In Sorel, E. (Ed.), Family, Culture, & Psychobiology. (1990). New York: Legas.

TABLE 15

RESTRICTION ENZYMES MAKES SEQUENCE-SPECIFIC CUTS IN DNA

Since then, restriction enzymes that cut specific sequences have been Isolated from some 230 bacterial strains, and over 91 different specific cleavage sites have been found.

Watson JD, Tooze J, Kurtz DT: *Recombinant DNA: A Short Course.New York: Scientific American Books, 1983, pp. 58-59.*

TABLE 16

SOME RESTRICTION ENZYMES AND THEIR CLEAVAGE SEQUENCES

Microorganism	Abbreviation	Sequence 5'—3' 3'—5'
Bacillus amyloliquefaciens	bam HI	G GATCC CCTAG G
Brevibacterium albidum	BalI	TGG CCA ACC GGT
Escherichia coli	Eco RI	G AATTC CTTAA G
Haemophilus aegyptius	HaeII	Pu G C G C Py Py C G C G Pu
Hoemopbilus aegyptius	HEIII	G G C C CC GG
Hoemopbilus haemolyticus	Hbal	GCG C CTGCG
Hoemophilus influenzae Rd	HindII	G T Py Pu A C C A Pu Py T G
Hoemophilus influenzae Rd	HindIII	A AGCTT TTCGA A
Haemophilus para influenzae	Hpal	GTT AAC CAA TTG
Haemophilus parainfluenzae	HpaII	C CGG G G C C
Providentia stuartii	PstI	CTGCA G G ACGTC
Streptomyces albs G	SalI	G TCGAC CAGCT G
Xanthomonas eryzae	xerII	CGATC G G CTAGC

Watson JD, Tooze J, Kurtz Dr: *Recombinant DNA: A Short Course.* New York: Scientific American Books; 1983, pp. 59.

B:18

*ETHNICITY AND PSYCHOPHARMACOLOGY: RECENT FINDINGS AND FUTURE RESEARCH DIRECTIONS**

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Introduction

The last decade has witnessed noteworthy progress in the field of cross-ethnic psychopharmacology. Capitalizing on recent advances in cross-cultural research methodology as well as bioassay methods, a number of studies have attempted to quantitatively examine the issues of ethnic differences in psychotropic responses. Utilizing research strategies such as chart reviews, single-dose pharmacokinetic studies with volunteer subjects, and longitudinal assessment of drug responses with serial determinations of serum drug concentrations, some of these studies have reported ethnic differences in therapeutic dose ranges, side effect profiles, pharmacokinetic parameters, as well as neuroendocrine responses to psychotropics.

Despite the progress, however, many issues remain unresolved. Factors contributing to the controversies include: (1) small sample size; (2) variation in the pharmacological and pharmacokinetic properties of psychotropics; (3) subcultural differences within each broadly-defined ethnicity category; (4) lack of coordination among researchers from divergent settings utilizing divergent research methodologies; (5) the neglect of "non-pharmacological" factors.

In order to ensure further progress in the field, interdisciplinary collaboration is necessary, and systematic efforts should be made

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average neuroleptic dosage of 1138 mg CPZ equivalent, which was similar to the above mentioned report. Also using a similar study design, Lu *et al.* (1987) recently compared 51 Asian, 40 Caucasian, 32 Black and 35 Latino psychotic patients consecutively hospitalized in an acute inpatient ward. Although both the maximum and discharge CPZ equivalent dose for Asians (1180 mg/day and 665 mg/day respectively) were lower than those of the other ethnic groups (1220 to 1365 mg/day for the maximal and 870 to 946 mg/day for the discharge doses), these differences also did not reach statistical significance. When the dosage requirement of recent immigrants (less than 5 years) was examined separately, they found that both recent Asian and Latino immigrants received significantly less neuroleptics (maximal CPZ doses 624 mg/day for the former and 864 mg/day for the latter) as compared to the rest. Rosenblatt & Tang (1987) reviewed charts of 33 Asian patients and 33 matched Caucasian patients receiving chlorpromazine, haloperidol, trifluoperazine and amitriptyline. After controlling for differences in body weight, the maximal doses used for these drugs were higher for Caucasians than Asians. However, except for amitriptyline, these differences did not reach statistical significance. The paper did not report the sample sizes for each of the drugs used for the comparisons. It could well be that the differences were not significant because of problem related to small size. Adams et al (1984) reviewed the charts of 980 patients treated with oral antipsychotics in five public community clinics in Houston, including approximately equal number of Hispanics, Blacks, and Caucasians. They found no apparent differences among the three groups (mean CPZ dosage for Hispanics: 430 mg/day; Blacks: 539 mg/day; Caucasians: 431 mg/day).

