Appendix

Terms of reference for the working groups. The working groups will:

1) Review relevant research completed, under way, or planned for the purpose of: (i) ensuring that the proposed methods of disposal of high-level radioactive wastes, whether into geological formations on land, below the seabed, or on the seabed, provide the degree of containment necessary to protect the biosphere from undue risks of radiation originating from the wastes; (ii) estimating with sufficient accuracy any radiation exposure to man that may result from such disposal; and (iii) assessing any harm to ecosystems from such disposal.

2) Conduct the reviews so that account is taken of the relevant behavior of nuclides following loss of any man-made containment of the wastes.

3) Principally base their reviews on the relevant activities of the IAEA, NEA, the Commission of the European Communities, and the Council for Mutual Economic Assistance, but extend these to national agencies where necessary to complete the reviews.

Membership of the working groups. The membership of Working Group No. 1, Terrestrial Disposal, included Dr. V. Babuska, Czechoslovak Academy of Sciences; Dr. W. S. Fyfe (chairman), University of Western Ontario; Dr. D. I. Norton, University of Arizona; Dr. N. J. Price, Imperial College of Science and Technology, United Kingdom; Dr. E. Schmid, Anglo-American Corporation of South Africa Ltd.; Dr. S. Uyeda, University of Tokyo, Bunkyo-ku; and Dr. B. Velde, Université Pierre et Marie Curie.

Working Group No. 2, Marine Disposal, included Dr. Kurt Bostrom, University of Lules; Dr. Egon T. Degens, Universität Hamburg; Dr. E. K. Duuersma, Delta Institute for Hydrobiological Research, Netherlands; Dr. Charles D. Hollister (chairman), Wood's Hole Oceanographic Institution; Dr. Ronald Pusch, University of Lulea; Dr. John C. Swallow, National Environmental Research Council, United Kingdom; and Dr. Gleb Udintsev, U.S.S.R. Academy of Sciences.

Working Group No. 3, Environmental Pathways, included Dr. B. G. Bennett, Environment Measurements Laboratory, New York; Dr. Y. Inoue, Kyoto University; Dr. R. H. Clarke (chairman), National Radiological Protection Board, United Kingdom; Dr. P. Jumans, University of Washington; Dr. J. P. Massue, Council of Europe; Dr. F. Morley, National Radiological Protection Board, United Kingdom; Dr. I. Nerethnicks, Royal Institute of Technology, Sweden; and Dr. J. B. Robertson, U.S. Geological Survey.

References and Notes

1. The full reports can be obtained from the International Council of Scientific Unions, 51 Boulevard de Montmorency, 75016 Paris, France.
2. A list of the references consulted by the working groups and steering committee would fill several pages. Moreover, this article provides only the conclusions of a study that directly involved about 30 individuals. It is suggested, therefore, that readers interested in specific details refer to the ICSU report with its 174 citations. The most comprehensive coverage is contained in the various reports and proceedings of the International Atomic Energy Agency in Vienna and of the Nuclear Energy Agency. Probably the best place to begin is *Underground Disposal of Radioactive Wastes* (International Atomic Energy Agency, Vienna, 1980). The Council for Mutual Economic Assistance also publishes material of relevance to the countries of Eastern Europe, but mainly in the Slavic languages. Many papers from the region, however, are included in several of the publications from The International Atomic Energy Agency. In addition, various regional groups have sponsored studies, seminars, and workshops on different aspects of waste disposal. From all of these it is relatively easy to investigate the literature of any aspect of radioactive wastes.

Heroin-Related Deaths: New Epidemiologic Insights

A. James Ruttenber and James L. Luke

The epidemiology of heroin use and associated mortality has been well described in a number of cities (*1–7*). Frequency of heroin use and overdose fluctuates widely over time and depends on geographical and cultural factors as well as drug availability. Heroin overdose also appears to be related to the concentration of heroin in street preparations and the loss of tolerance to heroin (*2, 7*). Over the past 30 years, the types of individuals using heroin and their patterns of heroin use have also changed. However, relatively little is known about why epidemics of heroin-related deaths (HRD's) develop, whether particular groups are at high risk for fatal overdose during these times, or how demographic and toxicologic variables during epidemics differ from those that precede and follow such periods.

The changes in heroin usage require continuous surveillance by medical and social support communities to provide appropriate emergency intervention, treatment, and rehabilitation. We describe an epidemic of HRD's in Washington, D.C., from 1979 through December 1982. We have identified risk factors for HRD's and suggest possible causes of such epidemics.

The Office of the Chief Medical Examiner investigates all deaths in the District of Columbia not demonstrated to have resulted from natural causes. When circumstances of death or postmortem findings suggest drug involvement, subjects receive autopsy examination and complete toxicologic screening. Since 1971, medical-legal investigations have been performed there with uniform methods and interpretive criteria (*2, 7, 8*).

