*Vina R. Spiehler,*[1] *Ph.D.*

# Computer-Assisted Interpretation in Forensic Toxicology: Morphine-Involved Deaths

**REFERENCE:** Spiehler, V. R., **"Computer-Assisted Interpretation in Forensic Toxicology: Morphine-Involved Deaths,"** *Journal of Forensic Sciences*, JFSCA, Vol. 34, No. 5, Sept. 1989, pp. 1104-1115.

**ABSTRACT:** Case data from 200 morphine-involved deaths (Spiehler, V. and Brown, R., *Journal of Forensic Sciences*, Vol. 32, No. 4, July 1987, pp. 906-916) were analyzed for patterns and relationships using artificial intelligence (AI) computer software. Case parameters were blood unconjugated morphine, blood, brain, and liver total morphine, sex, age, frequency of use, time of death after injection, cause of death, and presence of other drugs. The programs used were Expert 4 (Biosoft-Cambridge), BEAGLE (Warm Boot Ltd.), and KnowledgeMaker (Knowledge Garden Inc.). Interpretation was defined as estimating the dose, response, and time after drug dosing.

The AI programs were used to advise on time and response outcomes for cases, to calculate the probability of the estimate being true, to develop rules for interpretation of morphine-involved cases, and to diagram a decision tree. On known cases the AI programs were successful 70 to 90% of the time in classifying the cases as to response and time. No data on dose were available in this database. The success rate in individual cases was proportional to the program-estimated probability. All three programs found the case parameters of most value in predicting response to be blood unconjugated morphine, blood total morphine, and liver total morphine. The case data most useful in estimating time of death since drug injection were blood unconjugated morphine, percent unconjugated morphine in blood, and brain total morphine. The rule induction programs found that morphine overdoses were characterized by blood unconjugated morphine greater than 0.24 μg/mL, liver morphine greater than 0.50 to 0.75 μg/g, brain morphine greater than 0.08 μg/g or greater than blood unconjugated morphine, and percent blood unconjugated morphine greater than 37%. Rapid deaths were characterized by percent unconjugated morphine greater than 44 to 50%; blood unconjugated morphine, as a function of other drugs present, greater than 0.09 to 0.21 μg/mL; and brain total morphine greater than 0.16 to 0.22 μg/g.

This work demonstrates that inexpensive AI programs commercially available for personal computers can be useful in interpretation in forensic toxicology.

**KEYWORDS:** toxicology, morphine, computers

In this study, artificial intelligence (AI) computer software is used for computer-assisted interpretation in forensic toxicology (CAIFT). AI programs are designed to emulate the performance of humans, such as control of a robotic arm in manufacturing or laboratory work. The branch of AI known as expert systems attempts to create computer programs which emulate decision-making and diagnosis by experts. Forensic toxicology is an appropriate application area for a test of these programs. Interpretation in forensic toxicology often can-

This paper was presented in part at the 40th Annual Meeting of the American Academy of Forensic Sciences, Philadelphia, PA, 15-20 Feb. 1988. Received for publication 23 Sept. 1988; revised manuscript received 9 Dec. 1988; accepted for publication 10 Dec. 1988.

[1]Technical director, Diagnostic Products Corporation. Los Angeles, CA.

not be done by numeric calculations alone or by simple formulae. For many drugs, clinical pharmacokinetic models are not successful in interpretation of toxic doses or postmortem levels. Interpretation in forensic toxicology requires trained, experienced human judgment. Since the goal of AI expert system programs is to automate some aspect of expert human judgment, there may be areas in forensic toxicology interpretation which could be amenable to automation through AI.

One aspect of interpretation in forensic toxicology which might benefit from automation is the review of large collections of case data for patterns or the unbiased recall of patterns for interpretation. If, in this way, AI programs can be of assistance as tools in forensic toxicology interpretation, this would increase the productivity of existing experts and aid in the training of new toxicologists. Case data collections are growing beyond easy recall, and rules of classification are needed to handle this case database and to train students. It was the objective of this work to evaluate commercially available AI programs for personal computers for evaluation and interpretation of patterns and relationships in a forensic toxicology case database.

