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Toxicological Analyses in Cases of Sudden Infant Death: A National Feasibility Study

Sudden infant death syndrome (SIDS) is associated with more infant deaths, ages two weeks to twelve months, in the United States than any other single, definable cause. It is associated with approximately 10 000 deaths per year and is second only to the general category of accidental deaths for all children under the age of 15 years [*1*]. Unlike many disease entities, the diagnosis of SIDS is made not by an attending physician, but at postmortem examination; the determination is based not on firm definitive findings, but only on the exclusion of all other possible causes. Indeed, very few histological, biochemical, or physiological changes that might be considered pathologically diagnostic in these infants have been observed [*1,2*]. Although SIDS-associated deaths represent a major proportion of all infant fatalities, their frequency is such that even in jurisdictions of greater than one million population medical examiners and coroners encounter relatively few of these cases, typically 40 to 60 cases a year [*2*]. In an attempt to overcome the limitation of the small number of SIDS cases available for study in any one area, the Office for Maternal and Child Health, Department of Health, Education, and Welfare, is studying the feasibility of a national SIDS registry [*2*]. Such a registry could draw on the case experiences of many investigators so that statistically valid correlations and conclusions would be possible; both biomedical and sociological information, drawn from a variety of sources, could be gathered and analyzed. To establish such a data center, it would also be necessary to have strong guidelines specifically designed to control the quality of the data and the methods used in their collection. The formulation of a standard protocol for the investigation of sudden infant deaths that could be used at all sites contributing information would be a first essential task.

The value of toxicological studies in the postmortem investigation of infant deaths is questionable. Several studies have reported that forensic toxicology has little to add, either to the immediate investigation and determination of the individual cause of death or to the overall understanding of the SIDS phenomenon [*3,4*]. However, routine forensic toxicological procedures applied in cases involving infant deaths are generally designed to detect agents at concentrations known to be significant in adults. Although previous studies have not found anything of apparent value, the analytical procedures used were not tailored to the requirements of infants. Nor did they address the question of a possible contributory role of low concentrations of therapeutic or environmental substances.

The concern about the value of analytical toxicological data in a SIDS registry and their place in a standard protocol hinged upon two questions: (1) Is it feasible to devise a valid, practical scheme of analysis, suitable for autopsy specimens from infants under twelve months of age? and (2) If such a scheme is possible, would the data then be of value to a

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registry? This report presents the results, the data, and some conclusions of a two-year search for answers.

Study Design

The project involved the active participation of 27 medical examiners' and coroners' offices across the United States, offices which represent both urban and rural jurisdictions and range from large metropolitan areas, such as Los Angeles and Philadelphia, to predominantly rural populations, such as the entire states of Montana and Utah. Table 1 lists the sites, jurisdictional areas, and population for the 27 participants. The total U.S. population covered by these offices represents 54.9 million people. A key staff person, generally a pathologist or toxicologist at each site, was requested to provide specific autopsy specimens from all infants under twelve months of age who died suddenly or unexpectedly within their jurisdiction. This individual also acted as the liaison for all aspects of the study. They were asked to send specimens from all infants who died, not only from suspected SIDS cases. Fatalities other than SIDS served as a control population. Table 1 gives the number of cases contributed according to their final diagnosis, differentiating SIDS from the non-SIDS control group. As can be seen, 889 cases were received; 715 of these were determined by the pathologists at the site to be true SIDS deaths. The remainder, 174 or 19.6% of all cases received, fell into the non-SIDS category. These non-SIDS deaths resulted from a variety of causes, ranging from accidental traumatic deaths to fulminating infections. All cases were received "blind," that is, it was not known until the end of the study which cases represented SIDS deaths and which were control cases.

In addition to the autopsy specimens, investigation reports and autopsy protocols were collected for each case. Information related to the infant's background and to the circumstantial history of his death were correlated with the toxicological results.

Arrangements were made at each site for specimen handling and shipping so that a minimum amount of time elapsed between the postmortem examination and receipt of the specimens, generally 24 to 36 h. Although the quantity and the types of tissue specimens requested from each site were conservatively specified at the beginning of the survey, the actual tissues and the amounts received often exceeded the minimum anticipated. However, the factor that most often limited the laboratory procedures was the lack of a particular specimen or its inadequate quantity. Table 2 lists the postmortem tissues received with greatest frequency and the average quantity that was available at autopsy. Blood and liver were the most frequently available specimens and were the primary samples used in the screening procedures for the wide variety of drugs and toxic agents included in the survey. In addition to these two samples, cerebral spinal fluid (CSF), bile, urine, and gastric contents were frequently used for confirmation of presumptive positive analyses obtained during the initial screening.

Toxicology: Analytical Procedures

The analytical screening procedures were designed to accommodate the types and amounts of specimens that are generally available from infants. A series of nine separate drug screens were developed. Each case was processed through all of the screens regardless of the infant's past history or the circumstances of death.

