PANG L. MAN, M.D.
CALVIN H. CHEN, M.D.

Plasma levels of neuroleptics vs clinical response

ABSTRACT: The authors summarize the correlation of blood-plasma levels to clinical responses of all available psychotropic drugs and related medications. The optimal therapeutic plasma levels are tabulated. Ten different factors influencing the blood drug levels are discussed.

Even though psychoactive drugs have made possible fundamental changes in patient management, including the establishment of community psychiatry, they have been administered for a quarter of a century without scientific guidelines. This is true in spite of the well-known fact that patients with the same diagnosis, severity, and chronicity, treated by the same psychiatrist, respond differently to the same psychoactive drugs. For example, one patient may respond to 5 mg of haloperidol three times a day and recover completely from psychosis; yet another may not improve at all, even though the dosage of haloperidol is titrated up to 100 mg daily. Often, the medication is administered on a hit-and-miss basis. One of the most logical explanations of this variation is the difference of plasma levels, which vary from individual to individual because of various factors which will be discussed later.

In order for a drug to be effective, an optimal amount of the drug must be carried by the bloodstream to the site of illness in the body. In psychiatry, the medication should reach the brain and act on the neural receptor sites. For example, when lithium carbonate is used to treat manic depressive illness, it is mandatory that the plasma lithium level of each patient be diligently monitored to ensure therapeutic results and to prevent toxic effects. If we could determine the therapeutic plasma drug levels of psychoactive medication for each individual patient, we would be better able to bring psychiatry back to the mainstream of medicine.

In a thorough search, we were astonished by the scarcity of the literature concerning plasma levels of psychoactive drugs. Letters to all drug companies that market psychoactive drugs yielded little additional information. Currently, there are approximately 32 psychoactive drugs on the market, excluding lithium carbonate, stimulants, and sedatives. Twenty of the 32 are commonly prescribed, but only 10 have had their plasma levels studied; a few have been correlated with clinical responses. Therefore, the authors have prepared the accompanying Tables to serve as a reference for clinicians and to stimulate further research in this very important area. The Tables summarize all available data to date.

Discussion

As shown in the Tables, the relationship of plasma levels of psychoactive drugs and clinical responses is not a simple one. Curry and associates[58] and Garver and associates[14] were among the first to study the blood-plasma level of antipsychotic drugs. They found that there was a definite relationship between the plasma level of chlor-

promazine (CPZ) and therapeutic responses, but it was a nonlinear one; that is, there was an optimal plasma level below which there was less or no therapeutic response. This phenomenon has been referred to as the therapeutic window.

Rivera-Calimlim and associates,[4,59] after their study of plasma CPZ levels, also concluded that there was a nonlinear relationship; that is, patients who did not improve clinically showed low plasma levels, while those who improved significantly had plasma levels five

Antipsychotic Drugs

Drug	Dosage (mg)	Route	Frequency	Number of subjects	Av. subj. weight	Concentration in blood(B), plasma(P), serum(S), ng/ml	Time after last dose (hours)	Clinical response	Method	Reference
Chlorprothixene	50	Oral	Sirigle		Adult	40	8			1
	7,500	Oral		1	Adult	800	5 Days	Comatose		2
Chlorpromazine	2,000	Oral	Divided	1	100 kg	3,000		Death		3*
	400-800	Oral	Divided	50	Adult	50-300	12		Liq. gas chromatography	4
	100	IM		14	Adult	70	10			5
Thioridazine		Oral	Divided	6	Adult	2,400-11,800		Nonfatal overdose		6
		Oral		4	58 kg	1,100-6,200		Death		7
	420	Oral	Divided		Adult	1,300				8
	840	Oral	Divided	20	Adult	2,000-3,000				8
	100		Single	10	Adult	130-520			Quan. gas chromatography	9
	320		Divided	5	Adult	220-1,020			Quan. gas chromatography	10
Trifluoperazine		Oral		4	Adult	1,200-3,100		Nonfatal overdose		6
Prochlorperazine		Oral	Divided	4		1,200-1,600(S)		Nonfatal overdose		6
Butyrophenone	5-10	IV		37	Adult	0.5-10			Gas chromatography	11**
	20-200	Oral	Divided	6	Adult	5.8-245			Radio-immunoassay	12
	4	IV		3	Adult	20	1		Mass spectrometry	13
Butaperazine	80	Oral	Divided	10	Adult	40-321				14
	40	Oral	Divided	13	Adult	279 ± 70			Fluorometry	15†
Thiothixene	15-60	Oral	Divided	15	Adult	10-22.5	2-2.5		Mass fragmentography	16
Fluphenazine	25 Enanthate	IM		4	Adult	570	6-10 Days			17
	25 Decanoate	IM								
	25 Decanoate	IM		4	Adult	120-190	14-26 Days			17
Perphenazine	100 Enanthate		Divided	3	Adult	7,400	48-72		Gas chromatography	18††