Three AI computer programs developed to emulate decisionmaking and diagnosis by experts were applied to interpretation of morphine-involved deaths. Like the forensic toxicology experts, these programs can use both numeric and descriptive case data to classify a new, unknown case. Programs were chosen for this study which work from a database containing both toxicology results and case histories of known cases. The computer programs were used to discover patterns in the data base of morphine-involved cases and to express these patterns as rules. The rules were then evaluated as aids to classification and interpretation of morphine-involved cases. The programs were applied to the question of the time interval between dose and death and to the probability that the death was caused by a morphine overdose. Insufficient data were available to train the programs to estimate dose.

## Methods

### *Computer Programs Used*

Expert systems programs were chosen which represent three widely different approaches to the emulation of human reasoning from toxicology cases. The results were then compared to each other and to independently known values. The programs used were Expert 4 (Biosoft, Cambridge, U.K.) [*1*], BEAGLE (Warm Boot Ltd., Nottingham, United Kingdom) [*2*], and KnowledgeMaker (Knowledge Garden Inc., New York, New York) [*3*].

### *Expert 4*

The Biosoft Expert 4 uses similarity between cases to make inferences and to build prototypes of each diagnostic category such as rapid death or morphine overdose. Rivers finds this mimics the mental procedures doctors use in diagnosing illness [*1*]. In Expert 4, each case from the empirically collected case data becomes a rule or pattern against which other cases can be compared. The inferring mechanism is as follows: only cases that have more than 55% of their attributes in common (that is, a similarity rating of greater than 55) are taken into account. For each of these cases, support is added for the value it has on the attribute to be inferred. The amount of support is calculated according to the function

$$\text{added support} = \Sigma\,(C \times 4)^3$$

where $C$ is the proportion of values that two cases (the case with the value to be inferred and any one of the other cases with a similarity above 55%) have in common. Having gone through all the cases adding support, the value with the highest level of accumulated support

on the attribute to be inferred is the value inferred. Once the prototype is built from case data, in the consulting mode new cases can be entered and their attributes are predicted from the prototype using a pseudo-Bayesian combination of probabilities. The inference mode of Expert 4 was tested by erasing the known values of the cases one at a time from the computer memory and then noting the success of the program in inferring the missing value correctly.

### *BEAGLE*

BEAGLE uses a Darwinian evolutionary strategy to generate and select rules which converge on the required target estimate. Forsyth uses chi-square statistics and case data to allow the cases to dictate the rules [*2*]. After the data set is divided into a training set and a test set, the program generates a random collection of rules relating the attributes given for each case using a Monte Carlo method. Next, the program tests those rules for ability to predict the target (time of death, dose, response) in the training set and calculates a chi-square score for each rule. At the end of each generation, the rules with low chi-square scores are discarded. The rules with high chi-square scores are retained and mated. Premises and conclusions are exchanged, and numerical constants are "mutated" or varied slightly. These new rules are once again tested for their ability to predict the target. After many passes or generations, the evolved or surviving rules are much better at predicting the target than the beginning rules. The rules are developed one at a time. However, the greatest success is found by combining the evolved rules to test for complex patterns. The success of the rules in combination is determined by validation tests on cases from the test set which have not previously been seen by the learning program.

### *KnowledgeMaker*

KnowledgeMaker uses Quinlan's ID3 induction algorithm to build a decision tree. This program treats the uncertainty of the probability of classification as a measure of entropy and minimizes the entropy of classification [*3*]. If an object can be classified into $n$ difference classes, $c1 \ldots cn$, and the probability of an object being in Class $i$ is $p(ci)$, then the entropy of classification $H(C)$ is

$$H(C) = -\sum_{i=1}^{N} p(ci)\ \ln\ p(ci)$$

To determine how much information there is in knowing the value of one particular attribute, one can sort the cases on the values of that attribute, and the entropy of each resulting subset, $H(C \mid aj)$ can be calculated:

$$H(C/aj) = -\sum_{i=1}^{N} p(ci \mid aj)\ \ln\ p(ci \mid aj)$$

where $p(ci \mid aj)$ is the probability that the class value is $ci$ when the attribute has the $j$th value. The attribute having the smallest entropy and therefore the least uncertainty provides the most information about classification of the case. The validity of the decision tree was tested by applying the tree rules to cases which had not been used to build the tree.

