulations have also received experimental support in the findings relating personality traits to drug response in normal subjects.

Neuroleptics in Schizophrenia

The most direct of these pointers is clearly that comparing European and North American experience with the same drug, and one might think that if there were real differences here these would have been well documented long ago. The safety and latitude of most of the relevant drugs and the incomplete reliability of their effects, however, have meant that many psychiatrists use them "on demand," varying the dosage with the patient's progress or lack of progress; and no standard dosage is employed from one patient to another or from one hospital to another in the same country. In the chlorpromazine research surveyed by Heilizer (1960), for instance, the mean daily dosage in different studies ranges from 75 mg. to 2400 mg., and although the overall mean in North American studies (598.8 mg.) is almost three times that used in the British studies surveyed (207.1 mg.), the variation within each country was so great that this large difference in mean dosage is not statistically significant. This makes international comparison very difficult, and there are the further complications of possible differences in diagnostic outcome criteria, and in the manufacture of the drugs. In two instances, however, these difficulties have been faced and overcome. Psychiatrists crossed the Atlantic in both directions to ensure comparability of criteria and patient sampling, drugs were taken from the same batches, and the relatively rapid onset of extra-pyramidal side effects with the particular agents used provided guidelines to dosage. Definite results were thus obtained, but the question whether these results point to culture as a relevant variable can still be debated.

The drugs on which this comparative research has been done are the neuroleptics haloperidol and butaperazine; both have the newer disinhibitory effect rather than the sedative effect of chlorpromazine and both induce extra-pyramidal side effects quite early, though they otherwise show little toxicity. The results with haloperidol, though not followed up, were the more striking. When roughly comparable groups of psychotic patients were submitted to the drug in New York and Belgium, the U.S. patients required about ten times the mean dosage of the Belgian ones in order that equivalent clinical and therapeutic results might be obtained (Denber and Collard, 1962). The initial results with butaperazine in U.S. and Germany were less extreme, but no less significant (Denber, Bente, and Rajotte, 1962), and they have been reconfirmed with further strictly chosen samples (Denber *et al.*, 1961). Thus, when on the first trial the dosage was kept approximately equal (though adjusted to the individual patient and with the U.S.

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group having the higher average), 96 per cent of the German sample showed some improvement as compared with 40 per cent of the U.S. one, and the former group also showed a much more rapid development of neurological side effects. The results of that research are summarized in Table I.

TABLE I
EFFECTS OF BUTAPERAZINE TREATMENT IN COMPARABLE GROUPS OF U.S.
AND GERMAN PSYCHOTIC PATIENTS
(Summarized from Denber *et al.* 1961)

Clinical Outcome	U.S.	German
Marked improvement	4	18
Some improvement	4	7
Unchanged	11	1
Worsened	1	0
Side Effects		
Extra-pyramidal	8	18
Dyskinesia	0	8

On the second trial, dosage was not kept even but was progressively increased with each patient to the point where side effects discouraged further advance, and here it was found that the U.S. patients could tolerate roughly double the dosage level which the German ones could, showing at that higher level approximately the same clinical improvement as the German group did with the lower dosage. This last finding might suggest that the essential difference lay in the absorption of the drug (perhaps at the blood-brain barrier), but the latest and most interesting finding suggests that this is not the answer. Bente, studying the EEGs of the two samples taken before and at regular intervals during the trials, found not only differences in the time of onset of such EEG changes, but differences in their character (Bente *et al.*, 1968). These drug-induced EEG changes, different in different peoples, appear to be a most promising tool for transcultural psychiatry, especially if patients can be studied under different environmental conditions. In the present instance they correlated well with the side effects picture, but less well with the clinical improvement scores.

