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A National Assessment of Propoxyphene in Postmortem Medicolegal Investigation, 1972–1975

Propoxyphene in its various proprietary forms is among the most commonly prescribed drugs in the United States. As an analgesic which physicians find useful to bridge the gap between aspirin and the narcotics, propoxyphene has reached general application unparalleled by any other "pain-killer." It is inevitable for any drug with such widespread usage that if it has any toxicity at all, in whatever form or circumstance, it will eventually come to the attention of forensic pathologists and toxicologists. So it has been with propoxyphene in the 1970s through a series of papers in the scientific literature [*1–8*] suggesting that propoxyphene was increasingly implicated in medicolegal investigations of drug-related deaths. Many groups of cases have been reported by toxicologists in particular areas such as Dallas [*3*], North Carolina [*5*], Southern California [*1*], and the San Francisco Bay area [*6*], but generally in terms of the analytical toxicology findings alone, and usually as a "snapshot" of an incidence at one point in time.

This rate of appearance of such reports is not unexpected, since a method for the quantitation of low levels of propoxyphene in biological fluids and tissues was initially published in 1968 [*9*]. Subsequently, the original procedure was modified from gas-liquid chromatographic to ultraviolet spectrophotometric procedures [*10,11*] and, consequently, routine toxicological analyses for propoxyphene in the forensic toxicology laboratory were not instituted until late 1971. Thus, the most recent publication on the incidence of propoxyphene-related deaths reported a trend of increasing deaths over a period from 1972 to 1975 [*5*]. It was clear by late 1975 that a national assessment of the role of propoxyphene in these forensic cases was needed to place the role of the drug in perspective against demographic and epidemiological information about the deceased individuals.

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Survey Method

The survey was carried out in late 1975 and early 1976 and was designed to examine such questions as these: Is there an increasing trend of propoxyphene-related deaths and if so, is the trend unique against other drug-related deaths? Is propoxyphene the primary toxic agent in these cases? Is it a common suicidal agent? What is the mechanism of toxicity, and are current analytical methods adequate for detection and pharmacological interpretation? Can a general picture be built describing the deceased and the circumstances of death that would be useful in predicting potential toxic situations?

Eighteen medical examiners' and coroners' offices were asked to participate in the study. The sites were selected to reflect the national scene based on demographic circumstances; they are listed in Table 1 and depicted in Fig. 1. These sites represent urban,

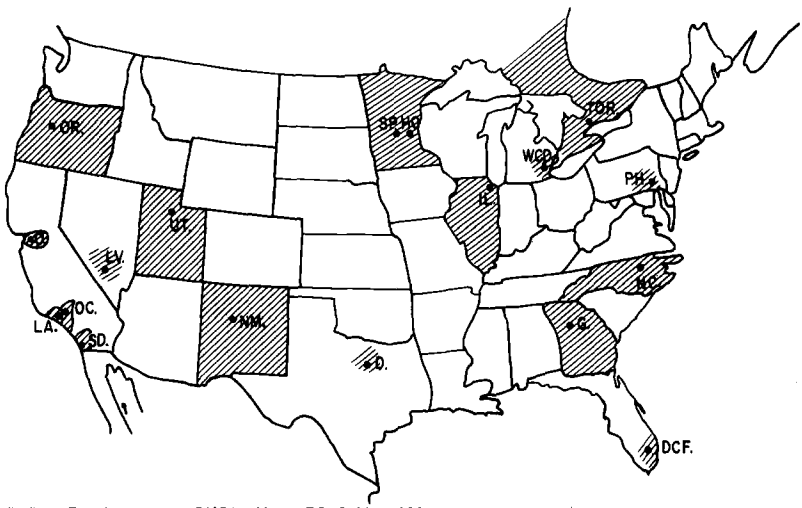

FIG. 1—*Geographic area and sites surveyed.*

rural, and mixed areas; state, county, and city jurisdictions; and both high and low population densities. Toronto and the Province of Ontario were chosen to help define whether the cases were limited to the U.S. This area also represents a balance demographically of rural Ontario and urban Toronto, and is close to the United States, but maintains distinctive Canadian social characteristics. A total population of 52.6 million was included in the survey, covering approximately 21% of the U.S. population.

Questionnaires were designed to address the broad questions in the study and then used at each site to gather the data from the case files. Site and personnel information was confined to one questionnaire while other questionnaires were used to extract identical information (where possible) from each case file. Visits of one or two days were made to each site. The file for each case involving propoxyphene was examined by the survey staff member, and only that information indicated on the questionnaires was recorded.

After the collection of the data was completed, the task of collating and compiling salient facts and features was undertaken. In order to do this a number of working

TABLE 1—*Survey sites, population, and demographic classification.*

	Site	Site Code	Jurisdiction Population, millions	Demographic Classification[a]
1	Alameda County (Oakland) Calif.	O	1.1	U
2	Dade County, Fla.	DCF	1.5	U
3	Dallas City and County, Tex.	D	1.3	U
4	Wayne County and Detroit, Mich.	WCD	3.0	U
5	Georgia (state)	G	4.9	U/R
6	Hennepin County, Minn.	HC	1.0	U
7	Illinois (state)	IL	6.0	R
8	Las Vegas City and County, Nev.	LV	0.3	U/R
9	Los Angeles City and County, Calif.	LA	7.0	U
10	St. Paul, Minn. (state office)	SP	3.0	R
11	New Mexico (state)	NM	2.1	R
12	North Carolina (state)	NC	5.0	U/R
13	Orange County, Calif.	OC	1.5	U
14	Oregon (state)	OR	2.0	R
15	Philadelphia City and County, Pa.	PH	2.0	U
16	San Diego City and County, Calif.	SD	1.4	U
17	Utah (state)	UT	1.2	R
Total U.S. population surveyed		...	44.3	...
18	Toronto and Province of Ontario, Canada	TOR	8.3	U/R
Survey totals		...	52.6	U = 9 areas R = 5 areas U/R = 4 areas

[a] Demographic code

U = Urban, containing a city of greater than 500 000 population.

R = Rural, no city of greater than 500 000 and overall population density less than 50/mi^2 (50/2.6 km^2).

U/R = Combination urban and rural, city greater than 500 000 but overall population density less than 50/mi^2 (50/2.6 km^2).

definitions were made for information more complex than simple facts like age and sex. These definitions are as follows:

1. Medical History: Any reported prior medical history, surgery, hospitalization, recent visits to a physician, acute or chronic medical complaints.
2. Psychiatric History: Any reported prior suicide attempts, past acute or chronic emotional problems, drug abuse history (other than alcohol), or overt mental illness requiring psychiatric treatment.
3. Terminal Symptoms: Symptoms observed and reported following drug ingestions.
4. DOA (Dead on Arrival): Individual was dead when found.
5. Time Interval: Interval from "last seen alive" to death; in hours to the nearest quarter hour.
6. Manner of Death: Officially stated manner of death as per death certificate: natural, accident, suicide, homicide, undetermined.
7. Cause of Death: Official cause as stated on the death certificate.
8. Proprietary Drug Name: The trade name of the pharmaceutical preparation associated with the case by investigator's report or physical evidence.
9. Cause of Death Includes Propoxyphene: Propoxyphene or a proprietary name is stated in the official cause of death on the death certificate.
10. Multiple Drug Ingestion: When stated as such on the death certificate.
11. Cause of Death—Propoxyphene: When propoxyphene was the only drug (excluding salicylate, phenacetin, and caffeine) detected by toxicological analysis and stated on the death certificate.
12. Alcohol Involved: Only when detected and quantitated by toxicological analysis.
13. Other Drugs Involved: (a) Detected by toxicological analysis or (b) available to the individual as indicated in the investigator's report or by physical evidence.
14. Alcoholic or "Problem Drinker": Alcohol abuse problem established by medical history or indicated in investigator's report.

Results

Survey Overview and Incidence of Propoxyphene Cases: 1972–1975

Table 2 gives the number of cases by year for each site surveyed and the incidence per million population for 1974, the last full year for which data are available. The total number of cases finally included in the survey is 1022. Because only those cases that were carefully documented and that could be substantiated were included, these data almost certainly represent the minimum incidence of propoxyphene-associated cases. Although propoxyphene is now routinely included in toxicological screening analyses of blood and liver specimens, not all potential cases are referred by the pathologist for toxicology and not all referred cases are screened. An absolute criterion for admission as a propoxyphene-related case was the presence of propoxyphene in body fluids or tissues determined analytically. The 44.3 million U.S. population surveyed represents approximately 21% of the current national population [*12*], and the resulting 851 cases from the U.S. certainly permit reasonable inferences to be drawn from the data.

It is important to note that the cases which form the bulk of this report occurred between 1972 and 1975, although some sites did have cases involving propoxyphene as early as 1969. These are also shown in Table 2. The cutoff date for case data collection was 31 July 1975.[3]

[3] The reader should be aware that many cases reported in this survey have been previously reported in other communications [*1,3,5–7*]. These data are *not*, therefore, additive with other reports from these sites during the reported time interval.

TABLE 2—*Number of propoxyphene-associated cases.*

Site	1969	1970	1971	1972[a]	1973	1974	1975	Total	Number of Cases Per Million Population[b]
O	...	3	3	3	9	11	3	32	10.0
DCF	...	...	...	2	13	10	11	36	6.7
D	...	...	...	14	10	16	27	67	12.3
WCD	...	...	...	8	12	31	42	93	10.3
G	...	1	2	5	6	6	4	24	1.2
HC	...	...	4	1	1	1	6	13	1.0
IL	...	...	...	2	3	9	10	24	1.5
LV	...	...	...	2	1	2	5	10	6.7
LA	...	...	...	37	33	63	32	165	9.0
SP	...	...	...	1	2	3	3	9	1.0
NM	...	...	...	...	4	8	11	23	3.8
NC	2	3	2	23	23	32	25	110	6.4
OC	...	...	...	8	12	15	10	45	10.0
OR	...	...	...	1	0	0	5	6	0.0
PH	...	...	...	25	22	28	18	93	14.0
SD	...	...	...	20	24	23	14	81	16.4
UT	...	...	...	...	7	11	2	20	9.2
U.S. totals	2	7	11	152	182	269	228	851	6.1
TOR	...	...	...	44	39	46	42	171	5.5
Survey totals	2	7	11	196	221	315	270	1022	6.0

... = no data available; 0 = no cases that year.

[a]Data for this survey are documented cases occurring from 1 Jan. 1972 through 31 July 1975.

[b]Based on 1974, the last full year for which data are available.

The calculated annual percentage increases are, for 1972–1973, 12.8%; and for 1973–1974, 42.5%. It is evident that the annual rate is increasing. Examination of the data by three-month intervals revealed no evidence for cycling within the years or for seasonal variations.

As previously noted, the survey sites were classified as urban, rural, or a combination (see Table 1). This was done to determine if significant demographic differences could be detected in the occurrence of propoxyphene cases. The data were rationalized to cases per million population for 1974 to permit site comparisons. If one compares the urban versus rural sites it is apparent that the incidence of propoxyphene-associated deaths is greater in the urban areas. If the incidence per million of population is calculated for the nine urban sites (Table 2) and the five rural sites, the incidence is 10 per million (urban) versus 2.2 (rural). The mixed urban and rural sites are intermediate at 4.6. However, the ranges are wide, and the smallest urban (Hennepin County, Minn.) almost equals the largest rural (Utah) site. San Diego County is greatest, and with Dallas and Philadelphia, forms a trio numerically ahead of all other sites. The smallest incidence rates are from the largest geographically, the states of Oregon and Minnesota.

The trend of increasing deaths, while apparent in the overall totals by year, does show slight variations by site. For example, in Table 2, San Diego appears almost uniform from 1972 through 1975, while the Wayne County–Detroit area exhibits a progressive increase through the same years.

Figure 2 was constructed from epidemiological data collected at 7 of the 18 sites in an effort to place propoxyphene-associated deaths in perspective relative to other medical examiner and coroner cases. In Figure 2 the average number of cases per million population, for five different categories of drug deaths and suicides, from seven of the study sites, is plotted for each year. The 1975 case averages are calculated from a value extrapolated to December 31. In general, the graphs are self-explanatory. The only increasing case type identified in this survey is the propoxyphene-associated deaths. It can also be seen that at these seven sites propoxyphene cases account for approximately 1/6 of the total drug deaths and that suicides involving propoxyphene are about 1/10 of all drug suicides. The average suicide rate (all causes) for these sites is slightly higher than the national average of 110 to 120 per million population per year [*12*]. It should be noted that suicide as a mode of death is listed by the coroner or medical examiner with some reluctance. Therefore, it is quite probable that a number of the accidental or undetermined mode of death cases are actually suicides. This will be borne out later in the discussion on the psychiatric case histories.

Characteristics of the Deceased

An important part of the study was a conscientious attempt to characterize the deceased in terms of their vital statistics and social background. If they could be described as a special population with either identifying idiosyncrasies or eccentric personal histories it might be possible to alert physicians, toxicologists, and medical investigators to potential toxicities. The information could form a reference for more confidently identifying and interpreting propoxyphene-associated fatalities in postmortem forensic investigations.