We reviewed records of all drug-associated deaths reported to the Medical Examiner's Office from 1 January 1976 through 31 December 1982. A death was considered heroin-related either (i) when postmortem toxicology was positive for morphine (a metabolite of heroin) but no trauma or natural disease contributed to death or (ii) when death occurred during hospitalization for effects of documented heroin administration. We excluded any overdose deaths with toxicologic evidence of other narcotics alone or in combination with morphine. Heroin-related deaths are the cases in the case-control analyses.

Two control groups were used for comparisons with HRD's. The general control (GC) group consists of all deaths due to natural or traumatic causes with either cutaneous stigmata of intravenous narcotic use or positive blood morphine levels. The morphine-positive control (MPC) group is composed of members of the GC group that had positive blood morphine levels and no measurable level of any other narcotic drug. Comparison to the MPC group adjusts for the possibility that some controls were not active heroin users at the time of death. We excluded autopsy toxicologic data for cases and controls if an individual was admitted to a hospital, survived longer than 12 hours after injection, or if medical treatment after drug overdose was not specified.

From the autopsy protocols of cases and controls, we abstracted the number

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of recent individual injection sites, the number of anatomically distinct areas with hyperpigmented needle tracks, the combined weight of both lungs, the weight of liver, gross pathologic evidence of liver disease (normal, fatty metamorphosis, or cirrhosis), height, and weight. Liver abnormalities noted on gross examination were also evaluated microscopically by an anatomic pathologist (J.L.L.) who did not know the diagnosis made from gross examination or whether the decedent was a case or a control. Slides were graded as either normal, trace, one-plus, or two-plus for both fatty change and cirrhosis. The presence of cirrhosis other than Laennec's and central necrosis were also noted when present.

Tissue samples collected at autopsy were frozen before analysis, whereas blood samples collected at autopsy were stored at 4°C. The elapsed time between death and autopsy and the time between sample collection and analysis were similar for both cases and controls. Twenty-gram lung samples were screened for basic drugs (including quinine) by ultraviolet spectroscopy and gas-liquid chromatography at both low and high temperatures (*9*). Acidic and neutral compounds in whole blood were extracted with chloroform and analyzed with high-performance liquid chromatography after the chloroform was evaporated.

Beginning in January 1980, samples of blood, urine, and bile from decedents with measurable opiate levels were quantified by radioimmunoassay (*10*) after appropriate extraction procedures with high-performance liquid chromatography (electrochemical detector). Between January 1976 and December 1979, morphine in blood, urine, and bile was quantified by the enzyme multiplied immunoassay test (*11, 12*). Volatile compounds (including ethanol) were measured in whole blood by head space gas–liquid chromatography. Detection limits for opiates were 0.001 mg per 100 ml by radioimmunoassay and 0.05 mg per 100 ml the enzyme multiplied immunoassay test; for ethanol, 10 mg per 100 ml; and for quinine, 1 μg/ml.

Case-control analyses were evaluated through two-by-two table analytical techniques (*13*). Adjusted odds ratios, calculated by the conditional maximum likelihood estimates, were evaluated for uniformity over the stratified two-by-two tables and were reported only if there was no significant difference from uniformity ($P > 0.05$). Confidence intervals were determined by exact conditional maximum likelihood estimates (*14*).

During the past decade, the District of Columbia Metropolitan Police Department has purchased heroin on the street to facilitate arrests. The Washington, D.C., regional laboratory of the Drug Enforcement Administration routinely analyzes such samples for heroin concentration (diacetylmorphine only). Since 1976, this laboratory has analyzed some samples for quinine and other common adulterants, including monoacetylmorphine. Heroin obtained by this program does not constitute a random sample of street preparations, but it does provide the best available data on the composition of heroin marketed for illicit use.

The relation between street drug composition and price, mean quarterly blood ethanol and blood morphine concentrations, and heroin-related mortality was explored by linear regression analysis for various periods between January 1972 and September 1982. The absence of data for certain times precluded analysis of all variables for the entire period of interest. Models were considered suitable after they were evaluated for (i) normality and constant variance by assessing the standardized residuals and (ii) stability by removing outlying data (*15*).

Summary. Deaths associated with injected street preparations of heroin increased substantially in the District of Columbia between April 1979 and December 1982. The 1981 population-based mortality rate (17.4 per 100,000) is possibly the highest ever reported. A case-control study based on toxicologic analyses of postmortem blood samples indicates that concentrations of both heroin and ethanol are substantial risk factors for heroin-related deaths. Analyses of the composition of street-level preparations of heroin and quarterly mortality indicate that the quantity of heroin in packages sold on the street, the price of heroin in these packages, and the quinine weight per package each predict deaths equally as well. An increase in the casual use of heroin in combination with ethanol and quinine is the probable cause of this epidemic.