But naturally, when one obtains such neurological data, the first explanation which comes to mind is a genetic or, at least, biological one rather than a cultural one, and this was initially proposed, though it is difficult to see why the U.S. patient samples should regularly differ so greatly from the European, since all were white, and probably mainly of West-European origin. Hence a more complex explanation seems

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likely. The sociocultural explanations which have been suggested relate to the greater demands put on patients in the U.S. hospital than on patients in the European hospitals, the types of interaction which the patients are exposed to, and the general climate of action in the two continents; but these explanations also seem insufficient. Itil, a former collaborator in these studies, has recently argued that the psychopathological patterns of different patients may provide a more economical explanation than a combination of genetic and sociocultural factors (Itil, Keskiner, and Fink, 1966), and the increasing realization that the various neuroleptics have a selective action on different symptoms makes this a promising line to follow. But, of course, we know today that culture can influence the relative prominence of symptoms and hence the total psychopathological pattern, so that a more thorough investigation of possible cultural influences here still seems called for.

Personality Traits and Drug Response

The comparative studies with haloperidol and butaperazine make no reference to "paradoxical" reactions and relatively little reference to Sarwer-Foner's theory of interference with defences which consideration of such paradoxical reactions gave rise to, although that theory could be quite relevant to these findings. Sarwer-Foner states: "The typical pharmacological effect removes or interferes with activities used by the patient as the major defences against unconscious underlying conflicts." "Such patients respond to the 'chemical' interference with panic, agitation, increased despondency, paranoid reactions, distortions of body image, increased withdrawal, increased agitation, or markedly enhanced anxiety" (Sarwer-Foner, 1960). "Much of the efficacy of the medication, therefore, depends . . . [on] factors such as the attitudes of doctors, nurses and orderlies towards the patient, as well as their attitude towards the drug and towards the patient's responses" (Azima and Sarwer-Foner, 1961). On this theory we could expect that cultural determinants of defence systems would lead to cultural variation in the frequency of such paradoxical reactions, quite apart from the cultural determinants of the caring situation. Such a variation has not yet been demonstrated for schizophrenics, but something very similar has been found, and there is a growing body of literature on the influence of personality type on drug response which indicates where cultural differences might be found.

Research into the relevance of personality types can be said to have started at the Massachusetts Mental Health Center in the late 1950's,

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when it was found that many apparently normal subjects reacted in "paradoxical" fashion to small doses of reserpine and phenyltoloxamine (Klerman *et al.*, 1959). Comparing the orthodox and the paradoxical reactors on a battery of psychological tests, it was found that the orthodox tended to have a moderately high anxiety level coupled with limited ego strength, an intellectual orientation, and a passive disposition, whereas the "paradoxical" or "counter-reactors" scored significantly higher on ego strength, lower on anxiety, and were athletically oriented. Further research at the same center suggested that these two personality types reacted differently not just to reserpine and phenyltoloxamine, but to chlorpromazine and secobarbital, with the athletically-oriented becoming irritable, apprehensive and confused under the influence of these drugs while the intellectually-oriented became calmer, showed better social rapport, and performed better at mathematical tasks (Heninger, DiMascio, and Klerman, 1965). Elsewhere, a team studying diazepam with normal subjects arrived at a similar division of personalities in terms of anxiety level and activity orientation, but with this drug found a different combination of traits to be relevant; low anxiety plus low activity was the combination which yielded the most abnormal results (Frostad, Forrest, and Bakker, 1966). However, McDonald, questioning some of the methodology of the last-named study (McDonald, 1967*a*), repeated it with his own techniques and with female in place of male subjects, and obtained results which came closer to those cited earlier (McDonald, 1967*b*).

These studies were all carried out with neuroleptics, tranquilizers, or sedatives in low dosage, and their trend was to support Sarwer-Foner's theory. Other more recent work, however, has indicated that a more complicated relationship must exist. The "paradoxical" effects obtained by the Massachusetts team with chlorpromazine could not be reproduced with trifluoperazine, one of the first disinhibitory group of neuroleptics (DiMascio, 1968). Imipramine increased the MMPI depression score of subjects who had low scores previously (DiMascio *et al.*, 1967), although this would not seem to be predicted by Sarwer-Foner's theory. The paradoxical reactions elicited by chlordiazepoxide and diazepam disappear when the dose is increased, and at that level produce actually a greater reduction in anxiety among the low-anxious than among the high-anxious (DiMascio, 1968). We need not pursue such matters further. Almost certainly, future research will show that present formulations are oversimple, and that, for instance, a distinction will need to be made between conscious and unconscious orientation (Azima and Sarwer-Foner, 1961). An academic experiment in a college setting,