For details of the programming and statistical procedures used by each program, the reader is referred to the literature [*4–7*].

*Case Database Used*

The database used was case data from 203 morphine-involved deaths [*8*]. Free morphine was determined by radioimmunoassay (RIA) and gas chromatography/mass spectrometry (GC/MS) [*8*]. Total morphine was determined by GC/MS [*8,9*]. The cases were randomly divided into a training set and a test set. Case parameters were blood unconjugated morphine, blood, brain and liver total morphine, percent unconjugated morphine in blood, sex, age, frequency of use, time of death after injection, cause of death, and presence of other drugs. Interpretation was defined as estimating the dose, response, and time after drug dosing. Time was entered as rapid, moderate, long, or unknown based on the case investigation and witness statements. Deaths occurring in 3h or less were characterized as "rapid" following Garriott and Sturner [*10*]. Deaths occurring longer than 12 h after the last dose were considered "long." Frequency of use was acute, chronic, or unknown based on case investigation and the presence of needle marks on the deceased. Cause of death or response was indicated as due to a direct overdose or not due to a direct overdose. Other drugs were entered as none, multiple, cocaine, ethanol, opiates, benzodiazepines, or unknown. Unconjugated and total morphine values were obtained by GC/MS using a deuterated internal standard [*8*]. Percent unconjugated morphine was calculated as the fraction (unconjugated morphine/total morphine) $\times$ 100.

## Results

*Information Value of Attributes*

All three programs found the case parameters of most value in predicting whether the case was a direct morphine overdose to be blood unconjugated morphine, percent unconjugated morphine in blood, blood total morphine, liver total morphine, and brain total morphine. The case data most useful in estimating time of death since drug injection were blood unconjugated morphine, percent unconjugated morphine in blood, and brain total morphine. This information value was expressed by Expert 4 as the probability of classification. This is given in Table 1. Higher probabilities indicate relatively greater value in predicting the target. The prototype values generated by Expert 4 are given in Tables 2 and 3.

*Induced Rules for Overdose*

The rule induction programs found that morphine overdoses were characterized by blood unconjugated morphine greater than 0.24 $\mu$m/mL, liver morphine greater than 0.50 to 0.75 $\mu$g/g, brain morphine greater than 0.08 $\mu$g/g or greater than blood unconjugated morphine, and percent blood unconjugated morphine greater than 37% (Table 4). The BEAGLE program converged on these same rules and the same or close critical decision values after different passes on the complete data base or after experiments on randomly selected training set cases. About 100 to 200 generations or cycles of the BEAGLE program were required to reach a stable, best rule. The value of each rule alone is expressed as a chi-square score. The chi-square scores and the true and false positive and negative prediction of direct overdose are summarized in Table 5. When the rules are used in combination, the conclusions which can be drawn are much stronger. Table 6 gives the success rate of the rules induced by BEAGLE for predicting a direct overdose when applied in combination and their associated probabilities.

*Induced Rules for Time Interval*

Rapid deaths were characterized by percent unconjugated morphine greater than 44 to 50%, blood unconjugated morphine, as a function of other drugs present, greater than 0.09

TABLE 1—*Probability of immediately classifying case calculated by Expert 4.*

| Attribute | Probability |
|---|---|
| FOR RESPONSE | |
| Blood unconjugated morphine | 0.44 |
| Percent unconjugated morphine | 0.36 |
| Blood total morphine | 0.35 |
| Liver total morphine | 0.27 |
| Brain total morphine | 0.25 |
| Age | 0.08 |
| Other drugs | 0.07 |
| Frequency | 0.02 |
| Sex | 0.00 |
| Time | 0.00 |
| FOR TIME | |
| Blood unconjugated morphine | 0.23 |
| Percent unconjugated morphine | 0.16 |
| Liver total morphine | 0.16 |
| Brain total morphine | 0.13 |
| Other drugs | 0.09 |
| Age | 0.08 |
| Blood total morphine | 0.06 |
| Frequency | 0.02 |
| Sex | 0.02 |
| Response | 0.00 |

