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FINAL REPORT
ON
REVIEW OF THE SCIENTIFIC LITERATURE
AND PREPARATION OF AN ANNOTATED BIBLIOGRAPHY
ON
EFFECTS OF CIGARETTE SMOKING AND NICOTINE
ON HUMAN PERFORMANCE

Volume 1

Submitted by:

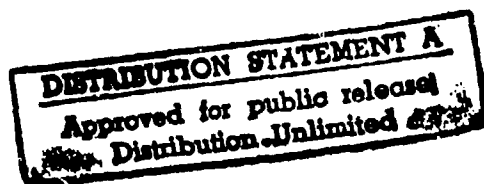
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Per Dr. James Vogel, US Army Res. Institute of Environmental Medicine

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I. INTRODUCTION

→ U.S. Army combat personnel typically consist of foot soldiers and mechanized infantry assigned to vehicles such as tanks, armored personnel carriers, and weapons carriers. Such personnel are exclusively male and predominately belong to the youngest age group of 18 to 30 years. Factors that encourage smoking in the military include the example of commanding personnel who smoke, the practice of giving work breaks for smoking, and military (Post Exchange) price discounts on cigarettes.

Various surveys have been conducted on the prevalence of cigarette smoking within military organizations. Typically, between 60% and 80% of men associated with ground forces are smokers who increase their consumption of tobacco during their military duty.

→ A typical practical result of the high incidence of smoking is the difference (between smokers and nonsmokers) of 130 days of inpatient care per 1,000 men per year in annual admission rates for acute respiratory diseases.

Acute effects of tobacco noticeable in Army activities of individuals range from gross decrements in running endurance to subtle effects on cognitive abilities, tracking task performance, reaction time, and other psychomotor functions. Habitual smoking

→ men

could

is associated with decreased hand steadiness and impaired short-term memory.

Acute physiological responses to nicotine, a central nervous system stimulant, include increases in heart rate, blood pressure, cardiac output, stroke volume, myocardial contractile force, coronary blood flow, myocardial oxygen consumption, arrhythmia induction, and electrocardiographic (ECG) changes.

Correspondingly, cessation of smoking produces decreases in heart rate, blood pressure, excretion of epinephrine and norepinephrine, blood glucose levels at 30 sec after eating, and oxygen consumption; and increases in body weight, pulmonary compliance, skin temperature, and hand steadiness. General withdrawal symptoms after nicotine addiction may include nausea, headache, constipation/diarrhea, increased appetite, fatigue/insomnia, inability to concentrate and irritability. Craving for cigarettes by former smokers has been noted up to nine years following cessation of smoking.

Obviously, such physiological effects and withdrawal symptoms are capable of producing decrements in psychomotor test scores as well as actual field performance of the soldier. Moreover, when attired in full battle gear designed for modern chemical warfare, the soldier is unable to smoke.

The critical parameters determining the effects of habitual smoking include the number of cigarettes smoked per day, nicotine content per cigarette, puff rate, extent of inhaling, and physical condition of the smoker.

Cigarette smoke contains a number of chemical compounds that are pharmacologically active. Nicotine is the primary active agent that functions to both establish and reinforce the smoking habit. Although the pulmonary circulation is affected first, nicotine rapidly circulates to the peripheral respiratory chemoreceptors (aortic and carotid bodies), strategically located in the systemic circulation, that stimulate pontomedullary respiration and cardiovascular centers reflexly.

In addition to reflex stimulation of the central nervous system (CNS), nicotine crosses the blood-brain barrier. In the brain, nicotine acts upon specific cholinergic (nicotinic) receptors, mimicking the activity of the neurotransmitter acetylcholine. Central serotonin receptors (and others as yet unidentified) also play a probable role in mediating the central effects of nicotine. Nicotinic stimulation of the chemoreceptor trigger zone in the medulla oblongata results in nausea and vomiting when large doses of nicotine are administered.

Secretion of endocrine hormones from the hypothalamus and pituitary gland result from nicotinic stimulation. Central effects on learning, memory and vision also have been reported.

Peripherally, nicotinic effects associated with autonomic ganglia increase motility and secretions of the gastrointestinal tract, resulting in diarrhea and electrolyte/water imbalance.

Catecholamine (epinephrine and norepinephrine) secretion by the adrenomedullary and sympathetic neuronal chromaffin tissues produces diffuse physiological changes that contribute to the state of arousal upon which a smoking habit may depend. The radial muscle of the iris in the eye contracts to produce the mydriasis which is characteristic of this arousal. The electroencephalogram (EEG) shows evidence of increased high-frequency and decreased low-frequency waveforms. The cardiopulmonary system increases the cardiac output and oxygen delivery to some tissues (e.g., CNS) by tachycardia and bronchodilation. Systemic hypertension increases tissue perfusion pressure, but also increases flow resistance by vasoconstriction to some regional vascular beds (e.g., cutaneous) that may actually decrease blood flow and oxygen delivery locally.

The aforementioned effects are generally considered acute. As the duration of nicotinic stimulation increases, the pharmacological effects decrease. Such adaptation of nicotine

receptors to stimulation produces tachyphylaxis wherein fewer pharmacological effects of nicotine are experienced by the habituated smoker than a novice. The acute response of nicotine withdrawal may involve either normalization or hypersensitivity of previously desensitized (down-regulated) nicotinic receptors.

The nicotine withdrawal syndrome involves normalization of heart rate and systemic blood pressure that increases delivery of oxygen to previously underperfused tissues. Physiological signs of arousal (e.g., mydriasis and high-frequency EEG) decrease. Indeed, increases in sleeplike EEG activity have been observed. Drowsiness, fatigue, and sleep disorders are among the most common arousal symptoms associated with nicotine withdrawal. Constipation frequently accompanies withdrawal.

Nicotine stimulates adipokinesis, increasing the concentration of nonesterified (free) fatty acids and lipoproteins of low and very low density (LDL, VLDL) in the systemic circulation. Central effects on hypothalamic feeding control centers decrease appetite (anorexia). The complex interaction of these effects usually results in desirable decreases of body weight and adipose tissue. Therefore, it is not surprising that increased appetite, weight gain and increased fat storage accompany nicotine withdrawal.

Performance of smokers on complex tasks, especially those requiring good sensorimotor coordination and visual tracking (e.g., driving and flying simulation) and vigilance (e.g., psychomotor tasks) is reported to be impaired during nicotine withdrawal. Affective (mood) disorders including increased anxiety, irritability and aggression are commonly associated with withdrawal.

Because arousal, mood, learning, memory, psychomotor and visual performance, nutrient intake, body fat composition, tissue oxygen delivery, blood pressure and heart rate are all important determinants of overall human performance, it is predictable that nicotinic stimulation and withdrawal affect soldier readiness.

Additionally, environmental stress, interaction with other drugs, and personality factors may play significant roles in determining the ultimate effects of nicotinic stimulation and withdrawal on human performance and soldier readiness.

Generally, the scientific literature on nicotinic stimulation and withdrawal has been published for a specialized readership and in most cases, does not directly address military applications. Therefore, Associate Consultants Inc. has developed an informative scientific database, the data elements of which are easily accessible and encompass the complex acute effects of nicotinic stimulation and withdrawal on human performance and soldier readiness.

The major objectives of the work were as follows:

1. To develop a scientific database on the subject of effects of smoking and nicotine on human performance;
2. To extract data from the database which are relevant to the performance of foot soldiers and combat system crews;
3. To provide USAMRDC with a report and annotated bibliography summarizing previous research, identifying data gaps, emphasizing significant aspects, and indicating possible areas of future research.

The database is a compilation of research reports covering all aspects of physiological and psychological effects of nicotinic stimulation and nicotine withdrawal. Research reports and surveys were restricted to those concerning human subjects and their reactions to smoking or to nicotine intake by any route of administration. Copies of source documents were retrieved using routine procedures at technical libraries starting from bibliographic citation listings.

The reports were analyzed for results and data concerning the smoking effects variables. Data found to be suitable were stored in a computerized database according to physiological and psychological variables of interest. The machine-readable data elements contain age ranges 18-30 years, 31-40 years, 41-50 years, 51-60 years; male and female sexes; ranges of nicotine dosage corresponding to low, medium, and high; and routes of administration. Each computer record contains document accession numbers,

bibliographic information, index terms, quantitative and descriptive data keyed to index terms, and a short abstract.

The final report was prepared by retrieving index terms keyed to quantitative and descriptive data. The annotated bibliography was prepared by retrieving bibliographic information and the abstract from the computerized database. The computerized database is on machine-readable magnetic tape compatible with that of the USAMRDC VAX system.

The final report focuses on the single substance, nicotine, a component of smoke; data on other substances found in smoke such as tars (which are carcinogenic) and carbon monoxide (which produces polycythemia and increases hemoglobin on the blood), were not analyzed per se, except for any reports on their interaction with nicotine. Effects of rapid smoking, used to create an aversive reaction in withdrawal therapy, were not considered.

The acute effects of nicotine stimulation and withdrawal on physiological and psychological functions, responses, and performance are discussed relevant to their potential effects on soldier readiness and performance.

II. METHODS

- A. Search Strategy**
- B. Screening of Citations**
- C. Retrieval**
- D. Data Extraction**
- E. Final Report**
- F. Annotated Bibliography**
- G. Computerized Database**

II. METHODS

ACI completed the following tasks to establish a database and prepare the final report:

1. Searching for relevant (hit) documents;
2. Retrieving hit documents;
3. Searching, accession numbering, and logging in retrieved documents;
4. Extracting data;
5. Computerizing data;
6. Analyzing data;
7. Writing final report including text and annotated bibliography

The search for hit documents was based on constructing broad and narrow search terms defining the boundaries of the subject matter. In the present case, suitable broad search terms included "physiological effects," "psychomotor testing," "withdrawal symptoms," etc. Whenever these search terms occurred in the title or list of keywords of a research report, the citation was flagged as a possible hit, and the source document was retrieved. Searching was also conducted manually by scanning bibliographies and electronically by use of existing computerized databases.

The retrieval of hit documents involved ordering copies of reports from private or government libraries that contained information relevant to the effect of smoking and/or nicotine and/or nicotine withdrawal on human performance. After the copies were retrieved, they were marked with accession numbers and a suitable description entered into a logbook. A current record of all document transactions was maintained and available at all times for checking the progress of the work, avoiding loss of documents, and avoiding duplication of effort.

The documents were then screened to select those that contained relevant research data. At this point, the relevant variables were entered into a matching-readable database for intercomparison and evaluation. As the documents were processed, a form attached to the document cover was completed in order to historically record the processing.

Once the database was computerized, the data were analyzed. Brief summaries of results and evaluations of experimental tests, their ambient and environmental conditions, and statistical methods were written. Contradictions, inconsistencies, and gaps in the data were examined as possible indicators of need for areas of future research.

1. Search Strategy

Computerized literature searches covered a large portion of the outstanding database holdings in a few selected operations. High-speed searching was performed by matching search terms against key words or index terms drawn from article abstracts. The following computerized databases, consisting of scientific research reports published since 1969, contained holdings within the subject areas of human smoking:

- Agline
- American Statistical Index
- Biosis Previews
- Chemical Industry Notes
- Comprehensive Dissertation Index
- Dialog
- Health Planning and Admin.
- INPADOC
- Int. Pharmaceutical Abs.
- Life Sciences Collections
- Medline
- NTIS
- PAIS
- Pharm. News Index
- Pollution Abs.
- Psychinfo
- Public Health Service Office on Smoking and Health Database
- Scisearch
- Excerpta Medica
- Federal Index
- Federal Register Abs.
- SSIE

A total of 337 relevant source documents were identified by computerized searching of the aforementioned databases. Approximately 58% of the documents identified were disqualified for inclusion in the nicotine database because they were

inappropriate for scientific data extraction and analysis. Many were secondary sources, review articles, and/or nonscientific sources.

To identify additional references published before 1969 relevant to the database, lists of bibliographic citations were developed by manually searching reference books, research articles, and special bibliographies. As works were acquired from these lists, their included bibliographies were also scanned. This process produced 627 additional bibliographic citations. Library reference works used for the manual search included the following:

- Abs. Chem.-Biol. Activities of Chem. Substances
- Analytical Abstracts
- Biological Abstracts
- British Medical Abstracts
- British Medicine
- Bulgarian Med. Bull. and Abs.
- Chemical Abstracts
- Drug Literature Index
- Excerpta Medica
- Govt. Reports Announc. and Index
- Index Medicus
- Intnl. Abs. Biol. Sci.
- Monthly Catalog, U.S.G. Publications
- News Russ. Med. Biochem.
- Psychological Abstracts
- Ref. Zh. Biol. Khim.
- Russ. Chem. Revs.
- Russ. Pharm. and Toxicol.
- Sci. Abs. China: Chem. and Chem. Tech.
- Science Citation Index
- Technical Abstracts Bulletin

Search terms were used to identify relevant source documents that report research data on human subjects wherein carcinogenesis of nicotine and/or smoking was not the primary research focus. The primary research focus considered to be relevant to the database included nicotine administration by any route (including cigarettes and other tobacco products) and/or nicotine withdrawal. A major interest was the acute effects of nicotinic stimulation and nicotine withdrawal.

2. Screening of Citations

Bibliographic citations and abstracts of source documents were reviewed by the principal investigator to determine the suitability of the source document for inclusion in the database. Suitable documents were identified as hits. Criteria for designating a hit document were as follows:

- * Source document emphasized primary research on the effects of nicotine and/or nicotine withdrawal in humans;
- * The primary focus of research is not carcinogenesis; and
- * The document is not a textbook, review article, or secondary source.

Bibliographies from textbooks, review articles, and secondary sources were searched to identify relevant research documents for screening but were not used as primary source documents for purposes of data extraction and analysis.

3. Retrieval

A total of 964 documents were identified as possible hits and photocopied from journal or book. Upon review, 441 of these were designated for inclusion in the database; 126 were identified by computer search and 315 by manual search.

4. Data Extraction

Upon retrieval, each hit document was reviewed by the principal investigator and categorized according to the specific research method or test employed.