Figure 1 shows a schematic diagram of the methods used for determining ethanol (alcohol), other volatile compounds, and the basic drugs. Cerebral spinal fluid was routinely used for the alcohol screen; 100 μl of this mixture was gas chromatographed (GC) on a 0.2% Carbowax-Carbopack column at 90°C. In the event that CSF was not available, blood was used as the preferred alternative specimen. Confirmation was made by duplicating the initial screen and by analyzing an additional, different specimen.

TABLE 1—*Collaborating sites and number and type of cases submitted.*

Site	Jurisdiction	Code	Jurisdiction Population (Millions)	SIDS	Non-SIDS	Total
Albuquerque, N. Mex.	New Mexico, state	NM	2.1	37	10	47
Auburn, Ala.	Alabama, state	AB	3.5	0	1	2
Baltimore, Md.	Maryland, state	MR	4.0	122	23	145
Buffalo, N.Y.	Erie County	BU	1.1	2	6	8
Chapel Hill, N.C.	North Carolina, state	NC	5.5	60	25	85
Chicago, Ill.	Illinois, state	IL	6.0	6	0	6
Clayton, Mo.	city of St. Louis	SL	0.6	4	0	4
Great Falls, Mont.	Montana, state	MT	0.7	1	1	2
Hauppauge, N.Y.	Suffolk County	SU	1.1	9	0	9
Indianapolis, Ind.	city of Indianapolis	IN	1.1	1	0	1
Las Vegas, Nev.	Clark County	LV	0.3	12	0	12
Los Angeles, Calif.	Los Angeles County	LA	7.0	3	0	3
Memphis, Tenn.	Tennessee, state	TN	3.9	3	4	7
Miami, Fla.	Dade County	DD	1.5	25	8	33
Minneapolis, Minn.	Hennepin County	HC	1.0	24	0	24
Oakland, Calif.	Alameda County	AL	1.1	42	6	48
Oklahoma City, Okla.	Oklahoma, state	OK	2.5	5	0	5
Philadelphia, Pa.	Philadelphia County	PH	2.0	12	1	13
Pittsburgh, Pa.	Allegheny County	PT	1.6	3	0	3
Portland, Ore.	Oregon, state	OR	2.0	5	1	6
Providence, R.I.	Rhode Island, state	RI	1.0	141	9	150
Salt Lake City, Utah	Utah, state	UT	1.2	84	38	122
San Diego, Calif.	San Diego County	SD	1.4	73	25	98
San Francisco, Calif.	San Francisco County	SF	0.7	12	8	20
Santa Ana, Calif.	Orange County	OC	1.5	15	5	20
Sheridan, Wyo.	Wyoming, state	WY	0.3	1	1	2
Spokane, Wash.	city of Spokane	SK	0.2	13	1	14
	Totals		54.9	715	174	889

TABLE 2—*Postmortem tissues: type, number, and quantity received.*

Tissue	Total Received, *n*	Cases, %	Average Quantity Received
Liver	776	87.3	40 g
Blood	737	82.9	7 ml
Lung	669	75.2	30 g
Gastric contents	657	73.9	5 ml
Bile	650	73.1	1 ml
CSF	589	66.2	3 ml
Urine or kidney	401	45.1	5 ml or g

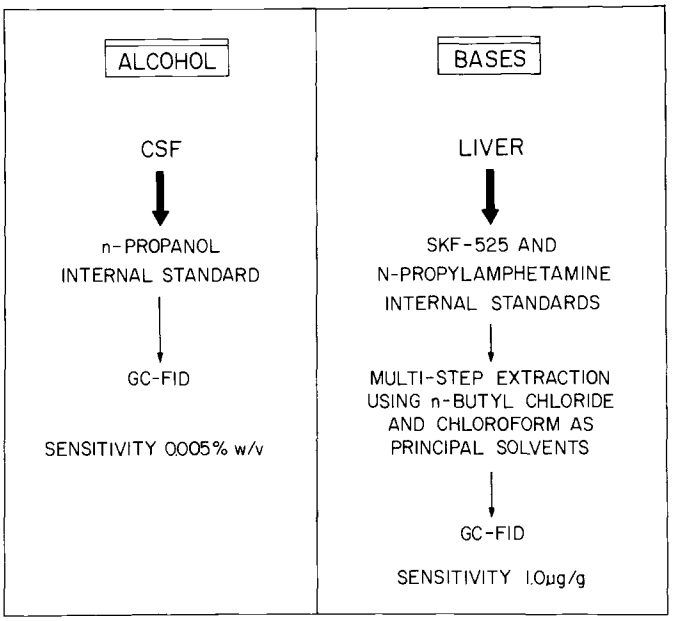

FIG. 1—*Schematic outline of analytical procedures for alcohol and organic bases.*

The bases (drugs which extract into organic solvent at alkaline pH values) were analyzed by using 5 g of liver homogenate. The homogenate was adjusted to pH 9 with borate buffer and extracted into 15 ml of *n*-butyl chloride, which in turn was back-extracted with sulfuric acid. The acid phase was made alkaline and extracted with chloroform, the solvent evaporated, and the residue dissolved in methanol and injected into a 3% OV-17 GC column, programmed from 130 to 270°C. The sensitivity limit for the various drugs included in the analysis ranged from 0.5 to 1.0 µg/g. Specific qualitative confirmatory analysis was carried out with electron impact gas chromatography-mass spectrometry (GC-EIMS). Blood was the alternative sample and was analyzed by a GC-nitrogen phosphorus detection (GC-NPD) method [*5,6*].