TABLE 2—*Expert 4: protytpe values for response.*

| | For Direct Overdose | | | For Not-A-Direct Overdose | | |
|---|---|---|---|---|---|---|
| Attribute | Value | AI[a] | DI[b] | Value | AI[a] | DI[b] |
| Unconjugated morphine | 0.21-0.30 | W | VG | 0.11-0.20 | M | M |
| Total morphine | 0.41-0.50 | VW | VG | 0.21-0.30 | VW | P |
| Percent unconjugated | 51-60% | VW | VG | 10-20% | M | G |
| Brain total morphine | 0.16-0.20 | VW | G | 0.05-0.10 | VW | M |
| Liver total morphine | 1.26-1.5 | W | VG | 0.26-0.50 | W | M |
| Age | 31-40 | M | VG | 31-40 | W | VP |
| Sex | male | VS | VG | male | VS | VP |
| Time | rapid | S | VG | moderate | M | M |
| Frequency | chronic | VS | VG | chronic | VS | VP |
| Other drugs | none | VS | VG | none | W | N |

[a]AI = Association Index: VW = Very Weak, W = Weak, M = Medium, S = Strong, VS = Very Strong.

[b]DI = Distinguishability Index: VP = Very Poor, P = Poor, M = Medium, G = Good, VG = Very Good, N = None.

to 0.21 μg/mL, and brain total morphine greater than 0.16 to 0.22 μg/g. These rules were also repeatedly chosen or evolved by BEAGLE on different passes on the complete data base or on randomly selected training set cases. The chi-square scores for these rules were 62, 48, and 45, respectively. The probability that the death was rapid when all three rules were true was 0.89. The probability of a rapid death when all three rules were false was 0.02. The truth tables for BEAGLE rules for time are given in Tables 7 through 9.

Rule 2 takes the form UNCONJUGATED MORPHINE > (OTHER DRUGS * 0.000 015). When

TABLE 3—*Expert 4: prototype values for predicting time interval.*

| | Rapid Time Interval | | | Moderate Time Interval | | | Long Time Interval | | |
|---|---|---|---|---|---|---|---|---|---|
| | Value | AI[a] | DI[b] | Value | AI[a] | DI[b] | Value | AI[a] | DI[b] |
| Unconjugated morphine | 0.31-0.40 | W | VG | 0.11-0.20 | M | M | 0.01-0.05 | M | VG |
| Total morphine | 0.31-0.40 | VW | G | 0.51-0.60 | VW | P | 0.21-0.30 | W | M |
| Percent unconjugated | 51-60% | W | VG | 21-30% | W | G | 10-20% | M | M |
| Brain total morphine | 0.26-0.30 | VW | VG | 0.16-0.20 | W | G | 0.05-0.10 | M | VG |
| Liver total morphine | 1.26-1.5 | W | VG | 1.0-1.25 | W | M | 0.10-0.25 | M | VG |
| Age | 31-40 | M | G | 31-40 | M | P | 31-40 | M | VP |
| Sex | male | VS | G | male | VS | P | male | VS | VP |
| Direct overdose | yes | VS | G | yes | M | VP | no | M | N |
| Frequency | chronic | VS | G | chronic | S | P | chronic | VS | VP |
| Other drugs | none | VS | G | none | S | P | none | M | N |

[a]AI = Association Index: VW = Very Weak, W = Weak, M = Medium, S = Strong, VS = Very Strong.
[b]DI = Distinguishability Index: VP = Very Poor, P = Poor, M = Medium, G = Good, VG = Very Good, N = None.

TABLE 4—*Rules induced by BEAGLE for predicting a direct morphine overdose.*

| | |
|---|---|
| Rule 1: | liver morphine greater than 0.50 to 0.75 μg/g |
| Rule 2: | blood unconjugated morphine greater than 0.24 μg/mL |
| Rule 3: | brain morphine greater than 0.08 or greater than blood unconjugated morphine |
| Rule 4: | percent blood unconjugated morphine greater than 37% |
| Rule 5: | frequency of use: chronic |