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moreover, confronts the subject with a very different situation from that which confronts the person who has been labeled sick or crazy, and we have to see the drug not as reacting with the personality but as intervening between the person and his situation. However, cultures do vary in the degree to which they encourage the development of activity-oriented or passivity-oriented personalities, and such studies suggest that it could be valuable to make a formal comparison between their patients on this question of drug response, though probably only when low doses are used. Certainly, the one experiment which has (heuristically) turned up a significant association between ethnicity or culture and drug response possessed just those elements, namely, low levels of dosage and two cultures which can more easily be differentiated on their activity orientation than on most other variables. But, as if to underline the difference between the experimenting with students and clinical applications, the association between personality trait and paradoxical response was in the opposite direction to that which the studies with "normals" would have predicted.

Ethnic Differences between "Paradoxical" and Orthodox Reactors

The research being referred to is that of Slater and Kastenbaum (1966) into the reactions of an institutionalized geriatric population to small doses of thioridazine and dextro-amphetamine. Ethnicity or culture was not intended to be one of the studied variables, but was discovered when a thorough comparison of the demographic backgrounds of the orthodox reactors and "counter-reactors" was carried out. The picture with which the researchers were confronted was that when low doses of the relevant drugs (7.5 mg. dextro-amphetamine or 30 mg. thioridazine daily) were given to their geriatric subjects, many of the latter exhibited the paradoxical reaction of lowered affectivity and vivacity under the stimulant and increased affect, irritability and self-criticism under the tranquilizer. Others, however, yielded the expected responses, and a detailed comparison of the two groups (the paper is very complete and indicates the exceptional thoroughness of these researchers) showed that they differed on four main dimensions. In the first place, the orthodox reactors were more active and concerned with keeping busy than the counter-reactors. Secondly, they were more concerned about themselves, their situation and their body; thirdly, when they were given a number of psychological tests which included the Draw-a-Person, the reactors followed the customary North American pattern of drawing a male figure first (regardless of the sex of the

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subject), whereas the counter-reactors predominantly drew a female. Finally, when their demographic characteristics were looked into, the orthodox reactors proved to be predominantly of Anglo-Saxon background and Protestant, whereas the counter-reactors were mainly of Irish background and Catholic. Table 2 (see below) gives the eleven variables out of the eighty-eight investigated which yielded differences at the 0.05 level, and although one would like to see the whole work replicated in order to reduce further the risk of the differences having appeared by chance, the whole hangs together. The concern with keeping busy, the greater involvement with the interviewer and the nursing staff, and perhaps the greater concern with their body's efficiency are much as one would expect from an Anglo-Saxon Protestant background, especially if one takes into consideration Zola's (1963) analysis of the reasons why different subgroups in Boston seek medical attention. The drawing of a female figure first and the acceptance of inactivity, on the other hand, fit what has commonly been written about Irish culture. The authors offer two main hypotheses to explain why it is the Irish group that should be counter-reactors, but conclude

TABLE 2
ITEMS DIFFERENTIATING ORTHODOX AND COUNTER-REACTORS
TO DEXTRO-AMPHETAMINE AND THIORIDAZINE IN A GERIATRIC POPULATION
(Summarized from Slater and Kastenbaum, 1966)

	Orthodox Reactors Mean Score	Counter- Reactors Mean Score	p.
A. Interview Check-List			
Copious in speech and performance	6.6	4.5	0.01
Audibility	8.5	6.7	0.05
Abstract thinking	6.7	4.8	0.05
B. Ward Behavior Check-List			
Thinks a lot about body	1.8	1.4	0.02
Attaches importance to keeping busy	1.7	1.2	0.05
Often looks tired	1.5	2.0	0.05
Usually sleeps soundly	2.4	2.8	0.05
C. Medical Record Items			
No. of notes on psychosocial matters	8.5	2.4	0.01
History of hypertension (No. of cases)	1.0	6.0	0.05
D. Psychological Tests			
Draws male figure first	87%	22%	0.05
E. Ethnicity			
Irish	7.7%	66.7%	} 0.02
Anglo-Saxon	61.1%	16.7%	

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that they have too little evidence to justify sponsoring either, and we can only follow them in this. However, the study forms an interesting bridge between the schizophrenia comparison series and those concerned with the personality traits of healthy reactors and counter-reactors, encouraging us to look further.