The remaining screening analyses outlined in Figs. 2 and 3 were routinely carried out with blood as the primary specimen.

The benzodiazepine drugs require 0.5 to 1.0 ml of blood and are assayed with GC-electron capture detection (GC-ECD), following a single-step extraction into a solvent system consisting of toluene/heptane/isoamyl alcohol (76:20:4). The limit of sensitivity for

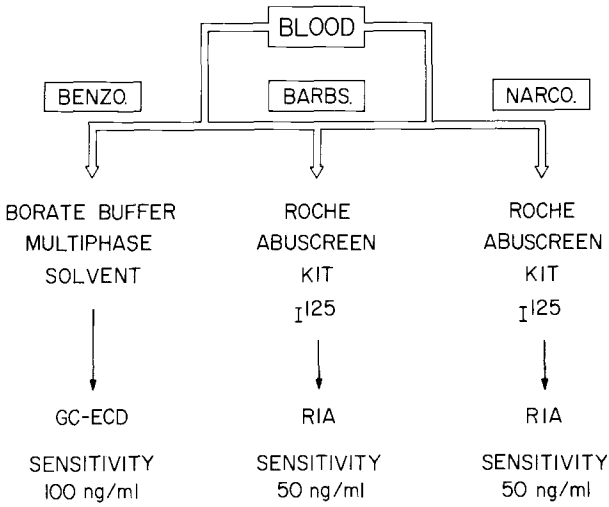

FIG. 2—*Schematic diagram for the analysis of benzodiazepines, barbiturates, and narcotic drugs in blood.*

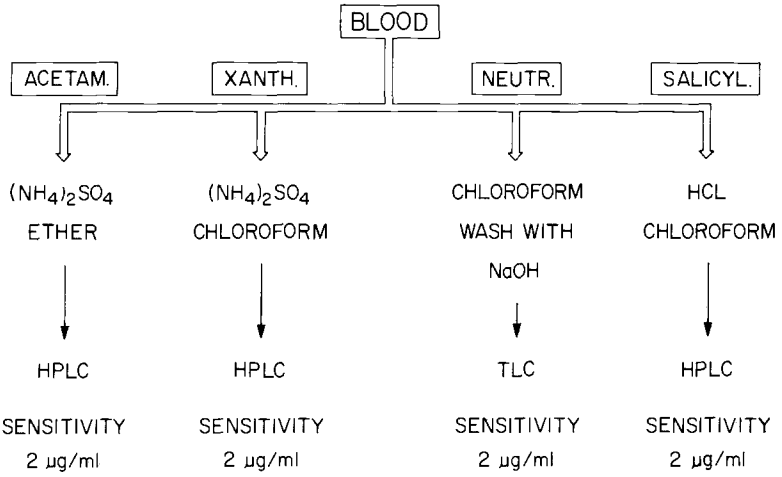

FIG. 3—*Schematic diagram for the analysis of analgesics, xanthines, and organic neutral drugs in blood.*

this technique is 50 to 100 ng/ml. Homogenized liver was found to be a practical alternate specimen. Confirmation required high pressure liquid chromatography (HPLC) equipped with a 254-nm ultraviolet spectrophotometric detector and an elution solvent system of 55% methanol-45% sodium acetate buffer at pH 4.

Radioimmunoassay (RIA) was used for screening barbiturates and opiate narcotic drugs in blood. Only 50 µl of blood is required for this method, which is both rapid and reliable. The practical limit of sensitivity is 50 ng/ml. The alternative to the use of blood for the RIA-barbiturate screen is liver homogenate, with confirmation analysis using GC-NPD. If blood was not available, bile or urine was used for the narcotics tests; presumptive positive results were confirmed by a silyl derivative GC-flame ionization detection (GC-FID) procedure.

The acetaminophen assay requires 100 μl of blood saturated with ammonium sulfate. This mixture is extracted with diethyl ether, and the separated solvent evaporated to dryness. The residue is dissolved in 50 μl of methanol, 10 μl of which is analyzed by HPLC with a 3- by 250-mm Spherisorb ODS column, running 10% methanol-90% sodium acetate buffer, pH 4, at a flow rate of 1.6 ml/min. The absorbance of the eluant is monitored at 254 nm, which allows a sensitivity of 2 μg/ml in the blood sample. If blood is not available, CSF is an adequate alternate specimen. Confirmation analyses are carried out by means of a silyl derivative GC-FID technique.