*Trihexyphenidyl reduced CPZ level by 44.7%; produced high sedation **Half-life 12.6 hr.
†Half-life 12.4 ± 2.3 hr. ††Produced extrapyramidal symptoms

to ten times higher. The tricyclic antidepressants have been studied primarily by the Scandinavian investigators. Asberg and associates,[5] Kragh-Sorensen and associates,[27] and Whyte and associates[60] found poor clinical responses both at low and high plasma levels, but good improvement at intermediate levels. Their findings of nonlinear relationship were confirmed by the studies of CPZ previously mentioned.[4,14,58,59] Further study by Garver and associates[61] found that phenothiazine RBC levels may correlate with the clinical response better than does the plasma level.

Thus, research in this area is still in its infancy. The reasons for this are many. First, it has taken medical technology a long time to develop sufficiently accurate methods to detect the miniscule amounts (nanograms per milliliter) of psychoactive drugs in the plasma. In addition, at least the following ten factors that influence the clinical response must be taken into consideration.

1. *Dosage schedule.* This is probably the factor most commonly presumed to affect the plasma level. The amount of medication necessary to obtain a desirable plasma level varies according to the frequency of administration and the half-life of the medication. More frequent administration is obviously necessary for a drug with a half-life of four hours than one with a half-life of 12 to 24 hours. Conversely, it would be unnecessary to administer the latter more than once a day.

2. *Route of administration.* The rapidity of action varies according to the route of administration, with the intravenous route the fastest, the oral route the slowest, and the intramuscular route in between. Because of the possible complications with intravenous administration and the quick absorption into the blood with intramuscular ad-

Antidepressants

Drug	Dosage (mg)	Route	Frequency	Number of subjects	Av. subj. weight	Concentration in blood(B), plasma(P), serum(S), ng/ml	Time after last dose (hours)	Clinical response	Reference
A. Tricyclic compounds									
Amitriptyline	55-75	Oral	Divided	3	56 kg	74-106	6		19
	3,000-5,000	Oral		4	70 kg	3,000-15,000		Death	7
Desipramine	82	Oral	Divided	8	68 kg	21-64	7		20
		Oral		1	50 kg	3,000(B)		Death	21
Imipramine	215	Oral	Divided	60	Adult	200 ± 137	8		22
	150	Oral	Divided	10	74 kg	8-105	7		23
	625	Oral		1	Adult	5,000(B)		Death	24
Doxepin	3,000	Oral		1	50 kg	9,000		Death	21
Protriptyline	40	Oral	Divided	28	Adult	400-1,430 N Mol/liter	12		25*
Nortriptyline	75-225	Oral	Divided	29	Adult	33-164	13		26†
	150	Oral	Divided	30	Adult	48-238 (av. 175)	4 Weeks		27
B. Monoamine oxidase inhibitor									
Ethchlorvynol	500	Oral	Single	8		6,500(S)	1		28
						2,000(S)	6		
	5 gm	Oral		1		85,000(B)	4	Death	29

*630-900 N Mol/liter effective level
†50-139 ng effective level

ministration, the latter is generally preferred. Oral administration is the slowest and least reliable method because of several factors: interference from the gastric juices; the food content; the concomitant use of other medications; the variability of absorption from the small and large intestines; the metabolism in the liver; and excretory processes in the kidneys. For example, the combination of magnesium and aluminum hydroxide interferes with absorption of chlordiazepoxide.[15] The importance of absorption, metabolism, distribution, and excretion in relation to the plasma level and the clinical response was emphasized at the 1977 Annual Meeting of the American Psychiatric Association, where an entire scientific section was devoted to this subject, under the term "pharmacokinetics."