In an earlier study, Binder & Levy (1981) reported significantly higher percentage of extrapyramidal side effects in 20 acute schizophrenic Asian patients, as compared to 40 Caucasians and 20 Blacks with comparable clinical conditions and diagnoses. In contrast, Keepers & Casey (in press) recently reviewed the charts of 107 White, 16 Black, 11 Indochinese and 1 Hispanic patients treated with similar doses of neuroleptics, and observed no difference in the incidence of dystonic reactions (31% in Whites, 41% in Blacks, and 36% in Asians).

In a survey of 126 inpatients treated in six psychiatric hospitals in Japan, Binder *et al.* (1987) found that 14.2% had moderate or severe tardive dyskinesia, and 20.6% had at least mild tardive dyskinesia. These results appeared to be comparable to those reported from North America and Europe (mean prevalence 20%, ranged between 0.5% to 56%). In contrast, in a longitudinal study recently conducted by Lin *et al.*(1989) two out of 26 Asian, compared to none out of 26 Caucasian schizophrenic patients prospectively treated with comparable doses of haloperidol developed delayed-onset movement disorders. It thus remain controversial whether the proposed ethnic differences between Asians and Caucasians in EPS side effects also applies to tardive dyskinesia or tardive dystonia.

II. Pharmacokinetic Studies

Most of these studies involve repeated measurement of serum or plasma drug concentrations over a predetermined period of time after the administration of a small test dose of the medicine being studied. Using these data, pharmacokinetic parameters are then calculated, which can be compared among individuals or groups of individuals, as well as across ethnic groups. These studies are most often conducted with normal volunteers. Studies of this nature may be difficult to perform with patient populations because of problems in subject recruitment and protocol compliance. These and a few other studies are briefly describe below:

(A) Neuroleptics: Lin, Peland, Lau, *et al.* (1988) studied the pharmacokinetics of haloperidol in 12 Caucasian, 11 American-born Asian and 11 foreign-born Asian healthy male volunteers.

Haloperidol (1.0 mg p.o. or 0.5 mg i.m.) was administered in random order on two separate days at least two weeks apart. Repeated blood samples were obtained for the measurement of haloperidol and prolactin concentrations, both by radioimmunoassay. The haloperidol (after both i.m. and p.o. administrations) and prolactin (after i.m. administration) concentrations of both Asian groups were significantly higher than those of the Caucasians. The differences in haloperidol concentrations remained highly significant after controlling for body surface area in the p.o. portion of the study ($F=6.83$ and 4.73; $p<.005$ and .025, respectively, for

nortriptyline concentrations between the two groups, however, may not be easily explained by these methodological problems. While receiving only half as much nortriptyline (50 mg) as the test dose, the Japanese subjects have significantly higher AUC (1150 ng x hr/ml) compared to the Caucasians (730 ng x hr/ml), even though the test dose was 100 mg. In a similarly designed study, Pi, Simpson, and Cooper, (1987) however, reached a different conclusion. They studied the kinetics of desipramine in 20 Asian healthy volunteers after the ingestion of 50 mg of the test drug, and compared these with 20 Caucasian subjects after the ingestion of 75 mg of the same medicine. They found no significant difference between the two groups in terms of several kinetic parameters including elimination half life, clearance, and volume of distribution. However, Asians were found to reach peak serum concentration significantly faster (4 hours) as compared to Caucasians (6.9 hours), and when normalized peak serum concentrations were compared, there was a trend toward Asians having higher concentrations (42.4 ng/ml vs 31.4 ng/ml, p=.08). Despite this, the authors concluded that there were no substantial pharmacokinetic differences between these two ethnic groups. Several methodological problems may have limited the comparability between this and the other two studies. The Asian and Caucasian groups were studied at different locations and during different time period. The serum samples were probably analyzed by different laboratories. Further, they also received different doses of desipramine. These factors tended to increase the variance and diminish the chance of proving statistical differences. Gaviria, Gil and Javaid (1986) compared nortriptyline kinetics between 10 Hispanic and 10 Anglo healthy, nondepressed volunteers matched for age, sex, and weight. All subjects were given a single oral dose of 75 mg of nortriptyline, and blood samples were drawn at various times over the next 96 hours. They found large inter-individual differences but no statistically significant ethnic differences in any of the kinetic parameters calculated from these data. They suggested that previous reports of hypersensitivity in Hispanic depressed patients may be due to ethnic differences at the pharmacodynamic rather than kinetic level.