The fraction containing neutral drugs, which extract from aqueous solution into organic solvent at any pH, is obtained in chloroform from 3 ml of blood. The chloroform is washed with sodium hydroxide and then evaporated to dryness. The residue is dissolved in 50 μl of methanol, 30 μl of which is spotted on a silica gel thin-layer chromatography (TLC) plate and eluted in a chloroform/acetone/ethanol (80:16:4) solvent system. The plate is sprayed with a solution containing 2% starch and 1% potassium iodide following exposure to chlorine. The residues from all TLC positive cases were assayed by GC-FID, with a 3% OV-17 column, and confirmed by GC-EIMS. The sensitivity limits for these drugs ranged from 1 to 5 μg/ml.

The xanthine class of drugs is of particular interest because theophylline is used to control a variety of respiratory problems in infants [7]. These drugs were screened; 250 μl of blood was used. The blood sample is saturated with ammonium sulfate and then extracted with 5 ml of chloroform. The chloroform is taken to dryness and the residue reconstituted in 50 μl of methanol; 10 μl of this solution is applied for HPLC analysis and eluted with 25% methanol–75% sodium acetate buffer, pH 4, at a flow rate of 1.2 ml/min. By recording the absorbance at 280 nm, a sensitivity of 2 μg/ml is achieved. In the absence of blood, liver homogenate is an adequate second choice. Confirmation of positive findings was made by GC-FID, after derivatization with diisopropyl acetal in *N,N*-dimethylformamide.

The salicylate screen requires 200 μl of blood that has been acidified with hydrochloric acid. Salicylates are extracted into chloroform from the acid blood. The phases are separated by filtration through phase-separating paper; the chloroform is then evaporated to dryness. The residue is dissolved in methanol and analyzed by HPLC using 15% methanol–85% sodium acetate buffer, pH 4, at 1.2 ml/min. The eluant absorbance is monitored at 280 nm and permits a sensitivity of 2 μg/ml. The GC-FID analysis, after silylation of the dry residue, provides reliable confirmation.

All of the analytical methods were subject to quality control procedures throughout the study. These included the use of prepared blank specimens, quantitative standards, and controls in appropriate biological media that were extracted and analyzed through the various methods. Qualitative specificity and quantitative accuracy and precision were monitored to ensure acceptable performance standards.

The development of analytical procedures sufficiently sensitive to detect therapeutic and subtherapeutic concentrations of drugs and their metabolites, as well as other agents commonly available for infants, in the very small amounts of autopsy specimens, was perhaps the most difficult undertaking of the project. A major proportion of the time and effort required for the study was spent on this problem. It was necessary to establish and validate relatively simple screening methods that were rapid and accurate to detect the presence or absence of a broad range of drugs and metabolites in a particular specimen. These methods and the presumptive positive findings then had to be supported by separate and independent procedures for qualitative confirmation and quantitation.

Results: Case Background Data

In addition to the autopsy specimens, data were collected on the personal backgrounds of the deceased infants and the circumstances surrounding their deaths. These data were

then separated into SIDS and non-SIDS deaths so that they could be used for comparison purposes, both within this study and between this and other SIDS epidemiological studies.

Of the 715 SIDS deaths, the sex was known in 591 cases; of the 174 non-SIDS control deaths the sex was known in 163 cases. Males represent a major portion of the SIDS deaths (55.7%), giving a male to female ratio of 1.25. The non-SIDS cases show a slightly smaller male to female predominance (m/f = 1.14). Although previously noted in other SIDS populations [*1,8-10*], the predominance of males in this survey is consistent with the bias that is seen in the national average for the birthrate of all infants [*11*] and, therefore, apears to have little peculiar significance.

The age distribution for the deceased is given in Fig. 4. The SIDS cases (n = 588) showed a marked cluster in the two- to three-month age range, which is consistent with reports from earlier studies [*8,12-14*]. The age profiles are markedly dissimilar between the SIDS and non-SIDS deaths. The peak frequency of the control cases is in the one-month age group, but actually ranges from one to four months. The large representation of infants older than nine months in the non-SIDS cases (n = 164) can be attributed to the request for specimens from control infants up to 18 months of age. This served to expand the number of control cases and to provide assurance that they were not SIDS deaths.

Of the 715 SIDS deaths 589 were specified by race; for the non-SIDS deaths, 160 cases were reported by racial origin. The number of cases serving as the data base for this figure precludes determination of any significant difference between the two subpopulations of the study deceased. Whites in both categories were in the majority but when compared to the national profile [*11*] the nonwhite groups were overrepresented. This is not necessarily surprising, because infant mortality from all causes, including SIDS, is known to be higher in these groups than would be predicted solely on the basis of population statistics, a factor apparently more directly related to socioeconomic status than racial or hereditary factors [*1,8,15*].