The sex ratio within the 1022 cases did not equal the national average. The percentages of 55% female and 45% male formed a ratio (F/M) of 1.22, while the national ratio for all ages is 1.05 F/M [*13*]. Figure 3 shows the age distribution for all the cases and the differences for males and females. Almost all of the victims were adults. Slightly greater than 55% of the males in the study were between ages 21 and 40 years, as contrasted with 24% of the females. The prominent 21 to 50 years group in Fig. 3 was broken down to half-decades to expose fine age differences. The females were evenly distributed, but the males peaked in their early twenties. There was a negligible number of children; in

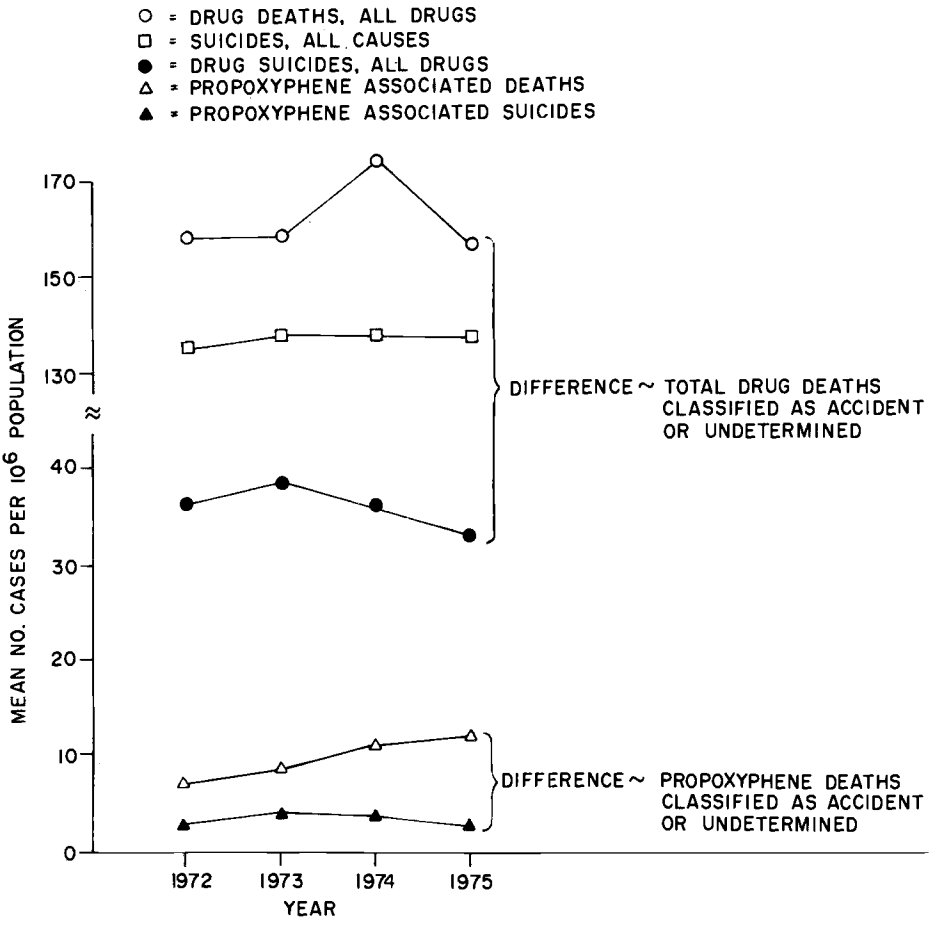

FIG. 2—*Average number of cases per million population, per year, from selected sites (O, WCD, NC, OC, PH, SD, and UT) for the years 1972 through 31 July 1975.*

fact, there is no evidence that propoxyphene is significantly associated with pediatric poisoning. Inquiries at some of the sites, local hospitals, and the Intermountain Poison Control Center, University of Utah Hospital, revealed that propoxyphene is not a commonly encountered drug in pediatric clinical toxicology.

An analysis of the victims' body weights was uninformative; they were unremarkably distributed between a minimum of 71 lbs (32 kg) and a maximum of 300 lbs (136 kg), and only 3.6% of the adults had weights in excess of 200 lbs (91 kg).

By examination of race frequency, residential address (when known), and occupation, the majority of the deceased could be classified as blue-collar workers and middle-class Caucasians. There were very few of the minority races represented and practically none of the professions such as medicine or law, business executives, or scientists. Many of the survey areas contained significant racial minority populations, making the conclusion even more striking. An overwhelming majority of the deceased died at home or at the residence of a friend or relative. Usually they were in or on a bed, on a couch, or on the bathroom, kitchen, or living room floor. Occasionally they were in a motel/hotel, but virtually never outside or in an automobile.

Almost half (42.6%) of the victims had a medical history as defined above. Most made

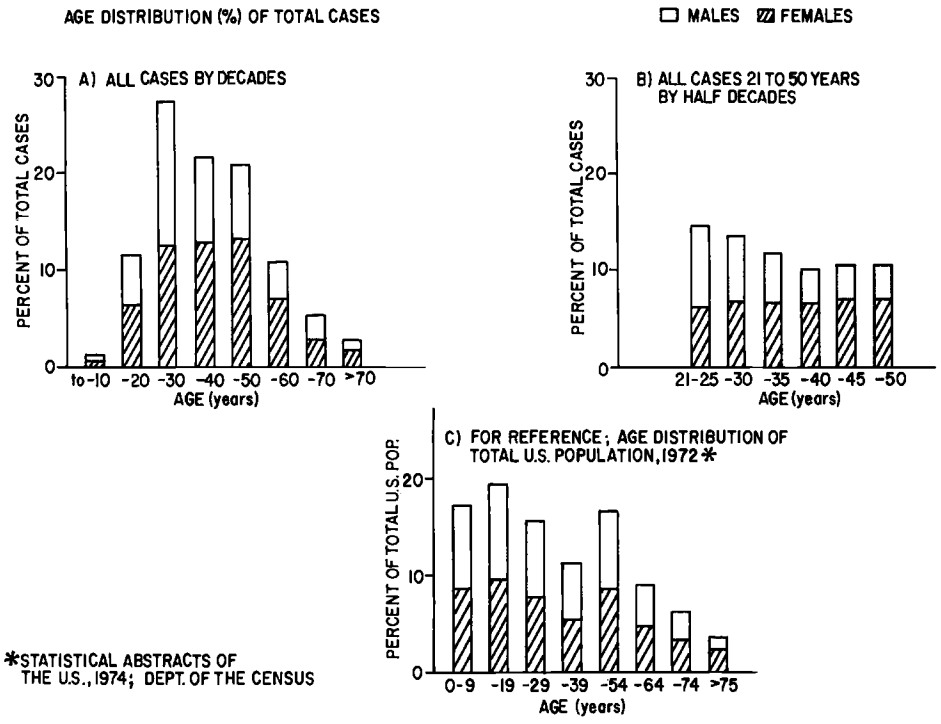

FIG. 3—*Age distribution (%) of total cases, of males and females, and of total U.S. population.*

frequent, regular visits to a doctor or hospital clinic. Many, but not all, complaints were chronic, minor illnesses such as "aches and pains," but above all, the case histories revealed that 82% had "emotional problems" and many were under psychiatric treatment. More than half of the 1022 cases, 50.7%, had a record of "self-destructive behavior"—either their death was classified as suicide or they had a documented history of prior suicide attempts. A total of 162 (15.8%) of the case histories revealed that the deceased had a record of "suicidal tendencies," suicide threats, or overt suicide attempts. Of these 162 cases, 69.1% were eventually classified on their death certificate as suicides. There were 50 cases in which a previous suicide attempt was indicated but the death was classified otherwise.

Table 3 summarizes the manner of death. The largest single category is clearly suicide, accounting for 45.8% of all cases. The female to male ratio for the suicides was 1.72, which was definitely biased towards the females compared to the total study population

TABLE 3—*Manner of death.*

Category	Cases, no.	Percent of All Cases Surveyed
Suicide	468	45.8
Accident	267	26.1
Undetermined	213	20.8
Natural	63	6.2
Homicide	1	...
Not Known	10	...
Total	1022	...

ratio of 1.22. It should be noted that 65.9% of all the cases had the word propoxyphene in the "cause of death" statement on the death certificate, and it was included in 9.5% of the cases determined as multiple drug overdose(s). Conversely, in 34.1% of the cases the cause of death was officially attributed to something other than propoxyphene alone.

Propoxyphene as a Drug of Abuse

It can be stated from this study that the deliberate, calculated abuse of propoxyphene, at least in commonly accepted terms of "street-drug abuse," did not cause the deaths of the study victims. They were not a part of the drug abuse scene, and very few were involved with heroin or other narcotics. The heroin user population in this study (3.3%) is negligible compared to the proportion of heroin fatalities in deaths from all drugs, which has reached an alarming number in many areas. By virtue of their medical and psychiatric histories the deceased had many drugs available to them and certainly misused their prescribed drugs through excessive self-medication, often in combination with alcohol. Table 4 shows their abuse history. Only 1.6% had a documented history

TABLE 4—*Cases involving a prior history of drug misuse.*

Prior History	Cases, no.	Percent of All Cases Surveyed[a]
Alcohol or drug abuse, or both	350	34.3
Drug misuse	175	17.1
Alcohol abuse only	139	17.0
Heroin abuse	34	3.3
Propoxyphene abuse	16	1.6

[a]Percentage values do not tally because of overlap between categories.

of propoxyphene abuse, and as might be suspected, the chief problem drug was alcohol (of which much will be said later in the report), often in combination with other prescription drugs. Approximately one third (350 cases) abused or misused some substance—alcohol alone, drugs alone, or a combination, and 17% were identified as problem drinkers or alcoholics. Almost 40% of those victims with a history of drug use (or misuse) had a defined drinking problem.

There is virtually no evidence that propoxyphene was obtained by the deceased from outside usual medical channels (see Table 5). For 98% of those cases in which the origin of the drug was known it was obtained by legal prescription. Although the source is unknown for almost half the cases, it is likely, in view of the hugely disproportionate

TABLE 5—*Apparent origin of propoxyphene used by the deceased.*

Apparent Origin	Cases, no.	Percent of All Cases Surveyed
Own prescription	483	47.3
Other's prescription	37	3.6
Forged prescription	1	0.1
Stolen	1	0.1
Placental transfer	1	0.1
Unknown	499	48.8

bias towards prescriptions, that a significant portion of the unknowns would reflect a prescription origin.

The route of administration can sometimes be a guide to abuse. This aspect was investigated and the results indicate that 758 or 74.2% ingested the drug orally. Only 4 of 1022 were identified as using the drug intravenously (0.4%). If it is accepted that any administration route other than oral could be construed as evidence of abuse, then the deceased did not abuse propoxyphene. The drug was generally obtained through legal, medical channels and was ingested orally as intended, although with definite tendencies to overuse.

Occurrence of Proprietary Propoxyphene and Other Drugs

There are about 30 trade name proprietary drugs containing propoxyphene in the United States and Canada. They embrace a variety of pharmaceutical forms, and the propoxyphene is present as either its hydrochloride or napsylate salt. In many of the products propoxyphene is compounded with other drugs, typically aspirin, phenacetin, and caffeine. Eighteen different proprietary forms of propoxyphene were encountered in the study, of which 40% were specific Lilly products, indicated by their trade names. An additional 33.5% were called "Darvon®," but the specific form was not identified. Examination of the specifically named Lilly products showed 81.6% of them to contain the hydrochloride salt of propoxyphene and 18.4% to contain the napsylate salt. Figure 4 shows the frequency with which the various proprietary forms of propoxyphene were

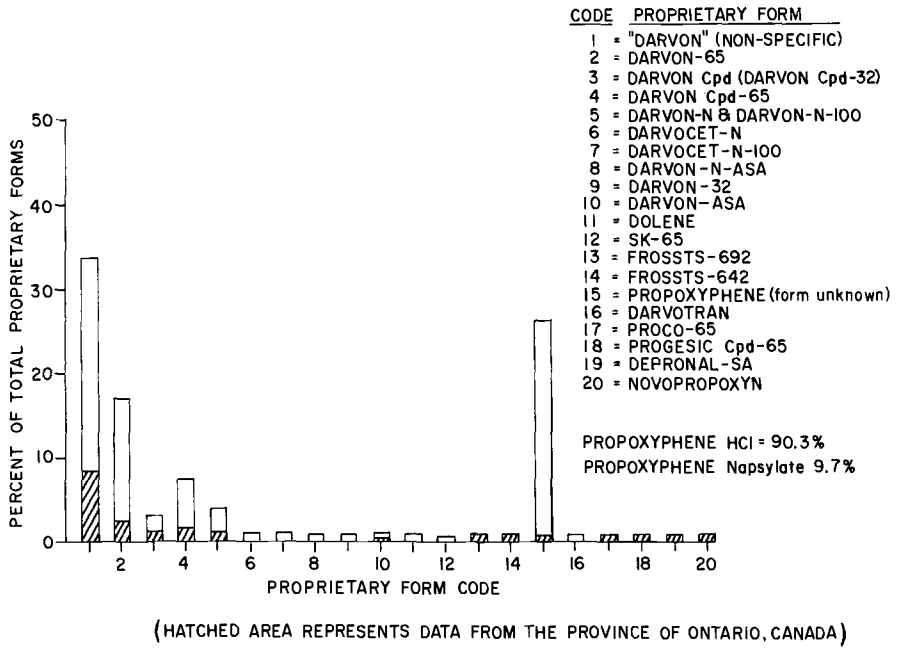

FIG. 4—*Frequency of appearance for proprietary forms of propoxyphene.*

encountered. Code 1 was used whenever unqualified Darvon® was stated in the case report to be the drug involved (343 cases), and Code 15 when propoxyphene was detected and identified analytically but not mentioned by name in the investigator's report (283 cases). By inspection of the figure it can be seen that Darvon-65® and Darvon Com-

pound-65® were the most frequently encountered specific forms. The proprietary name of the propoxyphene was known in 72% of all the cases. It is interesting to note that the frequency profile for most of the Canadian drugs is nearly identical to the U.S. profile, except that there were fewer unknowns (Code 15).

There were 244 cases (23.9%) of the 1022 study total in which propoxyphene, either alone or with at least one constituent of Darvon Compound®, was determined by analytical toxicology to be present in the deceased's blood. In 72 of these cases one or more constituent of Darvon Compound® (aspirin, phenacetin, and caffeine) was detected. It is acknowledged that it cannot be certain from toxicological analysis alone that these constituent drugs originated in the form of Darvon Compound®, but care was taken not to include minute amounts of caffeine and very high concentrations of salicylate which were likely to have originated with coffee or over-the-counter aspirin preparations.

Alcohol—Alcohol was involved in 429 (42.0%) of the total cases. It occurred uniformly in the major case types: 40.8% of suicides, 42.7% of the accidental deaths, and 43.2% of the undetermined cases. One hundred and eighty cases had alcohol and propoxyphene only, detected analytically, and a further 58 cases had alcohol and propoxyphene with either aspirin, phenacetin, or caffeine, or some combination. This high and uniform incidence of alcohol determined analytically clearly mirrors the circumstantial evidence in the investigator's reports which described the drinking habits of the victims and the omnipresence of alcohol.