Data for each of the following categories of data were entered into the machine-readable database:

A. Effects of nicotine withdrawal

A.1. Withdrawal syndrome

A.1.1. Symptoms

A.1.2. Craving for nicotine

A.1.3. Onset period

A.2. Appetite and body weight

A.3. Psychomotor performance

B. Psychological effects of nicotine

B.1. Stimulation-depression

B.2. Alertness-fatigue

B.3. Anxiety-tranquility, including Nesbitt's Paradox

- B.4. Irritability-tolerance
- B.5. Rigidity-flexibility
- B.6. Aggression-passivity
- B.7. Personality (combinations of factors)

C. Effects of nicotine on the central nervous system

- C.1. Effects on responses to visual stimuli
 - C.1.1 Reaction times
 - C.1.2. Thresholds
 - C.1.2.1. Flicker fusion threshold
 - C.1.3. EEG characteristics
 - C.1.4. Vigilance
 - C.1.5. Tracking tasks
 - C.1.6. Masking effects
 - C.1.7. Cortical potentials
 - C.1.8. Peripheral vision effects
 - C.1.9. Dark adaptation

C.2. Effects on responses to auditory stimuli

- C.2.1. Reaction times
- C.2.2 Thresholds
- C.2.3. EEG characteristics
- C.2.4. Vigilance
- C.2.5. Vestibular nystagmus
- C.2.6. Masking effects
- C.2.7. Cortical potentials

C.3. Recall and learning tasks

C.4. Attention and perception tasks

C.5. Reflex responses

C.6. Effects on other sensations or sensitivity

- C.6.1. Olfaction
- C.6.2. Taste
- C.6.3. Pain
- C.6.4. Pressure and touch

D. Effects on cardiovascular and pulmonary systems

- D.1. Parameters of the heart and circulation
 - D.1.1. Heart rate and blood pressure
 - D.1.2. Cardiac output
 - D.1.3. Stroke volume
 - D.1.4. Cardiac conduction (ECG) characteristics

- D.2.1. Vasoconstriction-vasodilation
- D.2.2. Size of blood vessels
- D.2.3. Regional blood flow
 - D.2.3.1. Blood flow in the finger
 - D.2.3.2. Blood flow in the hand
 - D.2.3.3. Blood flow in the arm
 - D.2.3.4. Blood flow in the gastric mucosa
- D.2.4. Vascular contractility

- D.3.1. Respiratory rate
- D.3.2. Minute ventilation
- D.3.3. Bronchoconstriction
- D.3.4. Airways resistance
- D.3.5. Oxygen consumption and aerobic capacity
- D.3.6. Diffusion capacity

- E.1. Muscle tone, strength, and tension
- E.2. Physical endurance
- E.3. Tremor and Steadiness

- F.1. Effects on blood chemistry
 - F.1.1. Blood oxygenation
 - F.1.2. Secretion of hormones
 - F.1.2.1. Vasopressin
 - F.1.2.2. Catecholamines
 - F.1.2.3. Thyroxin
 - F.1.2.4. Insulin
 - F.1.2.5. Growth hormone (Gh)
 - F.1.2.6. Cortisol
 - F.1.2.7. Thyroid stimulating hormone (TSH)
 - F.1.2.8. Follicle stimulating hormone (FSH)
 - F.1.2.9. Luteinizing hormone (LH)
 - F.1.2.10. Testosterone
 - F.1.2.11. Prolactin
 - F.1.3. Blood glucose
 - F.1.4. Fibrinolysis, coagulation, and wound healing

- F.1.5. Leukocyte count
- F.1.6. Blood lipids, including cholesterol
- F.1.7. Carboxyhemoglobin and carbon monoxide

F.2. Gastrointestinal effects

- F.2.1. Acid secretion
- F.2.2. Enzyme secretion
- F.2.3. Ulcer production
- F.2.4. Motility

F.3. Kidney function and diuresis

F.4. Total metabolic rate

F.5. Effects on oral cavity

- F.5.1. Saliva
- F.5.2. Gums
- F.5.3. Teeth

F.6. Effects on skin

- F.6.1. Conductance and galvanic response
- F.6.2. Temperature

G. Nicotine-drug interactions

- G.1. Nicotine-alcohol interaction
- G.2. Nicotine-caffeine interaction

H. Nonacute studies

- H.1. Respiratory function
- H.2. Cardiovascular function
- H.3. Psychomotor performance, mood and personality functions

follows:

The fields of the database are characterized as

1. All fields of the computer (unit) record except the short abstract are searchable.
2. The abstract (ABS) field constitutes the bibliographic citation as the first sentence annotation for the annotated bibliography and includes a short statement of methods.

experimental design followed by detailed results relevant to effects of nicotine on human performance; a printout of the ABS field produces an annotated bibliography of the database.

3. The accession no. (ACC) field includes the chronological number that identified each "hit" document for computer searching.
4. The locator field includes the number that identifies each "hit" document for ACI monitoring of document processing.
5. The author (AU) field includes the first six authors of each "hit" document in the following order: last name, first initial, middle initial without punctuation (e.g., Vogel JA).
6. The title (TI) field includes the full title of the journal article or book chapter ascribed to the hit document.
7. The source title (SO) field includes the full (nonabbreviated) title of the journal or book in which the "hit" document was found.
8. The volume (VOL) field includes the chronological number assigned to the source collection in which the "hit" document is found.
9. The start page (SPAGE) field includes the first page of the article or chapter ascribed to the "hit" document within the source collection.
10. The last page (LPAGE) field includes the last page of the article or chapter ascribed to the "hit" document within the source collection.
11. The publication year (PUBYR) field includes the year in which the "hit" document was published.
12. The issue (ISSUE) field includes the issue number or date that is subordinate to the volume number within a journal source collection and may exist independently as a date when the source collection is a report.

13. The publisher field includes the publisher of a book or report necessary for bibliographic citation but blank when the hit document is found within a journal source collection.
14. The language (LANG) field includes the language in which the original document is written.
15. The statistics (STAT) field includes a list of codes for the different types of statistics that are presented in support of the statistical rating.
16. The statistical rating (STATRAT) field includes a number 1-5 that reflects the complexity and sophistication of statistical analysis (Appendix B).
17. The document type (DOCTYPE) field includes a letter code indicating whether the source is a book, journal, or report.
18. The document condition (COND) field includes a letter code reflecting the readability of the archival copy of the source document (pp. 11-13).
19. The subject category (CAT) field includes a code indicating the specificity of the research question or topic addressed by the source document.
20. The performance variable (PVI-PV10) field includes descriptive scientific terminology for each variable that involves human subjects interacting with the external environment (performance definition); psychological and physiologically significant variables measured that do not reflect performance but indicate changes in the "internal milieu" (internal environment) are indexed separately in the index terms field.
21. The subject number (SUBNO) field indicates the total number of subjects studied.
22. The male number (MALENO) includes the total number of male subjects studied.

23. The female number (FEMALENO) field includes the total number of female subjects studied.
24. The age field includes codes reflecting the age ranges of the subjects studied; 1 = 18-30; 2 = 31-40; 3 = 41-50; 4 = 51-60.
25. The subject type (SUBTYPE) field indicates whether the subjects are light, medium, heavy, or nonsmokers (see performance coding record instructions).
26. The abstinence period (ABSPER) field indicates the interval in hours that smoking subjects abstained from smoking before experimentation.
27. The disease category (DISCAT) field indicates whether the subjects are normal or patients with diagnosed diseases.
28. The SPECIES field indicates whether the subjects are human or lower animal species; if nonhuman, designated species are given.
29. The DRUG field includes the names and numbers of drugs, doses, routes of administration, form, and level of exposure studied.
30. The index terms (IT1-IT50) field includes descriptive scientific terminology for each nonperformance, physiological variable studied and each topic, research question, or specialized jargon that scientists, archivists, or administrative personnel might find useful for identifying the source document.

Coding instructions for the database appear in the
APPENDIX.

Each computer record consists of data relevant to a single source document. Index terms are designated by the experimental methods used and scientific variables studied.

5. Final Report

An analysis of the data extracted is reported in writing under the title, "Effects of Cigarette Smoking and Nicotine on Human Performance" and constitutes the Results Section of the present report.

Research findings in each of five major areas of interest to USAMRDC are reviewed scientifically and properly referenced by author and year of publication with parentheses in the text.

6. Annotated Bibliography

All bibliographic references cited in the final report are abstracted in an annotated record.

The annotated record gives the bibliographic citation first, according to published guidelines (Appendix A).

The abstract text includes the following:

- A. A brief introductory description of the experimental design and methods with special emphasis on the dependent physiological, psychological, and performance variables measured.
- B. A series of clear, concise statements indicating the effects of nicotine or other independent variables on each dependent variable with statistical significance.

III. RESULTS

- A. Central Nervous System**
- B. Cardiopulmonary and Musculoskeletal Effects**
- C. Metabolic Effects**
- D. Withdrawal Effects**
- E. Summary and Effects on Soldier Readiness**

III. RESULTS

Data have been extracted from the computerized database to reflect the breadth of research that has been performed on human subjects to answer the research question, "What are the effects of cigarette smoking and nicotine on human performance?"

The relevant research areas of the database have been highlighted and organized into the following major topical subsections:

- A. Central Nervous System and Psychological Effects
- B. Cardiopulmonary and Musculoskeletal Effects
- C. Metabolic Effects
- D. Withdrawal Effects
- E. Summary and Effects on Soldier Readiness

A. CENTRAL NERVOUS SYSTEM AND PSYCHOLOGICAL EFFECTS

A. Central Nervous System and Psychological Effects

1. Arousal, Alertness, and Sedation
2. Attention and Vigilance Task Performance
3. Mood
4. Learning and Memory
5. Vision
6. Taste
7. Pain
8. Motor Functions

1. AROUSAL, ALERTNESS, AND SEDATION

Kumar et al. (1977) failed to detect a clear effect of smoking on EEG, although there was a tendency for beta activity to be systematically increased both during and after an intravenous dose of nicotine. Analyses of self-ratings made for both mood and anxiety failed to show any consistent effects after either doses of inhaled smoke or intravenous nicotine. However, there was a trend in the infusion study for subjects to rate themselves more drowsy and relaxed as the experiment progressed; paradoxically they also reported feeling more energetic. Herning et al. (1983) studied the effect of smoking on EEG changes during tobacco withdrawal (10-17 hours) in 18 heavy smokers. Theta and alpha power increased significantly during withdrawal, and were decreased by nicotine cigarette smoking but not by placebo smoking. The peak alpha frequency was lower during withdrawal. The decreases were not always significant. Increased theta power during withdrawal may be a correlate of drowsiness and may resemble a mild version of a stimulant withdrawal syndrome. Although changes in alpha have been attributed to differences in arousal or cognitive processing of smokers, changes in alpha power and peak frequency may be simply secondary to the theta power changes. Philips (1971) found decreased power of the predominant alpha frequency consistent with an alerting or arousal effect in 6 smokers following 2 hours abstention and the smoking of one cigarette.

Brown (1973) reported differences in "rhythmic beta," alpha abundance, and variability of alpha frequency between very heavy smokers and other smoker and nonsmoker groups, but subjects did not smoke during EEG studies making it difficult to suggest an acute effect of nicotine. Similar studies have been used to suggest differences in cortical arousal and personality that may contribute to smoking behavior. Very heavy smokers had half the abundance of alpha per unit time and rhythmic beta amplitude nearly twice that of smokers and former smokers.

Kanekar and Dolke (1970) studied the relationship of smoking to extroversion and neuroticism measured by the Eysenck Personality Inventory in 4 groups of male Indian smokers and nonsmokers. There was a positive relationship between amount of smoking and degree of extroversion. The relationship between the amount of smoking and degree of neuroticism was negative. These results are consistent with Eysenck's theory of personality; that the amount of smoking is directly related to extroversion.

DeGood and Valle (1978) found that users were significantly different from nonusers of nicotine in their ability to control alpha EEG activity. Users of nicotine and users of both nicotine and alcohol were not significantly different. Results were consistent with the hypothesis that nonusers of nicotine are better able to regulate their EEG in a biofeedback training

situation than are users. Because of the 4 hour abstinence prior to each training session, it was likely that nonacute (i.e., longer lasting) effects of chronic nicotine use were observed.

Hall et al. (1973) found that decreased amplitude of visual evoked potential occurred at both 12 and 36 hours during abstinence in 8 out of 9 smokers. The first cigarette following abstinence produced increased amplitude of visual evoked potential, an effect consistent with increased cortical arousal. Evoked potential decreased with withdrawal and increased after resumption of smoking, consistent with the hypothesis that tobacco increased arousal. In addition, there was a differential effect favoring responsiveness to weak over strong stimuli. Amplitude changes occurred between 100 and 125 milliseconds after the onset of the stimulus, suggesting that smoking selectively enhanced the perception of weak stimuli. Behavior, mood rating scales, and kinesthetic figural after-effects showed no change with either abstinence or resumption of smoking. Friedman et al. (1974) reported decreased amplitude of visual evoked potentials during 12 hours abstinence that increased after smoking, an effect also consistent with increased cortical arousal in smokers. However, auditory evoked potentials showed effects opposite to visual evoked potentials; increased amplitude during abstinence; and decreased amplitude after smoking with even greater decreases after sham smoking. These findings are

consistent with the hypothesis that nicotine increases some determinants of cortical arousal while decreasing others and that smokers report increased mental alertness while simultaneously experiencing a tranquilizing effect (Nesbitt's Paradox).

The Nesbitt Paradox exists because nicotine produces simultaneous increases in physiological arousal and decreases in emotional experience or behavior. The effects of nicotine on physiological arousal and emotion are not homogeneous, but represent the resultant of different processes. Therefore, indices of each must be evaluated to determine the overall effects. Vogel et al. studied the EEG driving response, defined as EEG waves at fundamental or harmonic frequency of photic stimulation for 1 second. Significant difference between EEG driving response before and after smoking occurred in both smokers ($P < 0.001$) and nonsmokers ($P < .05$). It was hypothesized that central adrenergic stimulation in smokers experiencing tranquilizer effects (Nesbitt's Paradox) are related to central adrenergic insufficiency in smokers that may be reflected in the EEG driving response.

The smoking of one or two cigarettes or the administration of an equivalent amount of nicotine produces sympathomimetic symptoms, the most notable of which includes an increase in resting heart rate of from 5 to 40 beats per minute (Domino 1973; Hill &

Wynder, 1974; Roth et al., 1944), increased blood pressure (5 to 20 mm of Hg), increased serum levels of epinephrine and adrenocortical hormones (Herxheimer et al., 1967; Hill & Wynder 1974; Jarvik, 1970), and significant vasoconstriction (Herxheimer et al.). Two studies found that high nicotine cigarettes produced significantly greater increases in heart rate than low nicotine cigarettes in moderately arousing emotional settings (Gilbert, 1978; Nesbitt, 1973). However, a study by Erwin (1971) found that heart rate did not change significantly in subjects performing their daily routines. Murphree et al. (1967) reported quantitative EEG effects of smoking for smokers and nonsmokers of both sexes (21-43 yrs) who smoked plain and mentholated cigarettes with and without filters. A rapid, initial effect of smoke inhalation in which EEG changes for a nonsmoker smoking a cigar were similar to inhaling it was reported. Although subjects exhibited individual differences, these data showed effects of smoking to be stimulant rather than tranquilizing.