(C) Anxiolytics: Ghoneim *et al.* (1981) studied the kinetics and sedative effects of diazepam between 12 Caucasian and 13 Asian normal volunteers. While no difference in the level of sedation was found between the two groups, the rate of metabolism of diazepam was significantly slower in Asians, resulting in slower total body clearance, smaller volume of distribution, and higher levels of diazepam and desmethyldiazepam in the Asian subjects compared to their Caucasian counterparts. In a pharmacokinetic study of alprazolam in 28 Asian (14 foreign-born and 14 American-born) and 14 Caucasian volunteers, Lin *et al.* (in press) demonstrated higher peak plasma alprazolam concentrations (C max) and AUC in both Asian groups after both p.o. and i.v. administration of alprazolam. These differences either reached statistical significance (AUC and CL after p.o. administration; C max after i.v. administration) or approached significance (C max after p.o. administration, AUC after i.v. administration). These statistical differences either remained significant or became significant (for the p.o.-C max and i.v.-AUC) after body surface area was covaried. Although the T 1/2 after both p.o. and i.v. administration of alprazolam was substantially longer in both Asian groups compared to the Caucasians, these differences failed to reach statistical significance. In contrast to the differences between the Asians and the Caucasians, the pharmacokinetic parameters of the two Asian groups were remarkably similar. There was no significant difference between the two groups in any of the parameters examined.

(D) Lithium: Although substantial differences in the therapeutic dose range and serum concentrations of lithium between Asians and Caucasians have been repeatedly reported, so far there has only been one study which utilized the single-dose kinetic method to examine such differences. Chang *et al.* (1985) compared the kinetics of lithium between 22 Taiwanese and 30 Caucasian bipolar patients. All patients went through wash out for at least one week prior to the study. Serial serum lithium concentrations were then determined for up to 31 hours after a single 900 mg of lithium carbonate. They found that the two ethnic groups did not differ in terms of all the kinetic parameters calculated. In a similarly designed study, Shelley (1987) observed no significant differences between 10 Afro-Caribbean and 11 Caucasian healthy male volun-

each evaluation point. The results of the study are currently being analyzed.

(C) Lithium: Several recent cross-national comparison studies have replicated earlier reports from Japanese researchers regarding the need for lower doses of lithium as well as lower therapeutic lithium levels among Asians. Yang (1985) studied 101 Taiwanese bipolar patients treated over a two-year period with clinically determined doses of lithium. He found that 62 of the patients with less variation of lithium levels (less than 0.2 mEq/L) responded significantly better to the treatment than those with variation higher than 0.2 mEq/L. When analysis was limited to those 62 patients with stable lithium levels, he found that the lithium level of the majority of good responders ranged between 0.5 and 0.79 mEq/L. Although very interesting, the robustness of these data is limited by several potential problems including the lack of a fixed-dose design, and the possible confounding influence of concomitant use of other medications such as neuroleptics and tricyclic antidepressants. In two studies conducted separately in Shanghai and in Taipei, Chang *et al.* (1985; 1984) reported remarkably similar therapeutic lithium concentrations for these two Chinese groups residing in drastically divergent socioeconomic environments. These were significantly lower than the mean level of 0.98 mEq/L for the matched Caucasian-American patients, as well as the 0.8 to 1.2 mEq/L therapeutic levels generally reported in Europe and North America. However, recent reports by several experts in Europe (Hullin 1980; Coppen, Abou-Salek, Milla 1983) suggested that lithium concentrations in the range comparable to those reported in the Asian countries may be sufficient for prophylaxis of manic episodes for the Occidental patients as well.

Remaining Controversial Issues and Methodological Problems

Going through the literature, one is struck by the ingenuity and increasing sophistication in recent years of the research in this area, and the richness in the information that has become available through these research efforts. Yet at the same time, it is also evident that despite such progress, many areas of controversy continue to exist. For example, the chart review studies of neuroleptic dosages have yielded conflicting findings regarding differences between Asians and Caucasians. The effect of nativity and immigration status is still unresolved. With the neuroleptics, the steady-state study differed from the single dose study in terms of whether there are pharmacokinetic differences between Asians and Caucasians. With the tricyclics, several kinetic studies provided conflicting data regarding kinetic comparisons between Asians and Caucasians, and the kinetic study with Hispanic subjects failed to support previous clinical observations. Kinzie's study on Southeast Asian patients failed to replicate earlier observations made on Japanese and Taiwanese subjects, suggesting that different Asian subcultural groups may have different kinetic or dynamic profiles.