Descriptive Epidemiologic Data

The quarterly totals of HRD's for the years 1971 through 1982 clearly emphasize the rise that occurred between the second quarter of 1979 and the second quarter of 1982 (Fig. 1). Of the 266 documented HRD's from 1980 through 1982, 260 (99 percent) have demographic information, and 253 (98 percent) have autopsy data. The average age of these decedents was 31; 93 percent were black and 82 percent male.

For 1980 through 1982, 58 percent of HRD's occurred from May through September, whereas fewer than 8 percent of these deaths occurred in every other month but November ($\chi^2(11) = 62.60$, $P < 0.001$). Forty-two percent of these deaths occurred on either Friday or Saturday ($\chi^2(6) = 28.77$, $P < 0.001$) and 52 percent between 6 p.m. and midnight ($\chi^2(3) = 56.44$, $P < 0.001$).

Circumstantial investigations by the police and autopsy results indicate that decedents administered heroin almost exclusively intravenously and that most used disposable syringes and needles similar to those available to diabetics. Between 1980 and 1982, 91 percent of HRD's but only 66 percent of the GC

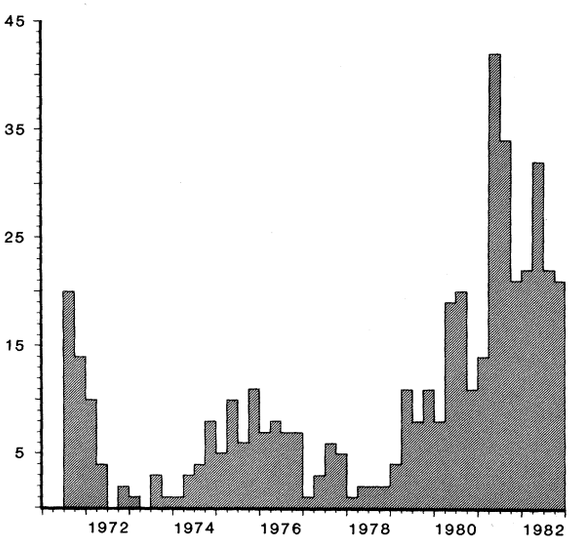

Fig. 1. Heroin-related deaths in the District of Columbia, 1971 through 1982.

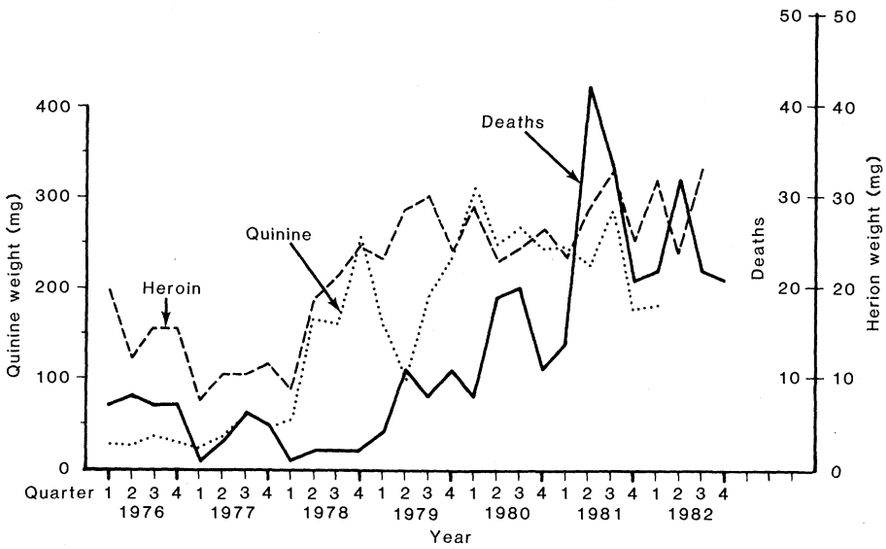

Fig. 2. Relation between heroin and quinine in street purchases and heroin-related deaths in the District of Columbia, 1976 through 1982. The dotted line represents quarterly mean quinine weight in packages purchased on the street; the dashed line, quarterly mean heroin weight in packages purchased on the street; and the solid line, heroin-related deaths, quarterly totals.

group had detectable quinine concentrations in the lungs. Only 5 percent of HRD's but 25 percent of GC's had measurable levels of phenmetrazine (an amphetamine derivative) in blood. Fourteen percent of GC's had detectable amounts of methadone in blood; 1 percent or less of HRD's and 3 percent or less of GC's had detectable amounts of diphenylhydantoin, tetrahydrocannabinol, amphetamine, cocaine, or secobarbital. Except for ethanol, no other toxic compounds or drugs were detected in the autopsy samples.