Roos (1977) examined whether nonsmokers differed from smokers in their tonic EEG levels and electrocortical reaction to various auditory stimuli (ranging from nonsignal sounds to emotionally laden words). Light smokers (less than 12 cigs/day) showed the greatest variability in alpha activity. Moderate smokers (12-18 cigs/day) exhibited the largest amounts of alpha activity of all groups, but were less reactive to mild stimulation than heavy smokers (more than 20 cigs/day), who had the smallest amount and exhibited little reactivity.

Ashton et al. (1974) found that amplitude of the negative EEG shift occurring prior to an anticipated stimulus (contingent negative variation, CNV) increased in some smokers, decreased in others, and were biphasic responses in still others. Subjects whose CNV amplitude decreased reported a sedative effect of smoking, and were found to be scored as introverts on the Eysenck Personality Inventory; subjects whose CNV amplitude increased reported a stimulant effect of smoking and were scored as extroverts. Sham smoking and placebo had neither cardiovascular nor CNV effects. Ashton et al. (1973) studied the CNV of the EEG following a weak, momentary flash of light; subjects were required to press a button as soon as possible after onset of a tone, which provided a reaction time measurement. Smoking significantly changed the magnitude of the CNV, which was decreased in some subjects and increased in others. The decrease in CNV occurred in 11 of 22 subjects, the increase in CNV in 7 subjects; and 4 subjects were biphasic. The authors hypothesized that increases in CNV amplitude represent stimulant effects and decreases represent depressant effects, suggesting individual variability in the effects of nicotine on arousal. Ashton et al. (1978) evaluated the contribution of nicotine by intravenous delivery of a nicotine dose that was similar to that obtained by a smoker who had inhaled a cigarette delivering 1-2 mg of nicotine. Nicotine produced the same changes as smoking while saline injections produced no significant changes. Doses of

nicotine (12.5-800 ug) produced a biphasic pattern in the CNV; with lower nicotine doses (12.5-50 ug) the CNV increased as dose increased, but with further increases in nicotine dose (100-800 ug) there was a progressive decrease in CNV amplitude.

The effects of intravenous (i.v.) injections of nicotine bitartrate on the CNV were studied in 12 male volunteers (Ashton et al.). In three subjects, nicotine (500-700 ug) produced an increase in magnitude of CNV; in 2 subjects, nicotine (750 ug) produced a decrease in magnitude of CNV. There was correspondence between i.v. nicotine and cigarette smoking in the direction and magnitude of CNV changes. Individual and mean dose-response curves were biphasic; smaller doses produced an increase in CNV (stimulant effect) and larger doses produced a decrease in CNV (depressant effect). Several experiments were performed to determine the effect of cigarette smoking and nicotine on the CNV. Extroverted subjects took smaller doses of nicotine per minute that produced increases in CNV magnitude; whereas, introverted subjects took larger doses that decreased CNV magnitude. When some of the same subjects received 2 intravenous infusions of 750 mg each, the CNV increased for some and decreased for others.

The effects of cigarette smoking on cortical, average visually evoked potential, and contingent negative variation (CNV) indices of cortical arousal suggest that nicotine influences cortical processes in a complex manner that can be either arousing or sedating, depending on the nature of the stimulus and the personality characteristics of the individual. Smoking has produced an arousing (increased response amplitude) effect on visual evoked potentials elicited by low-intensity stimuli and a sedative effect on potentials elicited by high-intensity stimuli (Hall, et al., 1973). On the other hand, Ashton, et al., (1974) reported that smoking produced cortical arousal (increased CNV magnitude) in extroverts, but had the opposite effect (sedation) in introverts.

Tibbling and Henriksson (1968) studied the vestibular nystagmus pattern of smokers; amplitude, frequency, speed of slow component, speed of fast component, and angular deviation of eyes were measured following rotation. Frequency showed the greatest change; heavy smokers had the smallest change. Only the speed of the fast component decreased after smoking. After smoking a conventional cigarette, nystagmus frequency increased but there was no change in nystagmus pattern after smoking nicotine free cigarettes. Intravenous nicotine also increased nystagmus frequency. The influence of smoking on heart rate varied proportionately to the influence on the nystagmus pattern (Tibbling & Hendriksson).

Sleep EEG studies have been used to determine the effects of intramuscular nicotine on sleep of six nonsmokers and two light smokers (Domino, 1967). Control injections of saline prolonged Stage I sleep compared to the no drug condition. Under conditions in which nicotine was given at bedtime, no evidence of a wake-up effect or facilitation of stage I sleep was obtained. The reason may be that the action of nicotine is relatively short, compared to a sleep cycle of 7-8 hours duration. No differences between light smokers and nonsmokers were observed in onset, duration, pattern of sleep, or responses to nicotine.

Domino and Baumgarten (1969) reported that depression of the patellar reflex was produced by smoking a nicotine-free lettuce cigarette. Following smoking of a nicotine cigarette, depression of the patellar reflex, observed within 30 seconds, was progressive and reached its peak at the end of smoking. After smoking, patellar reflex depression remained for 30-120 second followed by progressive recovery in 10 minutes. Reflex response returned to normal within 25 min after smoking. Cigarettes with a nicotine content of 0.80 mg produced approximately 45% depression of the patellar reflex and those with 1.69 mg, about 67% depression. Smoking a second cigarette 25 minutes after the first resulted in a reproducible depression indicating that no tachyphylaxis took place in this time interval. Although no significant

differences were observed between smokers and nonsmokers, tobacco smoking produced a short-term depression of the patellar reflex that seems to be related to nicotine content of the cigarette smoked.

An event related cortical potential (ERP) following smoking showed increased conduction velocity of the most positive potential identified with latency between 250 and 500 milliseconds (P300). The hypothesis that smoking speeds up stimulus evaluation processes, and that the effects of smoking help smokers concentrate has been tested by Edwards et al. (1983) who presented a series of digits to subjects singly at a rapid rate of 100 per minute. The task was to detect series of three consecutive odd or even digits. Alveolar carbon monoxide was measured before and after treatment in order to estimate the degree of inhalation, and cigarette butts were collected for analysis in order to assess puffing strength. Following 12 hours abstinence, the probability of correctly detecting a signal increased and reaction time decreased in the first 10 minutes after smoking. Although the improvement in reaction time was maintained over the final 10 minutes, correct detections decreased. In the nonsmoking condition, both correct detections and reaction times decreased over time. Performance after smoking was superior to that following the nonsmoking interval.

The immediate effects of cigarette smoking as related to different smoking habits in male subjects under smoking and nonsmoking conditions in two situations (low arousal and high arousal) showed no consistent differences between low-arousal smokers and high-arousal smokers under nonsmoking conditions (Myrsten et al., 1975). Smoking increased both epinephrine excretion and heart rate in both low-arousal and high-arousal situations. Self-estimates made at the end of the sessions indicated that smoking affected the two types of smokers differently. In the low-arousal situation, smoking increased the reaction time performance of low arousal smokers. Although high-arousal smokers reported decreased alertness and boredom while smoking during low-arousal sessions, smoking increased reaction time in high-arousal sessions.

Hartley (1973) studied the paced observing responses of 15 smokers. Following abstinence, detection scores increased during the test, but following smoking, they failed to increase. Smoking produced an increase in heart rate, and one cigarette produced nearly as large an effect as two. By the end of testing, heart rate decreased to the level of the nonsmoking condition, suggesting that smoking decreased the level of arousal during the latter part of the test and prevented changes in performance that usually accompany a prolonged test.

Philips (1971) used computer methods to examine form and duration of EEG changes under both resting and critical flicker fusion (CFF) vision task conditions, up to 20 minutes following the smoking of one cigarette. During the CFF task power spectral analysis revealed significant decreases in the peak alpha frequency component up to 20 minutes following smoking. Although no indications of increased high frequency activity were reported, these findings support the view that small amounts of nicotine act as a stimulant or activator. Golding and Mangan (1982) studied changes in electrodermal conductance, heart rate, and EEG alpha responding during the smoking of a 1.3 mg nicotine cigarette under aversive white noise (stress) and mild sensory isolation (relaxation) conditions. Under both the white noise and sensory isolation conditions, smoking produced increases in heart rate. Skin conduction was increased by stress, but was not significantly affected by smoking in the stress condition. Although smoking increased skin conductance during relaxation, strong cortical stimulant effects were indicated by significantly decreased EEG alpha activity. Under stress conditions, smoking produced mixed stimulant and depressant effects. Heart rate and alpha EEG activity increased; skin conductance was nonsignificantly increased. Sham smoking produced no effect on heart rate. The proportion of real smoking effect accounted for by sham smoking was calculated to be greater than 50% for both skin conductance and for EEG.

Contrary to the hypothesis that tobacco and nicotine produce central nervous system (CNS) tranquilizing effects, studies have typically shown that smoking-sized doses of nicotine (0.005 to 0.1 mg/kg body weight) produce EEG activity characteristic of CNS arousal (alpha desynchronization, increased dominant alpha frequency, and decreases in total energy). The EEG arousal may be observed immediately after the intravenous administration of nicotine and by the time the individual completes smoking a tobacco cigarette. Philips (1971) observed that the smoking of a single cigarette resulted in a significant increase in EEG arousal (mean alpha power decrease) for up to 20 minutes. Associated with restlessness and dysphoria (Shiffman & Jarvik, 1980). The EEG-activating effects of smoking have been interpreted as resulting from the behavioral act of smoking rather than from the physiological effect of nicotine or other pharmacologics in tobacco (Wechsler, 1958).

2. ATTENTION AND VIGILANCE TASK PERFORMANCE

Frankenhaeuser et al. (1971) found that smoking decreased performance on a choice reaction task. Decreases in simple reaction time suggested increased efficiency during a vigilance task that was associated with less restlessness, greater relaxation, and greater alertness during smoking compared to nonsmoking sessions. Following 8-12 hours abstinence, a group of smokers performed prolonged reaction time tasks. In the nonsmoking condition, the speed of reaction decreased over time; difference in reaction times between the smoking and nonsmoking conditions were significant. Myrsten (1971) studied six smokers (age 20-26 years) who performed prolonged simple and choice reaction time tests.. Smoking prevented the increase in reaction time which occurred over time in a nonsmoking condition. In complex reactions, smoking decreased reaction time. Myrsten et al. (1975) selected two groups of smoker subjects on the basis of their responses to a situational-smoking questionnaire. One group of eight reported that they typically smoked in highly arousing situations; the other group of eight reported that they typically smoked in low arousal situations. In a high arousal task, the reaction time of the smokers who smoked in highly arousing situations was improved, while the reaction time of the low arousal smokers was improved by smoking during the low arousal visual vigilance task. Frankenhaeuser et al. (1971) studied performance of the effects of smoking on efficiency using

a sustained visual reaction time test under monotonous conditions. The subject's task was to respond to a light signal given at irregular intervals of 1-3 seconds by pressing a button with his dominant hand. There were 1,600 stimuli given and reaction times were recorded with an accuracy of 0.001 seconds by an electronic counter. In a control session without smoking, efficiency decreased over time. In the smoking session where subjects smoked 3 cigarettes at 20-minute intervals, the initial level of performance was maintained throughout the session. Moreover reaction times were significantly shorter in the smoking than in the control session.

Lyon et al. (1975) studied 16 male smokers (20-25 yrs old) who were divided into smokers who had smoked 15-30 cigarettes daily for at least 3 years and nonsmokers who had never smoked. Each smoker was tested under six conditions consisting of three doses of alcohol and two doses of tobacco. Each nonsmoker was tested under three alcohol, no cigarette conditions only. Choice reaction time of smokers and nonsmokers involved responses to combinations of stimulus lights by removing a finger from a resting key and placing it on a response key. Latency between stimulus onset and removal of the finger from the resting keys was "decision time," and the interval between removal of the finger from the resting key and depression of a response key was

"motor time." A significant effect of tobacco (but not of alcohol) on decision time scores decreased decision time when administered after alcohol. Analysis of motor time scores did not yield any significant effects of tobacco or alcohol singly. Significant stimulant effects of nicotine were found following low and moderate doses of alcohol. No depressant effect of a moderate dose of alcohol was shown in the smokers whether smoking or not, although depressant effects were observed in nonsmokers. The stimulant effect of a small dose of alcohol on decision time was very pronounced in the smokers.

The behavioral efficiency of male subjects during performance of two visual reaction time tasks within a 100 minute interval was decreased by cigarette smoking, but impairment of hand steadiness complicated the analysis (Myrsten et al., 1971). Myrsten et al. (1972) further found that decreases in both hand steadiness and choice reaction time were associated with increased heart rate after each cigarette. When reaction time, hand steadiness, heart rate, blood pressure, skin temperature, catecholamine excretion, and subjective reactions were measured after smoking 4 cigarettes, simple reaction time increased over time in the nonsmoking condition and remained the same in the smoking condition (Myrsten et al, 1971). Choice reaction time increased slightly in the nonsmoking condition and decreased in the smoking condition. The differences between smoking and nonsmoking

conditions were statistically significant for only simple reaction time. Smoking significantly impaired hand steadiness. Heart rate and systolic blood pressure were significantly increased; catecholamine excretion was unaffected. Self-estimates of subjects' reactions indicated that smoking counteracted disagreeable feelings (e.g., boredom, irritation, concentration) induced by the experiment. These studies suggest that cigarette smoking may facilitate performance in prolonged visual tasks.

Myrsten and Andersson (1978) studied the combined effect of alcohol intake (whiskey 0.72 g/kg body wt.) and cigarette smoking (5 cgts within 175 min) in male subjects during a 3 hour interval in which they performed visual reaction time tests. Although blood alcohol concentrations were greater when alcohol was combined with smoking, the difference was not statistically significant. Subjective evaluation of intoxication was slightly greater during the combined alcohol and cigarette condition than in the alcohol condition. The main effects of alcohol as compared to control conditions (with water substituted for alcohol) were a slight increase in heart rate and skin temperature, a decrease in hand steadiness, and an increase in visual reaction time. Cigarette smoking increased the heart rate, which remained elevated throughout the trials following the first cigarette. Hand steadiness was consistently impaired. Alcohol and cigarette combined caused a progressive increase in

heart rate and a marked deterioration of hand steadiness. Maximum impairment was observed 75 minutes following alcohol intake. The largest epinephrine excretion occurred when alcohol and cigarettes were combined. These studies suggest a synergistic interaction may exist between cigarettes and alcohol for the heart rate and hand steadiness variables while an antagonistic one may exist for the skin temperature and reaction time variables. After smoking, subjects were given 10 minutes of training followed by 25 minutes of choice reaction time in studies by Lyon et al. Decision time was significantly decreased in the smoking condition.