THE INTERNATIONAL SURVEY

One method of looking further is to enquire whether psychiatrists working with cultures or ethnic groups still more different than the Germans and Americans had noticed other differences in drug response. In the literature one comes across occasional references of this type in course of other discussions, as for instance when Aall-Jilek (1964) remarks on the low doses of phenobarbital needed to suppress epileptic attacks in the Wapogoro, an East African tribe. But these are too few and too difficult to locate for much reward to be likely, and an international enquiry of the type that the editors of this journal had used successfully with respect to the revelation of cultural differences in schizophrenic (Murphy *et al.*, 1963) and depressive (Murphy, Wittkower, and Chance, 1967) symptomatology seemed more likely to yield results, even though one would have to work only with impressions. For this reason it was decided to invite readers of the journal to report any impressions which they had with respect to possible ethnic differences in psychotropic drug response, and, more specifically, to invite such impressions from colleagues who had assisted in our previous international surveys.

The result of these attempts proved less informative than the results of our enquiries into symptomatology. It became fairly clear from remarks made to us that psychiatrists are so accustomed to tailor their pharmacotherapy to the individual patient's apparent requirements that broad comparisons between groups of patients are difficult to make. One switches from one drug to another, combines two or more, has modest goals for one patient and stops pushing the drug when these are reached, whereas with another patient one has higher goals and pushes one's therapy to the extremes of tolerability or safety. Accordingly, this proved not to be a subject on which many psychiatrists had already established opinions, and the volume of answers was smaller than on the two previous occasions. Nevertheless, what was received proved informative and did confirm our expectations that as cultural (and genetic) differences become more marked, impressions of a difference in drug response become more frequent.

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TABLE 3
GEOGRAPHIC DISTRIBUTION OF RESPONSES TO INTERNATIONAL ENQUIRY*

REGION MAINLY REFERRED TO	NEGATIVE	POSITIVE	
		Phenothiazines	Other Drugs
North America	2	2	1**
South America and Caribbean	4	0	0
Australia	1	0	0
Europe and Israel	9	1	0
Sub-total	16	3	1
Far East	2	2	0
South-East Asia	2	6	0
Middle East (excl. Israel)	1	3	0
North Africa	0	2	1
Sub-Saharan Africa (incl. Mauritius)	2	2	1**
Sub-total	7	15	2
TOTAL	23	18	3

* Where respondents refer to people from more than one region, it is the region of the patients most emphasized in the answer that is given.

** In the two cases indicated, only other drugs and not phenothiazines were named.

Table 3 gives an overview of the written answers received, and since it is more likely that someone would trouble to answer if he had noticed a possible difference than if he had noticed none, the large number of negative answers suggests that even when an interest in cross-cultural comparisons exists, differences between ethnic groups with respect to drug response are difficult to perceive. However, there is a considerable variation in the ratio of positive to negative responses when one compares different regions, and this is in itself informative. When respondents are reporting mainly or wholly on patients of European origin (whether they live in Europe or overseas), negative answers greatly exceed positive ones, and of the positive answers two relate to Asian immigrants. Apart from one answer referring to the butaperazine comparison study cited at the beginning of this paper, therefore, we have a written reply from only one psychiatrist who believes that drug response differences can be recognized in European or American peoples. (Other oral comments on differences between Europe and North America have been received, but these are not counted here.) On the other hand, a clear majority of respondents reporting on Asian or African patients, and usually but not necessarily contrasting

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them with Euro-American ones, do suggest that differences may exist, although the intensity of this belief varies both with the people referred to and with the background of the respondent.