Other Drugs—At least one other drug in addition to propoxyphene (excluding aspirin, phenacetin, and caffeine) was involved in 76.1% of the total cases. Table 6 shows

TABLE 6—*Drugs other than propoxyphene and ethanol detected in autopsy specimens and corresponding availability indicated by investigation.*[a]

Drug	Cases Detected in Autopsy Specimens, no.	Occurrences of Corresponding Proprietary or Generic Drugs Indicated by Investigation, no.
Diazepam	292	280 Valium
Secobarbital	62	39 Seconal
Phenobarbital	53	8 Phenaphen 8 Donnatal 21 Phenobarbital
Chlordiazepoxide	40	5 Novopoxide 76 Librium
Pentobarbital	33	26 Nembutal
Meprobamate	32	30 Miltown, Equanil Deprol, Pathibamate Equagesic
Codeine	29	13 Codeine 37 Empirin Compound with Codeine Phosphate
Ethchlorvynol	29	19 Placidyl
Amitriptyline and nortriptyline	27	16 Triavil 29 Elavil 6 Etrafon 3 Aventyl
Unspecified "barbs"	27	15 . . .
Amobarbital	25	6 Amytal 4 Dexamyl
Morphine	25	. . .
Methaqualone	20	9 Quāālude
Trichlorethanol and chloralhydrate	20	25 Noctec
Diphenylhydantoin	19	32 Dilantin
Flurazepam	17	59 Dalmane

TABLE 6—*Continued.*

Drug	Cases Detected in Autopsy Specimens, no.	Occurrences of Corresponding Proprietary or Generic Drugs Indicated by Investigation, no.
Methadone	14	6 Methadone
Butabarbital	13	4 Butisol
Glutethimide	11	14 Doriden
Methyprylon	11	8 Noludar
Imipramine and desipramine	10	1 Norpramin
		10 Tofranil
		2 Presamine
Thioridazine	10	17 Mellaril
Amphetamine and methamphetamine	9	4 Dexamyl
		8 Amphetamine
Doxepin	8	12 Sinequan
Chlorpromazine	6	15 Thorazine and Largactil
Pentazocine	6	18 Talwin
Acetaminophen	4	30 Tylenol
Diphenhydramine	4	5 Mandrax
		11 Benadryl
Acetone	3	1 Acetone
Meperidine	3	6 Demerol
Quinidine	3	1 Quinidine
Carisprodol	2	6 Soma
Ethinamate	2	4 Valmid Pulvules
Isopropanol	2	1 Rubbing alcohol
Methapyriline	2	3 Sominex
Promazine	2	4 Sparine
Promethazine	2	6 Phenergan
Chloroquine	1	1 Chloroquine
Cyclazocine	1	
Digoxin	1	7 Lanoxin
Hydroxyzine	1	2 Vistaril
		2 Atarax
Lidocaine	1	1 Xylocaine
Orphenadrine	1	1 Norflex
Oxazepam	1	3 Serax
Oxycodone	1	10 Percodan
Phencyclidine	1	. . .
Unspecified phenothiazines	1	. . .
Phentermine	1	1 Ionamin
Phenylbutazone	1	5 Butazolidin
Prochlorperazine	1	1 Combid Spansule
		11 Compazine
Propranolol	1	2 Inderal
Quinine	1	2 Quinine
Theophylline	1	1 Quibron
Trifluoperazine	1	7 Stelazine

[a] 57 different drugs, 894 total cases.

specific drugs and the number of cases in which that drug was determined analytically in autopsy specimens. This table also shows the corresponding number of instances in which that agent was known to be available to the deceased by investigators. Diazepam heads the list by a huge margin. It is the most commonly prescribed drug in the United States [*14*], and it is generally recognized by toxicologists as a drug prone to excessive and casual use by many "patients" wishing to relax and control nervous tension. It was involved in 451 cases (44%), as determined by toxicological analysis or by

case investigation. Psychotropic/ataractic agents (40.1%), sedative/hypnotics (21.2%), and pain-killers (analgesics) (12.1%) accounted for approximately three fourths of all the drug occurrences. Of the psychotropic/ataractic agents the benzodiazepines were quite dramatically the most prominent: the occurrence of diazepam was almost four times greater than chlordiazepoxide, which in turn was about three times greater than amitriptyline before the main body of other drugs was reached. A benzodiazepine, flurazepam, also led the sedative/hypnotic class. Illicit drugs were a very small percentage.

Forensic Toxicology and Pharmacology

Signs and Symptoms

The symptoms exhibited by the victims in the time interval between drug ingestion and death were very carefully assessed with a view to their prospective clinical diagnostic value, to ascertain whether there was any clue to the physiological mechanisms involved in propoxyphene toxicity, and finally to determine if the frequency of occurrence and consistency of type made them a useful retrospective tool for the forensic scientists. Only those cases in which the symptoms were clearly described by a witness and officially documented in the case report were used for evaluation. There were 180 such cases (17.6% of the total); it is a small proportion, but the cases are reliable and undoubtedly most of the remainder exhibited some unobserved symptoms before dying. Of course, it is not known how many died without showing symptoms of any kind, but it is unlikely to have been great [*15*]. Figure 5 graphically presents the types of symptoms involved

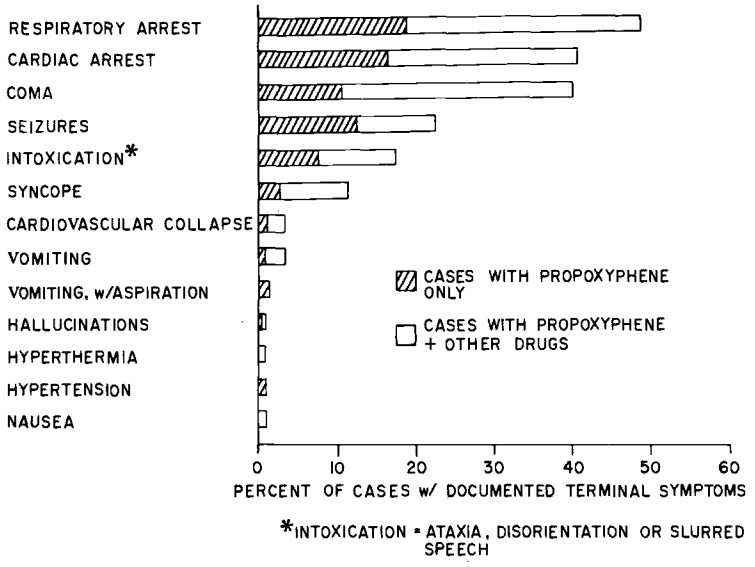

FIG. 5—*Types of terminal symptoms expressed as a percentage of relative frequency of occurrence.*

and their frequency of occurrence and shows the differences for those cases involving propoxyphene only and those in which a combination of drugs was ingested. Approximately 50% of all the cases in which symptoms were reported indicated that respiratory arrest was the final physiological event. The cases in which propoxyphene was the only

drug involved are probably a surer diagnostic guide. The addition of other drugs may well change the frequency profile, and, as can be seen in Fig. 5, seizures are more commonly seen, relative to other symptoms, in the cases involving propoxyphene only.

In those instances where the deceased collapsed and died suddenly (54 cases) the types of symptoms were the same but their relative frequency was very different. For example, respiratory arrest has a relative frequency of 85% in those who died quickly and is much greater than cardiac arrest, whereas in the cases shown in Fig. 5 respiratory and cardiac arrest are approximately equal. This certainly indicates a predominantly central nervous system response in those cases where death occurred rapidly.

In a laboratory research study [*15*] dogs, rats, and mice all exhibited symptoms consistent with those seen in the case victims. Clonic and tonic convulsions, ataxia, and weakness and profound respiratory depression prior to death followed large acute dosage with propoxyphene hydrochloride. Laboratory rats at the Center for Human Toxicology were given doses of 75 mg/kg or 125 mg/kg intraperitoneally of propoxyphene hydrochloride in a test experiment. Within 1 min after receiving the drug they were sedated, at 7 and 8 min they suffered clonic-tonic convulsions, and at 10 min they experienced sudden respiratory arrest. Cardiac arrest followed approximately 15 min after drug ingestion. The scientific literature reports and the foregoing experiment lend credence to the terminal symptoms observed in the survey cases. Although these symptoms may well be seen in other medical crises and drug toxicities, the forensic toxicologist should be aware that investigator's reports describing this terminal pattern could be implying an acute propoxyphene poisoning. Similarly, if propoxyphene is detected by postmortem toxicology analysis in an otherwise unsuspected case the presence of these symptoms can be accepted as consistent with acute toxicity.

Very few cases received hospital treatment and there were only 72 (7.0%) in which a hospital physician's report was available, but they generally reflected the same symptoms terminating in cardiac arrest following respiratory difficulties and failure. Almost no cases were diagnosed by a clinical laboratory in the hospital, and unless circumstantial evidence was available the subjects were treated symptomatically.

In contrast to the dramatic terminal symptoms observed there were virtually no characteristic diagnostic observations at autopsy. General pathology associated with central nervous system depression and failure was the rule. Pulmonary and cerebral edema and visceral congestion were typically the only findings. As expected, there were some instances of aspiration and gastrointestinal evidence of drug ingestion, but usually it was the circumstances surrounding the case and the terminal events that aroused suspicion that drug toxicity could be the cause.

Survival Time Estimations

The length of time between drug ingestion and death, and the subject's behavior during that period, can be of value in understanding physical patterns of toxicity. This is only true, however, if a sufficiently large number of reliably observed cases are available for study and if apparent common symptoms and time lapse can be confirmed. In order to draw objectively supported conclusions the time interval must be related to some other factors such as drug dose, the blood concentration of the drug, the appearance and determination of metabolites, or liver to blood concentration ratio. Only then can the various time intervals be rationalized and examined to determine if acute or chronic ingestion, alcohol-drug ingestion, and drug combinations are related to survival time, and, in turn, to analytical toxicological findings. If reliable inferences can be established, then recognition and diagnosis of toxicity may be improved and the toxicologists will have another useful characteristic to consider in assessing the consistency of a postmortem analytical finding within the general framework of the case.

An attempt was made to deal with this problem directly by portraying as a distribution the frequency (as a percentage) with which particular time intervals occurred throughout the study cases. The time intervals from "last seen alive to death" were available for 769 cases and are displayed in Fig. 6. The time interval on the abscissa is in hours;

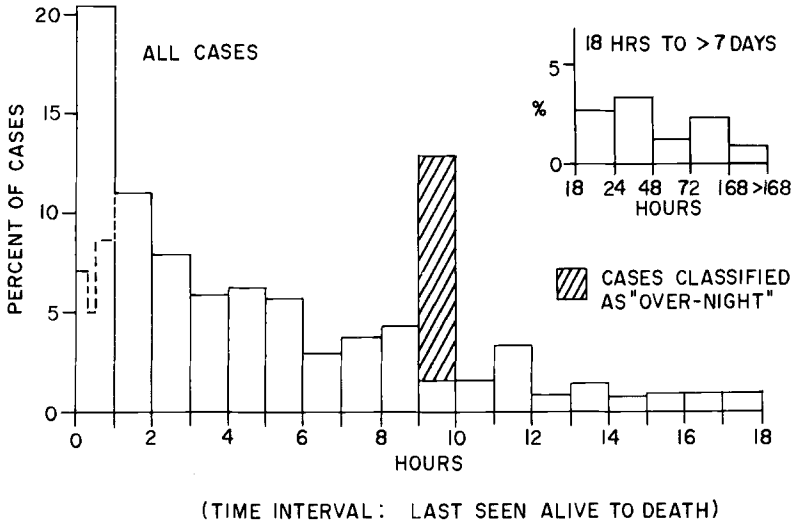

FIG. 6—*Interval from time last seen alive until death; distribution in percent for all cases surveyed. One case represents 0.13% of total cases.*

however, the first hour is subdivided into 0 to 15, 15 to 30, and 30 to 60-min periods to display the earlier time periods representing relatively rapid death. It should be clearly noted that the time interval used in these studies is *not* a "stop-watch" period beginning with observed drug ingestion and ending when the victim was pronounced dead. It is an estimate of survival time, sometimes accurate, and sometimes deduced from case investigation information. In some cases the time was known accurately, but those are distributed through the whole range, from those who died suddenly to those who died following long hospital care. Many of the times were taken from the medicolegal investigator's report of when the deceased was last seen alive and when found dead.

Those who were last seen in the evening and found dead the next morning were numerous, approximately 11% (85) of all the cases in the time interval study. These were assigned to an "overnight" classification and given a 9 to 10-h time interval. As can be seen from the discussion that follows, it is reasonable to infer that they probably died more quickly and the time intervals assigned for these cases should be distributed from 0.25 to 10.0 h. As the time interval increases beyond 10 h, it becomes progressively less reliable as an estimate of survival time. Very few cases greater than 10 h had the time course of intoxication observed; they were generally found dead, and obviously had died much earlier. There are several other factors which should be considered before the data are taken at face value. These are social, behavioral, and environmental considerations, and their significance increases as the time interval becomes longer.

Obviously, extreme age and poor physical health will alter the ability to survive; whether collapse occurs with the subject in a warm bed or undressed, lying on a cold floor also affects survival. If the subject lived alone, then the chance of succumbing without any assistance that might have saved life was increased, whereas those with frequent social friends and family near at hand often received some first aid. Of course,

the extent of medical attention affects survival. Whether the ingestion takes place during day or night is a factor which may determine when attention is first drawn to the victim. Very young or old people are often attended during the night, and some were discovered before death.

In general, it can be inferred from examination of Fig. 6 that almost all will die within 8 h unless they receive prompt and appropriate medical treatment. Approximately 81% of the 769 cases for which time is available died within 10 h, and 52% died in 5 h or less. The greatest percentage is in the 0 to 1-h period and represents 20% of the cases.