Smith et al. (1977) studied 8 smokers under 6 conditions comprising combinations of 200 mg caffeine or no caffeine with no cigarette; one 0.3 mg nicotine cigarette; or one 1.3 mg nicotine cigarette. Subjects performed a choice-reaction time task and a hand steadiness task. Both caffeine and nicotine decreased hand steadiness. There was no drug-drug interaction; each drug alone increased heart rate, but in combination the drugs appeared to have antagonistic effects. The level of nicotine exposure appeared to be the cause of the stimulant effects of smoking on decision time. Frankenhaeuser et al. (1969) studied the effects of cigarette smoking on adrenomedullary, cardiovascular, and psychomotor functions in 9 male subjects (19-24 years old) over 90 minute intervals. Epinephrine excretion increased after low

nicotine cigarettes (1.3 mg/cgt) by about 38%; after high nicotine cigarettes epinephrine excretion was 83%. A corresponding decrease in norepinephrine excretion was 8% after low nicotine cigarettes and 12% after high nicotine cigarettes. Smoking increased heart rate and blood pressure and decreased skin temperature and hand steadiness. Changes were more pronounced following high nicotine cigarettes. Choice-reaction time tended to be decreased after smoking; however, changes were not statistically significant. The interrelationship between reaction time and motor inhibition may account for the findings of Frith (1967, 1968b), who showed that nicotine antagonized the normal accumulation of inhibition associated with telegraph key tapping and pursuit motor learning tasks.

Morgan and Pickens (1982) measured reaction time after smoking. The test required matching a randomly selected lighted color button to various auditory tones. Performance was significantly slower after ad libitum smoking of subjects' own cigarettes than after both ad libitum and controlled smoking (prescribed puff rate) of a standard cigarette. Leigh et al. (1977) reported subjects performed better after smoking on an auditory divided attention task which lasted 15 minutes. Subjects wore two earphones with each connected separately to a two-channel stereophonic audio tape recorder; one channel of the tape contained a series of bursts of random noise and the second

channel contained a series of clicks. Mean error rate for click detection was decreased in the smoking condition; a significant increase in error rate was found with alcohol, but no interaction of alcohol with smoking was found. Tone localization scores increased after alcohol and there was a significant nicotine-alcohol interaction. In similar studies, subjects were required to process information by detecting auditory sequences of three consecutive odd digits that occurred about once per minute (Tong et al., 1977). Performance was measured by correct detections, and it was found that although the smoking group had the lowest initial level of detections following smoking, that they were the only group to improve over time.

Wesnes and Revell (1984) found mixed results when a series of digits was presented on a visual display unit at the rate of 100 digits/minute. Subjects were instructed to press a response button when sequences of either three consecutive odd or even digits appeared. Nicotine increased reaction time in the first experimental interval, but decreased reaction time in the second interval. Moreover, nicotine increased errors in both intervals. Scopolamine (1.2 mg) decreased the probability of detection in both intervals and increased reaction time, but increased errors in the second interval only. Nicotine and scopolamine in combination produced effects similar to placebo. Stroop testing revealed that subjects were slower following scopolamine than

either placebo, nicotine, or nicotine/scopolamine combination. Compared to placebo and scopolamine alone, nicotine and nicotine/scopolamine combination produced more rapid information processing, suggesting that nicotine antagonized the performance decrements associated with scopolamine.

Heimstra et al. (1967) showed that smoking prevents the normal deterioration in performance during a monotonous vigilance task involving simulated driving. Reaction times increased significantly over 6 hours in nonsmokers and abstaining smokers, but not in smokers who smoked while driving. Nonabstaining smokers also performed a meter vigilance task at a constant level compared to nonsmokers whose errors increased with time while driving. Brake light vigilance was decreased in abstaining smokers compared to both nonsmokers and nonabstaining smokers. Tong et al. (1978) reported that mean velocity estimates were underestimated and time estimations were overestimated under tobacco treatment for three stimulus speeds. Greatest overestimation occurred in the no smoking condition with the fastest velocity. Underestimation occurred at slowest velocity under the smoking condition. Although smoking interacts with stimulus velocity and time on task to influence judgment of velocity, the effect was less for velocity than for time estimation. In both tasks, influence of tobacco was decreased with time on task.

Weenes et al. (1983) used a classical vigilance test, "the continuous clock task" in which subjects monitored the second hand of a clock during an 80 minute session for brief pauses, which they signaled by depressing a button. Two of the groups were heavy smokers who abstained from smoking from the evening preceding the experimental morning. During the testing period, one of these groups was permitted to smoke cigarettes with a nicotine delivery of 1.4 mg at 20 minute intervals, while the other smoker group and the nonsmoker group placed the end of a pencil in their mouths during these smoking periods, as a control for the oral effects of smoking. Performance was analyzed using signal detection theory. The advantage of such an analysis is that it incorporates both correct detections and false alarms into a single measure of performance, stimulus sensitivity, which is independent of the motivational factors affecting performance. It was found that highly significant decrements in stimulus sensitivity occurred over time in both the nonsmoking group and in the abstaining smoker group. The stimulus sensitivity of the smoking group remained constant over time and was significantly higher than that in the other two conditions. Additionally, the effects of smoking on the performance of an auditory vigilance task were studied in a group of 12 male heavy smokers who performed the 80 minute vigilance task on two occasions; once while smoking cigarettes having 2.1 mg nicotine delivery and once while

smoking nicotine-free herbal cigarettes. The task involved listening to 0.05 second bursts of white noise and detecting those bursts which also contained a faint tone. The smokers maintained baseline stimulus sensitivity throughout the session when smoking the 2.1 mg nicotine cigarette; a significant decrease in sensitivity occurred over time in the nicotine-free condition.

Performance in terms of both correct detections and the speed of response was significantly greater following the high nicotine delivery cigarette than that following either of the two lower delivery cigarettes. Smoking antagonized the decrease in performance over time. The efficiency of performance actually increased relative to baseline during the first 10 minutes after smoking each cigarette. This increase was greatest for the high nicotine delivery cigarette; both correct detections and reaction times were improved above the rested baseline level. Smoking improved both the speed and accuracy of performance above the pre-smoking baseline levels; whereas, performance significantly decreased over time in both of the control conditions. Statistical analysis revealed that there were highly significant differences between the levels of efficiency in the two cigarette conditions and those in the control conditions. Subjects were significantly faster and more accurate after smoking the two

higher nicotine than after the low nicotine cigarettes. Smoking antagonized the decrease in performance which occurred in the control conditions and improved speed and accuracy compared to baseline.

Elgerot (1976) compared the performance of a group of 12 habitual smokers after abstaining from cigarettes for 15 hours with that following subjects who smoked at least one cigarette before testing, and then smoking freely during the testing period. Performance was superior in the abstinence condition. Although there were no differences in the Bourdon test of perceptual speed and proof-reading in the abstinence condition, there was a trend towards improvement in a reasoning test, and significant improvements in mental subtraction and "Raven's Progressive Matrices," a nonverbal reasoning test. In contrast the effects of smoking cigarettes on immediate memory and letter cancellation were studied by Williams (1980). On four occasions following overnight abstinence, 48 smokers performed the two tasks before and after smoking. No effect of smoking was found on immediate memory, but improvement was significant for a letter cancellation task after smoking.

Ashton et al. (1972) compared behavioral and physiological responses of cigarette smokers and nonsmokers exposed to varying degrees of stress produced under controlled laboratory condition.

The stress consisted of a driving test with the following three levels of task difficulty: response to light signals, response to a driving film plus light signals which always corresponded to the driving requirements of the film, and response to the film plus signals wherein some signals conflicted with the movements of the car in the film. Subject were instructed to give precedence to the light signals. Heart rate, respiration, calf blood flow, and blood pressure were recorded during and after the tasks. During the first half of the test, smokers smoked one cigarette with 1.0, 1.4, or 2.1 mg of nicotine. No significant differences were observed between smokers and nonsmokers during nonsmoking intervals. However, there were differences detected during the first half of the test while smokers were smoking. Shorter reaction times among smokers and the tendency for smokers to anticipate signals more than nonsmokers indicated that smoking may have had a stimulating or alerting effect. Lack of difference in performance between smokers and nonsmokers in simpler and less stressful pursuit rotor and reaction tests indicated that the effects of smoking may be subtle and more important in complex situations associated with higher magnitudes of stress. No differences in performance were reported between high and low nicotine cigarette smokers. Of the physiological measurements, only heart rate showed significant differences between smokers and nonsmokers. Results of the Cattell Sixteen Personality

Factor Questionnaire showed that smokers were significantly more extroverted and more self-reliant than nonsmokers, but did not differ in other personality characteristics.

Boyd and Maltzman (1982) studied the effect of cigarette smoking on bilateral skin conductance in eight smokers and eight nonsmokers to determine the relative activation of each of the two cerebral hemispheres by nicotine. Smokers abstained from smoking for 3 hours before the experiment. Bilateral measurements were taken of skin conductance during rest and following smoking a cigarette containing 1.1 mg nicotine. Results indicated that smokers had relatively larger spontaneous skin conductance magnitudes in their left hands when not smoking and larger spontaneous skin conductance magnitudes in their right hands following smoking. Smokers did not differ significantly from controls in either condition. This skin conductance asymmetry was interpreted to indicate that the right hemisphere may be stimulated more than the left hemisphere following smoking in smokers. Auditory tasks were given to differentially activate the cerebral hemispheres. While nonsmokers demonstrated task-appropriate changes in skin conductance magnitude asymmetry (i.e., larger magnitudes in the right hand during right hemisphere activation), smokers did not demonstrate any similar interaction between task and hand. The effect of smoking on lateralization of hemisphere activation may override the phasic fluctuations in utilization that would normally occur during changing task demands.

3. MOOD

Smoking and experimental nicotine administration produce significant increases in physiological arousal, especially of autonomic end organs. Frequently, decreases in behavioral and self-report measures of emotion suggest feelings of increased tranquility. A biphasic response in which arousal is followed by relaxation has been reported (Ashton et al., 1978; Gilbert, 1978; Golding & Mangan, 1982; Myrsten et al., 1975). Nesbitt (1973) described this phenomenon and more recent researchers have termed it "Nesbitt's Paradox."

Thomas (1973) studied smoking behavior of medical students over a 17-year interval and related findings to habits of nervous tension, habits of daily life, and other psychobiological characteristics. A computer program performed discriminate analyses of 21 variables. Subjects included 386 nonsmokers and occasional smokers, 141 heavy smokers (20 or more cgts/day), and 165 moderate smokers. Lifetime nonsmokers showed the lowest scale scores for anxiety, anger, and depression compared to cigarette smokers. Number of cups of coffee per day and alcohol frequency had the most discriminating power. When smokers were dichotomized into heavy and light on the basis of number of cigarettes smoked before age 30, strikingly different psychological profiles for the two groups emerged. Heavy smokers had higher mean values

for all 10 psychological variables. Anger was associated with heavy smoking. Feelings related to depression and tiredness on waking were frequently reported in smokers. Heightened awareness of nervous tension, particularly feelings of anger and anxiety, were associated with increased use of cigarettes, coffee, and alcohol.

Ague (1973) used a mood adjective checklist (MACL) and activation scale (AS) to measure subjective reports on mood changes in habitual male smokers. The MACL was sensitive to changes in mood within short periods of time. The AS linked subjective responses to physiological parameters. A significant trend was found for the sensation of pleasantness to be associated with smoking cigarettes of increasing nicotine content. Decreases in "inner tension" were significantly related to nicotine content. Frankenhaeuser et al. (1970) observed that subjects abstaining for 15 hours reported subjective well being after smoking.

Myrsten et al. (1972) reported that smoking during reaction time tasks decreased self-estimates of irritation and boredom compared to the nonsmoking condition. Ague (1973) studied subjects who smoked after 8 hours abstinence. Subjects reported on the mood adjective checklist that they were more relaxed one hour after smoking high nicotine cigarettes compared to after

smoking low or no nicotine cigarettes. There was a non-significant trend for nicotine to decrease anxiety and aggression. Schechter and Rand (1974) found that abstaining smokers performed 37% more aggressively compared to nonabstaining smokers. Two possible aggressive responses of smokers have been studied: subtracting money from or administering a blast of white noise to a fictitious person (Cherek, 1981). The former response was considered more aggressive. The nonaggressive response resulted in the subject's accumulating money. Smoking produced dose-dependent decreases in both types of aggression responses under conditions of both low and high provocation. The more aggressive option was more sensitive to the effects of smoking. Smoking also increased nonaggressive responding, indicating that the suppressant effect of nicotine was probably not associated with a nonspecific depressant action.

Hutchinson and Emley (1973) studied the behavioral effects of nicotine during the introduction of noxious or frustrating events. Masseter (jaw muscle) contraction patterns were recorded electromyographically. A recording of triceps muscle contractions served as a control. Seven of eight subjects showed increases in the frequency of jaw clenching following cessation of smoking and in the duration of high-force (160 microvolts or greater) jaw contractions. Each of the five subjects who completed a month-long observation period in a smoking withdrawal

clinic showed a progressive decrease. In another experiment, the effects of intravenous nicotine administration upon bite contraction during stressful episodes were studied in nonsmoking subjects without their immediate awareness. Subjects drank 5 ounces of distilled water each day 15 min prior to testing. When performance was stable after two days, 5 mg of nicotine were added to the water. Nicotine decreased the frequency and intensity of jaw contractions, and also produced a disproportionate decrement in jaw contractions occurring immediately after a stressful 3,000 Hz auditory stimulus.

Anxiety reduction has been demonstrated in humans after smoking (Pomerleau, 1984). It is also possible that a nicotine-stimulated increase in arousal and attention capacity with corresponding improvement in performance indirectly antagonizes anxiety (Myrsten et al, 1977). Other sedating or tranquilizing effects have been observed following smoking, including decreased skeletal muscle tension and depression of spinal reflexes (Domino, 1969 and 1973), stabilization of mood, and decreased aggression (Cherek, 1981; Hutchinson and Emley, 1973).

