Assessment of the current state-of-the-art of drug analysis is a challenging assignment, and is likely to be of short-term validity because of the rapidly changing situation. Although no comprehensive prior assessment focused on the analysis aspects of drugs-and-driving was located, several reports on closely related topics are pertinent as summaries of applicable technological developments in recent years (1-6). A massive body of applicable literature has also appeared in recent monographs, annual review volumes, and other periodicals; space limitations prevent their consideration here.

The practice of drug analysis has undergone great changes in the last decade, culminating in the present analytical capability to search for, identify, and quantitate all of the commonly used drugs, and many of their metabolites, in suitably small specimens of biological fluids. The changes of greatest impact on the problems of drugs and traffic safety, apart from the increased interpretative information, have been developments in the "monitoring" of concentrations of therapeutic drugs, advances in emergency analytical toxicology, and the development of immunochemical methods of analysis for many new drug analytes.

Special constraints apply to drug analysis in connection with traffic safety, as summarized in Table 1.
TABLE 1. Special Factors in Drugs/Driving Toxicology

- Limited Access to Subject
- Limited Specimen Quantity
- Need to Fix Time vs. Effect
- Lack of Information About Tolerance/Habituation/Dependency
- Probability of Court Challenge

For these reasons, it is useful to be aware of the drug analyte universe of potential interest as well as of recently obtained results in drugs/driving surveys. In the United States, the former is well reflected in an annual prescription survey (7) based on the National Prescription Audit (conducted annually by IMS America, Ltd., Ambler, PA); comparable data no doubt exist in other countries. Published data documenting the results of drugs/driving analyses in living drivers are scarce (8-10); a recent example for the State of Virginia, USA (11) is given in Table 2.

TABLE 2. Positive Drugs/Driving Results in Order of Frequency: Virginia 1978#

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diazepam</td>
</tr>
<tr>
<td>2</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>3</td>
<td>Methaqualone</td>
</tr>
<tr>
<td>4</td>
<td>Diphenylhydantoin</td>
</tr>
<tr>
<td>5</td>
<td>Amobarbital</td>
</tr>
<tr>
<td>6</td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>7</td>
<td>Amphetamine</td>
</tr>
</tbody>
</table>

#Data Base: 788 Blood Specimens of Drivers with BACs of 0-100 mg/dL; 16.5% of the Analysis Results Were Positive for Drugs.
The currently leading toxicological analysis methods of greatest applicability to drugs/driving are listed in Table 3.

**TABLE 3. Leading Toxicological Analysis Methods Applicable to Drugs/Driving**

- Chromatographies
  - GLC; N/P Detector
  - HPLC; Reversed Phase Liquid Chromatography
  - Thin-Layer Chromatography
- Gas Chromatography/Mass Spectrometry
- Immunochemical Techniques
  - Hemagglutination Inhibition
  - Homogeneous Enzyme Immunoassay
  - Radioimmunoassay
- Spectrofluorometry
- UV and IR Spectrophotometry

Of the many advances in drug analysis in recent years, those most relevant to problems of drugs-and-driving are highlighted in Table 4.

**TABLE 4. Highlights of Recent Relevant Advances in Drug Analysis**

- Developments in Therapeutic Drug Monitoring
- Proliferation of Immunochemical Assays
- Manageable Mass Spectrometry Instrumentation
- Expansion of Non-invasive Sampling: Breath, Saliva, etc.
- Ready Availability of Many Drug and Metabolite Standards
- Refinements in Systematic Analysis Schemes
- Automation of Some Analysis Methods
- Proficiency Testing in Toxicological Analysis
- Expanded Specialized Toxicology Literature
Among the methodological advances, those in immunochemical analysis have been the most dramatic. Some immunoanalysis variants, e.g., homogeneous enzyme immunoassay, combine great sensitivity and adequate selectivity or specificity with rapidity and simplicity of analysis. Tables 5 and 6 contrast the steps of a classical "wet" toxicological analysis with those of a typical homogeneous enzyme immunoassay. The total time required for the latter is typically 1-2 minutes.

TABLE 5. Schema of Classical Toxicological Analysis
- Sample Measurement
- Sample Pretreatment (Hydrolysis, etc.)
- Extraction(s)
- Reaction (Derivatization, Color Formation, etc.)
- Instrumental Measurement(s)
- Result Calculation

TABLE 6. Schema of Typical Homogeneous Enzyme Immunoassay
- Sample Measurement and Dilution
- Reagent(s) Addition
- Momentary Incubation \{ May be Automated \}
- Photometric Kinetic Measurement
- Result Calculation

The net result of recent developments in analytical toxicology has been to produce the current situation summarized in Table 7.

TABLE 7. Resultant Drug Analysis Enhancements
- Increased Sensitivity of Analysis to $10^{-12}$ g or less
- Smaller Specimen Requirements
- Improved Selectivity and Specificity
- Simplification of Techniques
- Increased Speed of Analysis & Decreased Turn-Around Time
- Reduction in Analysis Costs
Some of the most significant advances have occurred in the past 5 years in the analysis of cannabinoids in biological samples. Particularly useful are the written proceedings of symposia on cannabinoids assay held in 1976, 1977, 1978, and 1980 (12-15). These include details of the detection and quantitation of cannabinoids in whole blood, plasma, urine, and other bio-samples by radioimmunoassay, homogeneous enzyme immunoassay, gas chromatography, mass spectrometry, high-pressure liquid chromatography, and combinations of these techniques. The clustered evolution of these methods for cannabinoids assay in biological systems is illustrated by the fact that details of such analyses were omitted entirely from leading analytical toxicology texts published as recently as 1974-76 (16-18). Reports of medium and large-scale applications of these methods, especially the immunochemical assays, to the analysis of cannabinoids in traffic fatalities and in living drivers have begun to appear (19-21).