Sudden, unexplained death, partially defined as death occurring within 15 min or less after ingestion, comprises 7% (54) of the cases with a known time interval. They appear in Fig. 6 under the 0 to 15-min interval in the 0 to 1-h bar. For the cases involving only propoxyphene, data on survival time were available for 91 cases. This is graphically displayed in Fig. 7 in a manner analogous to Fig. 6. In this group there are only two

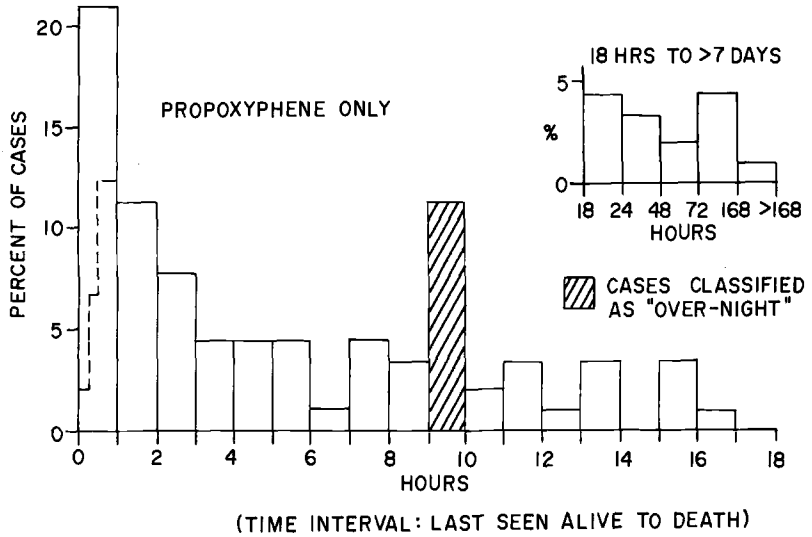

FIG. 7—*Interval from time last seen alive until death; distribution in percent for those cases involving propoxyphene only. One case represents 1.1% of total cases.*

cases (2.2%) in the 0 to 15-min time period. While the number is small, it would appear that propoxyphene per se is not a prominent cause of the relatively early deaths. Further evidence for this can be seen in Figs. 8 and 9. Figure 8 shows a similar time frequency distribution for 125 cases involving propoxyphene and alcohol. Figure 9 is identical in format and illustrates 43 cases involving propoxyphene and diazepam. Although the numbers are smaller, the distribution in the first hour indicates a large proportion died within 15 min. This further suggests that the sudden deaths result from drug combinations rather than propoxyphene alone.

A graph was constructed on the basis of blood propoxyphene concentration versus time interval for those cases in which only propoxyphene was detected. It was anticipated that there might be a valid negative correlation to the relationship, but despite all efforts to manipulate the data statistically they would not yield. Figure 10 shows the plotted data and, as can be seen, it is tempting to equate the higher blood concentrations with the shorter time intervals. There is definitely a bias in that direction, but unfortunately only a discussion of empirical observations is possible.

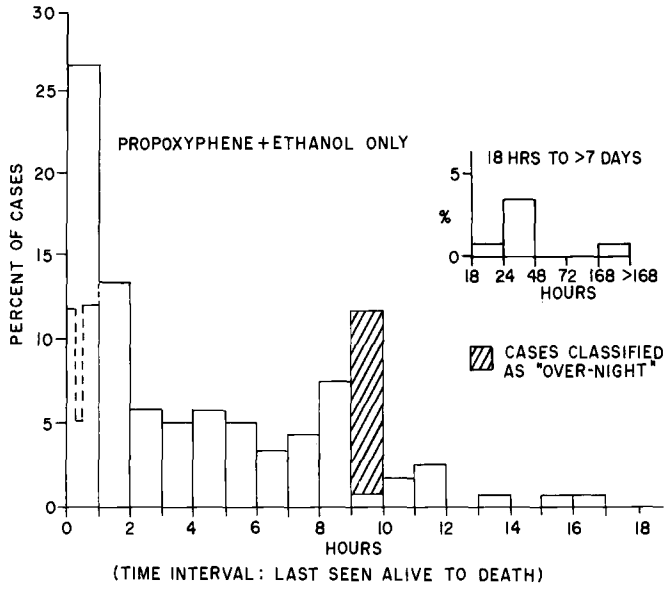

FIG. 8—*Interval from time last seen alive until death; distribution in percent for those cases involving propoxyphene and ethanol only. One case represents 0.8% of total cases.*

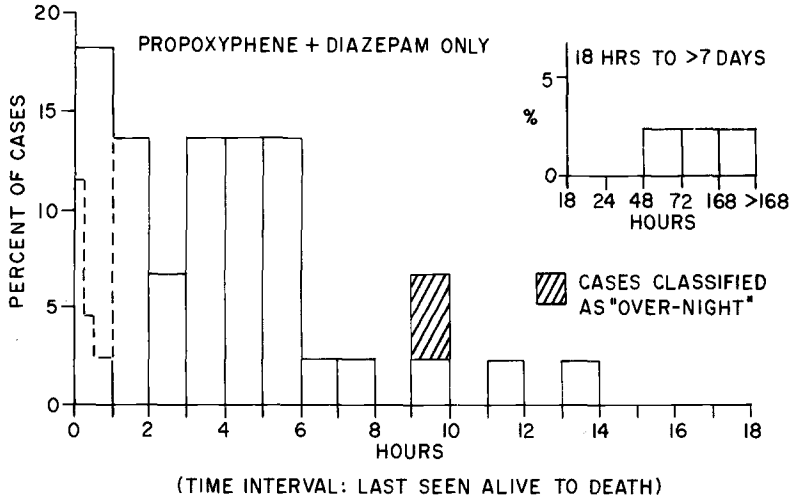

FIG. 9—*Interval from time last seen until death; distribution in percent for cases with propoxyphene and diazepam only. One case represents 2.3% of total cases.*

Line A in Fig. 10 was arbitrarily drawn so that 95% of the cases fall within the confines of the line and the axes. There is great variability in blood propoxyphene concentrations at any given time, especially at low values. No attempt has been made to quantitate this variability. To accept a valid negative correlation with survival time some pharmacodynamic assumptions are necessary, such as a quantitative relationship between the drug dose, the rate and amount absorbed, and the resulting blood concentration with time. Given these assumptions and the bias seen in Fig. 10, the data do support the

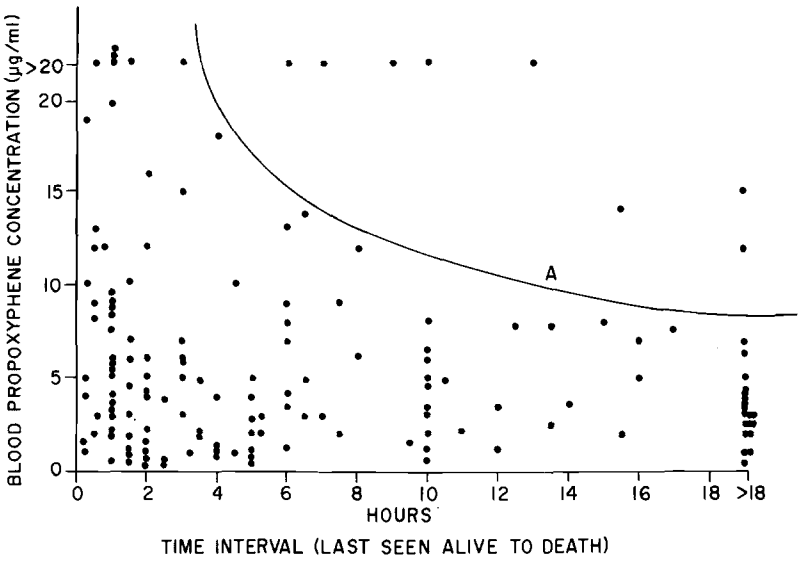

FIG. 10—*Blood propoxyphene concentration versus interval from time last seen until death for those cases involving propoxyphene only.*

primary supposition that the time intervals reported in the study cases are reasonable estimates of true survival time. Although there is no apparent mathematical relationship between blood concentration and survival time useful for dogmatic interpretation of case findings, Fig. 10 can be used as a guideline to assist rational interpretation or to reconcile case investigative information with laboratory analytical results. For example, five cases in every hundred do not fall under Line A in the figure; therefore, in a forensic laboratory where 50 propoxyphene cases per year are investigated it may reasonably be expected that no more than two or three cases each year will fall beyond this line.

Figures 11*A* and *B* show another attempt to relate survival time to analytical toxicology data. The 293 cases in which blood and liver propoxyphene concentrations were both available are plotted on an ordinate of blood concentration and an abscissa of liver concentration. It has been suggested for some drugs such as barbiturates [*16*] that in cases of large, acute dosage and rapid death the postmortem ratio of liver/blood drug concentrations will be very high, and decrease in inverse proportion to survival time. Further, it is sometimes assumed that drugs which are tissue bound or exhibit a hepatic "first-pass effect" [*17*] will also fit the liver/blood ratio theory. Propoxyphene is known to satisfy the former requirements, but as can be seen from Figs. 11*A* and *B* it emphatically denies the ratio theory. All of the cases are randomly scattered, there is no clustering of values along any particular ratio line, and the ratios from cases in which the survival time was not greater than 1 h are also indiscriminately scattered. It can be argued that there is the merest tendency for the cases of less than 1 h survival to have liver/blood ratios greater than 10/1, but it is almost an illusion, and in general the high ratios are of no assistance in predicting short survival times. The calculation of liver/blood ratios is a poor practice for this purpose and it cannot be recommended from this study.

Analytical Methods

The analytical methods used at each laboratory in the survey were documented and the toxicologists interviewed concerning their experience and method applied to postmortem

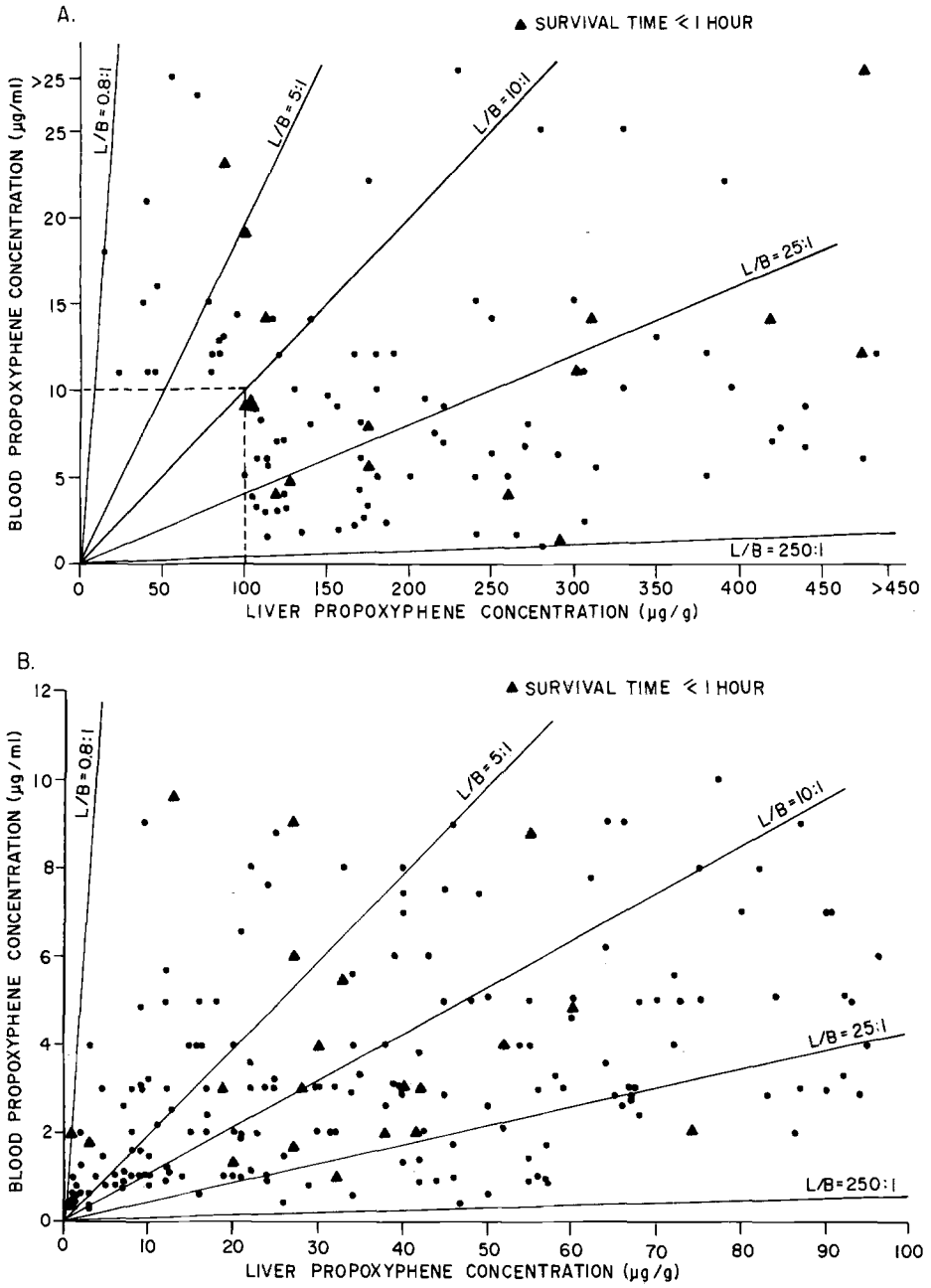

FIG. 11—*Blood propoxyphene concentration versus liver propoxyphene concentration for all cases;* (A) *cases where concentrations exceed 10 μg/ml for blood and 100 μg/g for liver;* (B) *cases where concentrations are less than 10 μg/ml for blood and 100 μg/g for liver.*

cases. Both qualitative screening procedures and quantitative methods are in routine use at the study sites for the determination of propoxyphene and its metabolites in blood and tissues taken at autopsy. The only specimens routinely analyzed for propoxyphene were whole blood, usually taken from the heart, and liver tissue. Although there were three

different types of methods in use, in fact only two methods with occasional technical variations predominated. They are the ultraviolet (UV) spectrophotometric method of McBay [*10*] and the gas chromatographic (GC) method of Wolen [*9*]. Wallace's steam distillation-derivative UV method [*11*] was the third, but was used rarely at only two sites. Ten sites used only GC, two without resort to any internal standard for quantitation. Six sites used only UV spectrophotometry. Two sites used both, making a choice of quantitation following qualitative detection of propoxyphene. The choice depended on a number of variables in the circumstances of the case.

Of the total 1022 cases examined, there were only 22 in which concentrations of norpropoxyphene were reported. Toxicologists in only four of the surveyed laboratories routinely determined the metabolite concentrations, although almost all used a GC procedure which recognized the metabolite(s) and used their presence as qualitative confirmation of propoxyphene ingestion. It is possible that the quantitative importance of propoxyphene and norpropoxyphene to a sound toxicological interpretation of a case is not appreciated as essential, or that the technical difficulties involved in the metabolite analysis, which are not negligible by any means, have not yet been surmounted.