TABLE 5—*BEAGLE rules for response evaluated one at a time.*

| Rule | Chi-Square Score | True Positives | False Positives | False Negatives | True Negatives |
|---|---|---|---|---|---|
| 1 and 2 | 47 | 90 | 7 | 15 | 17 |
| 3 | 42 | 101 | 15 | 4 | 9 |
| 4 | 41 | 74 | 6 | 31 | 18 |
| 5 | 16 | 25 | 4 | 80 | 20 |

TABLE 6—*BEAGLE rules for response evaluated in combination.*

| Rule | | | | Total Cases Matching | Target True Cases | Probability of Direct Morphine Overdose |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 5 | | | |
| 0 | 0 | 0 | 1[a] | 12 | 4 | 0.36 |
| 0 | 0 | 1 | 1 | 20 | 11 | 0.55 |
| 1 | 1 | 1 | 1 | 94 | 90 | 0.95 |

[a]1 = true; 0 = false.

TABLE 7—*Rules induced by BEAGLE for predicting time between dose and death.*

| | |
|---|---|
| Rule 1: | percent unconjugated morphine > 44% |
| Rule 2: | blood unconjugated morphine greater than 0.09 to 0.21 μg/mL depending on other drugs present |
| Rule 3: | brain morphine greater than 0.22 μg/mL |

TABLE 8—*BEAGLE rules for time evaluated one at a time.*

| Rule | Chi-Square Score | True Positives | False Positives | False Negatives | True Negatives |
|---|---|---|---|---|---|
| 1 | 62 | 44 | 19 | 5 | 61 |
| 2 | 48 | 43 | 30 | 13 | 60 |
| 3 | 45 | 36 | 20 | 13 | 60 |

TABLE 9—*BEAGLE rules for time evaluated in combination.*

| Rule | | | Total Cases Matching | Target True Cases | Probability of Rapid Death |
|---|---|---|---|---|---|
| 1 | 2 | 3 | | | |
| 0 | 0 | 0 | 36 | 2 | 0.02 |
| 0 | 0 | 1[a] | 9 | 1 | 0.02 |
| 0 | 1 | 0 | 13 | 1 | 0.15 |
| 1 | 0 | 0 | 5 | 0 | 0.05 |
| 1 | 0 | 1 | 6 | 3 | 0.40 |
| 1 | 1 | 0 | 19 | 10 | 0.40 |
| 1 | 1 | 1 | 33 | 31 | 0.89 |

[a]1 = true; 0 = false.

evaluated for the possible values for other drugs using the program hash values, this yields the following critical decision values: when no other drug was reported, the critical decision value was unconjugated morphine greater than 0.21 μg/mL; when cocaine or ethanol or both were present, the value was 0.09 μg/mL; and when multiple drugs were present, the value was 0.19 μg/mL.

### *Decision Tree for Time Interval and Response*

KnowledgeMaker, using the ID3 algorithm, produced a tree or logic diagram of the decision steps in classification of a case. An example of the decision tree for prediction of time interval between last drug dose and death is shown in Fig. 1; the decision tree for prediction of response is shown in Fig. 2. KnowledgeMaker also induced rules (example in Fig. 3), but did not provide the probability calculations used or the certainty factors for conclusions reached at different levels of the decision tree.

### *Validation of the Expert Systems Knowledgebase*

Validation was carried out by testing the rules or advisor in a consultation mode using cases from the test set which had not been used in the generation of the rules. An example of a case consultation for the KnowledgeMaker decision-tree derived rules is shown in Fig. 3. The results of validation tests for all three expert system programs are summarized in Table 10. The heuristic rules induced by BEAGLE when used in combination produced the greatest number of correct predictions and the fewest incorrect answers.

## Discussion

The interpretation of the cases and the rules developed by all three programs were consistent with each other, although each program used a totally different logical and programming approach to the task. The rules developed were also intelligible to experienced forensic toxicologists and consistent with the judgments of human experts.