As the topic is apparently complex and multi-dimensional, many issues may be involved and responsible for these ongoing controversies in the field. These not only include factors relevant to the biological aspect of the topic that has thus far been the focus of most of the research endeavors, but also a number of important "non-pharmacological" factors that also exert powerful influences on drug effects but have thus far eluded serious attention of investigators. In the following, we will discuss some of the most important issues, the resolution of which we believe are of utmost importance for the further progress of the field:

I. Pharmacokinetic/Pharmacodynamic Issues

Psychotropic medications have divergent pharmacological properties, interact with different brain receptor-neurotransmitter systems, and are biotransformed by complex enzyme systems (Gilman, Goodman and Rall, 1985; Lader, 1980), which are at present still not completely understood. Ethnic differences in a particular enzyme system may result in differences in responses to some but not other drugs belonging to the same category of psychotropics. For example, while the majority of benzodiazepines are metabolized by mitochondrial oxidating enzymes, some of them, such as lorazepam and oxazepam, only require conjugation before excretion (Greenblatt and Shader, 1987). Kinetic findings derived from studies with benzodiazepines requiring oxidation, such as diazepam and alprazolam, may not be applicable to those not undergoing oxidation. For studying ethnic variation in drug phar-

Ethnicity definitely exerts strong influences on the way family members interact with patients (Lin 1987; McGoldrick, Pearce and Giordano, 1982). However, research is lacking in terms of a clear delineation of how these interactive patterns vary across cultures. For example, we do not yet have empirical information on the relative frequency of high EE families in different cultures, although limited research data have suggested that American Anglo families are more likely to be rated as high EE compared to their British counterparts, and Hispanic families tend to have significantly lower EE ratings as compared to Anglo-Americans and the British (Jenkins, Karno and De la Selva, in press). It is possible that such cultural differences in family atmosphere may have important influences on drug treatment across cultures.

VI. The Role of Personality Styles

Earlier studies have suggested that patients as well as normal volunteers with different personality styles tended to respond to sedating or tranquilizing drugs differently (Slater and Kastembaum, 1966; Heninger, Dimascio and Klerman, 1965; Frosted, Forrest and Bakker, 1966). Those who are action oriented tend to have "paradoxical reactions" to these drugs by exhibiting increase in agitation, tension, anxiety. If we subscribe to the common stereotype of Occidentals being more "action-oriented" (Slater and Kastenbaum, 1966), according to this theory we would then expect them to be less responsive to sedating drugs, and perhaps require higher doses of these medications to achieve the desired effects. Personality styles could conceivably influence receptor responsivity to drugs in such a way that significantly alter the therapeutic dosage and concentration ranges. However, without empirical data to support or refute these hypotheses, these issues remain as speculations.

Discussion

It is seemingly paradoxical but not unexpected that, along with the resolutions of some of the key questions in the field, more new issues have emerged. As elaborated in the previous section, future progress of the field depends on the further refinement of existing methodology, as well as the development of new approaches. Of

progress of the field depends on the further refinement of existing methodology, as well as the development of new approaches. Of continuing importance certainly is the further clarification of ethnic variations in both pharmacokinetics and pharmacodynamics. In terms of the pharmacokinetics, it is important to search for newer research designs that will allow for more specific information regarding more detailed mechanisms underlying ethnic differences.

Ultimately, it is important to identify the enzyme systems that are responsible for such differences, and to determine whether these differences in enzyme activities are genetically or environmentally determined. In terms of the pharmacodynamics, it may be especially fruitful to explore newer and more direct assessment methods of receptor-drug interactions. These newer imaging techniques include the Single Photon Emission Computerized Tomography (SPECT) and Computerized Electroencephalography (Sedgwick and Edwards, 1984; Sedvall, Farde and Persson, 1986; Trimble, 1986). To enhance the power of the studies, it will be important to strive for higher degree of homogeneity in the study populations. It is clearly very important that, to the extent possible, future studies should be interdisciplinary in nature. Collaboration among researchers of different research backgrounds, especially between clinicians, behavioral scientists, and biomedical researchers should be fostered. Finally, cultural influences on drug responses through "non-pharmacological" mechanisms, as discussed in previous section, should be systematically clarified.

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