As practiced then at the survey laboratories, GC was most often used to determine parent propoxyphene only. A wide variety of instrument conditions, columns, and liquid phases were used, but all were common and adequate to separate the parent drug and metabolites. The choice of internal standards was equally imaginative and included pyrroliphene, SKF-525A, and benzhexol. A recurring problem was multiple GC peaks for propoxyphene, but this usually can be traced to thermal degradation. It often results in the final stage of the extraction from overheating the tip of the evaporation tube after the organic solvent has gone to dryness or because the GC injection port is maintained at too high a temperature. To avoid this latter problem the temperature at the GC injection port should not exceed 225 °C.

The McBay UV method measures both parent propoxyphene and norpropoxyphene simultaneously, giving an aggregate concentration value. It was favored largely for its speed and technical simplicity, but it does compromise metabolite analysis and requires a 10-ml blood sample to reach a useful concentration range. The sensitivity limit was stated variously as 0.5 to 1.0 μg/ml, which suffices because the aggregate concentrations are obviously higher than the parent drug alone quantitated by GC. The GC methods, by contrast, are sensitive to at least 0.1 μg/ml with a 5-ml sample. If the UV method is followed *exactly* as published it provides accurate results and, inasmuch as it expresses a value for both drug and metabolite, may reflect the circulating concentration of propoxyphene in toto at the time of death.

In studies[4] using blood and liver tissue homogenate fortified to 20 μg/ml with propoxyphene, the GC method of Wolen [*9*] recorded 21 μg/ml against the results of the UV procedure of 20 to 25 μg/ml. Also, the summation of propoxyphene and norpropoxyphene concentrations following GC analysis of test samples approximated the UV aggregate value for the same test sample. In addition, it is known from laboratory studies[4] that only 40 to 50% of the norpropoxyphene is determined by the UV method. However, its absorbtivity value (1 cm light path and wave length 255 nm used for quantitation) is 1.25 to 1.5 times greater than propoxyphene.

The poor recovery of the metabolite undoubtedly results from its chemically unstable, labile character which cannot withstand harsh hydrolysis or very strong alkaline conditions, both of which are inherent to the extraction method in the UV procedure. The calibration curves for parent drug and metabolite match each other very closely but linearity cannot be relied on beyond an absorbance difference of 0.5 at 255 nm before

[4] Personal communications, Dr. Arthur J. McBay, State Medical Examiner's Office, North Carolina and Dr. Frank Nash, Eli Lilly and Co., Indianapolis, 19–23 Jan. 1976.

and after irradiation. It is absolutely essential, as the published method clearly states, to dilute the sample before irradiation to achieve an absorbance value of approximately 0.3. The shelf life of propoxyphene and metabolite standards is poor and unreliable in virtually any medium, including water. Again, it is essential to analyze freshly prepared standards in blood or tissue homogenate at the time the case samples are analyzed if the best, most accurate results are to be obtained. This of course applies to both GC and UV methods.

Figure 12 depicts the metabolic pathways of propoxyphene and forms the basis for discussing problems of analytical methods, although, in fact the forensic toxicologist is only interested in the parent drug, norpropoxyphene, and possibly dinorpropoxyphene. The two metabolites as their amide derivatives are difficult to resolve on common GC

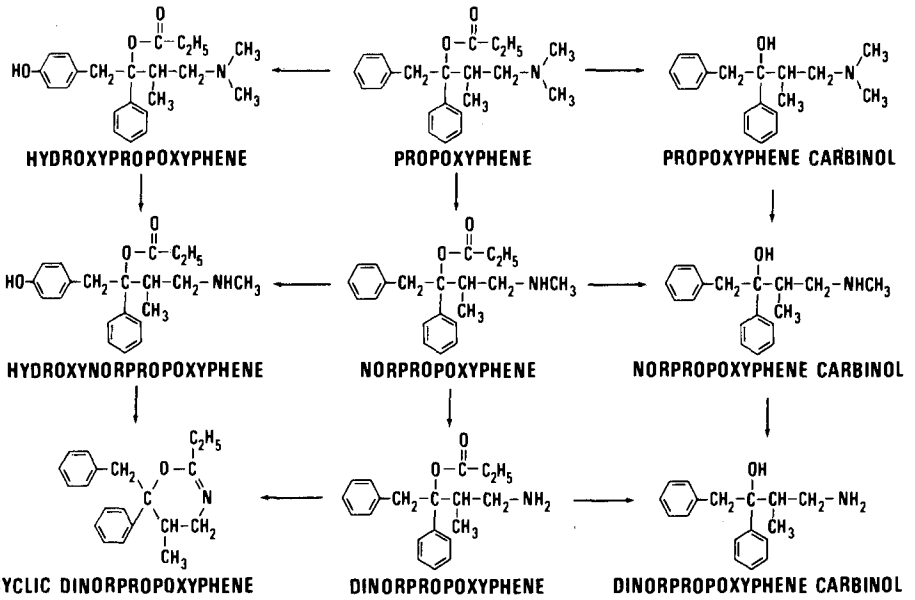

FIG. 12—*Metabolic pathways for propoxyphene (courtesy of Dr. Robert E. McMahon, Eli Lilly and Co., Indianapolis, Ind.).*

liquid phases, but it is not a critical matter because the ratio of norpropoxyphene to dinorpropoxyphene is usually greater than 9:1, and dinorpropoxyphene is often in negligible concentrations. Figures 13 and 14 show important chemical rearrangements of the metabolites which occur during typical blood and tissue analytical extraction schemes.

Figure 13 illustrates the modification of norpropoxyphene to a stable amide which is suitable for GC analysis. This reaction goes to completion at pH 11 or greater, but some conversion to the amide occurs at any pH value above neutral. Dinorpropoxyphene is subject to the same type of rearrangement to form its own amide. Unlike norpropoxyphene, the dinorpropoxyphene metabolite undergoes a second reaction, cyclization to form a stable cyclic compound (Fig. 14). This cyclization can occur spontaneously at pH 7.4, at 37°C in the presence of albumin, and is therefore present in blood prior to analysis. The cyclic metabolite can be extracted from blood at pH 5 with hexane, thus separating it from the parent drug and other metabolites. The cyclic to dinorpropoxyphene ratio is usually about 1:1. In a test analysis[5] of a blood sample drawn from a dog

[5] Personal communication, Dr. Robert E. McMahon, Eli Lilly and Co., Indianapolis.

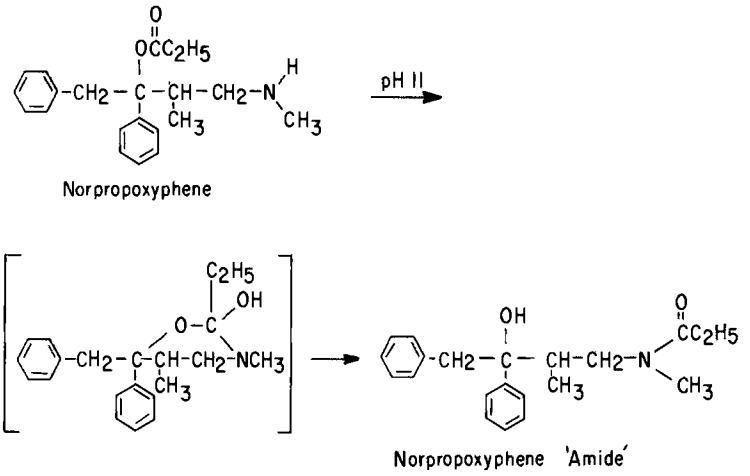

FIG. 13—*Base-catalyzed rearrangement of norpropoxyphene (courtesy of Dr. Robert E. McMahon, Eli Lilly and Co., Indianapolis, Ind.).*

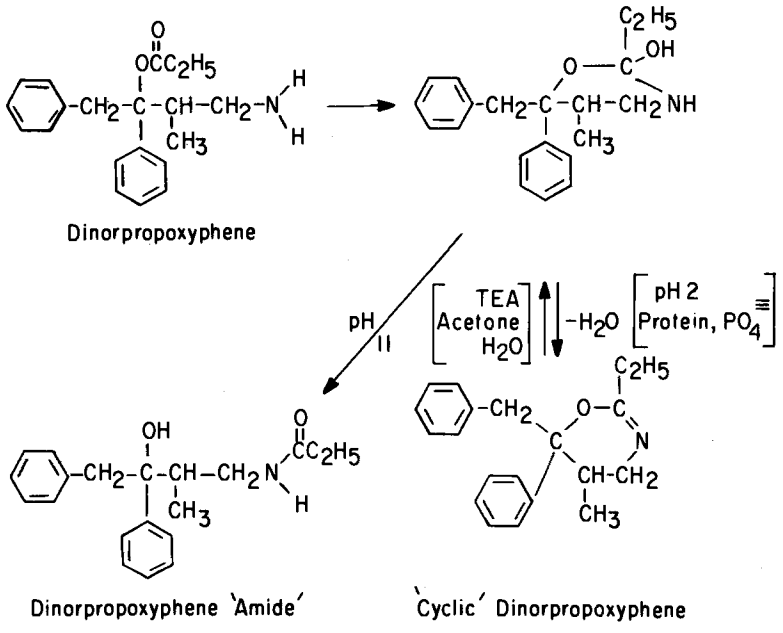

FIG. 14—*Rearrangements of dinorpropoxyphene (courtesy of Dr. Robert E. McMahon, Eli Lilly and Co., Indianapolis, Ind.).*

given toxic (but not lethal) doses of propoxyphene, the concentrations in μg/ml were propoxyphene, 2.2; norpropoxyphene, 32.0; dinorpropoxyphene, 2.8; and cyclic, 2.8.

There can be little doubt that GC methods employing a suitable internal standard and capable of quantitating the propoxyphene and norpropoxyphene (as its amide) provide the most useful and accurate data. As will be discussed later in the report, this information is required if a sensible toxicological interpretation is to be made of the analytical results. The extraction method described by Wolen [*18*] provides a proven procedure

which can be used by forensic toxicologists. By substitution of an appropriate internal standard the method is suitable for GC, flame-ionization detection. The survey revealed that 10 (55%) of the study sites had a GC-MS instrument, some with chemical ionization source, and 9 had computer-data systems. Despite this analytical powerhouse none of the laboratories were using the instrument for quantitative analysis by mass fragmentography. Nonetheless, the method of Wolen [*18*] by either electron impact or chemical ionization is ideal and is recommended as the method of choice. It is superior to all other methods in sensitivity, specificity, accuracy, precision, and simplicity of operation once it has been established in the laboratory.

Figure 15 shows the distribution (as a percentage) of blood propoxyphene concentrations for all of the 1022 study cases, separated according to GC analysis or McBay UV

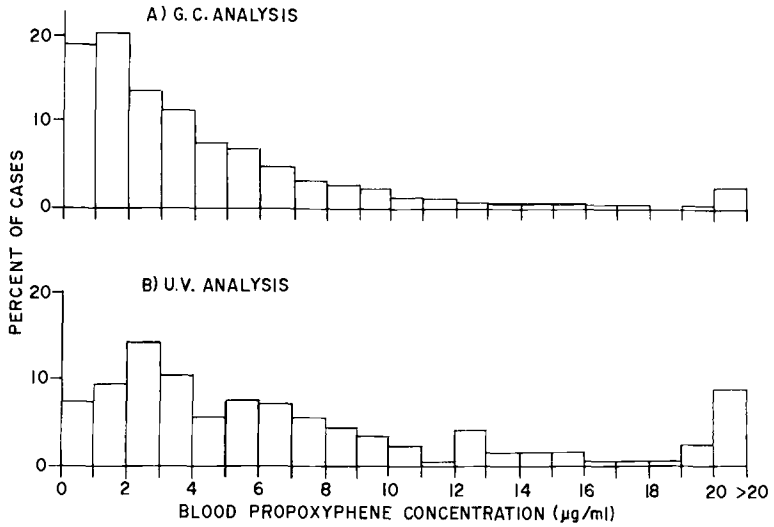

FIG. 15—*Distribution, in percent, of blood propoxyphene concentrations for all cases analyzed by gas chromatography* (A) *and ultraviolet analysis* (B) *according to the method of McBay et al* [10].

method. There are almost twice as many GC cases as UV. The profiles are obviously different but predictably so if the GC graph represents only parent propoxyphene concentrations and the UV graph includes aggregate values for parent drug and metabolite. The UV concentrations are skewed to high values, particularly for those greater than 20 μg/ml. It should be noted that 45% of these very high values occurred at one site. It is very unlikely that the parent drug is completely absent in any of the case samples, given the typical survival times and the fact that propoxyphene has a half-life approximately 12 h. The peak at 12 to 13 μg/ml in Fig. 15*B* is probably a UV method phenomenon and may be related to the presence of norpropoxyphene metabolite or to a UV standard calibration curve anomaly. It does not appear in any of the GC illustrations. The apparent paucity of cases at 4 to 5 μg/ml in the UV graph is equally inexplicable. Neither of these phenomenon can be readily explained by consideration of the pharmacodynamics of the parent drug plus metabolite.