Comparisons between HRD's and both control groups reveal no significant difference in height or weight (t-test, $P > 0.10$) or in racial distribution (for GC, $\chi^2(2) = 4.82$; for MPC, $\chi^2(2) = 3.59$). Table 1 shows autopsy results for cases and controls. The median blood, urine, and bile morphine concentration of HRD's each significantly exceeds that of GC's and MPC's. Median ethanol concentrations are significantly higher for HRD's than for either control group, and the removal of cases and controls with no measurable blood ethanol does not change this relation. Blood ethanol concentrations for HRD's (median, 100 mg per 100 ml) during the epidemic (April 1979 through December 1982) were significantly higher (Wilcoxon test, $P = 0.0002$) than those for the preceding period (January 1976 to March 1979, median 0 mg per 100 ml).

Epidemic Risk Factors

Of the studies of heroin-related mortality in U.S. cities (*2–7, 16–20*), some do not clearly differentiate between deaths due exclusively to heroin and those due to narcotics in general or to specific combinations of heroin and other drugs. Even if the unspecified deaths are considered heroin-related, the 1981 District of Columbia population-based mortality rate of 17.4 per 100,000 is the highest rate documented. The high 1980 population-based mortality rate, 8.8 per 100,000, is similar to rates reported for previous epidemics (*6, 21, 22*). The increase in the number of HRD's is not likely to have resulted from an expanding population, since the District's total population declined slightly during the epidemic years, and the population in the age group at risk (18 to 44 years of age) remained stable.

In the recent District of Columbia epidemic, the decedents averaged about 3 years older at death than in previous periods (*2, 7*). This epidemic is thus not due to the recruitment of young and inexperienced users, as has been noted in the past (*23*). The average blood morphine concentration in HRD's resembles that reported for other cities for both endemic and epidemic periods (*2, 6*). This average concentration is twice that reported by Richards *et al.* (*19*) for decedents that had negative blood alcohol levels but like that for decedents with detectable levels of both blood morphine and ethanol.

Compared with MPC's, epidemic cases (Table 2) were 22 times as likely to have blood ethanol concentrations greater than 100 mg per 100 ml than they were to have concentrations below this level and 15 times as likely to have blood morphine concentrations greater than 0.02 mg per 100 ml than concentrations below this. Adjustment for confounding variables does not alter these risks appreciably. Cases in the epidemic were also more likely than MPC's to have gross evidence of fatty metamorphosis in their livers, but no more likely to have either microscopic evidence of fatty change or either gross or microscopic evidence of cirrhosis (χ^2, $P > 0.05$).

Table 1. Autopsy data measures of central tendency for heroin-related deaths (HRD's) and general (GC) and morphine-positive (MPC) controls in the District of Columbia, January 1980 to December 1982. Unless otherwise specified, variables do not have normal distributions and medians and P values for the Wilcoxon rank-sum test are reported; each control group is compared with the HRD group.

Variable	HRD's	GC group	P	MPC group	P
Age	30 (260)*	31 (188)	0.3630	31 (96)	0.5129
Blood ethanol (milligrams per 100 ml)	90 (229)	0 (116)	<0.0001	0 (51)	<0.0001
Blood morphine (milligrams per 100 ml)	0.03 (225)	0 (115)	<0.0001	0.01 (50)	<0.0001
Lung quinine (milligrams per 100 g)	0.40 (242)	0.20 (143)	0.0001	0.40 (59)	0.2265
Bile morphine (milligrams per 100 ml)	0.40 (229)	0.30 (91)	0.1059	0.95 (46)	0.0097
Urine morphine (milligrams per 100 ml)	0.10 (180)	0.20 (74)	0.6706	0.80 (35)	<0.0001
Recent injection sites	1 (174)	0 (102)	<0.0001	0 (50)	<0.0001
Track areas	2 (246)	2 (150)	0.0081	2 (66)	0.2695
Lung weight (g)†	1270 (228)‡	1019 (116)‡	0.0001	900 (51)	<0.0001
Liver weight (g)	1919 (252)	1718 (158)	0.0002	1520 (69)	<0.0001

*Parentheses denote numbers of decedents; size of variable groups for cases and controls is different because all variables were not evaluated for some decedents. †Combined weight of both lungs. ‡Means and t-test reported for variables that are normally distributed.

Blood ethanol levels probably explain the associations between fatty metamorphosis and HRD's. The use of phenmetrazine in combination with heroin is related to a reduction in the likelihood of heroin-related death. Elevated concentrations of morphine in both bile and urine also appear to be protective factors during the epidemic.