4. LEARNING

Andersson and Post (1972) used a task in which subjects were given 30 successive learning trials under both nicotine and nicotine-free conditions; in each condition the same list of nonsense syllables was presented and the subjects were required to correctly predict the next syllable in the sequence. A group of 12 male light smokers performed the recall task, once smoking 2.1 mg nicotine delivery cigarettes after trials 10 and 20, and on another occasion smoking nicotine-free cigarettes. Correctly anticipated syllables decreased in the nicotine condition but not in the nicotine-free condition. Recall was poorer in the nicotine condition until after the second cigarette had been smoked and from then to the end of the study there were no differences in recall between the two conditions. This suggests that state dependent learning occurred; the material learned before smoking was more difficult to recall immediately. Andersson (1975) studied effects of smoking on verbal rote learning, and recall was decreased immediately after smoking, also suggesting a state dependent learning effect. This decreased recall tended to recover on successive trials, as nicotine levels decreased. After a 45 minute intermission, recall in the two conditions was identical, which may also be interpreted as state dependent learning. Peters and McGee (1982) required subjects to immediately recall as many nouns in a list as they could recall following smoking. Recall 24 hours later suggested a state dependent effect; there were no differences between "same state groups."

Andersson and Post (1974) studied the effect of nicotine-free cigarettes and nicotine cigarettes on learning a nonsense syllable line. No evidence was presented for nicotine induced interference with information acquisition. Learning curves were parallel after the first nicotine cigarette; there was facilitation of information acquisition after the second cigarette. Houston et al. (1978) studied learning in smokers on immediate and delayed recall tests. Nicotine intake was associated with a decrease in both immediate and delayed retention on a 75 item free recall test 2 days after learning.

Peeke and Peeke (1984) tested the effects of smoking one cigarette on verbal memory and attention. A 50 word list was presented twice followed by both immediate and delayed recall tests; the delayed recall was at 10 and 45 minutes after learning. The high nicotine cigarette improved performance on both immediate and delayed recall tests. The low nicotine cigarette was less effective at improving recall than the high nicotine cigarette. No differences between light and heavy smokers were observed for recall. Correlation ($r=0.5$) between heart rate immediately after smoking and mean number of words recalled suggested a relationship between stimulation level and performance on word recall tests.

Andersson and Post (1974) studied moderate smokers who learned 2 lists of 7 nonsense syllables; each smoked nicotine and nicotine-free cigarettes. The mean number of correctly anticipated syllables decreased after the first nicotine cigarette compared with the first nicotine-free cigarette. After the second nicotine cigarette, there was reversal of the previous response. Mean number of correctly anticipated syllables increased from 0 to 22 (out of 30) syllables in 30 trials compared to nicotine-free cigarettes. Epinephrine excretion increased significantly during learning in both conditions. Diuresis increased from 0.6 to 0.9 ml/min after smoking both types of cigarettes (nicotine and nicotine-free). Mean heart rate increased after one nicotine cigarette from 70 to 85 bpm, further suggesting a relationship between learning and stimulation level.

However, the findings of Andersson et al. (1975) on the effects of cigarette smoking on arousal and correct responding in a rote nonsense syllable learning task suggested that arousal and learning may be negatively correlated. During the smoking condition, there was a significant decrease in the number of correct responses on a learning task. Significant heart rate increases following smoking coincided with impaired learning performance and served as an indirect measure of physiological

arousal. Long-term retention of learning was assessed by a delayed retention test 45 minutes following the end of the learning period (when the arousal level had returned to pre-smoking levels), and was found to be better in the smoking condition.

Williams' (1980) analysis of performance in subjects who were required to work as fast as possible without errors crossing out each instance of an "E" found in sheets of randomly ordered letters, suggested a more complex association between arousal and learning. Average gains in letters cancelled (with different cigarettes smoked) increased in smokers who reported smoking both in low and high arousal conditions. The greatest increase was associated with use of moderate nicotine cigarettes. Gains in immediate memory errors occurred in both low arousal subjects and in high arousal subjects. With increasing cigarette strength, gains in letter cancellation speed increased during smoking; immediate memory accuracy progressively deteriorated. Smokers with greater desire to smoke in situations of low arousal appeared to react more strongly to cigarettes and showed superior gain in cancellation speed on smoking. Andersson and Hockey (1977) studied the effect of cigarette smoking on an immediate memory task in 2 groups of 25 female students (19-39 yrs old). The memory task, requiring immediate serial recall of 8 words showed no differences between smoking and nonsmoking groups. For

incidental recall (position of words on the screen in any of 4 corners), the nonsmoking group was superior to the smoking group. Heart rate increased after smoking; no change in heart rate occurred in the nonsmoking group. The incidental learning memory data suggest that smoking decreases subjects' attention to irrelevant information. These results agree with results obtained with noise induced arousal and with the view that attentional selectivity may be greater during increased arousal.

Wesnes and Warburton (1984) studied 12 nonsmokers who performed a rapid visual information processing task of identifying and responding to consecutive odd digits in a series presented at 100 digits per minute. Nicotine antagonized the decrease in both speed and accuracy which occurred over time in the placebo condition. Nonsmoking subjects performed significantly better than smoking subjects on anagram word-in-context and concept tests, but did not differ from the smoking subjects on a card sorting task (Stevens, 1976). This suggests that subjects who smoke do not perform as well on learning tests as do nonsmoking subjects. This difference was found to be related to amount of smoking rather than to smoking per se because the light-smoking group did as well as the nonsmoking group. The effect of smoking on the learning process was detected only in the group of subjects who smoked in excess of 12 cigarettes per day. Carter (1974) required each subject to take

two separate letter-digit substitution tests of 20 trials and a serial-learning test of 12 nonsense syllables. These syllables were of intermediate difficulty; four testing sessions were required, as each task was presented separately. There was no difference between 10 smoking and 10 nonsmoking subjects on number correct.

These studies suggest that knowledge learned under the effects of nicotine may be recalled better under the effects of nicotine (i.e., in smoking subjects) than when nicotine is not administered (i.e., in abstaining smokers). Furthermore, there is evidence that nicotine from smoking improved long-term memory. The mechanisms for this effect are not known but could involve stimulation by nicotine of acetylcholine and vasopressin (or both). The improvement of memory by nicotine may be the result of noradrenergically mediated enhancement of selective attention. The problems of state-specific learning, test-retest reliability, performance versus learning, task specification, and motivation, furthermore, present formidable obstacles to research on smoking and memory learning.

5. VISION

Attia et al. (1978) studied withdrawal from smoking in 100 cigarette smokers with chronic simple glaucoma who stopped smoking for one month. During this period, the intraocular pressure (IOP) was measured once daily for each patient; visual acuity was tested weekly and the central visual field was plotted monthly. Cessation of cigarette smoking in these glaucomatous patients decreased IOP in 40% of subjects; the IOP decrement varied between 2 and 7 mm Hg without changing the dose or frequency of pilocarpine treatment.

The visual acuity group of 30 students, aged 20-39 years, was performed using an apparatus specifically constructed for simulating glare conditions existing when cars meet at night (Johansson, 1964). The luminance of an experimental surface corresponded to that of a concrete road surface 30 meters in front of a car with full headlights measured at eye level above the driver's seat. Five detection time measurements were made after allowing 1 minute for adaptation to the light intensity of the apparatus. Ten redetection time measurements were made, these being separated by one minute intervals to allow for readaptation. A few blind trials were inserted at random among these measurements, as a control of the reliability of the subjects' reactions. On these trials, the glare occurred as

usual without the signal being presented afterwards. Five more detection time measurements were made after allowing 1 minute for adaptation. The difference between the smoking and non-smoking conditions was 0.15 second for detection time and 0.08 second for redetection time. Detection time was greater for the smoking condition but differences were not found to be significant: $P = 0.79$ for the detection time, and $P = 0.12$ for the redetection time. These results suggest that the effect of tobacco smoking on the ability to detect objects on the road while driving at night is negligible.

Sheard (1946) studied the effect of smoking cigarettes on the levels of dark adaptation in several subjects and found that 1) there was definite decrease of light sensitivity (0.25 to 0.75 log unit) in both rods and cones that persisted for 15-30 minutes after inhaling smoke from two standard cigarettes. The effects were practically the same when the smoke was drawn into the mouth and not inhaled and there was no effect on the adaptation levels when the nicotine was removed (less than 5% remained) from the smoke by suitable filters. The responses of cones were less affected and the recovery was more rapid than for the rods. There was no effect of smoking cubebs, corn-silk cigarettes and similar types of material containing no nicotine. Troemel et al. (1951) measured dark adaptation in smoking subjects; the dose of nicotine was low (one inch of a standard brand cigarette smoked

in 2 minutes) or heavy (1 inch of two cigarettes smoked consecutively in 2 minutes each). Nicotine increased the speed of dark adaptation in the absence of caffeine (0.1% confidence level). A small dose of caffeine (3 grains) in combination with nicotine did not antagonize the effect of nicotine. A high dose of caffeine (6 grains) in combination with nicotine showed speeding of dark adaptation as with nicotine alone. In contrast, Calissendorff (1977) studied the effect of cigarette smoking upon dark adaptation and found that dark adaptation after smoking was slower than after a nonsmoking interval. The difference was greatest during the first 10 minutes and was insignificant after 20 minutes. The mesopic range (the intermediate stage in which activities of cones and rods overlap) was most affected by smoking.

Edwards et al. (1983) studied male smokers who smoked more than 15 cigarettes daily while performing a rapid visual information processing task requiring detection of a sequence of three consecutive odd or even digits in a series presented singly on a video screen, at a rate of 100 digits/minute. Smoking resulted in subjects detecting targets significantly more quickly and accurately on the information processing task in the first 10 minutes following smoking. There was no evidence of trade-off between speed and accuracy. Event related potentials measured by applying signal-averaging techniques to the EEG were studied by

their P300 components, a peak having approximately a 300-millisecond latency that showed decreased latency following smoking. These results suggest that rapid visual information processing is enhanced by smoking.

The critical flicker fusion threshold (CFF) is the frequency at which the flickering of a light source can no longer be detected. Although it is really a psychophysical measurement, it is sometimes confusingly termed vigilance, and it may be indicative of the level of attention to visual tasks under specific conditions. Warwick and Eysenck (1968) reported increased critical flicker frequency after smoking, suggesting that smoking increased visual vigilance. Larson et al. (1950) examined the effects of smoking on CFF using a group of 20 smokers. The first cigarette of the day whether taken in the afternoon or in the morning produced a significant decrease of the threshold during smoking. No effects occurred if the smokers were allowed to smoke normally beforehand or if they smoked a very low nicotine cigarette. Larson et al. (1950) found that the first cigarette smoked produced an immediate increase in the flicker fusion frequency with gradual return to normal in about 15 minutes after cessation of smoking. With continued smoking throughout the day, the effect became nonsignificant. Increased flicker fusion frequency resulting from smoking was found to be due to the nicotine content of the cigarette tobacco, since it did not occur

when cigarettes containing less than 0.2% nicotine were smoked. Fabricant and Rose (1951) reported that smoking a cigarette (1.8 mg nicotine) increased flicker fusion frequency the increase being greater and more significant the longer the time elapsed following the last smoking period. Warwick and Eysenck (1963) studied five smokers and four nonsmokers who each smoked a single cigarette. A significant change in CFF was found only for the smokers who abstained from smoking prior to smoking. Nonsmokers who did not inhale were assumed not to have absorbed significant CFF changes. In a second series, 15 subjects were tested under one of three conditions; no drug, oral placebo or 0.1 mg nicotine tablets. Nicotine increased CFF threshold, and was assumed to be more efficiently absorbed from tablets than from smoking cigarettes. It was found that cigarette smoking as a technique for nicotine administration was not of much value because the amount absorbed depends on whether the subject was an inhaler or noninhaler. Smoking increased CFF when the subjects were allowed to smoke normally before testing.

Garner et al. (1952) studied 108 subjects and found that CFF was decreased in 35 and increased in 21. Unfortunately, the results were not reported as groups of smokers and nonsmokers; therefore, the findings from this study are uninterpretable. Garner et al. (1954) studied the effect of cigarette smoking on flicker fusion threshold (FFT) in 53 normal nonsmokers and 55

smokers who had abstained from smoking 10-12 hours preceding each test; 96 of the subjects were student nurses with only a short smoking history. Of the nonsmokers, 15 showed an increase in flicker fusion frequency; 11, a decrease; 18, no change; and 2, an initial sharp increase immediately following smoking, with return to baseline in 2-4 minutes, followed by a secondary decrease. Of the smokers, 20 showed an increase; 10, a decrease; 22, no change; and 3, initial increase, followed by a secondary decrease. In 8 of the 35 subjects showing an increase in flicker fusion frequency, smoking a second cigarette after FFT had returned to baseline again resulted in an increase, but of lesser degree. In the group of 21 subjects showing a decrease in flicker fusion frequency after smoking, an increase occurred in 14 on repeated smoking of a denicotinized cigarette, except for minor decreases in 6 of the subjects who showed a decrease in response to smoking regular cigarettes. The subjects absorbed sufficient nicotine by sitting in a smoke-filled room (passive smoking) to affect the flicker fusion frequency.

Ausman and Arneth (1951) reported that 10-40 mg of bentyll hydrochloride (di-ethylaminocarbethoxybicyclohexyl hydrochloride) intravenously antagonized the changes in flicker fusion frequency associated with smoking.

Warwick and Eysenck (1968) reported that nicotine produced greater visual masking threshold in nonsmokers than smokers; placebo and no drug conditions produced effects opposite to nicotine wherein visual masking thresholds were lower in nonsmokers than smokers. There was a significant effect of nicotine that increased CFF threshold, but two-flash threshold analysis showed no significant differences between smokers and nonsmokers.

Schalling and Waller (1980) studied the effects of tobacco smoking on psychophysiological and pain variables. In the first experiment, the effect of smoking on critical flicker fusion (CFF) was measured by a computerized forced-choice interactive technique which is an indicator of central nervous system efficiency or cortical arousal. There was a marked improvement in CFF performance 8 minutes after the first puff. Performance was significantly higher in the smoking condition than in the non-smoking condition. When the most and least improved groups in the smoking condition were compared, the improvement group had significantly higher scores on an extroversion scale.

Warwick and Eysenck (1969) evaluated the statistical significance of the independent variables sex and smoking habits to determine the effects of nicotine on behavior. Results from serial reaction time, spiral after-effect, visual masking and CFF tests failed to show differences in male or female responsiveness.

Measurement similar to CFF is the two-flash fusion (TFF) threshold which is the point on a scale of inter-flash intervals below which the subject consistently fails to discriminate between two successive flashes. Tong et al. (1974) studied the effects of cigarettes and alcohol on the TFF. During one of the two placebo alcohol conditions, eight smokers smoked two 1.3 mg nicotine delivery cigarettes before TFF testing, but smoked none in the other. Smoking produced a significant decrease in the threshold.