3. *Optimal therapeutic level.* Studies by Curry and associates,[58] Rivera-Calimlim and associates,[59] and Garver and associates[61] on plasma CPZ levels illustrate this factor. If the optimal therapeutic plasma level was reduced by 50%, the symptoms would return. More research is needed in this area.

4. *Paradoxical phenomenon.* Paradoxical reaction must also be considered. Methylphenidate, a stimulant, is well known to have the opposite (calming) effect when given at a much higher dosage than used to stimulate—as evidenced in its use as a treatment for hyperkinetic children. Alcohol and amphetamines are other good examples of this phenomenon.

5. *Cumulative effect.* Because of the possible cumulative effect, a lower dosage may be required to maintain the blood level once the effective plasma level has been established. Hence, determination of plasma drug levels is essential, just as in the case of lithium-carbonate maintenance therapy for patients suffering from mania.

6. *Side effects.* Sometimes a psychoactive drug may be highly effective, but the accompanying side effects are such that the patient is not able to tolerate them. Although there are medications that may help to control these side effects, they may produce other side effects or cause drug interactions. The use of antiparkinsonian drugs for treatment of extrapyramidal symptoms is such an example.

7. *Drug interaction.* This is a well known fact. For instance, barbiturates reduce the plasma level of chlorpromazine, and trihexyphenidyl reduces the plasma CPZ level by as much as 44.7%.[59]

8. *Age.* With the same dosage, the blood-plasma levels of psychoactive drugs are higher in older people. This may be due to the fact that drug metabolism in the liver is lower in this age group.

9. *Blood-brain barrier.* This factor is especially important in determining the effectiveness of psychoactive drugs because the seat of mental illness is the brain. Therefore, any medication that is to af-

Antianxiety Drugs

Drug	Dosage (mg)	Route	Frequency	Number of subjects	Av. subj. weight	Concentration in blood(B), plasma(P), serum(S), ng/ml	Time after last dose (hours)	Clinical response	Reference
Diazepam	10	Oral	Daily			225-84			30
	30	Oral	Daily	5	76 kg	700-1,500(P)			31
		Oral		8	Adult	3,200-14,000		Comatose	32
Chlordiazepoxide	30	Oral	Single	3	Adult	500-1,600			33
	300-500	Oral		3	Adult	3,000-25,000		Comatose	2
Meprobamate	1,600	Oral	2x800 mg in 1.5 hours	5	80 kg	1,860-2,660	2	Sedated	34
	16-40 gm	Oral		12		142,000-346,000	7-26	Death	35
Oxazepam	45	Oral	Single	8	Adult	880-1,440	2		36
	90	Oral	1		Adult	500(S)	18	Lethargic	37

fect the brain, hence the mind, must pass this barrier into the cerebrospinal fluid (CSF) in order to exert its influence. Some drugs may reach a high level in the blood circulation, but may be barred from passing through the blood-brain barrier. Obviously such drugs would have no value in psychiatric treatment. Therefore, we believe that the CSF level is even more important than the plasma level. The drawback, of course, is that it is not practical to obtain the CSF for drug level determination.

10. *Heredity.* Everything else being equal, sometimes the clinical results still vary among patients.

Sedatives

Drug	Dosage (mg)	Route	Frequency	Number of subjects	Av. subj. weight	Concentration in blood(B), plasma(P), serum(S), mg/ml	Time after last dose (hours)	Clinical response	Reference
Amobarbital	600	Oral	3x200 mg in 3 hours	5	75 kg	5,300-7,000	4.5	Sedated	34
		Oral		6	68 kg	4,700		Death	21
Aprobarbital	750	Oral	Single	3	68 kg	11,000-20,000	3		38
		Oral		9	Adult	50,000		Death	39
Barbital	1,500	Oral	Single	4	72 kg	19,000	2		38
		Oral		3		133,000		Death	21
Butabarbital	600	Oral	3x200 mg in 3 hours	5	76 kg	12,300	0.5	Sedated	34
		Oral		4	68 kg	58,000		Death	21
Hexobarbital	750	Oral	Single	3	75 kg	3,600	0.5	Sedated	40
Pentobarbital	600	Oral	3x200 mg in 3 hours	5	75 kg	3,000	0.5	Sedated	34
		Oral		55	72 kg	30,000		Death	21
Phenobarbital	600	Oral	3x200 mg in 3 hours	5	70 kg	18,000	0.5	Sedated	34
		Oral		5	74 kg	96,000		Death	21* 41
Primidone	500	Oral		26	Adult	6,700(P)		Antiepileptic	1
		Oral	Divided	1	68 kg	65,000		Death	7
Chloral hydrate	1,000	Oral	Single	5	70-108 kg	7,600		Sedated	42
	15-30 gm	Oral		4	54 kg	265,000	2-3	Death	7
Flurazepam	90	Oral	Single	2	82 kg	13	1		43
		Oral		1	64 kg	1,800	4-8	Death	7
Glutethimide	2,000	Oral	2x1000 mg in 1.5 hours	5	83 kg	10,200	2	Sedated	34
		Oral		11	70 kg	45,000		Death	21
Paraldehyde	10 ml	IM	Single	1	Adult	77,000	1.2		44
		Oral		4	Adult	936,000(B)		Death	45