Odds ratios calculated for the endemic period (Table 2) indicate that ethanol use is a significant risk factor, but that the influence of this variable upon HRD's is less than it is during the epidemic. Blood morphine concentration is not a risk factor during the endemic period, but the discrepancy between this finding and the odds ratio for the epidemic period could be due to the different analytical techniques that were used in the measurement of this drug for endemic and epidemic periods. Elevated concentrations of morphine in bile and urine are not significant protective factors during the endemic period.

Because the minimum lethal blood morphine concentration may range from 0.02 to 0.04 mg per 100 ml (*2, 21, 24, 25*), and because heroin-related decedents in this study were 15 times more likely than controls to have blood morphine concentrations of 0.02 mg per 100 ml, or greater, the pharmacologic effects of heroin played an important role in the current epidemic deaths. This conclusion conflicts with the interpretation of Cherubin *et al.* (*23*) and Monforte (*21*).

Seventy-four percent of our case subjects had positive ethanol levels. The average blood ethanol concentration for ethanol-positive cases for this epidemic (158 mg per 100 ml) also exceeds that reported for ethanol-positive cases in previous epidemics (*6, 19*). Blood ethanol concentrations from autopsy samples reflect only minimum levels because concentrations in the living decrease by about 100 to 200 mg/liter per hour (*26*). Many reports have noted that ethanol is commonly found in the blood of heroin overdose victims (*2, 7, 20, 21, 23*), but no data have specifically shown ethanol to be a risk factor or ethanol abusers to be a high-risk group.

Our data provide statistically significant evidence that the combination of ethanol and heroin substantially influences mortality. The acute effects of blood ethanol appear more prominent than the chronic effects, since liver pathology does not significantly increase the risk of HRD after the confounding influence of blood ethanol is removed. The sizable differences between endemic and epidemic periods in odds ratios for high blood ethanol concentrations and for median blood ethanol concentrations also suggest that this epidemic was influenced by an increase in ethanol consumption by heroin users, or an increase in heroin consumption by ethanol abusers, or by a combination of these influences.

The statistically significant concentration of HRD's during the spring and summer, on Friday and Saturday, and from 6 p.m. through midnight suggests that heroin injection leading to overdose and death may be associated with casual or recreational use rather than classic addiction, which would cause deaths to be distributed more uniformly over time. This temporal concentration did not occur in deaths in the same city between 1971 and 1979 (*7*). Other suggestions of recreational heroin use by the decedents of this epidemic include the combined use of heroin and ethanol, the protective effect of phenmetrazine (a drug that is injected along with heroin and probably preferred by experienced users more than by novices) (*27*), and the significant protective effect of comparatively high concentrations of heroin in bile and urine, which suggests that the cases used the drug less chronically than the controls (*24, 28*). The recreational use not only of heroin but also of heroin and alcohol may cause fatal overdoses.

Price and Purity of Street Drugs

The quarterly mean weight of both heroin and quinine in street-purchased samples increased during the epidemic period (Fig. 2). Numerous adulterants commonly found in street samples were also detected by the Drug Enforcement Administration, but only quinine was consistently present in concentrations recognized as pharmacologically active. Three sets of price data (all expressed as U.S. dollars per milligram of pure heroin) were analyzed since three different agencies collected this information, and they all used slightly different methods.

Table 3 presents a summary of linear regression analyses for quarterly data from both endemic (January 1972 through March 1979) and epidemic (April 1979 through September 1982) periods combined. Heroin-related deaths are associated with the amount of heroin and quinine in street packages and the concentration of heroin (percentage of dry weight) in street samples. The price of heroin is also inversely associated with heroin-related mortality and to an extent similar to that of the separate effects of heroin and quinine weight. Likewise, linear combinations of heroin and quinine weight and heroin price are also

Table 2. Case-control analysis of risk factors for endemic and epidemic periods January 1976 through December 1982. Because the technique for morphine analysis was changed in January 1980, the endemic period is defined as January 1976 to December 1979 and the epidemic period as January 1980 to December 1982. The effect of this change upon reported relations is considered negligible.