The studies described in this section provide clear evidence that both CFF and TFF are decreased by smoking under specific testing conditions. These findings are consistent with increased cortical excitability and suggest that smoking may have a beneficial effect upon the processing of visual information.

Wesnes and Warburton (1983) studied the effects of smoking cigarettes on varying nicotine delivery and tar levels on both accuracy and speed of target detection. Although performance deteriorated over time after abstinence and smoking of nicotine-free cigarettes, smoking improved both speed and accuracy of target detection.

The effects of smoking on peripheral movement detection were determined in male subjects (18-30 yrs old) who were tested under four conditions and combinations thereof (smoking, high illumination; abstaining, low illumination) (Scoughton et al., 1975). No significant differences were observed between smoking and nonsmoking subjects for either the low- or high-illumination conditions. Abstaining subjects were significantly better than smoking subjects at detecting and responding to movement in the peripheral visual fields, particularly at the highest velocity. Nonabstaining smokers demonstrated decreased ability to estimate the time of interaction of a moving target than abstaining smokers.

Frankenhaeuser et al. (1971) studied sustained performance in a visual reaction time test in 12 moderate smokers. In the non-smoking condition, efficiency decreased over time. When three cigarettes were smoked at 20 minute intervals, subjects maintained their initial level of performance. The difference in performance in the two conditions was significant. Smoking was also found to significantly increase heart rate and excretion of epinephrine, but did not affect self-ratings of wakefulness and mood. These results suggest that nicotine may counteract the impairment in visual performance typical under monotonous conditions. Schori and Jones (1974) studied subjects required to perform a complex task consisting of three visual monitoring

subtasks (meter, white-light, and red-light), an auditory monitoring subtask, and a mental arithmetic subtask, all of which were performed simultaneously. Only on the auditory subtask was a significant effect of smoking detected. Whereas at the low level of task complexity smokers reported fewer significant mood changes than did nonsmokers and abstaining smokers, the smokers reported more significant mood changes at the high level of task complexity that may have had an indirect effect on visual attention. Indeed, the relationship between smoking and mood change may depend on the nature of the situation.

6. TASTE

Salmon and Blakeslee (1935) found that heavy smokers were just as likely to have a low threshold for detection of the bitter taste of phenylthiocarbamide (PTC) as a high one, and vice versa. Hall and Blakeslee (1945) determined taste threshold for phenylthiocarbamide (PTC) in 60 subjects (32 habitual smokers, 28 nonsmokers, 24 men, 36 women) after 9 or more hours of abstinence from tobacco, then immediately after smoking 2 cigarettes in 10-15 minutes, and thereafter at 15 minute intervals for 1-2 hours. After smoking, 73.3% of the subjects required stronger solutions of PTC in order to taste, while 20% of them tasted weaker solutions. Only 58% of the subjects had returned to the resting threshold within an hour and some took several hours for recovery; this time varied with the individual. In a second series of experiments, 10 of the subjects from the first series, both smokers and nonsmokers, were tested except that the cigarette was drawn through a dry flask for cooling and then into the nose through a sterilized nosepiece, with the mouth kept closed so that the smoke did not touch the tastebuds. Six of these subjects showed an initial stimulation, followed by a depression, in contrast to the initial depression showed by the majority of 60 subjects when smoking was done by mouth. It was concluded that the true effect of nicotine on taste may be the same as for

other nerves tested - an initial stimulation followed by depression. Krut and Perrin (1961) studied the taste threshold of smokers and nonsmokers to determine the immediate effect of smoking a cigarette. In both groups, smokers and nonsmokers showed no significant differences in mean thresholds for sweet, salt, or sour. The mean threshold for bitter, however, was significantly higher for smokers. Light smokers had a significantly lower threshold for bitter than moderate and heavy smokers. Smoking of a cigarette had no immediate effect on taste perception. Ability to taste PTC did not differ between smokers and nonsmokers, and suggested that the decreased acuity for bitter among smokers does not appear to have a genetic basis.

Sinnot and Lauth (1937) reported that the mean taste threshold for sugar was decreased and for salt was increased in smokers compared to a similar population of nonsmokers. The smokers were again tested after they had quit smoking; the mean threshold for sugar was still found to be decreased and for salt increased compared to subjects who never smoked. Differences between the subjects before and after smoking were statistically significant; those between the nonsmokers and the smokers during their nonsmoking period were not. During the tests on the smokers, several broke their resolutions to stop smoking and smoked for 2 days; taste thresholds showed an immediate increase and decreased promptly again after smoking cessation. Grunberg (1982) found that nonsmokers ate more sweets than did smokers

smoking and somewhat more sweets than nonabstaining smokers. There were no differences in consumption of salty and bland foods. Abstaining smokers ate more sweets than did nonabstaining smokers, suggesting that smoking specifically decreases consumption of sweet-tasting foods.

7. PAIN

Smoking has been shown to increase both pain awareness and pain endurance thresholds for aversive shock during nicotine withdrawal. Schalling and Waller (1980) studied the effects of tobacco smoking on pain variables. Experimental pain responses studied in 24 subjects during smoking and nonsmoking conditions using electrocutaneous stimulation showed that stimulation during smoking intervals increased pain tolerance. Pomerleau et al. (1984) studied cold pressor pain induced using ice water in combination with anxiety generated by challenging the subject to unscramble an unsolvable six-letter anagram presented on a card. Thresholds for pain awareness were greater in 5/5 subjects when they smoked. Decreased perception of pain after subjects smoked their usual cigarette was reported by 3/5 subjects. Peripheral skin temperature of the nonimmersed hand decreased more after smoking the subject's usual nicotine cigarette than after a non-nicotine cigarette. Subjective ratings of anxiety decreased more after smoking the usual nicotine cigarette than after the non-nicotine cigarette. Milgrom-Friedman et al. (1983) studied the relationship between smoking and pain perception by comparing the pain thresholds, tolerances, and qualitative pain experiences of 78 subjects of whom 17 were nonabstaining smokers, 15 were smokers given nicotine gum, 15 were smokers who abstained for 1 hour before the trial, 15 were smokers abstaining for 12 hours,

and 16 were nonsmokers. Pain was applied by draining the blood from the arm with a rubber bandage which was not removed until a blood pressure cuff was inflated above systolic pressure. A stopwatch was started when the cuff was secured and subjects rated the sensations on an 11-point scale with 1 no pain and 11 unbearable pain. Pain estimates were made when a recorded tone sounded at random intervals, as well as when first pain was felt regardless of a tone. The procedure was stopped when subjects could no longer tolerate pain or when 20 minutes had passed. Subjects then completed part two of the McGill pain questionnaire with 20 categories divided into sensory, affective, evaluative, and miscellaneous subscales. Deprived smokers and nonsmokers had the shortest mean time to pain onset. The longer smokers abstained the longer the time to onset. Smokers had the shortest mean tolerance time, which was significantly different from nonsmokers, and the abstaining smokers had a decreasing rate of pain tolerance as the abstinence interval increased. These studies indicated that abstinence may lower a smoker's awareness of pain significantly below that of smokers; whereas, smoking cigarettes (rather than just absorbing nicotine) heightens awareness to a level equal to or above that of smokers.

8. MOTOR FUNCTIONS

A number of findings are consistent with the possibility that some of the tranquilizing effects of nicotine may result from the tendency of nicotine to decrease skeletal muscle tension. Depression of the patellar tendon reflex (knee jerk) and associated musculature has been demonstrated following the administration of small amounts of nicotine (Domino and Baumgarten, 1973). Clark and Rand (1968) suggested that decrease of the knee-jerk was due to the nicotine in cigarette smoke and the tranquilization effects of smoking may be related to inhibition of reflex mechanisms. Decreases of aversive stimulation-induced jaw contractions and associated muscle potentials have been reported in human and monkey subjects following both smoking and the intravenous and oral administration of nicotine (Hutchinson & Emley, 1973).

Fagerstrom and Gotestam (1977) detected increased electromyographic (EMG) activity of the trapezius muscle during smoking; however, mean EMG activity decreased during sham smoking. Future studies should determine whether differences in EMG responses to nicotine reported for specific skeletal muscles may be related to differences in functions between specific muscles studied.

Faden et al. (1981) concluded on the basis of studying subclinical neuropathy in 23 patients with chronic obstructive pulmonary disease that neuropathy was correlated with cigarette consumption.

Frankenhaeuser et al. (1968) studied the effects of smoking on catecholamine excretion, blood pressure, hand steadiness and skin temperature. Urinary epinephrine excretion increased continually after two, four and six cigarettes smoked during the experiment, but norepinephrine excretion decreased after two cigarettes, being unaffected by further smoking. Heart rate was increased by cigarettes smoked at the rate of one every 20 minutes, to an optimum dosage of four cigarettes. The heart rate increase produced by two cigarettes remained above baseline for 80 minutes and was accompanied by increased blood pressure and decreased hand steadiness.

Warwick and Eysenck (1968) used a task which involved subjects holding a stylus in each of seven holes of different diameters for 15 seconds. Subjects were not allowed to rest their elbows or support their arms. Nicotine had no effect on the frequency of side contacts but increased the length of time that the stylus remained in contact with the sides, suggesting that nicotine decreased hand steadiness.

B. CARDIOPULMONARY AND MUSCULOSKELETAL EFFECTS

B. Cardiopulmonary and Musculoskeletal Effects

1. Blood Flow
2. Cardiac Dynamics
3. Exercise and Musculoskeletal Functions
4. Blood Pressure
5. Respiration

1. BLOOD FLOW

Roth et al. (1944) studied circulatory, cutaneous, and metabolic changes during cigarette smoking or intravenous nicotine in 6 healthy smokers (aged 22-41 years). Cutaneous temperatures of the extremities of all subjects decreased while resting after smoking two standard cigarettes or tobacco cigarettes with ashless cigarette paper or standard cigarettes with a filter holder. When two corn silk cigarettes were smoked, there was little change in cutaneous temperatures. When fully clothed subjects were sitting or walking slowly, the decrease in temperature of the extremities after smoking two standard cigarettes was the same as when the subjects were in a resting position. An increase in the basal metabolic rate occurred after the smoking of two standard cigarettes, although the rate decreased after the smoking of corn silk cigarettes. Consistent changes in the electrocardiographic (ECG) tracing taken after the smoking of two standard cigarettes showed an increase of heart rate and decrease in the amplitude of the T wave. Such changes were negligible after the smoking of corn silk cigarettes. When saline solution was given prior to the intravenous injection of nicotine, there was a slight decrease in cutaneous temperatures of the extremities, but when nicotine was added to the solution, the decrease was rapid and pronounced. After the injection of nicotine, the ECG tracing demonstrated a definite increase in

heart rate and a decrease of T wave amplitude greater than that after the subject had smoked two standard cigarettes. There was an increase of blood pressure and heart rate after smoking two standard cigarettes or the intravenous injection of nicotine. After smoking two corn silk cigarettes, there was little or no change in blood pressure and heart rate. Some subjects showed parallelism between hyperreaction to the cold pressor test and hypersensitivity to tobacco. Two hyperreacted to one or the other alone. After subjects had smoked standard cigarettes, blood pressure, heart rate, and the ECG returned to normal within 5-15 minutes. Peripheral vascular constriction indicated by cutaneous temperatures of the extremities persisted 30-60 minutes and in some cases longer.

Vasoconstriction in the finger has consistently been reported following smoking in normal persons, but does not occur in heavy smokers with peripheral vascular disturbances (Lucchesi et al., 1967).

Suter et al. (1983) studied the effect of smoking cigarettes with different nicotine deliveries on the subcutaneous blood vessels at different sites of the body in 15 healthy female smokers (aged 19-34 yrs). Heart rate increases were dependent on the individual mouth intake of nicotine. The vasoconstrictive response to nicotine was considerable in finger, modest in foot,

and absent in forehead and ear recordings. The magnitude of this vasoconstriction in the finger correlated positively with personality traits of neuroticism. Whelan (1968) studied changes in hand blood flow measured qualitatively (by oxygen saturation) and also quantitatively. Intra-arterial (i.a.) injection of nicotine produced initial vasoconstriction associated with pain followed by vasodilation of 15-45 minutes duration.

Fewings et al. (1966) reported that the predominant effect of intra-arterial nicotine was vasodilation in the hands of healthy males. The response was complex: minor vasoconstrictor components involved a sympathetic reflex response to the pain of the nicotine injection and a vasoconstrictor component that was unmasked when sensory nerves were blocked by both denervation and the alpha adrenergic antagonist phenoxybenzamine. The vasodilator action of nicotine was not adrenergic, and was probably a direct local effect on smooth muscle. The ganglionic blocker hexamethonium bromide antagonized both vasoconstrictor and vasodilator effects of nicotine.

Ludbrook et al. (1974) studied the response of hand blood flow to ice application to the neck during smoking, sham smoking, intravenous nicotine, a foot movement procedure, mental arithmetic, and imaginary smoking in four experiments. Blood flow was measured simultaneously in both hands by venous

occlusion plethysmography. One hand was kept at 26 degrees and the other at 36 degrees C. In the first experiment, subjects were seven normal male and female smokers, aged 21-48 years who smoked 10-30 cigarettes per day. With both tobacco smoking and sham smoking, the ice response was depressed compared with resting conditions, i.e., there was significantly less vasoconstriction at all levels of flow in response to ice application. Ice application produced a 61% decrease in hand blood flow in the control condition, compared with 33% during sham smoking and 23% during tobacco smoking. There were no significant differences between the ice response during sham smoking and that during tobacco smoking. At the completion of 7 minutes of tobacco smoking, arterial blood pressure increased insignificantly, and heart rate increased significantly. Heart rate remained unchanged during sham smoking. When nicotine was administered into an antecubital vein, only infusions that produced tachycardia and other pronounced effects were evaluated. Compared with controls during saline infusion, there was a significant decrease of the vasoconstriction induced by ice application during nicotine infusion (56% and 31%, respectively). By the end of the 10-minute nicotine infusion, arterial blood pressure and heart rate had increased. When sham smoking and intermittent foot movement were studied to determine the effect of a procedure not affecting respiration but requiring the subject to respond to sensory input, foot movement decreased the

ice response compared with the control period, as did sham smoking. Ice application produced a 54% decrease in hand blood flow in the control condition, compared with 40% during sham smoking and 41% during foot movement. There was no significant difference between the effects of foot movement and sham smoking on the ice response, and there was no significant change in heart rate increase during sham smoking and heart rate decrease during foot movement. The effects of two procedures requiring cortical activity produced decreased ice responses, while imaginary smoking had no effect. Ice application produced a 63% decrease in hand blood flow in the control condition, 71% during imaginary smoking, and 43% during mental arithmetic. Heart rate increased during mental arithmetic, but during imaginary smoking the increase was not significant. The effects of tobacco smoking on hand blood flow are not likely to have deleterious consequences because other stimuli of everyday life have been shown to produce at least as great an effect on hand blood flow as smoking.