The body weights of the infants were calculated at time of death for the two populations and, surprisingly, both groups had a mean of 5.56 kg; that is, there was no difference between the SIDS and non-SIDS groups. In 494 of the SIDS deaths, the weights had been noted; 141 of the non-SIDS cases had the body weights recorded.

Considerable differences in the medical histories for the two weeks prior to death were evident between the two study populations, as shown in Fig. 5. The majority of the SIDS babies were considered medically healthy immediately prior to their deaths (55.6%). This proportion cannot be considered generally conclusive, but it does correspond to the

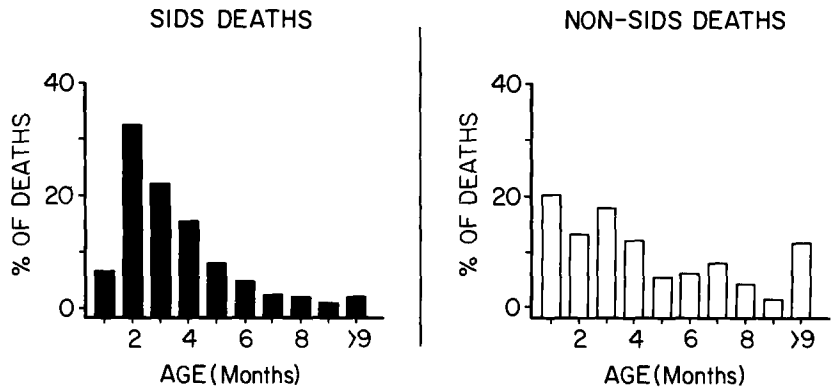

FIG. 4—*Age distributions.*

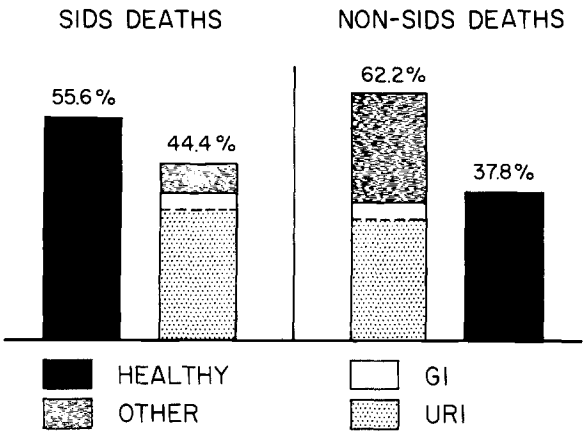

FIG. 5—*Prior medical histories.*

findings in at least one other study [*1*]. Those who were not healthy during the two weeks prior to their demise (44.4%) could not be considered seriously ill. Upper respiratory infection (URI) was the major complaint, often accompanied by gastrointestinal upset (GI). The "other" category represents less than one fourth of the unhealthy infants in the SIDS population and very few of them were seriously ill. In contrast, the pattern for the non-SIDS deaths is not only reversed but exaggerated, with nearly two thirds of the babies considered unhealthy prior to their death. Of this group approximately half had upper respiratory problems, the remainder being made up of the "other" category, some of which were serious medical problems.

A proportional distribution of the times of death for the two study populations is shown in Fig. 6. The greatest number of SIDS deaths occurred between midnight and 6:00 a.m., the second most-common time interval being from 6:00 a.m. to noon. This pattern has been shown to apply to other SIDS populations [*12,16*]. In most cases, the infant's death was not observed; therefore, the figure can only be used as an estimate of the time of death. The significance of this distribution is not yet apparent, but a noticeable difference can be seen when it is compared to the time distribution for the non-SIDS cases. Most control cases died during daylight hours, as opposed to the SIDS deaths.

The location of the child at time of death was recorded for 510 of the SIDS cases and 136 of the non-SIDS group. The majority in both groups were found in their own cribs (SIDS, 75.4%; non-SIDS, 61.5%). It is not surprising that a greater proportion of the non-SIDS deaths died in hospital (17.1% versus 3.5%); this probably reflects the greater incidence of prior medical complaints as well as traumatic deaths. Dying or being found dead in a parent's bed was more common in the SIDS cases (11.4%) than in the control group (5.7%). In these cases the possibility of smothering, at least as a contributory factor, must be seriously considered. This is an explanation that has been proposed by several investigators to explain at least a portion of supposed SIDS cases [*17-20*]. The remaining cases (SIDS, 9.7%; non-SIDS, 15.7%) represent a variety of locations; automobiles were most notably involved in the non-SIDS deaths.