The programs rediscovered rules which have been previously reported by forensic toxicologists. For example, Monforte [*11*] reported that acute narcotic deaths were characterized by blood unconjugated morphine concentrations greater than 0.25 to 0.30 μg/mL. Felby et al. [*12*] concluded that the minimum lethal blood morphine concentration in man is 0.20 μg/mL. BEAGLE found the critical values for direct morphine overdose to be 0.24 μg/mL for blood unconjugated morphine. KnowledgeMaker found a branch in the decision tree at 0.215 μg/g brain morphine, but used the percent unconjugated morphine rather than the absolute value of the unconjugated morphine as the primary decision node.

```
PERCENT UNCONJUGATED MORPHINE?
    < 21%
      TOTAL BLOOD MORPHINE?
        < 0.175 UG/ML === TIME INTERVAL IS LONG
        > 0.175 UG/ML
            TOTAL BLOOD MORPHINE?
              <0.205 UG/ML  === TIME IS MODERATE
              >0.205 UG/ML
                 UNCONJUGATED MORPHINE?
                   < 0.055 UG/ML === TIME IS LONG
                   > 0.055 UG/ML
                       BRAIN MORPHINE CONCENTRATION?
                          < 0.215 UG/GM === TIME IS MODERATE
                          >= 0.215 UG/ML === TIME IS LONG
    > 21%
        PERCENT UNCONJUGATED MORPHINE?
            < 51%
               DIRECT OVERDOSE?
                  NO === TIME IS MODERATE
                  YES
                    OTHER DRUGS PRESENT?
                       COCAINE === TIME IS MODERATE
                       ETOH    === TIME IS MODERATE
                       MULTIPLE === TIME IS LONG
                       NONE
                          BRAIN TOTAL MORPHINE?
                             < 0.165 UG/GM
                                 UNCONJUGATED MORPHINE?
                                    < 0.095 === TIME IS MODERATE
                                    >= 0.095 === TIME IS RAPID
                             > 0.165 UG/GM === TIME IS MODERATE
            >= 51% === TIME IS RAPID
```

FIG. 1—*KnowledgeMaker classification tree for time interval.*

Monforte [*11*] observed that in the presence of ethanol, three quarters of the deaths occured at free morphine concentrations less than 0.20 μg/mL rather than 0.30 μg/mL. For KnowledgeMaker, the critical level of blood total morphine for diagnosing a direct overdose was dependent upon other drugs present (none, 0.56; ethanol, 0.27; multiple drugs, 1.11; cocaine, any level).

All three programs found relationships between the presence and identity of other drugs and the time to death. BEAGLE found that the critical value for blood unconjugated morphine characterizing rapid deaths was dependent upon the presence and nature of other drugs in the case. Expert 4 ranked other drugs fifth in usefulness. The KnowledgeMaker decision tree considered other drugs when the percent unconjugated morphine was greater than 21% but less than 51% and the cause of death was a direct overdose.

All three programs found the percent unconjugated morphine in blood to be a very useful value in classifying the time between dose and death as rapid, moderate, or long. BEAGLE found rapid deaths characterized by percent unconjugated morphine in blood greater than 44 to 50%. This rule consistently had the highest chi-square score for classification of cases as to time. The exact critical value varied from different random starts and different randomly selected training case sets. Expert 4 found percent unconjugated morphine to be less useful than the absolute value of unconjugated morphine, but more useful than any other parameter. The Expert 4 Prototype value for a rapid death was 51 to 60%. KnowledgeMaker consistently started the decision tree every time with percent unconjugated morphine. The decision value varied from greater than 51% to greater than 54.5% for rapid deaths. The decision tree also had a node at 21% unconjugated morphine in the process of further classifying cases into moderate and long time intervals between last dose and death. These rules are consistent with the observations of Spiehler and Brown [*8*] and Reed [*9*] in overdose cases and with the pharmacokinetics of morphine in humans. Between 1 and 2 h after injection, the morphine glucuronide concentration exceeds the concentration of morphine in the blood [*13*]. Therefore, after 3 h or more, the ratio of the remaining unconjugated morphine to the

```
BRAIN MORPHINE?
  < 0.085 UG/GM
     LIVER MORPHINE?
        < 0.435, === NOT A DIRECT OVERDOSE
        >= 0.435
           BRAIN MORPHINE?
              < 0.065 === IS A DIRECT OVERDOSE
              >=0.065 === IS NOT A DIRECT OVERDOSE
  >= 0.085 UG/GM
     OTHER DRUGS PRESENT?
        COCAINE === IS A DIRECT OVERDOSE
        MULTIPLE
           TOTAL MORPHINE?
              < 1.115 UG/ML === IS A DIRECT OVERDOSE
              >= 1.115 UG/ML === IS NOT A DIRECT OVERDOSE
        ETHANOL
           TOTAL MORPHINE?
              < 0.27 === IS NOT A DIRECT OVERDOSE
              >= 0.27 === IS A DIRECT OVERDOSE
        NO
           TIME?
              LONG === IS A DIRECT OVERDOSE
              MODERATE
                 AGE ?
                    < 26 === IS NOT A DIRECT OVERDOSE
                    >= 26
                       PERCENT ?
                          < 29.5 === IS A DIRECT OVERDOSE
                          >= 29.5
                             FREE MORPHINE?
                                <.32
                                   AGE ?
                                      <29.5
                                         FREE MORPHINE?
                                          < 0.185 === IS NOT A DIRECT OVERDOSE
                                          >= 0.186 === IS A DIRECT OVERDOSE
                                      >= 29.5 === IS NOT A DIRECT OVERDOSE
                                >= 0.32 === IS A DIRECT OVERDOSE
              RAPID === IS A DIRECT OVERDOSE
              UNKNOWN
                TOTAL MORPHINE ?
                   < 0.56 === IS A DIRECT OVERDOSE
                   >= 0.56
                      LIVER ?
                        < 2.56
                           FREE MORPHINE ?
                              < 0.41
                                 FREE MORPHINE ?
                                    < 0.105 === IS NOT A DIRECT OVERDOSE
                                    >= 0.105 === IS A DIRECT OVERDOSE
                              >= 0.41 === IS NOT A DIRECT OVERDOSE
                        >= 2.56 === IS A DIRECT OVERDOSE
```