Variable	Odds ratio*	95 percent confidence interval†
Endemic		
Blood ethanol‡	5.2	1.1, 49.6
Blood morphine§	0.2	0.1, 1.5
Bile morphine‖	2.2	0.7, 7.1
Urine morphine¶	1.0	0.2, 4.0
Epidemic		
Blood ethanol‡	21.7**	5.4, 187.3
Adjusted for:		
Blood morphine	36.0	8.2, 335.0
Gross fatty metamorphosis	16.5	4.1, 145.4
Microscopic fatty metamorphosis	17.5	4.1, 160.1
Blood morphine§	15.2**	6.6, 37.4
Adjusted for:		
Blood ethanol	23.3	9.4, 64.0
Gross fatty metamorphosis	14.5	6.3, 37.3
Microscopic fatty metamorphosis	12.4	5.2, 32.4
Gross fatty metamorphosis	2.6**	1.4, 5.9
Adjusted for:		
Blood ethanol	2.1	0.9, 5.7
Phenmetrazine in blood	0.3	0.1, 0.8
Bile morphine‖	0.50	0.2, 0.9
Urine morphine¶	0.20	0.1, 0.5

*Heroin-related deaths are compared to morphine-positive controls; conditional maximum likelihood estimate of adjusted odds ratio. †Exact conditional maximum likelihood estimate of confidence interval. ‡Blood ethanol >100 mg per 100 ml compared with ≤100 mg per 100 ml. §Blood morphine ≥0.02 mg per 100 ml compared with <0.02 mg per 100 ml. ‖Bile morphine ≥0.50 mg per 100 ml compared with <0.50 mg per 100 ml. ¶Urine morphine ≥0.20 mg per 100 ml compared with <0.20 mg per 100 ml. **Crude odds ratio, not adjusted for another variable.

significant predictors of HRD's. It should be noted that for the combined endemic and epidemic periods, there is a strong linear association between heroin weight and quinine weight ($r^2 = 0.64$, $n = 25$, $P = 0.0001$). This relation makes it difficult to clearly implicate quinine as a causal factor in this epidemic, for quinine weight could serve as an indicator of a particular street mixture whose pharmacologic effects could be more closely related to heroin weight.

For endemic quarters before April 1979, only the average concentration of heroin in street samples and heroin price suitably predict HRD's (Table 4). During the epidemic, neither average quarterly street heroin weight, quinine weight, nor heroin concentration singly, or in combination, significantly predicts HRD's. Heroin price is the only adequate predictor of mortality for this period. The relation between average quarterly total price of a bag of street heroin and mortality was also examined by linear regression. No estimate of total price was significantly related to mortality for any period of analysis. Since the total price of a bag of street heroin is not associated with mortality, it appears that mortality is influenced by the extent to which a bag of street heroin is both inexpensive and of high heroin content.

Since the price of heroin could be influenced by the weight of heroin and thus lead to a spurious association between price and mortality, we explored the relations between heroin content (in terms of both weight and concentration of pure heroin) and both the price per milligram of pure heroin and the total price of heroin. Our analysis suggests that the chance for spurious associations is small, particularly during the epidemic period.

We should point out that linear regression models omit many potential variables, and thus could show spurious correlations if there is covariation between model variables and background variables not included in the analysis. We also evaluated the effects upon intraepidemic HRD's of changes in population composition, route of drug administration, age of decedents, and concentrations of blood ethanol and heroin metabolites in blood, urine, and bile. Our reported regression results appear to be independent of these factors.

The influence of both the concentration and the weight of heroin upon mortality corroborates findings in other studies (*7, 29*). Our results differ from these reports by relating quinine and the price of heroin to an epidemic of HRD's and by differentiating predictors of epidemic development from predictors of intraepidemic variance. These findings conflict with the accepted explanation that the potency of heroin is the primary cause of epidemics of HRD's (*2, 7, 30*). Our data suggest that the selection of the amount of heroin in street samples as the only independent variable for regression analysis may oversimplify the dynamics of HRD epidemics and lead to spurious conclusions.

We urge others also to examine the effects of the price of heroin and the concentrations of pharmacologically active diluents when applying regression

Table 3. Linear regression models for relation between deaths and street sample composition and price for combined endemic and epidemic periods in the District of Columbia, 1972 through 1982.

Period	Number of quarters	Model r^2	Independent variable	Regression coefficient	Standard error	P
January 1972 to September 1982	43	0.24	Heroin concentration*	4.72	1.31	0.0008
January 1976 to September 1982	27	0.39	Heroin weight†	0.87	0.22	0.0005
January 1976 to March 1982	25	0.26	Quinine weight	0.05	0.02	0.0099
January 1972 to September 1982	39	0.37	Heroin price‡	−3.23	0.70	0.0001
January 1975 to September 1981	24	0.23	Heroin price§	−6.24	2.40	0.0164

*Percentage of dry weight of total street sample. †All weights are in milligrams. ‡From original records of Zimney and Luke as summarized in (*7*) and updated with data from the Drug Enforcement Administration Domestic Monitor Program. §From Drug Enforcement Administration purchases and seizures. All prices are U.S. dollars per milligram of heroin, not corrected for inflation.

Table 4. Linear regression models for relation between deaths and street sample composition and price for endemic and epidemic periods in the District of Columbia, 1972 through 1982.