During the course of the survey, information was requested about the therapeutic agents that had been given to the child prior to death; this information proved to be very difficult to obtain. Of the 715 SIDS deaths, information about drugs and therapeutic agents given was available in only 37 cases; these 37 cases represented 46 occurrences of therapeutic agents. For the non-SIDS control group, information was available in only 15 cases and accounted for only 21 occurrences of pharmaceutical preparations. In both categories, antibiotics and preparations used for immunizations accounted for most of the

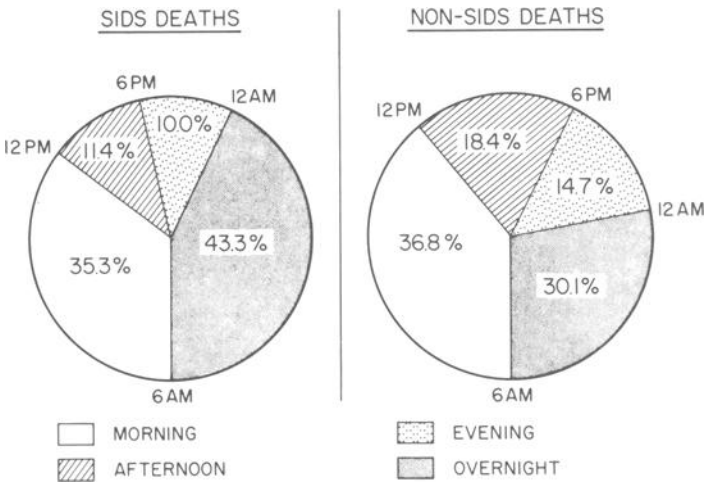

FIG. 6—*Times of death.*

known drugs received by the infants. In the SIDS cases, only five documented occurrences of aspirin were noted. Antihistamines were the only other noteworthy category of pharmaceuticals given to SIDS infants prior to death; these accounted for only nine occurrences. When these figures are compared with the analytical findings presented in this report, it will be seen that toxicological investigation based solely on a past history of drug use could be very misleading.

Results: Toxicology Data

The number of screening analyses (6870 separate procedures) carried out on all study cases is shown in Table 3. Although nearly 900 cases were received, the various combinations and amounts of tissues that were available occasionally precluded screening for a particular drug in a particular case. As a result, the barbiturate and narcotics screens, which require only minute amounts of specimen, were performed most often. Table 3 also lists the number of confirmed positive findings: 160 separate confirmation analyses were positive. Based on the total number performed, this represents a confirmation rate of approximately 0.2%. Of the individual screens, confirmed positive findings were most

TABLE 3—*Number of analytical screens and confirmation procedures performed on the total study cases.*

Analytical Screen	Screening Analyses, *n*	Confirmed Positive Findings, *n*
Volatile agents	764	53
Barbiturates	817	11
Narcotics	819	3
Benzodiazepines	771	3
Salicylates	763	24
Acetaminophen	724	9
Xanthines	736	10
Neutral drugs	764	16
Basic drugs	712	31
Total	6870	160

prevalent for the volatile agents (6.9% of the cases). The least-common confirmed findings were from the barbiturate and narcotics screens (0.4%). With the exception of the volatile agents, all other drugs and therapeutic agents were detected with a frequency of less than 5%.

Considerable effort was applied to the physical examination of the gastric contents collected in each case. In forensic toxicology, this procedure can often be a valuable guide to the possible presence of drugs and poisons. Table 4 lists the three major characteristics of all gastric contents that were noted. The macroscopic and microscopic examinations are extremely simple to perform and require a minimum of analytical equipment; therefore, in view of their potential value they should be performed in all investigations of sudden, unexpected infant death. By visual examination, most of the gastric contents were white to brown. The odor was generally pungent or slightly sour. A viscous liquid or a mixture of liquid and solid was the most frequent texture encountered, and in no case was there any visual evidence of pharmaceutical preparations in the gastric contents.

Amorphous sediment and fat globules were the most common components observed by microscopic examination (Table 5). The presence of crystals as possible evidence of pharmaceuticals was found in only 0.3% of those cases examined; however, the analysis of tissue samples from the cases that contained crystals in the gastric contents ruled out the presence of drugs. The distribution of gastric content pH values for the study population was generally in the range of 4 to 5. It is noteworthy that most of the samples with a pH of 7 or greater were putrified.

The specific agents that were identified and confirmed from the total study population are given in Table 6; 17 different agents were found in the total of 889 cases submitted and are listed in decreasing order of frequency. The mean tissue concentrations or the individual case concentrations (for those in which only two or three cases are represented) are also given. This table represents the first significant values that can be applied to

TABLE 4—*Macroscopic examination of gastric contents.*

Color	% of cases Examined	Odor	% of cases Examined	Texture	% of cases Examined
White	36.6	sour	32.3	liquid	61.4
Brown	54.9	pungent	54.7	solid	20.6
White and brown	1.0	putrified	12.4	liquid and solid	14.3
Green	1.6	yeast	0.6	mucoid	3.7
Yellow	5.5	total	100.0	total	100.0
Clear	0.4				
Total	100.0				