From the Far East, Chinese psychiatrists are very doubtful whether there is any difference in drug effect which cannot be explained in terms of lower body weight, though some psychiatrists with other backgrounds coming in contact with Chinese patients do have the impression that such a difference exists. From Japan, a country where there is considerable interest in cross-cultural studies, we have this time received so few replies that it seems highly probable that the psychiatrists there have noticed nothing in this direction. However, a North American respondent who keeps in contact with Japanese psychiatric journals has pointed out to us that the prescribing patterns in Japan are somewhat different from those in the West so that, for instance, diazepam may be used, presumably alone and successfully, in the treatment of schizophrenia; and this invites further attention. Also, the one positive answer from Japan is interesting insofar as it suggests that the Japanese may respond less well to the phenothiazines than North Americans, whereas virtually all other respondents see the North Americans as showing the least response.

From Africa and the Middle East the answers are more positive, and it is virtually only from South Africa that we have received definitely negative reports. The broad picture throughout these regions is that local peoples seem to respond better to the phenothiazines than West Europeans, or alternatively to require lower maintenance doses of such drugs, but our informants provide some further interesting details. Thus, patients from Upper Egypt and patients from the Black Sea part of Turkey are reported to show a stronger response to the phenothiazines than those respectively from Lower Egypt and from Mediterranean Turkey. Extra-pyramidal side effects appear, according to a brief but formal study in Kampala, to occur less frequently in local patients than in Europeans, and the same may be true in Nigeria, although recent theory would lead us to expect that if extra-pyramidal effects were weaker, therapeutic effects would also be. However, several informants from this region indicate that they are unsure whether what they are observing is a response to the pharmacotherapy or a response to the social setting (a comment which echoes Sarwer-Foner) and one respondent from Egypt points out that assessments can differ according to what one thinks should be the proper mode of symptom resolution. British schizophrenics, in his experience, tend to encapsulate their delusions as they improve whereas Egyptian schizophrenics more

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usually modify their delusions in order to merge them with the system of beliefs that surrounds them.

These comments all concern the neuroleptics, but from Africa and the Middle East there are also some interesting suggestions to the effect that tranquilizers, antidepressants and neuroleptics used for the purpose of reducing excitement may work less well with the indigenous peoples than with Europeans or those who have had a European education. In Mauritius, tranquilizers and antidepressants appear to work satisfactorily only with the better educated; in Turkey the regional group that is most sensitive to the phenothiazines is least sensitive to the antidepressants; in Egypt the phenothiazines do not appear to be as successful in suppressing excitement as the same respondent had found with the British. However, in Teheran, where a formal investigation of the question is under way, it is the impression that both the phenothiazines and imipramine are effective in lower dosage than in the West.

Thus, there is plenty of interest in these responses from Africa and the Middle East, but one must also admit that they are diffuse and relatively uncorroborated, with no more than two informants per culture area, and it is to South-East Asia that one must turn for focused, near-unanimity of opinion. There, one meets a striking contrast between a total absence of positive answers from India and Pakistan and a relative abundance of positive answers respecting the Malays and Indonesians. Despite the many contacts which we have in India, almost no written answers were received from there, and when we spoke with Indian colleagues, the answer was always that no difference in drug response had been noticed—this was also the answer concerning the East Indian population in the Caribbean. Regarding the Malays and Indonesians, on the other hand, we received reports from one British, one Chinese, one German, one Indonesian, and two U.S. psychiatrists, all suggesting that a greater sensitivity to phenothiazine therapy exists in these peoples than in other peoples they had worked with. Moreover, one of these informants makes the point that he is contrasting them not so much with Euro-Americans as with East Indians whom he had treated in the same hospitals and under the same conditions; and two further informants report that although they had not observed differences in therapeutic effectiveness, they felt that patients in Malaya and Indonesia suffered more from somatic side effects.