*15,000-25,000 ng effective level

This individual variation would have to be attributable to hereditary factors that cause variations in pharmacokinetics.[1]

Unfortunately, the above factors are not always remembered when a clinician prescribes a medication.

So far, the methods of determining plasma levels of psychoactive drugs have been mostly spectrophotometry and chromatography. The radioimmunoassay has been introduced recently, and it appears to be a more accurate method. More sophisticated methods indubitably will be developed and many more clinical laboratory and clinical investigations will ensue. It is

Stimulants

Drug	Dosage (mg)	Route	Frequency	Number of subjects	Av. subj. weight	Concentration in blood(B), plasma(P), serum(S), ng/ml	Time after last dose (hours)	Clinical response	Reference
Amphetamine	1,000	Oral	Divided	1	Adult	2,000-3,000			46
		Oral		1	76 kg	800		Death	38
		IV		3		4,500		Death	47
Methamphetamine	10	Oral	Single	1	72 kg	30	1		48
		Oral		1	Adult	40,000	5.5	Death	49
		IV		3	Adult	230		Death	50
Methylene-dioxyamphetamine	1,000	Oral		1	73 kg	1,800(B)		Death	51
				5	Adult	14,000		Death	52

Miscellaneous

Drug	Dosage (mg)	Route	Frequency	Number of subjects	Av. subj. weight	Concentration in blood(B), plasma(P), serum(S), ng/ml	Time after last dose (hours)	Clinical response	Reference
Disulfiram	500	Oral	Divided	14	Adult	2-400(B)	2-4		29
LSD	0.14	IV	Single	5	70 kg	5	1		53
						3	4		53
Methadone	15	Oral	Single	5	73 kg	50	2	Sedated	54
	100-120	Oral	Divided	5	76 kg	75 830	4	Maintenance	55
				6		1,900	2	Death	22
Lithium carbonate	1,800		3x600 mg			1.0-1.5 mEq/liter			56
Phenytoin	600	Oral	2x300 mg in .5 hr	5	75 kg	4,000	2	Sedated	34
	2,800	Oral		1	11.8 kg	112,000	70	Comatose	57* 41

*10-25 ng/ml effective level

possible that some simple methods may be developed in the future, including the use of saliva or urine, so that clinicians may use them in their daily practice, thus making psychopharmacotherapy a science, instead of mostly an art based on trial and error. □

Dr. Man is director of research and associate director of psychiatric education at the Northville State Hospital, Northville, Mich.; clinical assistant professor of psychiatry at Wayne State University; and consultant at the VA hospital, Allen Park, Mich. Dr. Chen is assistant chief of clinical affairs at Northville State Hospital and clinical associate professor of psychiatry at Wayne State University. Reprint requests to Dr. Man, 41001 Seven Mile Road, Northville, MI 48167.