Fatal Propoxyphene Concentrations: Blood and Liver

This section is devoted to an examination of the blood and liver propoxyphene (and metabolite) concentrations, and their interrelationships, as determined by the GC and UV methods discussed previously. Figures 16 and 17 present the distribution of blood

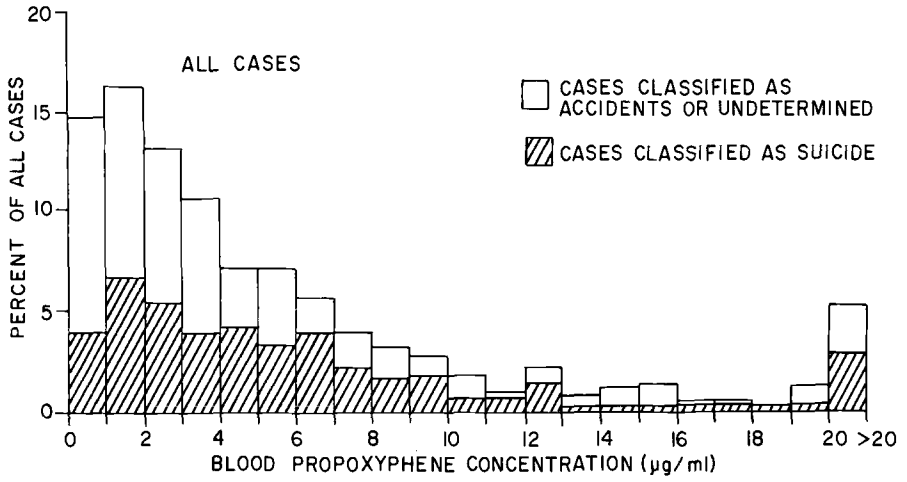

FIG. 16—*Blood propoxyphene concentrations for all cases surveyed, for cases classified as accidents or undetermined, and for cases classified as suicide. One case represents 0.1% of total cases.*

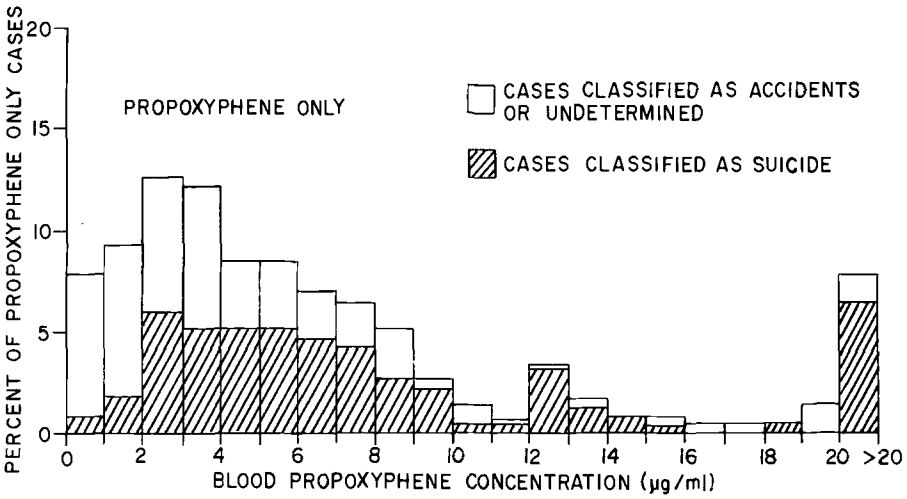

FIG. 17—*Blood propoxyphene distribution for cases involving propoxyphene only, cases classified as accidents or undetermined, and cases classified as suicide. One case represents 0.5% of total cases.*

concentrations, the latter for those cases in which propoxyphene was the only drug. They also separately identify the suicide cases. The concentration range for all cases in the survey with blood concentration reported was from less than 0.1 to greater than 20 μg/ml. Approximately 6% of the cases were from 20 to 189 μg/ml, and 40% of these very high values were from one site and are almost all UV analyses. In Fig. 16 the peak frequency was in the range of 1 to 2 μg/ml, and these represent 16% of the total cases. About 54% of the total cases are less than 4 μg/ml, and 15% of the cases are 1 μg/ml or less.

The suicide cases are distributed somewhat differently, being biased toward the higher concentration ranges. The frequency distribution of the data for all cases and the suicides

are different, as shown by inspection of Fig. 16. The peak for suicides is at the same concentration range as the other cases, but they are more evenly distributed between 1 and 10 μg/ml.

Figure 17 is concerned with those cases involving propoxyphene only. The peak frequency is shifted toward the higher blood concentration and is distinctly above 2 μg/ml. Some 9% of the cases are above 20 μg/ml. In this instance 42% are below 4 μg/ml, and only 8% are at 1 μg/ml or less. It is not surprising that the cases are skewed to the higher concentrations, because the deceased apparently ingested only the single drug, and in sufficient quantity to cause their death. A greater proportion are suicides as compared to the total study cases, and the suicide profile has a higher mean propoxyphene concentration value than the cases classified as accidents or undetermined. One possible explanation for the lower mean concentration seen in Fig. 16 for all the cases is that it includes the alcohol and multiple drug overdoses. In these instances it is reasonable to suppose that the lower concentrations of propoxyphene in combination with other agents are sufficient to induce fatal intoxication.

Figures 18 and 19 are analogous to the blood concentration distribution graphs but are concerned with liver tissue propoxyphene concentrations. When inspecting the graphs the

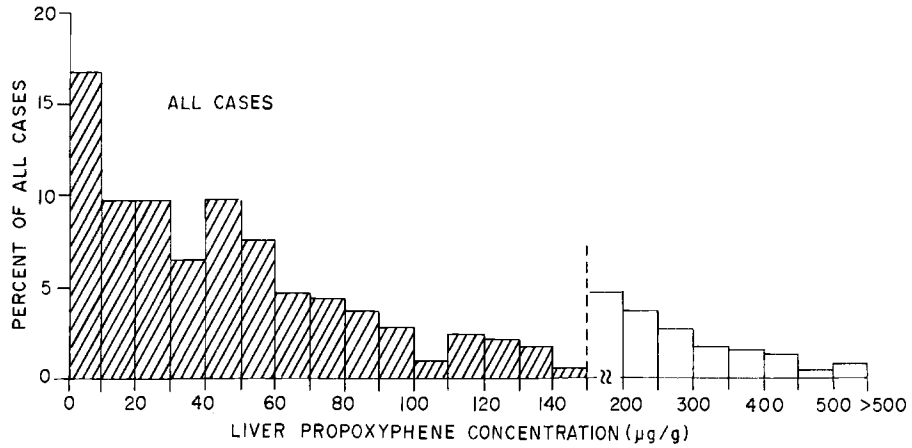

FIG. 18—*Liver propoxyphene distribution for all cases surveyed. One case represents 0.3% of total cases.*

change in the abscissa at 150 μg/g should be noted. In Fig. 18, one case represents 0.3% of the total, while in Fig. 19, one case is 0.9% of the total. In contrast to the blood values, the liver concentrations in both figures are spread over a truly enormous range, 0.5 to greater than 500 μg/g. Given these facts, the two graphic profiles are very similar, with perhaps the propoxyphene-only cases (Fig. 19) skewed slightly toward the higher concentrations. Again in contrast to the blood ranges in which 50% of all the cases were below 4 μg/ml, the liver concentrations representing 50% of all the cases were 50 μg/g or less. By referring to Fig. 11*B* it can be seen that the prominent peak below 10 μg/g liver concentrations in Figs. 18 and 19 are associated with the lower blood concentrations.

As was noted earlier (Figs. 11*A* and *B*), the liver to blood ratios vary from 0.8:1 to 250:1. Since the lower ratios seem to be associated with the lower concentrations in both tissues, it may be that those concentrations determined by UV tend to change the ratio at the higher concentration. This could be explained on the basis of metabolite concentrations which in time will represent an increasingly large proportion of the assayed aggregate concentration, perhaps preferentially in the liver tissues. Only 2.5% of the

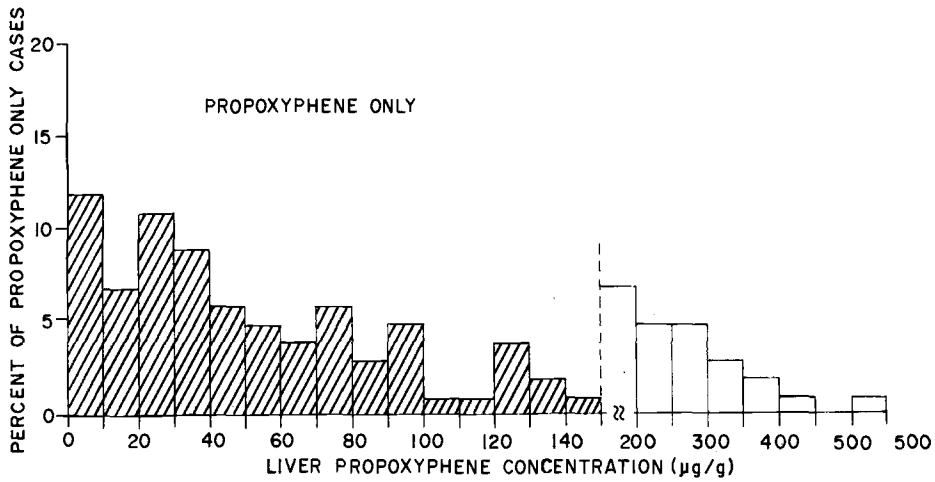

FIG. 19—*Liver propoxyphene distribution for cases involving propoxyphene only. One case represents 0.9% of total cases.*

cases had blood concentrations greater than the liver, and those only fractionally so, with none greater than 1.25:1.

It is clearly important to determine liver tissue concentrations of propoxyphene and norpropoxyphene no matter what values are obtained for the blood. This is particularly true if the blood concentration is less than 1.5 μg/ml; a liver to blood ratio of approximately 10:1 can be anticipated in these instances. Above all, it should not be assumed that because the blood concentration is low the liver concentration will be also, with the case therefore judged as one of marginal toxicity.

Figures 11*A* and *B* and 16–19 can be used as reference models for comparative purposes in medicolegal postmortem cases.

Fatal Propoxyphene Blood Concentrations Not Greater Than 1 μg/ml.

The cases with low blood concentrations were examined separately to ascertain whether propoxyphene was really significant in the toxicology of the case. There were 168 cases with blood concentrations not greater than 1 μg/ml; but 17 died from natural causes, 1 from homicide, and 7 from accidents, suicide, or undetermined causes in which propoxyphene was obviously not implicated in the cause of death (for example, suicide from gunshot wounds). These 25 cases were subtracted from the total to leave 143 cases (14% of the total) in which death was a result of drug overdose. There were 14 cases in this segment which involved propoxyphene only. In 60 cases (41.9%) in this group the deceased had a medical history almost the same as the 42.6% of the total survey population as defined above.

The following is a summary of the toxicological case types involved in the group (because of overlap, the total exceeds the actual number): 14 cases (9.8%) involved only propoxyphene; 61 cases (42.7%) involved propoxyphene and alcohol; 27 cases (18.9%) involved propoxyphene and diazepam; and 94 cases (65.7%) involved propoxyphene and at least one other drug, excluding alcohol and diazepam.

There is a striking contrast with the data from the total 1022 cases for these categories. The 9.8% for propoxyphene only is very low and the 65.7% for multiple drug ingestions high. No less than 90.2% of the 143 special study cases had another drug involved, as determined by analysis by toxicology laboratory.

Figure 20 shows graphically the frequency distribution (as a percentage) of the blood propoxyphene concentrations for the 143 cases. There are no cases involving only propoxyphene below 0.2 μg/ml, and the profile of the graph is generally as anticipated: a

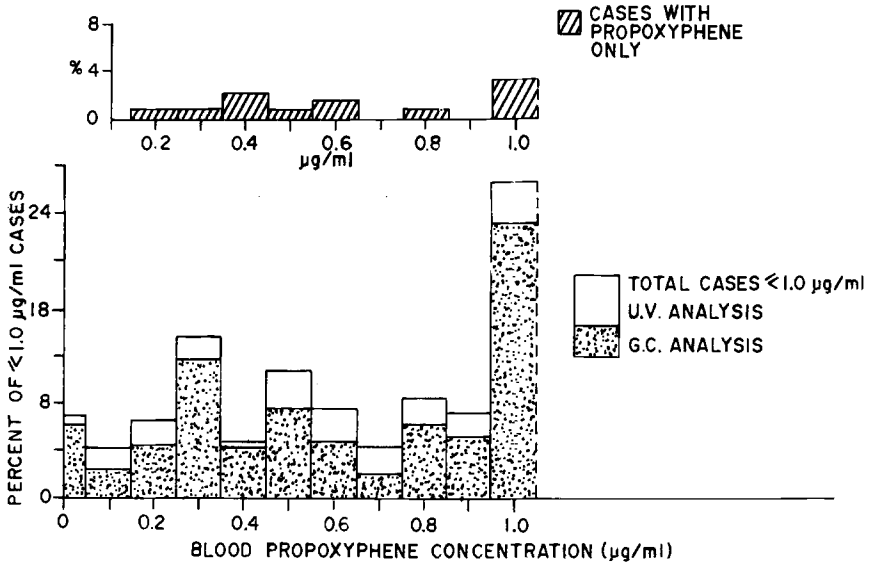

FIG. 20—*Distribution, in percent, of blood propoxyphene concentrations in the range <0.1 to 1.0 μg/ml for cases involving propoxyphene only. One case represents 0.7% of total cases.*

general increase in cases as the blood concentrations increase. The peaks and valleys in the graph should be assessed with the caution that these determinations are at the limits of sensitivity, precision, and accuracy of the analytical methods used.

In approximately 80% of the cases the drug concentration was determined by a GC method, and in 20% by UV analysis. Therefore, the values primarily represent parent propoxyphene and not metabolites. There were 5 cases which involved only propoxyphene in the range 0.2 to 0.5 μg/ml, four of which were determined by GC analysis, and the 1 case determined by UV analysis was 0.3 μg/ml. It is interesting to speculate that some of the cases in the 1.0 to 3.0 μg/ml range analyzed by the UV procedure might have been assayed at less than 1.0 μg/ml had they been determined by GC.

Figure 21 presents the case frequency for the group as a function of estimated survival time for 100 cases in which a time estimate is available. The profile is very similar to that for all of the cases surveyed; approximately 50% are within 6 h, 60% within 9 h, and 75% in 10 h or less, including "overnight" cases (about 18%). Nine percent of the victims died in 0.25 h or less, a close comparison to the 7% of all the survey cases classified as sudden deaths. However, it is very difficult to interpret these data statistically in terms of propoxyphene toxicity because more than 90% of the cases had other drugs involved and there are too few cases in which propoxyphene is the only drug to render interpretation.