Joined with the Malays in several informants' minds are the local Chinese and the Filipinos, but here we have less unanimity, and from Singapore (whose population is over 80 per cent Chinese) the most experienced local psychiatrist is of the opinion that any differences in

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drug response that he may have noticed are probably due to the lower average body weight of his patients.* Also, one respondent found his Filipino patients to be relatively unresponsive to drug therapy. This point must be left in abeyance, therefore. The reports on the Malays and Indonesians mention almost exclusively schizophrenia and the neuroleptics, and some respondents question whether it is a true schizophrenia that is yielding the better-than-expected responses, but those with the most experience locally do not seem troubled by this doubt. The only mention of antidepressants suggests that there is no difference in response with them, but two respondents suggest that there may be an increase in side effects with some of the tranquilizer group.

DISCUSSION

These are the essential results of our international enquiry—a broad impression that the effect of psychotropic drugs does vary with culture, and the specific impression that the action of neuroleptics in Malaysians deserves particular study. Such findings are slight in comparison with what we hoped we might achieve, but they have served our primary aim of locating a culture in which the question could be profitably pursued through intensive drug trials, and they remind us of an apparent paradox which deserves closer examination. The first report of an ethno-cultural difference in response to a neuroleptic was made in 1959, and our enquiry in 1967-68 shows that there are quite a number of locations around the world where similar, perhaps stronger, differences had been inferred. Yet, as far as the writer is aware, no laboratory, other than that of the original discoverers, has seriously studied the question, and although our respondents tell us of three or four comparative studies into the matter going on at present, these are relatively small affairs without the rigorous methodology that is today considered necessary when psychotropic drugs are evaluated. Of course, international comparison studies have been taking place, but their aim has usually been to see if psychiatrists can agree on some broad principles of diagnosis, treatment, and prognosis, not to investigate differences in response and thence hopefully to arrive at a better understanding

*We had initially assumed that mean body weight would be an important complicating variable, and had therefore asked correspondents to take it into account. However, an interesting comment from Egypt suggests that obese patients appear more susceptible to some neuroleptics than thin patients receiving the same unit dosage (and hence receiving a lower dose per kilo body weight).

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of drug action. Why has there been this neglect of a potentially valuable discovery?

Various factors come to mind, factors which make the required research less than easy; but there would probably be a greater effort to tackle them if there had not been a more basic problem, namely, that the discovery touches an unresolved weakness in our present thinking about mental illness, the division between psyche and soma. Socio-cultural factors are considered to impinge mainly on the former, drug therapy mainly or wholly on the latter, and most researchers belong squarely to one or other camp. Sarwer-Foner's formulations and the personality studies which have grown out of them offer a type of link, but one which re-emphasizes the dichotomy instead of reducing it, for he distinguishes sharply between the extra-pyramidal symptoms, assumed to be purely somatically mediated, and the "paradoxical" behavior which is assumed to result from the mind's reaction to what it feels is being done to the body that it inhabits. Bente's EEG findings were unforeseen by these formulations, and are unexplainable by them as they stand. Either an improved formulation is called for or there must be a readiness to go ahead investigating the problem without prior commitment to either point of view.

Of course, the presence of a sociocultural factor in the therapeutic effectiveness of psychotropic drugs can still only be inferred; it cannot be said to be proven either by the work on schizophrenics or by that on normal subjects. The clinical results could theoretically be explainable by genetic or dietary factors and the personality factors have still to demonstrate a relevance to therapy. But a genetic basis for the butaperazine findings is highly unlikely, given the very mixed background of New York patients and the probably by no means uniform ancestry of the Erlangen ones, while the use of intramuscular administration for one of the New York samples would seem to rule out the more simple interactions of diet and absorption. That is not to say that genotype is irrelevant or that the amount of drug reaching the brain could not be affected by diet, infections, etc.; but culturally-induced modes of psychosomatic adaptation seem at least equally relevant, whether one thinks of them operating at the level of drug metabolism, the blood-brain barrier, the arousal or vigilance level of the cerebral cortex, autonomic responses to drug-induced sensations, or subconscious reactions to the total treatment process. It would certainly be wrong to prejudge the matter and to assume that the differences reported, whether they relate to Americans and Germans or to Malays and East Indians, are culturally induced, but it would be equally wrong to ignore what

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the social scientist could tell us about the social backgrounds and settings of each group.