Period	Number of quarters	Model r^2	Independent variable	Regression coefficient	Standard error	P
			Endemic			
January 1972 to March 1979	29	0.33	Heroin concentration*	1.79	0.49	0.0011
January 1976 to March 1979	13	0.00	Heroin weight†	0.00	0.14	0.9972
January 1976 to March 1979	13	0.24	Quinine weight	0.02	0.01	0.0881
January 1972 to March 1979	29	0.22	Heroin price‡	−1.07	0.39	0.0103
January 1975 to March 1979	16	0.56	Heroin price§	−3.44	0.81	0.0008
			Epidemic			
April 1979 to September 1982	14	0.21	Heroin concentration	5.84	3.23	0.0962
April 1979 to September 1982	14	0.04	Heroin weight	0.55	0.81	0.5122
April 1979 to March 1982	12	0.01	Quinine weight	0.02	0.06	0.7167
April 1979 to September 1981	10	0.15	Heroin price‡	−5.35	4.53	0.2707
April 1979 to September 1981	8	0.77	Heroin price§	−23.06	5.18	0.0043
April 1979 to December 1981	11	0.44	Heroin price‖	−11.13	4.15	0.0251

*All concentrations are percentages of dry weight of total street sample. †All weights are in milligrams. ‡From records of Zimney and Luke (*7*) and updated with data from the Drug Enforcement Administration Domestic Monitor Program. §From Drug Enforcement Administration purchases and seizures. ‖From Narcotics Branch, Metropolitan Police Department, District of Columbia. All prices are U.S. dollars per milligram of heroin, not corrected for inflation.

analysis to the study of HRD's. Likewise, it may be useful to separately analyze data from endemic and epidemic periods. The inclusion of these analyses is obviously dependent upon a well designed program of street drug purchases. Our examination of currently available data from the District of Columbia and other cities suggests there is much room for improvement. Because mortality within the reported epidemic period appears to be influenced by other factors, we caution against assuming that HRD's result solely from increases in the amount of heroin in street drug preparations. During epidemics, high doses of heroin in street preparations may operate only as a threshold for high risk, and other factors, such as cost, frequency of heroin use, and combinations with ethanol and quinine, may affect mortality patterns.

Reports that cite lack of heroin tolerance as an important risk factor for mortality have implied that a heroin user is either consistently addicted or going through a period of strict abstinence when he is particularly susceptible to strong preparations of heroin (*30*). Preliminary interview data coupled with the previously cited risk factors and the role of ethanol as a substantial risk factor suggest that a pattern of polydrug use that includes injection of heroin may elevate one's risk for a heroin-related death.

A study of heroin overdose by military personnel supports this conclusion (*31, 32*). The recruitment of chronic alcohol abusers who have been former heroin users into the population of casual heroin users during periods when heroin is inexpensive and readily available might explain a portion of the mortality during the epidemic that we studied. Granted, this explanation only subtly alters previously posited ones (*7, 30*). It suggests, however, that a far different response may be necessary for public health intervention in contemporary epidemics (*33*).

Quinine and Heroin-Related Deaths

Quinine is a well-documented adulterant in heroin preparations, particularly those sold on the east coast of the United States (*3, 27, 34*). Most investigators have concluded that quinine probably does not contribute to HRD's because quinine concentrations in street samples are relatively constant (*2*) and because epidemics of HRD's occur on the west coast of the United States, where quinine rarely is added to heroin (*1, 7, 20*). Our data, however, do indicate a significant increase in both concentration and quantity per package of quinine during the initial stages of this epidemic. Likewise, regression analyses suggest that quinine dose may explain some of the difference in mortality between endemic and epidemic periods.

Doses of intravenously administered quinine (calculated by multiplying quarterly average street sample package weight by quarterly average quinine concentrations) ranged from 98 through 314 mg for the epidemic, assuming that a user may inject the entire contents of a package at one time. If these quantities were injected over a 10-second interval, dose rates would range between 10 and 31 mg/sec, 59 to 188 times the currently recommended maximum therapeutic rate of quinine dihydrochloride injection for humans, reported to be 10 mg/min (*35*). If only part of a package (average weight 750 g) were injected at one time, or if the injection interval were lengthened or shortened, the dose rate would be modified proportionately. Levine *et al.* (*36*) raised the issue of quinine toxicity with data from the literature and drew similar conclusions.

The potential lethality of these doses may also be evaluated by calculating the injection dose that would result in the reported minimum lethal blood concentration of quinine (30 μg/ml) (*37*), estimating total blood volume from 69 ml per kilogram of body weight (*38*) and assuming that the average user weighs 75 kg and that the cardiovascular effects of quinine would occur before significant metabolism of the drug. The minimum lethal dose according to these computations would be 155 mg, again suggesting the potential lethality of the quinine injected by decedents in this epidemic—particularly for short injection intervals—and contradicting studies that maintain that quinine concentrations in street samples cannot be considered toxic (*39*).