Firm conclusions are scarce for this segment of cases, but it is clear that they are not a special population. Their demographic and epidemiological data match well all other cases in the study, and it seems reasonable that they are representative of multiple drug ingestions. It is possible that these blood samples contained high concentrations of norpropoxyphene that were not assayed by the GC procedure; it is also possible that because of accuracy and precision limitations assay values between about 0.8 and 1.3

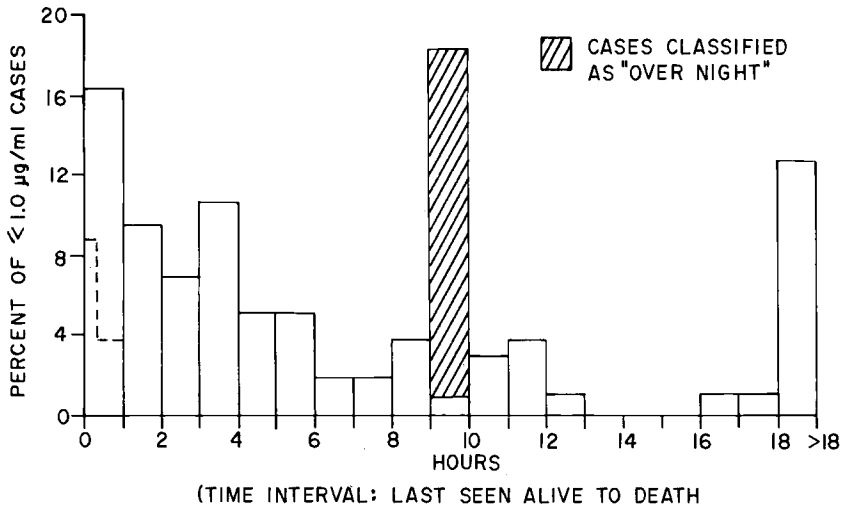

FIG. 21—*Interval from time last seen until death; distribution, in percent, for cases with blood propoxyphene concentrations in the range of <0.1 to 1.0 μg/ml. One case represents 1.0% of total cases.*

μg/ml were mathematically rounded to 1.0 μg/ml by the analyst, thus apparently increasing the number of cases at 1.0 μg/ml.

Therapeutic Propoxyphene Blood Concentrations

The following is not intended as a review or précis of current knowledge concerning the pharmacodynamics and kinetics of propoxyphene, but it does seem appropriate to provide a reference framework by which the results of analytical toxicology in this report can be judged. The most obvious points are blood and plasma concentration ranges of propoxyphene and norpropoxyphene achieved after single or chronic oral doses of the drug. There is a surfeit of data in the literature [*19–23*], but it is of variable value because much of it does not concern human subjects and few (if any) definitive studies using a statistically valid population have been reported. The clinical toxicology literature describing living subjects achieving toxic concentrations is virtually nonexistent.

Undoubtedly, the most reliable pharmacodynamic data and plasma half-life values for propoxyphene are those of Wolen et al [*18*]. Both hydrochloride and napsylate salts were tested. The plasma half-lives are approximately 12 h for propoxyphene and 36 h for the nor-metabolite, calculated following single oral doses. The values were reported after the plasma concentration curve had been plotted to 240 h after ingestion. The partial time course of blood concentrations obtained over 8 h, following oral ingestion of a single 300-mg dose of propoxyphene napsylate, is shown in Fig. 22. The maximum concentration was between 0.2 and 0.3 μg/ml and occurs for both propoxyphene and norpropoxyphene in less than 2 h. The rapid rise of norpropoxyphene metabolite is very striking and points out the importance of separate metabolite analysis in forensic toxicology cases. The pharmacodynamic behavior of the hydrochloride salt is very similar. The concentrations are maintained in the range of 0.2 to 0.3 μg/ml for about 2 h, that is, 4 h after ingestion. The norpropoxyphene is still at 0.2 μg/ml after almost 8 h.

It has been reported [*19*] that plasma concentrations reach 0.3 μg/ml of propoxyphene after chronic oral ingestion of 65 mg of the hydrochloride or 100 mg of the napsylate salt. In an unreported study of humans, tolerant patients ingested 300 mg of propoxy-

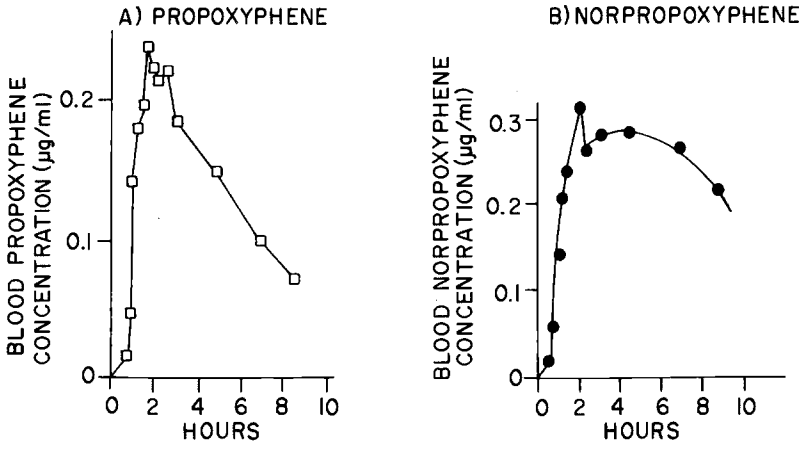

FIG. 22—*Blood concentrations of propoxyphene* (A) *and norpropoxyphene* (B) *after a single oral dose of propoxyphene napsylate (300 mg)(courtesy of R. L. Wolen, E. A. Ziege, C. M. Gruber, and the Lilly Laboratory for Clinical Research).*

phene napsylate four times each day for two weeks. Their plateau blood concentration was 2 μg/ml for both parent drug and norpropoxyphene. They apparently showed signs of ataxia and central nervous system depression but were not dangerously toxic. Dogs have been maintained at 3 to 5 μg/ml blood propoxyphene, with 20 to 30 μg/ml norpropoxyphene. However, these examples only serve to illustrate the gray area and overlap between maximum therapeutic concentrations and minimum lethal concentrations of which every toxicologist is aware. The health status of the individual, the environmental circumstances surrounding a death, and the possibility of other drugs complicating the pharmacology are factors which remove laboratory toxicity studies far from the realities of medicolegal postmortem investigation and the professional judgment required to establish a tenable manner and cause of death.

In essence, the knowledge gained from data developed from human patients or animals undergoing therapy can only be a reference point, never dogma. Triggering physiological, biochemical events which express themselves in the subject as symptoms of toxicity, or, in the extreme, as death can occur under an infinite number of complex circumstances, all of which are virtually impossible to predict. This study-report and the case data it presents only serve to emphasize this fact. Despite the analytical variability the 1022 cases probably serve as the best guide in their own right to propoxyphene toxicity in all its guises, without recourse to designed, pharmacological experiments for support.

Propoxyphene-Ethanol Interactions

As stated earlier in the report, approximately 42% of all the cases had an alcohol involvement. This large number of cases certainly deserves critical analysis, but as might be imagined the outcome of examination reveals a general picture in which two central nervous system depressants combine in additive effect. Figure 23 shows the distribution of blood alcohol concentrations for those 200 cases in which only propoxyphene and alcohol were detected. The mean blood alcohol concentration in the figure is 0.14%. This value is indicative of heavy social drinking, or an acute ingestion, but the concentrations cover the complete range seen in the drinking population. Figure 24 is somewhat more informative in that it attempts to relate blood propoxyphene and alcohol concentrations. An inverse relationship may be suspected. If those cases with a blood propoxy-

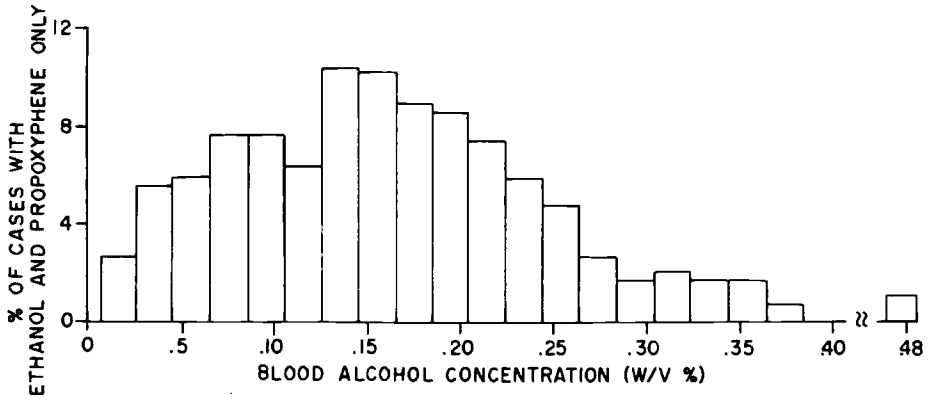

FIG. 23—*Blood ethanol distribution, in percent, for cases involving only ethanol and propoxyphene. One case represents 0.5% of total cases.*

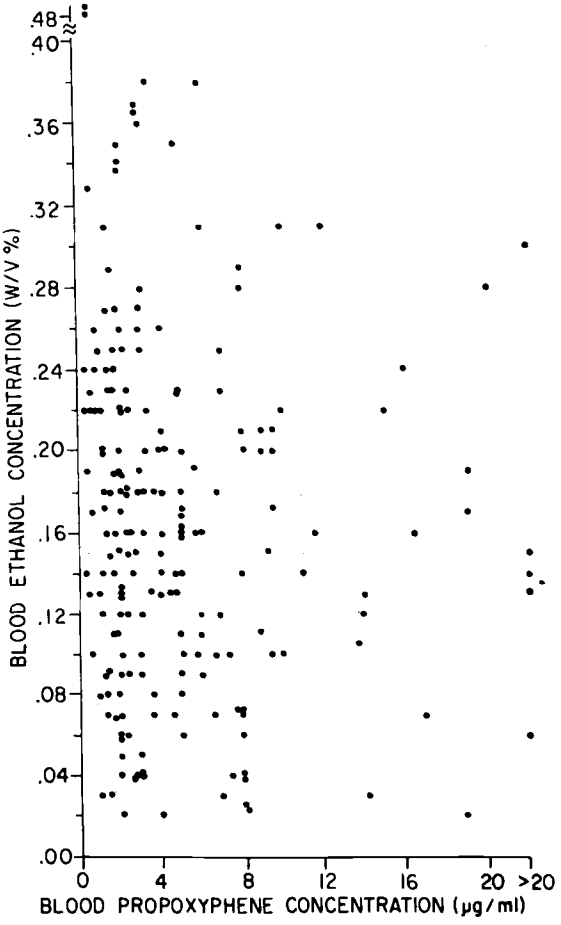

FIG. 24—*Relationship of blood ethanol to blood propoxyphene concentrations in those cases involving only ethanol and propoxyphene.*

phene concentration less than 1.0 μg/ml are inspected it can be seen that approximately 50% have blood alcohol values greater than 0.22%. Though the median for this group is 0.22%, the mean is slightly lower at 0.20%. This is a high and potentially dangerous alcohol concentration, particularly in combination with another central nervous system agent. In view of these data it is not surprising that many of the study cases involving alcohol were judged as accidental death or classified as undetermined.

Sudden Unexplained Deaths

Shortly after beginning the critique and analysis of the raw information collected for the total 1022 study cases, it became apparent that there was a small group that exhibited a common pattern of symptoms prior to death, the most dramatic of which was a survival time of 15 min or less. Once the time interval data for all of the study cases, expressing the observed or estimated survival time, were plotted graphically (see Figs. 7-9), it was evident that the sudden death group was worthy of separate treatment. Did the common characteristics in these cases confirm they were a discrete group or were they simply the low extreme of the normal population? Did they constitute a clinical entity, die from a single definable cause, or die from a combination of events occurring together? Each epidemiological and toxicological aspect of the group was examined in an attempt to answer these questions.

Fifty-six cases, all of whom apparently died in 15 min, were collated for study. Four cases were rejected because the deaths were not drug intoxications—1 died of gunshot wounds, 1 fell off a balcony, and 2 had heart attacks. There were 28 males and 24 females in the group, obviously no significant sex bias, but it is the reverse of the total study population. There were 37.2% suicides, 29.4% and 27.5% accidents and undetermined cases, respectively, and 5.9% natural deaths. The accidental and undetermined cases constituted a greater proportion than in the general study, and the suicides less.

The age distribution for the sudden death cases is given in Fig. 25. The greatest number are in the twenties and forties decades. On detailed analysis (Fig. 25*B*), it can be seen that the males are evenly distributed in the 20 to 30 years decade and predominate in the late forties. The females, by contrast, dominate the late teens and late twenties, and are normally distributed through the 36 to 55 years range. These age distributions are different from the total study cases shown in Fig. 3. However, caution must be exercised in assessing the significance because this group is small and the age distribution for the total U.S. population is similar to Fig. 25 in the 40 to 50 years range.

An examination of the body weights was not rewarding and, perhaps surprisingly, neither were their medical histories. Twenty percent had medical histories, but while there were few illnesses of note, 4 cases did have a "heart condition," and 1 each had hypertension, asthma, epilepsy, paraplegia, ulcers, and "recent head injury." The drug abuse histories were a little more interesting and are summarized in Table 7. There is a

TABLE 7—*Sudden death cases with a history of prior drug abuse.*

Prior History	Cases, no.	Percent of Sudden Death Cases
Alcohol or drug abuse, or both	20	40.0
Drug abuse	9	18.0
Alcohol abuse only	10	20.0
Heroin abuse	3	6.0
Propoxyphene abuse	1	2.0

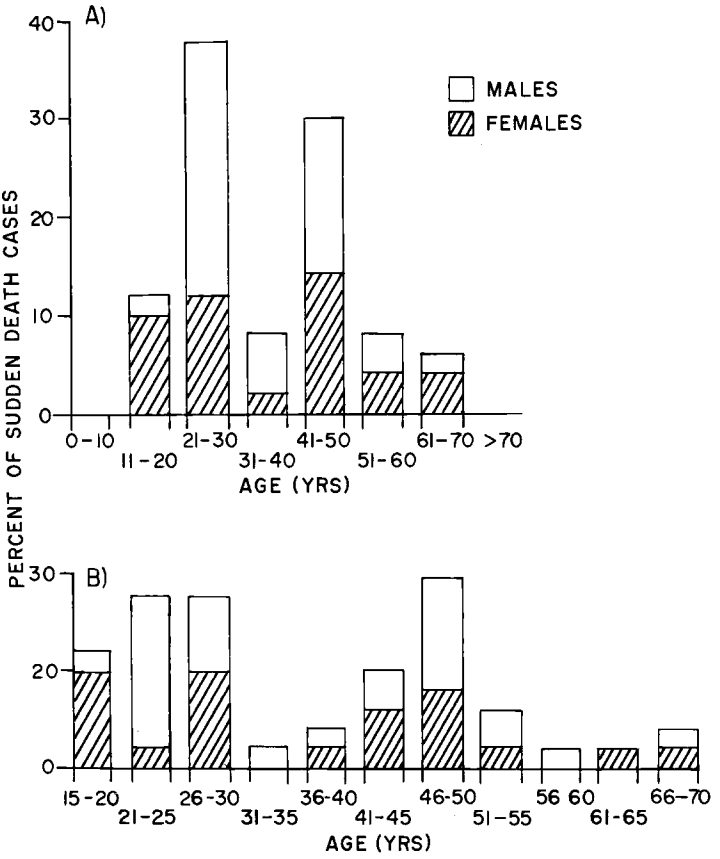

FIG. 25—*Age distribution, in percent, for sudden death cases by age decades* (A) *and by half-decades* (B), *for males and females.*

bias for the sudden death group to be higher in all categories compared to all cases (see Table 4). Of the sudden death cases, 44% had a documented history of abusing some substance (34.3% for all cases). There was no evidence of intravenous self-administration; in fact, all of the cases were stated as oral ingestions except 9, which were unknown.