REFERENCES

1. Perel JM, Mendlewicz J, Shostak M, et al: Plasma levels of imipramine in depression—environment and genetic factors. *Neurophysiology* **2**:193-202, 1976.
2. De Silva JAF, D'Arconte L: The use of spectrophotofluometry in the analysis of drugs in biological materials. *J Forensic Sci* **14**:184, 1969.
3. Algeri EJ, Katsas GG, McBay AJ: Toxicology of some new drugs: Glutethimide, meprobamate and chlorpromazine. *J Forensic Sci* **4**:111, 1959.
4. Rivera-Calimlim L, Castaneda L, Lasagna L: Effects of mode of management on plasma chlorpromazine in psychiatric patients. *Clin Pharmacol Ther* **14**:978-986, 1973.
5. Asberg M, Cronholm B, Sjoqvist F, et al: Relationship between plasma level and therapeutic effect of nortriptyline. *Br Med J* **3**:331-334, 1971.
6. Tompsett SL: The spectrophotometric determination of phenothiazine drugs in blood serum. *Acta Pharmacol Toxicol* **26**:298, 1968.
7. San Francisco Medical Examiner-Coroner's Office, California. Toxicology Laboratory Case Reports.
8. Berling R, Mjorndel T, Oreland L, et al: Plasma levels and clinical effects of thioridazine and thiothixene. *J Clin Pharmacol* **15**:178-186, 1975.
9. Marteusson E, Roos BE: Serum levels of thioridazine in psychiatric patients and normal volunteers. *Eur J Clin Pharmacol* **6**:181-186, 1973.
10. Dinovo EC, et al: Isolation of a possible new metabolite of thioridazine and mesoridazine from human plasma. *Res Commun Chem Pathol Pharmacol* **7**:489-496, 1974.
11. Forsman A, Martensson E, Nyberg G, et al: A gas chromatographic method for determining haloperidol. *Naunyn Schmiedebergs Arch Pharmacol* **286**:113-124, 1974.
12. Clark BR, Tower BB, Rubin RT: Radioimmunoassay of haloperidol in human serum. *Life Sci* **20**:319-326, 1977.
13. Marcucci F, Mussini E, Airoldi L, et al: Analytical and pharmacokinetic studies on butyrophenones. *Clin Chim Acta* **34**:321-332, 1971.
14. Garver DL, Dekirmenjian H, Davis JM, et al: Neuroleptic drug levels and therapeutic response: Preliminary observations with red blood cellbound butaperazine. *Am J Psychiatry* **134**:304-307, 1977.
15. Greenblatt DG, Shader RI, Harmatz JS, et al: Absorption rate, blood concentrations, and early response to oral chlordiazepoxide. *Am J Psychiatry* **134**:559-562, 1977.
16. Hobbs DC, Welch WM, Short MJ, et al: Pharmacokinetics of thiothixene in man. *Clin Pharmacol Ther* **16**:473-478, 1974.
17. Schreider EC, Grozier ML: Metabolic studies with long acting compounds. *Therapie* **28**:441-449, 1973.
18. Hansen CE, Larsen NE: Perphenazine concentration in human whole blood, a pilot study during anti-psychotic therapy using different administration forms. *Psychopharmacologia* (Berlin) **37**:31-36, 1974.
19. Braithwaite RA, Widdop B: A specific gas-chromatographic method for the measurement of "steady-state" plasma level of amitriptyline and nortriptyline in patients. *Clin Chim Acta* **35**:461, 1971.
20. Alexanderson B: Pharmacokinetics of desmethylimipramine and nortriptyline in man after single and multiple oral doses—a cross-over study. *Eur J Clin Pharmacol* **5**:1, 1972.
21. Orange County Coroner's Office, California. Toxicology Laboratory Case Reports.
22. Glassman AH, Perel JM, Shostak M, et al: Clinical implications of imipramine plasma levels for depressive illness. *Arch Gen Psychiatry* **34**:197-204, 1977.
23. Nagy A, Treiber L: Quantitative determination of imipramine and desipramine in human blood plasma by direct densitometry of thin-layer chromatograms. *J Pharm Pharmacol* **25**:599, 1973.
24. Edwards J: Fatal imipramine overdosage. *Med J Aust* **1**:839, 1966.
25. Tripp SL, Williams E, Wagner WE, et al: A specific assay for subnanogram concentration of reserpine in human plasma. *Life Sci* **16**:1167-1178, 1975.
26. Asberg M, Cronholm B, Sjoqvist F, et al: Correlation of subjective side effects with plasma concentration of nortriptyline. *Br Med J* **4**:18-21, 1970.
27. Kragh-Sorensen P, Asberg M, Eggert-Hansen C: Plasma nortriptyline levels in endogenous depression. *Lancet* **1**:113-115, 1973.
28. Cummins LM, Martin YC, Scherfling EE: Serum and urine levels of ethchlorvynol in man. *J Pharm Sci* **60**:261, 1971.
29. Cravey RH, Baselt RC: Studies of the body distribution of ethchlorvynol. *J Forensic Sci* **13**:532, 1968.
30. Kaplan SA, Jack ML, Alexander K, et al: Pharmacokinetic profile of diazepam in man following simple intravenous and oral and chronic oral administrations. *J Pharm Sci* **62**:1789-1796, 1973.
31. Van der Kleiju E, Van Rossum JM, Muskens ETJM, et al: Pharmacokinetics of diazepam in dogs, mice and humans. *Acta Pharmacol Toxicol* **29**:109, 1971.
32. Shaw R: Presented at the 19th quarterly meeting of the California Association of Toxicologists, Oakland, Calif., January 21, 1972.
33. Koechlin BA, D'Arconte L: Determination of chlordiazepoxide and of a metabolite of lactam character in plasma of humans, dogs and rats by a specific spectrofluorometric micro method. *Anal Biochem* **5**:195, 1962.
34. Parker KD, Elliot HW, Wright JA, et al: Blood and urine concentration of subjects receiving barbiturates, meprobamate, glutethimide or diphenylhydantoin. *Clin Toxicol* **3**:131, 1970.
35. Kazyak L: Determination of meperidine in biological specimens in conjunction with a case of Demerol intoxication. *J Forensic Sci* **4**:264, 1959.
36. Knowles JA, Ruelius HW: Absorption and excretion of 7-chloro-1, 3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (oxazepam) in humans. *Arzeim Forsh* **2**:687, 1972.
37. Shimkin PM, Shaivitz SA: Oxazepam poisoning in a child. *JAMA* **196**:662, 1966.
38. Lous P: Plasma levels and urinary excretion of three barbituric acids after oral administration to man. *Acta Pharmacol Toxicol* **10**:147, 1954.
39. Bonnichsen R, Machly AC, Frank A: Barbiturate analysis: Method of statistic survey. *J Forensic Sci* **6**:411, 1961.
40. Bush MT, Berry G, Hume A: Ultra-short-acting barbiturates as oral hypnotic agents in man. *Clin Pharmacol Ther* **7**:373, 1966.
41. Merritt HH: *A Textbook of Neurology,* ed 5. Philadelphia, Lea & Febiger, 1973, pp 764-768.
42. Kaplan HL, Forney RB, Hughes FW, et al: Chloral hydrate and alcohol metabolism in human subjects. *J Forensic Sci* **12**:295, 1967.
43. De Silva JAF, Strojny N: Determination of flurazepam and its major biotransformation products in blood and urine by spectrophotofluorometry and spectrophotometry. *J Pharm Sci* **60**:1303, 1972.
44. Maes R, Hodnett N, Landesman H, et al: The gas chromatographic determination of selected sedatives (ethchlorvynol, paraldehyde, meprobamate, carisoprodol) in biological material. *J Forensic Sci* **14**:235, 1969.
45. Figot PP, Hine CH, Way EL: The estimation and significance of paraldehyde levels in blood and brain. *Acta Pharmacol Toxicol* **8**:290, 1952.
46. Cravey RH, Jain NC: Testing for amphetamines: Medico-legal hazards. *Trauma* **15**:49, 1973.
47. Orrenius S, Maehly AC: Lethal amphetamine intoxication—a report of three cases. *J Leg Med* **67**:184, 1970.
48. Lebish P, Finkle BS, Brackett JW: Determination of amphetamine, methamphetamine and related amines in blood and urine by gas chromatography with hydrogen-flame ionization detector. *Clin Chem* **16**:195, 1970.
49. Cravey RH, Baselt RC: Methamphetamine poisoning. *J Forensic Sci* **8**:118, 1968.
50. Cravey RH, Reed D: Intravenous amphetamine poisoning. Report of three cases. *J Forensic Sci* **10**:109, 1970.
51. Kier LC: MDA poisoning. *Bull Int Ass Forensic Toxicol:* **9(2)**:5, 1972.