FIG. 2—*KnowledgeMaker classification tree for response.*

```
Target:  Time Interval

What is the value of total morphine?  2.1
What is the value of free morphine?   .86
What is the value of brain morphine?  .90
Is this a direct overdose?            yes
Were other drugs present?             no

Conclusion:  Time interval was moderate

Why?  Percent was less than 51% but greater than 21%
  and this was a direct overdose
  and no other drugs present
  and brain morphine was greater than 0.165 ug/gm
Therefore the time interval was moderate.
```

FIG. 3—*Example consultation using KnowledgeMaker decision tree derived rules.*

TABLE 10—*Validation of predictions using test cases.*

| Prediction | BEAGLE, % | Expert 4, % | KnowledgeMaker, % |
|---|---|---|---|
| Time interval | | | |
| correct | 71 | 46 | 76 |
| undetermined | 27 | 43 | 5 |
| wrong | 2 | 11 | 19 |
| Response | | | |
| correct | 64 | 52 | 65 |
| undetermined | 32 | 36 | 30 |
| wrong | 4 | 12 | 5 |

total morphine present (unconjugated plus that conjugated to the glucuronide) would be expected to be less than 0.5. The mean percent unconjugated morphine in rapid deaths has been reported as 68% [*8*] and 51% [*9*] compared with overall means for morphine related cases of 42 [*8*] and 38% [*9*] in these studies.

In diagnosing whether the death was caused by a direct morphine overdose based on the given case data, the programs, as do experienced toxicologists [*14*], considered the liver and brain morphine concentrations as useful as or more useful than blood morphine concentrations. BEAGLE and Expert 4 used blood unconjugated morphine ($>0.24$ μg/g and 0.21 to 0.30 μg/g, respectively), whereas KnowledgeMaker looked at blood total morphine. For KnowledgeMaker, the critical level of blood total morphine was dependent on other drugs present (none 0.56; ethanol 0.27; multiple drugs 1.11; cocaine, any level). All three programs found brain morphine useful in diagnosing a direct morphine overdose: BEAGLE at $>0.08$ μg/g, KnowledgeMaker at $>0.085$ μg/g, and Expert 4 in the range 0.16 to 20 μg/g. Pare et al. [*14*] reported that in all cases in which death could be attributed to a narcotic overdose, the morphine concentration exceeded 0.2 μg/g in one or more brain sections. Critical liver concentration was: BEAGLE $>0.50$ to 0.75 μg/g; KnowledgeMaker $>0.435$ μg/g and later $>2.56$ μg/g; and Expert 4 in the range 1.26 to 1.5 μg/g for the overdose prototype.