The three main differences in drug response which the present review has found are as follows:

- a) between European and American schizophrenics exposed to disinhibitory neuroleptics;
- b) between Malay and Euro-American schizophrenics exposed to various neuroleptics, but mainly to chlorpromazine; and
- c) between Anglo-Protestant and Irish-Catholic geriatric patients exposed to weak doses of a stimulant and a sedative.

Do we know anything about the broad cultural traits or symptomatology of these groups which would offer a clue as to why these differences were found?

Broadly speaking, American culture can be considered to differ most from the European ones which gave birth to it in its greater emphasis on independence and struggle, as opposed to the traits of interdependence and social adaptation. Hence, still very broadly speaking, one should expect in North America more of the athletically-oriented type of personality that is associated with the paradoxical reaction to small doses of psychotropic drugs than one would expect in Western Europe, and on the other hand one would expect greater trust in and acceptance of medical action (other things being equal) among the Europeans. McDonald (1967b) showed that the athletically-oriented reacted with increased hostility instead of with increased calmness to small doses of diazepam, and Lorr (see this journal, page 35) has shown that European functional psychotics show definitely less of the syndrome which he calls "hostile belligerence" than American ones do. The characteristics of hostile belligerence and independence, however, suggest an association not only with the athletic-orientation trait, but also with the vigilance which Bente, on the basis of EEG data, found to decline more rapidly under treatment in the European (Erlangen) schizophrenics than among the Manhattan ones (Bente *et al.*, 1968). Therefore, as a very tentative hypothesis one might suggest that West European schizophrenics require less of certain neuroleptic drugs to achieve a given result than American ones do because their cultures encourage greater orthodoxy of reaction, make the violation of independence less a thing to be feared, and encourage a lesser level of defensive vigilance by the individual. Furthermore, if one makes the assumption that European culture can only induce the traits of interdependence and social adaptability by means of inhibitions, then the use of disinhibitory drugs might achieve a greater effect there than in American culture

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where inhibitions are weaker. In part these hypotheses have to do with the placebo effect,* but they go beyond it insofar as they relate to symptomatology, inhibition, and vigilance, all aspects on which the neuroleptics have specific effects. It is not suggested that they can account for more than a part of the inter-group variation, and it is not suggested either that they cover all the cultural factors at work, but they are a beginning and should be worth testing.

Turning now to the difference between Malay and Euro-American and Indian cultures, the relevant dimensions might be seen as the same, up to a point. Traditionally, Malaysians are peaceful people with a great sense of propriety, restrained by strong inhibitions which burst explosively when frustration is too great, able to direct extreme hostility toward those their society calls enemies, but unable to ventilate hostility easily within their own society. They have a strong respect for and acceptance of leadership and also a desire to please by saying what they believe the listener would like to hear. Accordingly, just as the Western European might be expected to respond more easily to socially supported therapy of a disinhibitory type than the American, so the Malay might be expected to respond more strongly to such therapy than the European. However, there is still a further point of possible interest here. The Malays, as is well known, are the people among whom the culture-specific disease *latah*, now quite rare, was once common. *Latah* and Gilles de la Tourette's disease, while not identical, are very similar; both involve coprolalia and involuntary muscle movements, both come in episodes precipitated by strong emotional stimuli, and both are, to a slight extent, controllable by voluntary effort. Gilles de la Tourette's disease has recently been shown to respond well to some neuroleptics, notably those of the disinhibitory group such as haloperidol. Accordingly, if one believes that this disease has a psychodynamic rather than a purely organic etiology, then one might believe that a culture which produces a disease so similar to it as *latah* would also produce other mental disturbances which would be particularly susceptible to the neuroleptics, provided the correct social therapy were also used.