Similarly, Walsh et al. (1973) found that inhalation of tobacco smoke decreased the response of hand resistance vessels to distant ice application compared with the control response. Sham smoking, intravenous administration of nicotine (200, 400 or 600 ug/min for 10 minutes), a foot movement procedure, and mental arithmetic also had this inhibitory effect. Only sham smoking failed to decrease the ice response. A common central inhibitory action at a cortical level may be responsible for this antagonism of the cold pressor response.

Rottenstein et al. (1969) studied changes in cutaneous blood flow in toes estimated by changes in skin temperatures at constant environmental temperature (20 C). Nicotine was administered intravenously in a single dose of 1-2 mg in 1 minute or of 3 mg in 4 minute. Cutaneous blood flow decreased, and muscle blood flow increased. The period of the increase in muscle blood flow was found to be shorter than the decrease in cutaneous flow.

Koch et al. (1980) studied the effects of high nicotine (1.54 mg) and low nicotine (0.08 mg) cigarette smoking compared to sham smoking. Increased heart rate and systolic blood pressure, decreased pressure pulse transit time and digital blood flow were correlated with increased nicotine levels. The increases in heart rate and blood pressure were probably due to beta adrenergic action; decreased digital blood flow to alpha adrenergic action. Beta adrenoreceptor predominance over alpha adrenoreceptors produced increased arterial muscle blood flow after high nicotine cigarettes. Pressure pulse transit time (PPTT) decreased after high nicotine cigarettes; the original PPTT had not returned after 2 hours. The decrease in PPTT was less after a low-nicotine cigarette than after a high-nicotine cigarette. Digital blood flow decreased after high nicotine cigarettes, low nicotine cigarettes, and sham smoking.

Stromblad et al. (1959) studied the effect of intra-arterial administration of nicotine on vasoconstriction in the hand of 10 healthy subjects. A control injection of saline had no effects on vasoconstriction. Sensitivity to the vasoconstrictor effect of nicotine was not found to correlate with individual levels of habitual smoking, which ranged from no smoking to smoking more than 30 cigarettes per day. Injections of both hexamethonium and pentolinium antagonized the vasoconstrictor response to nicotine. Combined injections of dihydroergotamine and dibenamine also blocked vasoconstriction. Blockade by sympathicolytic and ganglionic-blocking agents suggests that nicotine mediates vasoconstriction by acting directly on the autonomic nervous system when administered intra-arterially.

Using fundus photographs examined under a dissecting microscope, Bettman et al. (1958) studied the effect of cigarette smoking on retinal blood vessels before and after smoking and after breathing pure oxygen. Four comparable retinal points were studied on each of the 18 subjects, a total of 72 points. After one cigarette, 7 of the 72 points showed vasoconstriction, and 2 showed vasodilation. Ten minutes after the cigarette was smoked, only 4 points showed vasoconstriction, and 2 showed vasodilation. After inhalation of oxygen for 5 minutes, 26 of the 72 points

(36%) showed vasoconstriction and none showed vasodilation. Of the 18 subjects studied, 7 showed an increase in blood pressure of 10 mm Hg or more after smoking, and 13 subjects showed an increase of 20 mm Hg or more. After oxygen inhalation, subjects showed a decrease of at least 10 mm Hg and none showed an increase. The skin temperature in 5 subjects increased one degree C or more. Skin temperature changes and blood pressure changes were not correlated. Smoking may constrict the retinal blood vessels in a few humans, but may actually dilate them on rare occasions. These studies suggest that smoking may increase the intraocular blood supply in some persons rather than decrease it.

Ruskin et al. (1969) described use of both fluorescence retinal cinematography and conventional still photography in evaluating the effects of vasoactive substances upon the retinal vasculature. Retinal arteriovenous transit time did not change after smoking 2 cigarettes; there was a small decrease in mean vessel diameter.

Matsubara and Sano (1972) studied the effect of smoking on the microcirculation. After smoking, calf blood flow and capillary filtration coefficient decreased. The venous system showed little effect of smoking, but arterioles constricted and precapillary sphincters closed as a result of smoking, suggesting

that release of norepinephrine may be responsible for both effects. Parker and Bradham (1969) found that skin temperature decreased an average of 2 degrees C for 18 of 20 peripheral vascular disease patients studied after smoking one cigarette. Tachmes et al. (1975) reported that no changes in leg blood flow, lung diffusion capacity, pulmonary blood volume, or lung functional residual capacity were detected after smoking.

Decreases in skin temperature following smoking have consistently been observed. Larson et al. (1961) reported that a large number of investigators have observed this phenomenon, with decreases ranging from 0 degrees to 4 degrees C for the finger and 0 degrees to 2.8 degrees C for the toe. Auge (1973) showed that skin temperature decreases were related only partially to nicotine content. When subjects smoked a cigarette with 2.11 or 1.02 mg nicotine, mean skin temperature decreased 3.5 degrees C below base levels. When they smoked a 0.75 mg nicotine cigarette, the mean decrease was 2.8 degrees C. With high nicotine cigarettes, temperature levels were still 1 degree C below baseline one hour after smoking. When subjects smoked lettuce-leaf cigarettes with no nicotine, their skin temperature decreased a mean of 2.0 degrees C and returned to baseline within 10 minutes.

Wechsler (1958) studied the effects of cigarette smoking and intravenous nicotine on the human brain. Ten normal subjects (17-85 yrs of age) were studied before and 3-8 minutes after smoking three regular sized cigarettes in 10 minutes. No significant changes in cerebral blood flow, oxygen consumption, vascular resistance, respiratory quotient, blood pH or blood gases were observed. EEG recordings made before, during and for 10 minutes after smoking revealed an intermittent flattening lasting 1-30 seconds. This pattern occurred primarily with puffing on the cigarette, but it also occurred to a lesser degree in subjects who did not inhale and in those smoking filtered and denicotinized cigarettes. This pattern could be an abnormal attentional response. Five men (19-22 years of age) were studied before and during the last 10 minutes of the administration of 8-10 mg nicotine given over a 3-minute interval. Dizziness, nausea, pain in the infusion arm, numbness, shaking and cold extremities occurred. Anxiety, tachycardia, and hyperventilation with a decrease in arterial PCO₂ and an increase in cerebral metabolism were observed in three subjects. Because of the side reactions, it is difficult to attribute the observed significant increase in cerebral metabolism (4.0-6.0 cc/100 gm/min, $P < 0.25$) to nicotine.

2. CARDIAC DYNAMICS

Roth (1956) reported that the mean resting heart rate increase associated with smoking was 36 bpm (range 20-52 bpm) in 425 observations on 100 smokers. Herxheimer et al. found that the effects of increased heart rate were observed about 2 minutes following the first inhalation. Elliot reported that smoking steadily throughout the day maintained subjects at a higher heart rate than on abstaining days and that the increased resting heart rate was observed even when the subjects were not actively smoking.

Elliot and Thysell (1968) studied 10 male smokers in the morning after a night's abstinence, smoking for 5 minutes, sham smoking, and deep breathing. The smokers rested at a heart rate of about 77 bpm upon awakening at 8:30 AM. The resting heart rate levels for the same smokers when tested at 11:30 AM again without having smoked since awakening, were about 74 bpm. The resting heart rate levels for these smokers when tested at 11:30 AM after smoking in their usual fashion since awakening (about 7 or 8 cigarettes) averaged about 88 bpm, an elevation of 14 bpm over the comparable resting levels. Neither sham smoking nor deep breathing increased heart rate. However, Erwin (1971) studied 10 smokers in their natural work environment for a total of 26 hours per subject by ECG telemetry. No statistically

significant heart rate changes were observed before, during or after smoking. In 20 young men, Squires et al. (1984) reported that cardiovascular effects of an oral smokeless tobacco product (snuff) were investigated in 20 young men and in 10 anesthetized dogs. Instrumented measurements were taken after the dogs were given a 2.5 g dose of moistened snuff. Increases were seen in heart rate, blood pressure, left ventricular pressure, left ventricular end diastolic pressure, and left ventricular dP/dt. Decreases in flow were noted in the coronary circumflex, renal and femoral arteries. In the experiment using humans, subjects were given a 2.5 g dose of the same snuff product; for twenty minutes following baseline, heart rate and blood pressure both increased.

Hopkins et al. (1984) reported that heart rate and exhaled carbon monoxide concentration were the most useful noninvasive indices of smoke uptake following one cigarette. Carboxyhemoglobin and plasma nicotine levels were the most useful invasive indices of smoking uptake.

Nyberg et al. (1982) studied the effects of nicotine chewing gum and a placebo gum administered in a double-blind cross over method to 8 subjects. Nicotine gum (4 mg) produced approximately a 16% increase in heart rate compared to a 4% increase following a placebo gum. Mean systolic blood pressure and hand blood flow

increased about the same amount following both placebo and nicotine gum. Changes in diastolic pressure, calf blood flow, and skin temperature were not significant for either nicotine or placebo gum. Nausea, dizziness and anxiety were reported after nicotine gum. Tachmes et al. (1978) reported that high-nicotine cigarettes increased systemic blood pressure more than a low-nicotine cigarette. Stroke volume remained relatively constant. The magnitude and duration of an increased cardiac output were shown to be directly related to the nicotine content of the cigarettes smoked.

Mo es et al. (1964) determined percentage changes in cardiac output, stroke volume, and heart rate in 7 healthy smokers after smoking, after glucose, and after smoking preceded by glucose. No significant changes occurred after glucose. There was a significant increase in cardiac output, stroke volume, and heart rate after smoking. Pretreatment with glucose did not change the heart rate increase, but the cardiac output increase was ameliorated.

Bekheit and Fletcher (1976) studied the effects of smoking on myocardial conduction in 28 smokers. Atrioventricular nodal conduction time during atrial pacing decreased after a few puffs of a cigarette. Smoking decreased the incidence of blocked beats in these subjects and in subjects with spontaneous Wenckenbach

block. Smoking did not affect conduction velocity in the anomalous pathways in subjects with Wolff-Parkinson-White syndrome. Subjects with atrial fibrillation showed increased ventricular rate after one to three puffs; smoking seemed to antagonize the cholinergic effects of the digitalis that these subjects were taking. These results indicate that smoking has a specific adrenergic effect on atrioventricular nodal conduction.

Analysis of 24-hour continuous recordings of arterial pressure, heart rate, and ECG from 9 regular smokers who were free to do as they pleased during the experiment was performed (Cellina et al., 1975). Cigarette smoking episodes signalled by the patient were analyzed. Forty-nine separate smoking episodes were indicated and analyzed. There was a significant increase in arterial pressure five minutes after smoking a cigarette. The systolic pressure increment was twice that of the diastolic increment and was present under different conditions of everyday life. No quantitative differences were found between normotensive and hypertensive subjects. There was no reproducible change in heart rate (mean increase +0.3 bpm) in the group as a whole. Smoking produced short-term decreases in arterial pressure and heart rate occurring over 8 to 10 heart beats immediately after the first inhalation of tobacco smoke, followed by a rebound increase in arterial pressure to a level greater than the pre-smoking level. Cigarette smoking caused angina pectoris in one subject, and showed ST-segment depression preceding the subject's awareness of pain.

The cardiovascular effects of healthy young adults were studied by ballistocardiography, electrocardiography and sphygmomanometry (Thomas et al., 1956). After one cigarette, systolic pressure, diastolic pressure, heart rate, cardiac output and cardiac index increased, while pulse pressure and stroke volume decreased significantly. The effects of sex, smoking, parental hypertension, parental coronary artery disease, and combined parental hypertension and coronary artery disease were statistically correlated with the measured parameters. Systolic pressure increased more in women than in men. Pulse pressure decreased more in men than in women. There were no significant differences to be found between smokers and nonsmokers. Statistically significant changes occurred in all measurements following the smoking of one cigarette. Subjects whose parents had hypertension exhibited greater increases in cardiac output and cardiac index than did subjects with parents free of hypertension. Subjects with parental coronary artery disease showed a much smaller increase in cardiac output and cardiac index than did subjects with parents free of coronary artery disease.

Rummel et al. (1975) studied 56 college students for two major purposes: to determine the effects on heart rate and blood pressure when a nonsmoker inhaled the exhaled smoke from a cigarette smoker, and to investigate the effects of such inhalation in relation to the attitudes of the nonsmoker toward

breathing exhaled smoke. In a closed environment after 5, 10, 15, and 20 minutes of exposure to exhaled smoke, the nonsmokers' heart rates and blood pressures were monitored. Subjects were also grouped according to whether they disliked, or were indifferent to, the presence of cigarette smoke. Results indicated that the "dislike" group had higher heart rates than the "indifferent" group on all trials. Systolic pressure was not significantly different between groups. It could not be determined if the higher heart rates in the "dislike" group were true or were caused by the anticipation of the situation.

Danaher et al. (1976) found that rapid smoking produced greater increases in heart rate than by regular smoking or rapid breathing with sham smoking. Differences in expired carbon monoxide (CO) and estimated blood carboxyhemoglobin were not significant. No changes in heart rate (baseline 75 bpm) were found with rapid breathing/sham smoking. Normal smoking with both low and high nicotine produced about the same increases in heart rate from baseline (72-78 bpm). Rapid smoking with no nicotine increased heart rate to peak of 85-90 bpm from baseline 78; rapid smoking with both low and high nicotine increased HR to peak of 105-110 bpm from baseline 75-80 bpm. Results showed that rapid smoking produces relatively greater stress on the cardiovascular system than normal smoking. To clarify the physiologic effects of nicotine during rapid smoking therapy (Sachs et al.,

1981) 21 smokers with symptomatic obstructive pulmonary disease or coronary heart disease were studied. Patients were studied at baseline, after 12 hours of abstinence from cigarettes, and during normal smoking. During normal smoking, patients inhaled every 60 seconds and during rapid smoking, every 6 seconds. Serum nicotine increased for normal smoking and rapid smoking. Heart rate increased significantly for normal and rapid smoking, but was not significantly different between the two groups. Systolic blood pressure was significantly higher for rapid smoking, and diastolic blood pressure increased significantly in all conditions. Arterial carboxyhemoglobin increased significantly for normal and rapid smoking, but was not significant between normal and rapid smoking. Arterial pH, PaO₂, and PaCO₂ did not change across conditions. The inverse relationship between serum nicotine and heart rate indicates that there is no simple, positive relationship between serum nicotine or nicotine consumption and cardiovascular change. Thus, for the patients in these two disease groups, consuming large amounts of nicotine for a smoking cessation program may not produce any more cardiovascular stress than small amounts.