52. Cimbura G: Analytical and forensic aspects of poisoning. *J Forensic Sci* **17**:329, 1972.
53. Aghajanian GK, Bing OHL: Persistence of lysergic acid diethylamide in the plasma of human subjects. *Clin Pharmacol Ther* **5**:611, 1964.
54. Inturrisi CE, Verebely K: Disposition of methadone in man after a single oral dose. *Clin Pharmacol Ther* **13**:923, 1972.
55. Inturrisi CE, Verebely K: The levels of methadone in the plasma in methadone maintenance. *Clin Pharmacol Ther* **13**:633, 1972.
56. *Physicians' Desk Reference*. Oradell, N.J., Medical Economics Co, 1976, p 1433.
57. Tenckhoff H, Sherrard DJ, Hickman RO, et al: Acute diphenylhydantoin intoxication. *Am J Dis Child* **116**:422, 1968.
58. Curry SH, Marshall HL, Davis JM, et al: Chlorpromazine plasma levels and effects. *Arch Gen Psychiatry* **22**:289-296, 1970.
59. Rivera-Calimlim L, Nasrallah H, Strauss J, et al: Clinical response and plasma levels: Effect of dose, dosage schedules and drug interaction in plasma chlorpromazine levels. *Am J Psychiatry* **133**:646-652, 1976.
60. Whyte SF, MacDonald AJ, Naylor GJ, et al: Plasma concentrations of protriptyline and clinical effects in depressed women. *Br J Psychiatry* **128**:384-390, 1976.
61. Garver DL, Davis JM, Dekirmenjian H, et al: Pharmacokinetics of red blood cell phenothiazines and clinical effects. *Arch Gen Psychiatry* **33**:862-866, 1976.