The third example of a difference in drug response between two cultural groups may at first sight appear to belie the foregoing hypotheses, but further consideration shows that this is not so. If one considers

*This is not the same as saying that the West European patient should lose his symptoms more rapidly than the American one; if his doctor is more pessimistic, he may retain them longer, and in certain social settings he is more likely to become catatonic, by this theory.

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the Anglo-Protestant Bostonian as representative of American culture and the Irish Bostonian as more representative of European, then the greater frequency of paradoxical drug responses among the latter goes against expectation. If instead, however, one thinks not in broad and largely irrelevant terms of European and American, but in terms of the commonly recognized traits or stereotypes of the Irish American, then the presence of paradoxical responses is much as one might predict. The stereotyped Irish American is an imaginative but labile individual, who is very susceptible to alcohol, strongly opinionated, often "agin the government," and has difficulty in turning his inner drives into positive action. He does not have the average West European's belief in the good intentions of authority, and he often does harbor hostilities toward members of his own society. Accordingly, even though he may be more intellectually than athletically oriented and may in later life be apparently content to rest inactive, this may represent not so much an inner calm as an inability to make action serve inner needs, and any apparently gratuitous action of the authorities in his direction would then be likely to engender suspicion and anxiety. Slater and Kastenbaum's Irish-American patients were inactive, but a significant proportion of them had a history of hypertension, and one could easily imagine that they regarded the drug experiments not as a means of help but as a form of exploitation.

Such evidence as we have been able to collect, therefore, can with some manipulation be arranged to point to two types of cultural influence on drug response. On the one hand, we can expect that some cultural backgrounds will facilitate the patient's acceptance of and identification with the total therapeutic effort, pharmacological as well as social and psychological, while others will obstruct that process to some degree. On the other hand, we can expect that culture will affect the symptomatology, the psychopathology, the extent of inhibition, of vigilance, and of intrapsychic complexity, so that when drugs which attack particular aspects of the pathological structure are used their success will be influenced. Further research can follow these clues. Plans are afoot for a comparative study of clinical response and side effects in Malays and Indians treated in the same unit, but many other lines of attack are called for. Bente has suggested to us that it would be profitable to make some cross-cultural comparisons of EEG abnormalities in patients with similar syndromes, and Sarwer-Foner has proposed to review his material on paradoxical reactions with cultural background in mind. What is probably most needed, however, is replication and expansion of the type of study which Denber and his

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colleagues have been carrying out, with ethno-cultural differences being searched for instead of being overlooked.

POSTSCRIPT

As this paper was going to press we received from Dr. W. M. Pfeiffer the preliminary report on a comparative study of Indonesian and German schizophrenics treated with fluphenazine which suggests that when due allowance is made for both body weight and duration of illness, the clinical results are relatively similar although the extra-pyramidal side effects are not. It is clear that the study has been admirably thorough, but that the comparison of the two sets of data has presented great difficulties. The German patients were relatively recent admissions to a university psychiatric unit. They had been admitted, if with an acute attack, within an average of four months of onset, and they were treated with group and occupational therapy in addition to the drug. The Indonesians were relatively chronic patients in a state mental hospital, and even when suffering from an acute attack it had taken them an average of thirteen months to be admitted. They received little or no psychiatric treatment besides the drug. In both groups the treatment was not given according to a set program but was adjusted in the light of the clinical response and the development of extra-pyramidal signs. If only patients with less than a year's duration of illness are considered, the Indonesian sample shows a better average improvement than the German, but the difference is not marked, and if patients with over a year's duration of illness are considered, the clinical results are equivalent. Side effects with the Indonesians were mainly motor weakness, but with the Germans were akathisia and the hypertonic types of disturbance (torticollis, etc.). The German patients received considerably higher total doses of the drug, but they were also considerably heavier.

This comparative study does not comprise that which was called for in the foregoing paper, since the two groups of patients were not matched for chronicity and were not being treated under the same conditions; but it is still a valuable contribution to the problem. It is to be hoped that Dr. Pfeiffer will be able to publish in full the details of his material. A larger abstract of his findings will be included in the next issue of this journal.

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