Quinine can cause a reduction in pacemaker discharge and conductivity, a prolonged effective refractory period, ventricular fibrillation, pulmonary edema, hypersensitivity, depression of myocardial contractility, peripheral vasodilation, and severe hypotension (*3, 19, 33, 40, 41*). Cases of apparent quinine cardiotoxicity in intravenous heroin users have also been reported (*42*). Alterations in cardiac conduction and rhythm and pulmonary edema are also known to be associated with both heroin (*36, 43, 44, 45*) and ethanol (*46, 47*), raising the issue of potential synergism among the three drugs. Quinine and heroin have been shown to be additive in producing pulmonary edema and death in mice (*40*), but whether heroin, ethanol, and quinine act synergistically or additively in humans is not known.

Conclusion

A detailed study of autopsy data for an epidemic of heroin-related deaths has suggested new explanations for the etiology of mortality increase: the vulnerability of ethanol abusers to the effects of heroin and the apparent increase in the recreational use of heroin. Since it is difficult to obtain accurate data on drug use patterns and risk factors through the interview process, the importance of autopsy data cannot be overstated. We feel a well-designed program of autopsy data review is invaluable to public health personnel for identifying new patterns of drug abuse and risk factors for drug-related mortality. Our data also show the value of the epidemiologic analysis of street drug composition data that are collected continuously and in a defined and replicable manner. Interpretation of these two data sources may lead to the identification of public health strategies for reducing drug-associated mortality (*33*).

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Who Will Pay for Medical Education in Our Teaching Hospitals?

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In the teaching hospitals of this country, the care of patients has always been intimately associated with clinical education and research. Medical students, house officers, and clinical fellows help take care of patients while they are being supervised and educated by the senior staff, even as the staff carry out clinical research studies. Indeed, it has been an article of faith among medical educators that these three elements—patient care, clinical education, and clinical research—are the essential ingredients of academic medicine—inseparable and mutually supportive (the academic medical "tripod"). Most educators believe that the sophisticated clinical services in the teaching hospitals owe their special quality in no small measure to the educational and research programs. They also believe that the best kind of clinical education takes place at the bedside and in the clinics in the teaching hospitals, under the close supervision of full-time faculty specialists who are also engaged in the care of patients and in clinically related research.

Phase One: Generous Research Grants

With this rationale, and in response to the generally perceived need to increase the number of medical graduates, clinical departments in the teaching hospitals—particularly departments of medicine—expanded rapidly in the decades following World War II. The initial support for the necessary growth in full-time faculty came largely from National Institutes of Health (NIH) grants, which were ostensibly awarded only for the support of research and research training. Although there was no explicit approval of the use of these funds to support education and patient care, there was no objection either. Generous NIH grants included salaries for faculty members who were mainly supposed to be doing research and training investigators, but there was no problem if they also spent some time teaching students and house officers and making clinical rounds. And, likewise, fellows and trainees were supposed to be spending most of their time in the laboratory, but the fact was that many were also teaching students, seeing patients, and learning how to become clinical specialists. No one really objected because at first there was plenty of NIH money to go around, and also because most of us were convinced that one simply could not be a competent clinical investigator without also seeing patients and doing some teaching.

In those early postwar years, although most schools were eager to increase their full-time faculty, they had no way of supporting them other than through NIH grants. Except in some well-financed state schools, institutional hard money was available for only a relatively few senior faculty. Income from practice was also limited because there were few or no departmental practice plans, and most patients on teaching services were uninsured.

Thus, it was that departments of medicine in the 1950's and 1960's built their new full-time faculties largely with NIH funding. That was not intended by Congress, nor was it often admitted in public, but deans and department chairmen knew what they were doing, and they rationalized it by talking about "troikas" and "three-legged stools." The fact was that we really had no other options. In those days, if you wanted to build a department, it was the NIH or nothing.

By 1965–1966, 53 percent of total medical school revenues came from the federal government, most of it in the form of research grants and contracts (*1*). For a relatively brief period, beginning in 1966, the government provided modest support for education in the form of per capita grants. Originally intended to fund "basic improvements" and to assist schools in financial straits, the grants were soon linked to expansion of class size. By the mid-1970's a gradual phasing-out began, which was completed in 1980, ostensibly because there was no longer any need for expansion of classes.

There never was any explicit federal commitment to the general support of medical education, but in any case, proposals that there ought to be soon faded away as the NIH purse strings began to tighten in the 1970's. With the coming of a new austerity in the NIH budgets also came the need to account for allocations of time and effort more carefully and to concentrate available resources on the support of research rather than education or patient care.

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