TABLE 5—*Microscopic examination of gastric contents.*

Microscopic Components	% of Cases Examined
Amorphous sediment	99.6
Fat globules	56.1
Vegetable material	24.7
Mucus	14.3
Epithelial cells	6.1
Starch granules	3.6
Yeast cells	1.5
Possible evidence of pharmaceutical preparations (crystals)	0.3

TABLE 6—*Tissue concentrations of drugs identified and confirmed.*

	Confirmed Assays, *n*	Mean Tissue Concentration or Individual Case Values, μg/ml or g			
		Blood	Liver	CSF	Urine
Ethanol	55	$\bar{x}$ = 0.03% w/v	...	$\bar{x}$ = 0.03% w/v	...
Caffeine	32	$\bar{x}$ = 5.5	$\bar{x}$ = 7.0	...	...
Salicylate	24	$\bar{x}$ = 36.8	6.3	2.1	...
			46.2		
			10.0		
Acetaminophen	15	$\bar{x}$ = 11.7	6.0	$\bar{x}$ = 7.9	1.0
Pheniramine	13	...	$\bar{x}$ = 2.0	...	...
Phenobarbital	12	$\bar{x}$ = 9.8	$\bar{x}$ = 8.7	...	...
Brompheniramine	6	0.8	$\bar{x}$ = 1.6	...	...
		0.1			
Codeine	6	$\bar{x}$ = 0.22	...	...	$\bar{x}$ = 16.2
Dextromethorphan	4	...	$\bar{x}$ = 0.95	...	...
Morphine	3	...	...	...	$\bar{x}$ = 4.6
Diazepam	3	$\bar{x}$ = 0.3	...	...	...
N-Desmethyldiazepam	3	$\bar{x}$ = 0.1	...	...	...
Pyrilamine	2	...	0.5	...	...
			0.1		
Lidocaine	2	86.6	3.2	...	...
Theophylline	2	4.1	...	...	...
		10.2	...	...	...
Phenylpropanolamine	1	...	4.3	...	...
Ephedrine	1	...	trace	...	...
Glutethimide	1	...	<1.0	...	...

fulfilling the second objective of the study, that is, the assessment of the possible role of exogenous agents in sudden unexpected infant death. With the possible exception of lidocaine, none of the average concentrations of the drugs or metabolites detected represent toxic or lethal amounts. The two occurrences of lidocaine were attributable to emergency therapeutic procedures in one of the SIDS cases. The most frequently encountered drug, ethanol, has a mean value that would be considered toxicologically insignificant in an adult; however, the effect on infant respiratory control could be important, particularly if the infant had a propensity for prolonged apnea while sleeping. The source of the alcohol, in most instances, was from liquid cough and cold remedies or other pharmaceutical elixirs. Although a few cases were found to have significantly high values, most of them were below 0.04% w/v. The mean values for caffeine and salicylate, the second most commonly detected drugs, are both below therapeutic blood concentrations for adults. The remainder of the drug concentrations shown in Table 6 are similarly of no apparent toxicological significance. They appear to represent the administration of small amounts of drugs commonly used in infants. Glutethimide is the one exception. Although glutethimide cannot be considered an appropriate therapeutic agent for infants, the concentration detected in this case is nevertheless in the range that would be considered therapeutic for adults.

Concerning the narrower question of the role played by drugs and common therapeutic agents in SIDS, a comparison of the presence of exogenous agents in the SIDS and non-SIDS deaths is instructive and can be made by an examination of Table 7. Of the 715 SIDS cases submitted to the laboratory for study, 91 (12.7%) showed detectable levels of drugs; in contrast, 44 of the 174 (25.3%) non-SIDS cases had drugs present. These figures would indicate that SIDS babies are approximately half as likely to have received drugs as those infants whose deaths are attributable to other causes. The most liberal interpretation would indicate that drugs, at least in acute administration, could have played a role in

TABLE 7—*Cases with positive toxicological findings.*

Drug	SIDS Cases			Non-SIDS Cases		
	Cases, *n*	% of Positive SIDS Cases	% of All SIDS Cases	Cases, *n*	% of Positive Non-SIDS Cases	% of All Non-SIDS Cases
Ethanol	42	46.2	5.9	13	29.5	7.5
Caffeine	21	23.1	2.9	5	11.4	2.9
Salicylate	12	13.2	1.6	12	27.3	6.9
Pheniramine	12	13.2	1.6	1	2.3	0.6
Phenobarbital	7	7.7	1.0	4	9.1	2.3
Acetaminophen	4	4.4	0.6	7	15.9	4.0
Diazepam	3	3.3	0.4	...	...	...
N-Desmethyldiazepam	3	3.3	0.4	...	...	...
Brompheniramine	2	2.2	0.3	4	9.1	2.3
Pyrilamine	2	2.2	0.3	...	...	...
Dextromethorphan	1	1.1	0.1	3	6.8	1.7
Theophylline	...	...	...	2	4.5	1.1
Codeine	1	1.1	0.1	2	4.5	1.1
Morphine	1	1.1	0.1	2	4.5	1.1
Lidocaine	1	1.1	0.1	1	2.3	0.6
Phenylpropanolamine	...	...	...	1	2.3	0.6
Ephedrine	...	...	...	1	2.3	0.6
Glutethimide	1	1.1	0.1	...	...	...