There were 13 cases that had reported terminal symptoms, and these did suggest a characteristic for this group. Table 8 shows the frequency with which the various symp-

TABLE 8—*Relative frequency of terminal symptoms observed in sudden death cases.*

Symptom	Cases, no.	Percent of Sudden Death Cases with Documented Symptoms
Respiratory arrest	11	84.6
Cardiac arrest	4	30.8
Syncope	4	30.8
Seizures	2	15.4
Coma	2	15.4
Intoxication[a]	1	7.8

[a]Intoxication = ataxia, disorientation, or slurred speech.

toms occurred. It can be seen immediately that compared with the data in Fig. 5 for all the cases in the survey, respiratory arrest is 1.75 times as frequent in the sudden deaths, and cardiac arrest less frequent (0.75 times). Seizure frequencies were approximately equal to the frequency in the overall population. Coma is difficult to assess because there is an obvious time component which is excluded from this group by definition. The physiological expression of toxicity as seen through these terminal symptoms, particularly the 84.6% with respiratory arrest, implies that the final collapse is centrally mediated and rarely cardiovascular.

There was a very high incidence of other drugs associated with the sudden death cases. A total of 84.5% of the cases had some other drug in addition to propoxyphene, as contrasted with 76% for all the cases. Of the sudden deaths, 52% had an alcohol involvement, as contrasted with 42% for the general study cases. The other drugs, reported through case investigation or toxicology analysis, were predominantly central nervous system depressants. There were 26 different drugs occurring 51 times. The frequency of appearance of psychotropic/ataractic agents was approximately equal to the general study. Nineteen cases (40%) had drug concentrations (other than propoxyphene), determined by laboratory analysis, that were significantly high in and of themselves. Diazepam was detected in 5 cases, morphine or codeine, or both, in 3 cases, barbiturates in 5 cases, and chlordiazepoxide in 2 cases. The others such as ethchlorvynol, methaqualone, and methyprylon each occurred once. The following tabulation is a summary of sudden death drug combination cases determined by blood and tissue analysis relative to those few sudden death cases involving only propoxyphene.

Propoxyphene only	8 cases	15.4%
Alcohol present	27 cases	52.0%
Other drugs present	20 cases	40.0%
Alcohol only	17 cases	32.7%
Diazepam present	12 cases	23.1%
Alcohol and other drugs	6 cases	11.5%
Diazepam only	4 cases	7.8%
Diazepam and other drugs	3 cases	5.8%
Alcohol and diazepam	3 cases	5.8%
Alcohol, diazepam, and other drugs	1 case	1.9%
Cases involving other drugs	10 cases	19.2%

It is quite certain from these data that alcohol and other drugs, in addition to the propoxyphene, played a major role in these sudden death cases.

This distribution of blood propoxyphene concentrations is given in Fig. 26. There are very few cases represented in the figure, so the data should be interpreted conservatively. There is no evidence for extraordinarily high concentrations. The peak (1 to 2 μg/ml) is similar to that for all the study cases. This suggests that these sudden deaths could have resulted from a massive dose, rapidly absorbed. For those cases containing propoxyphene only, the blood concentrations ranged from 1.0 to 19 μg/ml, with a mean of approximately 6.0 μg/ml. There were only 15 cases in the group with liver tissue propoxyphene concentrations, and on inspection they did not shed any further light on the sudden deaths.

The relationship of blood alcohol concentration to blood propoxyphene was plotted graphically (Fig. 27) and shows a mean alcohol concentration of 0.13%. There are two clusters of cases, at 0.08 to 0.12% and at 0.18 to 0.22%. The alcohol concentrations predominantly relate to the lower propoxyphene values; propoxyphene concentrations less than 2.5 μg/ml relate to 72% of the alcohol values. That is, 75% of these sudden death cases with alcohol had propoxyphene concentrations less than 2.5 μg/ml, sharply

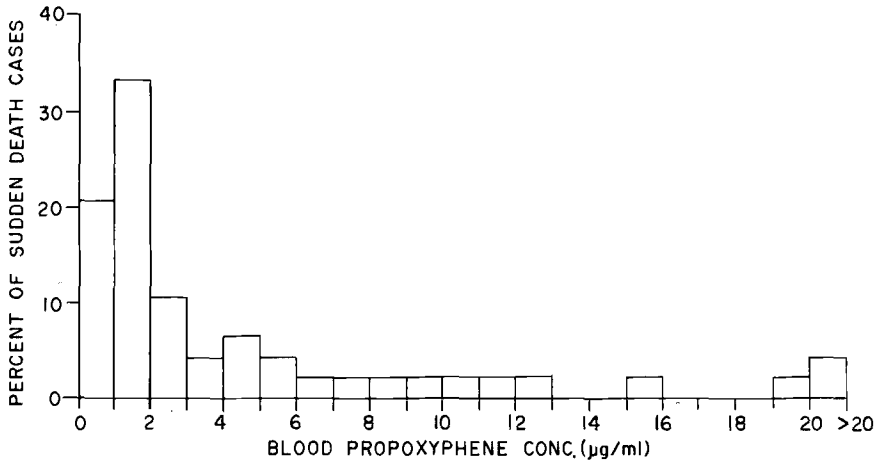

FIG. 26—*Blood propoxyphene distribution, in percent, for those cases classified as sudden death. One case represents 2.2% of total cases.*

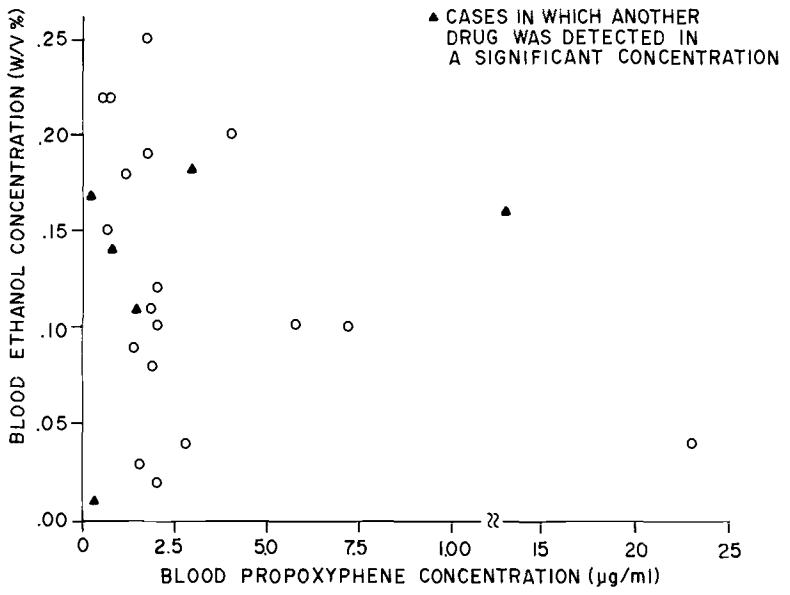

FIG. 27—*Blood ethanol concentration versus blood propoxyphene concentration in sudden death cases and in cases in which another drug was detected in a significant concentration.*

different from all the study cases in which 72% of the alcohol values related to propoxyphene concentrations less than 7.0 μg/ml.

In summary, the analysis of these sudden death cases shows that they are a separate group within the whole study (note age differences) and are characterized by a very short survival time following drug(s) ingestion (0.25 h). Their terminal symptoms appear to be centrally mediated, most often culminating in respiratory arrest. They have a stronger tendency to drug abuse than the general study population and almost invariably succumb as a result of alcohol or multiple drug ingestion (which includes propoxyphene), or both.

Their medicolegally certified cause of death may be little different from the other cases in the survey, but their manner of death certainly is. There is scant evidence for cardiovascular collapse, but there are sufficient data to support a verdict of central nervous system failure following acute respiratory depression caused by ingestion of multiple central nervous system depressant drugs with an emphasis on propoxyphene/alcohol combination.

Summary

Eighteen medical examiners, coroners, and forensic science laboratories and offices, representing a total jurisdictional population of 52.6 million, were visited during November 1975, and more than 1200 cases occurring in the four years from 1972 through 31 July 1975 were evaluated for inclusion in the study. The sites were distributed across the United States and Ontario, Canada, and included urban and rural, states, city, and county jurisdictions. Scientific data and circumstantial information was gathered consistently for each case and site by means of five questionnaires. Finally, 1022 cases were compiled and examined, and the data were analyzed to form the body of data from which this report is written. The following conclusions may be drawn.

1. The number of deaths involving propoxyphene is increasing each year, and at a faster rate than total drug deaths. The absolute numbers and rate are different in urban and rural areas, but the frequency reached 6.0 deaths per million population in 1974. Deaths attributed to suicide as well as those determined to be accidental deaths and undetermined have increased.

2. Approximately 66% of all the cases studied had the word propoxyphene included in the cause of death statement on the death certificate. Approximately 46% of the cases were classified as suicide (64% of them female and 36% male), 26% as accidents, and 21% as undetermined.

3. The deceased were mainly middle-class, Caucasian, urban dwellers, with male and female evenly distributed. Their ages were from 20 to 50 years, with few outside this range. Female ages were uniformly distributed, but males in their early twenties were very prominent. This is different from the U.S. population age distribution, which is currently dominated by teenagers. Propoxyphene does not appear to be a pediatric problem, as seen in the study.

4. The deceased were *not* part of the illegal drug abuse population and had no particular propensity for the use of heroin or narcotics, but rather they were a particular medical population of those who misuse prescription drugs and alcohol.

5. The deceased did have a marked tendency to hypochondria, chronic minor illnesses, and emotional problems. Some 43% had recent medical histories, and 82% had a documented psychiatric history which often included (51%) self-destructive behavior such as suicide attempts. Almost all received a wide range of prescription drugs, particularly tranquilizers, which they often misused in the sense of self-medicating, multiple drug ingestion, and combining alcohol with their medication. Approximately 34% had a history of misusing some drug, and 20% could be defined as abusers in that they were prone to excessive use of their medications; 44% had diazepam available to them, and 17% were either problem drinkers or alcoholics.

6. Most individuals died at home or other residence, and succumbed to a mixture of propoxyphene, other drugs, or alcohol, or a combination. In only 24% of the cases was propoxyphene the only drug involved; 18% had only propoxyphene plus alcohol. However, 42% of the cases had an alcohol involvement.

7. Darvon-65® and Darvon Compound-65® were the most commonly encountered

proprietary forms of propoxyphene, but unspecified "Darvon®" accounted for 33% and unspecified propoxyphene for 26% of the cases. Excepting alcohol, the most commonly encountered other drug by a huge margin was diazepam, with the tranquilizers as a group and the sedative hypnotics (especially flurazepam) accounting for 40% and 21% of the occurrences, respectively.

8. Autopsy findings were consistently reported in general terms and were without character or diagnostic specificity. Typically, pulmonary and cerebral edema and visceral congestion were reported.

9. Terminal symptoms were characterized by central nervous system depression: respiratory arrest and cardiac failure often preceded by seizures and symptoms of intoxication. Very few were treated in the hospital, since death usually occurred prior to discovery. Most died within 8 h, but 20% died within 1 h.

10. Propoxyphene is included in the general, analytical schemes of most toxicologists, but not all potential cases are referred for toxicological examination. Only two quantitative methods are in general use; one in which only the parent propoxyphene is usually assayed (gas chromatography) and the other in which an aggregate concentration of propoxyphene and its primary metabolites are determined (derivative ultraviolet spectrophotometry). Despite these limitations, it can be stated that most of the fatal blood concentrations were in the range of 1 to 4 μg/ml. This is 5 to 20 times the concentration resulting from usual therapeutic dosage. Approximately 15% of the cases had blood concentrations of 0.1 to 1.0 μg/ml, inclusive.

11. A small group of individuals (5%) survived a maximum of only 15 min after propoxyphene ingestion. They were classified as relatively sudden deaths. Death in these cases was heralded by very few symptoms other than sudden respiratory arrest and central nervous system failure. They were mainly drug combination deaths—propoxyphene plus other central nervous system depressants, not necessarily in individually lethal concentrations. The resulting blood concentrations of propoxyphene were not significantly different from the general population; neither were the characteristics of the victims except for age (15 to 30 years old and in the 40 to 50 decade), with a negligible number in their thirties. This group had a slightly higher incidence of drug abuse history relative to the others in the study, but they were not predominately suicides.

12. The study indicates the potential importance of propoxyphene-metabolite, particularly norpropoxyphene, toxicity. In view of the respective half-lives of propoxyphene and norpropoxyphene relative to survival time of the victims, it is conceivable that norpropoxyphene is toxicologically important in many cases. Virtually no toxicity data are available for norpropoxyphene in its own right.

The above paragraphs state the principal findings of the study and implicitly indicate the need for better understanding of propoxyphene toxicity. Also, improved analytical toxicology procedures are needed by which the propoxyphene and its principal metabolites can be individually assayed and specifically identified. This is very important for blood concentrations less than 1 μg/ml. Liver tissue analysis and problems associated with data interpretation are addressed in the body of the report.

The study confirmed that propoxyphene can be a dangerous drug when misused, deliberately or accidentally, most especially in combination with central nervous system agents such as alcohol, diazepam, and flurazepam. Although in an illegal drug abuse context it is not a drug commonly responsible for fatalities, its widespread use would indicate that notice of caution be issued, particularly regarding its use in conjunction with other depressant substances. From a toxicologist's perspective and the study data, propoxyphene appears no more dangerous than countless other drugs available to the public.

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