Toxicologists are often concerned about taking into account the effect of tolerance in the establishment of critical values for morphine in heroin users. Both BEAGLE and Expert 4 included the frequency of use in inferring response. If the deceased was a chronic user, then the probability of the conclusions was increased. Neither program found the critical values to be dependent on frequency of use, age, or sex. The time interval since last dose was accounted for by factoring in the percent unconjugated morphine in inferring response. KnowledgeMaker did not use frequency of use but did consider time, percent unconjugated morphine, unconjugated morphine, and, occasionally, age.

## Conclusions

The artificial intelligence programs were used to advise on time and response outcomes for cases, to calculate the probability of the estimate being true, to develop rules for interpretation of morphine involved cases, and to diagram a decision tree. The rules and decision tree were used to build an expert system for interpretation of morphine-involved deaths which could explain its interpretations. On known cases the AI programs were successful 70 to 90% of the time in classifying the cases as to response and time. No data on dose were available in this database. The success rate in individual cases was proportional to the program-estimated probability. This work demonstrates that inexpensive artificial intelligence programs commercially available for personal computers can be useful tools in interpretation in forensic toxicology.

## References

[1] Rivers, R., *Expert 4—A BioSoft Manual*, Elsevier Science Publishers, Amsterdam, the Netherlands, 1985.
[2] Forsyth, R., *Bionic Evolutionary Algorithm Generating Logical Expressions—User Guide*, Warm Boot, Ltd., Nottingham, U.K., 1986.
[3] Thompson, B. and Thompson, W., *KnowledgeMaker*, Knowledge Garden, Inc., Nassau, NY, 1987.
[4] Forsyth, R., *Expert Systems: Principles and Case Studies*, Chapman and Hall, London, 1984.
[5] Forsyth, R. and Rada, R., *Machine Learning*, Ellis Horwood, London, 1986.
[6] Thompson, B. and Thompson, W., "Finding Rules in Data," *Byte*, Vol. 11, No. 12, Nov. 1986, pp. 149-158.
[7] Spiehler, V., Spiehler, E., and Osselton, M. D., "Application of Expert Systems Analysis to Interpretation of Fatal Cases Involving Amitriptyline," *Journal of Analytical Toxicology*, Vol. 12, July/Aug. 1988, pp. 216-224.
[8] Spiehler, V. R. and Brown, R., "Unconjugated Morphine in Blood by Radioimmunoassay and Gas Chromatography/Mass Spectrometry," *Journal of Forensic Sciences*, Vol. 32, No. 4, July 1987, 1987, pp. 906-916.
[9] Reed, D., "Comparison of Spectrofluorometric and GC/MS Procedures for the Quantitation of Morphine in Blood and Brain," *Clinical Toxicology*, Vol. 14, No. 2, 1979, pp. 160-180.
[10] Garriott, J. C. and Sturner, W. O., "Morphine Concentrations and Survival Peroids in Acute Heroin Fatalities," *New England Journal of Medicine*, Vol. 289, 13 Dec. 1973, pp. 1276-1278.
[11] Monforte, J. R., "Some Observations Concerning Blood Morphine Concentrations in Narcotic Addicts," *Journal of Forensic Sciences*, Vol. 22, No. 4, Oct. 1977, pp. 718-724.
[12] Felby, S., Christensen, H., and Lund, A., "Morphine Concentrations in Blood and Organs in Cases of Fatal Poisoning," *Forensic Science*, Vol. 3, No. 1, Feb. 1974, pp. 77-81.
[13] Bruck, S. F. and Delle, M., "Morphine Metabolism in Man," *Clinical Pharmacology and Therapeutics*, Vol. 16, 1974, pp. 51-57.
[14] Pare, E. M., Monforte, J. R., and Thibert, R. J., "Morphine Concentrations in Brain Tissue from Heroin-Associated Deaths," *Journal of Analytical Toxicology*, Vol. 8, No. 5, 1984, pp. 213-216.

Address requests for reprints or additional information to
Vina R. Spiehler
Diagnostic Products Corp.
5700 W. 96th St.
Los Angeles, CA 90045