approximately 12% of the SIDS cases. However, the concentrations determined for the detected drugs and metabolites would appear to have had only minor, direct pharmacological effects. The greater proportion of non-SIDS cases in which drugs were present is attributable to the greater prevalence of illness in this population. In any event, the types of drugs found in both populations are generally what would be expected from professional or lay medical practice. The possible adverse effects of drug combinations were considered but it was found that only 13 of the 91 SIDS cases with positive toxicological findings had more than one drug present. Of these 13 cases, 9 had two drugs present and in only 4 were three drugs present. Of the non-SIDS cases, 10 of the 44 positive results showed more than one drug present, a slightly greater proportion than in the SIDS cases. Examination of all aspects of the toxicological results failed to indicate that drugs in combination are a significant factor in SIDS.

Inspection of the circumstantial information and case data for both the SIDS and the non-SIDS infants with positive toxicological findings demonstrates that most of these data correspond to the overall patterns seen in the entire survey population. The ages, sex, racial characteristics, and mean weight values for the SIDS and the control cases reflect those seen for the total study population. One notable exception was in the medical histories of those cases in which drugs were found: for the non-SIDS deaths, infants characterized as healthy in the two weeks prior to death represented a minority (see Fig. 7) because approximately 60% of the control infants were characterized as having had some medical complaint. If the control infants who had a drug present are examined separately, the proportion of "non-healthy" increases to greater than 80%. Although the greater frequency of concurrent illness in these positive cases is noteworthy, it would seem reasonable that sick infants are more likely to receive drugs than are those without medical problems. It is evident that this dramatic increase may be attributable to the individual infant's medical history rather than to some characteristic physiological or biochemical process. In any event, the correlation between ill health and the presence of drugs is much more pronounced in the non-SIDS group than in the SIDS group.

It would appear, even without separating the SIDS cases from the control population, that therapeutic agents do not play a major direct role in SIDS. It must be firmly kept in mind, however, that the only existing basis for the interpretation of drug concentrations and their significance *is based on data from adults*. What significance even small amounts of these agents might have in the complex of biochemical and physiological events that occur during a SIDS episode cannot yet be completely evaluated.

Summary and Conclusions

1. The case histories were generally consistent with previous reports for SIDS populations. There was no significant sex bias, ages clustered at 2 to 3 months, and nonwhites were overrepresented compared to the national racial profile. The SIDS infants were apparently healthy for the two-week period prior to death with the exception of minor upper respiratory infections or gastrointestinal upset. Most died between midnight and 6:00 a.m., more often in a parent's bed than for the non-SIDS group.

2. We now know that it is possible to design an analytical scheme for a sensitive and comprehensive drugs analysis of the limited autopsy specimens available from infants; moreover, such an analysis is also practical. The procedures described in this report provide toxicologists with the capability of conducting analytical studies that would be useful as part of the medicolegal investigation of any unexplained infant fatality. The new protocols could find immediate application in forensic toxicology laboratories.

3. It is practical to obtain the following minimum specimens from infants at autopsy for toxicological analysis: blood, 7 ml; liver, 25 g; bile, 1 ml; urine, 5 ml; and CSF, 3 ml. All of the gastric contents should be collected, and macroscopic and microscopic examination is recommended as routine.

4. Drugs were found in approximately 12% of the SIDS cases, representing approximately half the frequency with which they were found in the control group. In both populations the concentrations of drugs present would, by adult standards and current understanding of their pharmacological properties, be considered minimally effective if not insignificant. With the exception of a few cases, the types of agents found are precisely those to be expected in this population (that is, antihistamines, antitussives, analgesics, and "minor sedatives"). However, the study confirmed that drawing toxicological inferences based solely on a past history of drug use can be very misleading. If the cause and prevention of SIDS are to be found in a single biological phenomenon, it would not appear that drugs or other common toxic agents play a significant role, either directly or indirectly. However, the analytical toxicology data would surely be of value in a national registry, at least in the beginning. The relative simplicity of the complete analytical scheme, together with an anticipated 12% positive results, would make for a favorable cost-to-benefit ratio. If, after a statistically significant number of cases were recorded in the registry, a review indicated that the toxicology data were of little value, then the routine requirement for laboratory analysis could be deleted from the medicolegal protocol.

5. If the study has achieved little beyond the development and test of the analytical procedures, the resulting improvement in postmortem analytical toxicology would have fully justified the effort. Many of these procedures have established new techniques for the use of instrumentation such as HPLC, GC-NPD, and mass spectrometry.

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