New books received

Foundations of Biochemical Psychiatry,
by David S. Segal, Joel Yager, and John L. Sullivan, 346 pp, $19.95, Boston, Butterworths, 1976.

Psychodynamics of Hostility,
by Leon J. Saul, 233 pp, New York, Jason Aronson, 1976.

Psychiatry in a General Hospital,
by J. Crawford Little, 104 pp, $7.95 paperback, Boston, Butterworths, 1976.

Primer on Chemical Dependency,
by Joseph Westermeyer, 231 pp, $11.95, Baltimore, Williams & Wilkins, 1976.

Carl Rogers on Personal Power,
by Carl R. Rogers, 299 pp, $10, New York, Delacorte Press, 1977.

Emotional Disorders: An Outline Guide to Diagnosis and Pharmacological Treatment,
by Alberto DiMascio and Harold L. Goldberg, 134 pp, $8.95, Oradell, NJ, Medical Economics, 1976.

Abstracts of the Collected Works of C.G. Jung,
224 pp, $16.95, Rockville, Md, Planning Associates, 1976.

The Pain of Obesity,
by Albert J. Stunkard, 236 pp, $10, Palo Alto, Calif, Bull, 1976.

Aging and Dementia,
edited by W. Lynn Smith and Marcel Kinsbourne, 244 pp, $15, New York, Spectrum, 1977.

Coping with Physical Illness,
edited by Rudolf H. Moos, 440 pp, $25, New York, Plenum, 1977.

Psychiatric Diagnosis,
edited by Vivian M. Rakoff, Harvey C. Stancer, and Henry B. Kedward, 240 pp, $15, New York, Brunner/Mazel, 1977.

Psychopharmacology: From Theory to Practice,
edited by Jack D. Barchas, Philip A. Berger, Roland D. Ciaranello, and Glen R. Elliott, 557 pp, $17.95 cloth, $10.95 paperback, New York, Oxford University Press, 1977.

The Suicidal Patient: Recognition and Management,
by Ari Kiev, 157 pp, $12.95, Chicago, Nelson-Hall, 1977.

The Harvard Guide to Modern Psychiatry,
edited by Armand M. Nicholi, Jr., 691 pp, $29.50, Cambridge, Mass, Belknap Press of Harvard University Press, 1978.

Psychiatry: Essentials of Clinical Practice,
by Ian Gregory and Donald J. Smeltzer, 343 pp, $17.50 cloth, $12.50 paperback, Boston, Little, Brown, 1977.

The Role of Anxiety in Bodily Feelings,
by Peter Tyrer, 128 pp, $18, New York, Oxford University Press, 1976.

Manic-Depressive Illness: History of a Syndrome,
edited by Edward A. Wolpert, 604 pp, $22.50, New York, International Universities Press, 1977.

Biofeedback and Self-Control 1976/1977,
edited by Joe Kamiya, T.X. Barber, Neal E. Miller, David Shapiro, and Johann Stoyva, 614 pp, $22.95, Chicago, Aldine, 1977.