It seems certain that significant advances will continue in this now rapidly changing field of drugs-and-driving. The techniques which, in the author's opinion, are of greatest immediate-future promise and relevance to the drugs-and-driving field are listed in Table 8.

<table>
<thead>
<tr>
<th>TABLE 8. Promising Techniques for the Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atmospheric Pressure Ionization GC of Breath</td>
</tr>
<tr>
<td>• Expanded Immunochemical Analysis (especially Immunofluorescence)</td>
</tr>
<tr>
<td>• Individual Cell Analysis by Fluorescence Techniques</td>
</tr>
<tr>
<td>• Parent Drug/Metabolite(s) Ratio Measurement</td>
</tr>
</tbody>
</table>

The techniques in Table 8 and other applicable methods hold special promise for extending the application, to drugs-and-driving problems, of non-invasive methods of analysis. Ample demonstration of the potential of such schemes exists already; but breath, in particular, is likely to be a preferred specimen reflecting the circulating body burden of drugs when suitably sensitive analysis methods are
available. Intermediate collection schemes for end-expiratory breath, over time, seem feasible for this application, analogously to the currently practiced time-monitoring of atmospheric components for environmental and occupational safety purposes. Enhanced reliance upon saliva as a noninvasive specimen of interest is also probable.

A directly related concern is the interpretation of results of the many analyses for drugs now possible, often at very low concentrations and long after initial drug intake. Some of the issues in the interpretation of results of drug analyses, especially with respect to drugs-and-driving are given in Table 9.

**TABLE 9. Some Interpretation Issues in Drugs-and-Driving**

- Active Drug vs. Active/Inactive Metabolite(s)
- Concentration vs. Effect Curves
- Habituation and Tolerance Phenomena
- Dose/Time/Concentration Interrelations
- Pharmacodynamics and Pharmacokinetics Aspects

Until a specialized body of information is developed on concentrations of drugs and their metabolites in biological specimens in relation to driving fitness, reliance must be continued upon the relevant literature in pharmacology, clinical toxicology, and therapeutic drug monitoring. Computerized information services (e.g., MEDLINE, TOXLINE, and the Toxicology Data Bank/TDB of the U. S. National Library of Medicine) make much of this information readily accessible.

Advances in drug analysis have not been without accompanying problems. Several of the newer techniques lend themselves to "kit" form and invite use by the tyro and those without adequate analytical toxicology background, expertise, and skills. The application of these newer, very promising methods to this demanding special forensic use will require close supervision and control by qualified professionals. The present state of practice in labora-
tories routinely engaged in (mostly clinical) toxicological analysis can be appreciated from the data in Tables 10 and 11, which depict recent open proficiency testing results in the United States and hence can only reflect best analytical capability in the participating laboratories there. There is clearly much room for improvement.

**TABLE 10. Center for Disease Control Proficiency Testing Results for "Drug Monitoring," 1979**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Laboratories</th>
<th>Target Drug concentration, µg/ml</th>
<th>Mean Result</th>
<th>C.V.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>53</td>
<td>0.8</td>
<td>0.5</td>
<td>47</td>
</tr>
<tr>
<td>Diazepam</td>
<td>90</td>
<td>2.5</td>
<td>2.6</td>
<td>56</td>
</tr>
<tr>
<td>Glutethimide</td>
<td>73</td>
<td>5.0</td>
<td>5.4</td>
<td>53</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>289</td>
<td>12.0</td>
<td>9.3</td>
<td>14</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>284</td>
<td>18.0</td>
<td>19.6</td>
<td>19</td>
</tr>
<tr>
<td>Salicylate</td>
<td>263</td>
<td>150</td>
<td>146.2</td>
<td>26</td>
</tr>
</tbody>
</table>

**TABLE 11. College of American Pathologists Toxicology Survey Results, 1979**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Laboratories</th>
<th>Target Drug concentration, µg/ml</th>
<th>Mean Result</th>
<th>C.V.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>94</td>
<td>5</td>
<td>4.4</td>
<td>59</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>101</td>
<td>16</td>
<td>14.9</td>
<td>38</td>
</tr>
<tr>
<td>Methaqualone</td>
<td>127</td>
<td>8</td>
<td>8.0</td>
<td>30</td>
</tr>
<tr>
<td>Norpropoxyphene</td>
<td>27</td>
<td>1.6</td>
<td>1.5</td>
<td>53</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>298</td>
<td>25</td>
<td>23.9</td>
<td>11</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>66</td>
<td>0.8</td>
<td>1.2</td>
<td>80</td>
</tr>
</tbody>
</table>

Contributions to these developments, and these problems, have been of international character. Close cooperation between workers around the world, and better communication among them, is a necessity for effective application of future advances everywhere.
REFERENCES


11. Valentour, J. C., "Drugs and Driving in Virginia," presented at Society of Forensic Toxicologists Annual Meeting, Williams-