3. EXERCISE AND MUSCULOSKELETAL FUNCTIONS

Hiestand et al. (1940) studied the immediate effects of cigarette smoking on metabolic rate, heart rate, oxygen pulse, and respiratory rate in 39 subjects following smoking one cigarette. Of the 39 subjects observed, smoking was associated with increase in metabolic rate in 82% of the subjects; a decrease in 13%; and no immediate effects were observed in 5%. The average increase in metabolic rate was 8.9%; increases in metabolic rate for 18 men was 7.7% for 21 women, 9.9%. The maximum effect of smoking one cigarette on basal metabolism was reached immediately in some subjects and delayed as long as 45 minutes in other subjects. Smoking increased heart rate in 72% of the subjects; decreased it in 26%; and no change was observed in 2.5%. After 15 minutes following smoking, the heart rate increase for men was 5.9%; for women, 6.4%. Respiratory rate decreased immediately after smoking and returned to normal 45 minutes later. Smoking produced an immediate decrease in the oxygen pulse rate followed by an increase lasting about 45 minutes. The greatest physiological changes were observed in habitual smokers who inhaled and by persons unaccustomed to smoking. Dietz et al. (1984) reported that during exercise, increased heart rate occurred with increased norepinephrine (NE). Beta adrenenergic blockade (200 mg metoprolol, p.o.) shifted heart rate and blood pressure to lower values; beta blockade did

not antagonize smoking induced increases in blood pressure, heart rate and norepinephrine. Heart rate, systolic blood pressure, and diastolic blood pressure increased during and decreasing from peak values after smoking 5 cigarettes ($P < 0.01$). Heart rate and blood norepinephrine showed negative correlation both following smoking and during intravenous administration of norepinephrine (0.01-0.3 mcg/kg/min) without smoking. During exercise, increased heart rate and blood pressure occurred with increased norepinephrine.

Brundin (1980) studied thermal reactions to exercise programs of different durations before and after smoking. Increased heart rate after smoking was more pronounced than increase in cardiac output; stroke volume was decreased in response to smoking. Carboxyhemoglobin increased, and relative hyperthermia appeared during short-term exercise performed immediately after smoking. The temperature effect was paralleled by increased heat generation, reflected by an increase in total body oxygen consumption.

David (1968) studied the relationship between the number of packages of cigarettes smoked per day and performance on physical fitness tests of different levels of strenuousness. Performance was significantly decreased for more strenuous tasks (crawling test, dodge and jump test, and one-mile run), but was not significantly decreased for tasks that required only minimal activity

(climbing, and throwing accuracy). Comparison of six smoking levels revealed significant performance decreases as functions of smoking amount and task strenuousness. Decreases in performance with increased smoking may result from decreased oxygen delivery in tasks requiring high levels of physical activity. Seppanen (1977) studied physical work capacities at heart rates of 130, 150, and 170 beats per minute that decreased after both carbon monoxide inhalation and smoking, although the change was greater after smoking. The greatest decrease in calculated mean maximal work was after carbon monoxide inhalation.

Williams and Shields (1972) found that brief exercise decreased the blood carbon monoxide concentration that was first elevated by smoking.

Rabinowitz et al. (1979) reported that smoking a nicotine cigarette induces the same physiologic responses as isometric exercise. Klausen et al. (1983) studied physical endurance in healthy, male, moderate smokers using a cycle ergometer following either three unfiltered cigarettes or inhalation of an amount of carbon monoxide giving a blood carbon monoxide level equivalent to the three cigarettes. Decreases in maximal oxygen uptake were significant for both the smoking and carbon monoxide inhalation conditions as compared to the control condition of no smoking and no carbon monoxide exposure prior to testing. Endurance time was

significantly decreased following both experimental conditions, but smoking had a greater effect. Increased maximal and resting heart rates and decreased peak blood lactate concentration were demonstrated for the smoking condition only during maximal exercise.

McHenry et al. (1977) reported no significant differences in the prevalence of exercise-induced premature ventricular contractions when current smokers were compared with nonsmokers or former smokers among 586 men studied. The duration of maximal exercise was shorter in smokers and former smokers than in nonsmokers. Maximal heart rate during exercise was decreased more in smokers and former smokers than in nonsmokers. Aronow and Cassidy (1974) studied 10 male subjects with classic stable exertional angina pectoris and severe coronary artery disease during exercise and bicycle ergometry until onset of angina. After smoking one high-nicotine cigarette mean increases in heart rate, systolic pressure and diastolic pressure were associated with decreases in mean exercise time until angina from 243.4 ± 46.6 sec (controls) to 185.3 ± 43.5 (experimental). There was a greater decrease in exercise time until angina after smoking one marijuana than after smoking one high-nicotine cigarette. Amount of maximal ischemic S-T segment depression after smoking a high-nicotine cigarette and after onset of angina were similar.

Aronow and Swanson (1969) also studied 10 men with exertional angina pectoris who performed exercise four times in a nonsmoking state and four times after smoking a low-nicotine filter cigarette. All patients developed angina sooner if they smoked before exercising. All patients showed indications of an increase in myocardial oxygen consumption. Patients with diseased coronary arteries who exercise after smoking even low-nicotine cigarettes may not be able to meet the increased demand for myocardial oxygen and may therefore develop angina pectoris sooner.

Anderson and Brown (1951) studied the effect of cigarette smoking upon grip strength and recuperation from local skeletal muscle fatigue in 14 men, aged 18-21 years, who had smoked for at least one year. Grip strength was measured by having the subjects (all right-handed) squeeze a dynamometer with the left hand. Each subject squeezed the hand dynamometer at 10 second intervals for a period of six min then rested for three minutes, during which time subjects smoked the placebo or real cigarette. Subjects then squeezed the hand dynamometer at 10-second intervals for another period of six minutes, rested for three minutes, and squeezed the hand dynamometer three times. This sequence was performed in two tests separated by two days by each subject, once smoking a real cigarette, and the other, a placebo. Seven took the smoking test first, and seven took the nonsmoking

test first. A comparison of the group mean percentages of decrease in grip strength during smoking and nonsmoking tests showed that smoking one cigarette had no significant effect upon grip strength and recuperation from local fatigue of the flexors of the hand within the time period studied. When the data obtained during the first and second tests were compared, significantly higher mean grip scores were found for the second test, indicating that a slight training effect may have occurred. Kay and Karpovich (1949) found that smoking one cigarette by smokers had no effect on recovery from local skeletal muscle fatigue of the flexors of the hand. In contrast, Willgoose (1947) also tested the effect of smoking one cigarette on fatigue and strength of flexors of the hand, and reported that the percent recovery after smoking and rest and the percent recovery after a nonsmoking rest condition indicated that in every case, the percent of recovery was greater for the nonsmoking than for the smoking condition.

Shephard et al. (1979) studied responses of passive cigarette smoke exposure in healthy nonsmokers (23 men and women) who were performing intermittent bicycle ergometer work sufficient to increase respiratory minute volumes by a factor of 2.5. Cigarettes (7 or 9) were smoked by a standard machine; chamber carbon monoxide concentrations were 20 or 31 ppm and particulate levels were 4 mg/cu. m. The main subjective symptoms were odor and eye

irritation; cough, nasal discharge, stiffness, and throat irritation were also reported. A small increase of tidal volume and respiratory minute volume seemed to result from anxiety rather than from airway irritation. Static lung volumes were unchanged, but 3%-4% decreases were reported for forced vital capacity, 1 sec forced expiratory volume, and maximum flow at 25% and 50% vital capacity. Changes of dynamic lung volumes were of the order anticipated from the cigarette equivalent encountered by the passive smoker (< 0.5 cigarette/2 hr). These tests provide little evidence of respiratory responses to passive cigarette smoke exposure, despite the combination of high smoke concentrations and intermittent exercise.

4. BLOOD PRESSURE

Thomas et al. (1956) reported a mean systolic blood pressure increase of 2.9 mm Hg and a mean diastolic increase of 4.6 mm Hg in 113 smokers after smoking a standard cigarette. Sachs et al. (1981) studied the normal cardiovascular effect of normal rate smoking (inhalation once every 60 seconds) over a 16 minute period in 14 regular cigarette smokers with coronary heart disease but no hypertension. Serum nicotine levels increased significantly in both normal and rapid smoking conditions. Arterial carboxyhemoglobin increased significantly during both smoking conditions. Systolic blood pressure increased only during the rapid smoking condition; diastolic pressure increased significantly during both smoking conditions. Even for coronary heart disease patients, exposure to relatively large amounts of nicotine produced no more cardiovascular stress than small amounts.

Gunby (1982) reported on the effect of oral tobacco (snuff) in 20 male athletes. A 2.5 g pinch of oral tobacco was placed in each subject's mouth. Mean heart rate increased from 69 to 88 bpm. Mean blood pressure increased from 118/72 to 128/78 mm Hg. Both parameters returned to their original levels after the tobacco was removed. Benowitz et al. (1984) studied 10 heavy smokers while smoking their own brand of cigarettes while

abstaining. Cardiovascular effects were measured and urinary nicotine excretion was measured as a control. Blood nicotine concentrations were 4 times as high smoking high nicotine compared to low nicotine cigarettes. Smoking increased mean heart rate but heart rate effects did not differ as a result of high versus low nicotine exposure. Blood pressure tended to be higher while smoking, although plasma cortisol concentrations throughout the day did not change while either smoking or abstaining.

Seltzer (1974) analyzed cross-sectional and longitudinal data to compare the blood pressures of 794 subjects representing four categories of cigarette smoking habits. At admission into the study, current smokers had lower systolic and diastolic blood pressure than nonsmokers and former smokers, with age group controlled. Former smokers were heavier than nonsmokers, who were somewhat heavier than current smokers. At the 5 year follow-up, 104 subjects had quit smoking. Subjects had a significant increase in both systolic and diastolic blood pressure. Continuing smokers had unchanged systolic pressure and a modest decrease in diastolic blood pressure. Both groups had significant increases in body weight, but quitters gained more than twice as much as continuing smokers. Analysis of blood pressure changes by weight change groups showed that quitters had increased systolic blood pressure whether they gained or lost

weight, but diastolic pressure rose only when they gained weight. In contrast, continuing smokers had increased systolic blood pressure when they lost weight. When they lost weight diastolic pressure decreased. Quitters were far more likely than continuing smokers to have reached critical levels of hypertension. These epidemiological data suggest the surprising finding that cigarette smoking tends to inhibit increases in blood pressure and that smoking cessation contributes to increases in blood pressure even when weight decreases.

5. RESPIRATION

Hammond and Garfinkel (1963) studied lung histological specimens from 1,340 patients to determine changes in the parenchyma associated with smoking as a function of age and smoking habits. Tissue from each of four lobes from each of 1,340 patients that revealed changes in the degree of fibrosis and rupturing of alveolar septums, development of padlike attachments to the alveolar and arterioles as a function of smoking habits. The least change was noted for patients who had never smoked and the most change was noted for current smokers and those who smoked cigarettes most heavily. Current pipe and cigar smokers showed more changes than nonsmokers. Age was positively associated with histological changes; older patients tended to have more extensive changes in the parenchyma than younger patients. This was true of both smokers and nonsmokers. Ex-cigarette smokers matched with current smokers for age, race, occupation, and daily cigarette consumption showed less extensive histological changes than current smokers if they had stopped smoking at least three years prior to death. These findings suggest that cigarette smoking results in histological changes in the parenchyma as well as in bronchial epithelium and bronchial glands. These changes are believed to increase with continued smoking and advanced age. The clearance of ^{99m}Tc -DTPA among smokers was studied during and after smoking in 10 subjects with

a scintillation camera to evaluate the rate and uniformity of solute clearance from the lungs. The average clearance from the lungs of smokers with no significant airway obstruction was greater than that found in normal subjects by an average factor or more than 5. This abnormality was observed in all lung regions. Clearance decreased rapidly in the week after smoking was stopped. These data indicate that smoking results in a rapidly reversible increase in pulmonary epithelial permeability (Mason et al., 1983). Kollerstrom et al. (1977), found a lower ratio of sulfated to sialidated mucin in the nonsmokers. In addition, in both smokers and nonsmokers, there was a diminishing proportion of sulfated mucin down to the inferior lingular pathway from the trachea. Analysis of the logarithm of the ratio showed that the smokers' means to be 2.3 times higher than that of nonsmokers at each generation of branching, and for both groups, the ratio's average decrease down successive generations was given by a factor 0.9. The sulfated to sialidated ratio may be a sensitive measure of bronchial response to inhaled irritant, including cigarette smoke.

Hamosh and Da Silva (1977) examined the effect of chain-smoking three unfiltered cigarettes (each containing 2.5 mg of nicotine) on maximal and partial expiratory flow rates in order to assess the utility of these measures in monitoring airway response to irritants. Using 10 healthy heavy smokers, measures

of expiratory flow rates were obtained both before smoking and following a smoking rate of 10 puffs per 5-minute interval for each cigarette. Although there was a 5-minute interruption between cigarettes for taking measurements, results indicated a significant decrease in maximal midexpiratory and partial midexpiratory, end-expiratory, and instantaneous flow rates following acute intense smoking.

Swineford and Ochota (1958) studied chronic cough and other evidences of chronic lung disease after 25 patients stopped smoking, using a clinical questionnaire. Cough, dyspnea on exertion, asthma, frequent colds, and hay fever were recorded 96 times. Undiagnosed chest pain was reported 11 times. Eleven of these symptoms disappeared entirely upon cessation of smoking. Forty-one symptoms markedly improved (75%-90%). In 15 of the 25 patients, respiratory improvement was attributed solely to abstinence from smoking.

The acute effects of cigarette smoking were measured in 36 healthy subjects and 22 smokers with cardiopulmonary disease (Nadel and Comroe, 1961). Airways conductance decreased after smoking in both groups. Inhalation of an isoproterenol aerosol antagonized this effect. Additional experiments indicated that the decrease in conductance was not related to inhalation of nicotine or other volatile substances. Inhalation of nicotine

aerosol did not produce the effect, and variations in concentrations of nicotine in cigarettes produced no significant difference in effect. A cigarette with a charcoal filter decreased airways conductance, suggesting that submicronic particles in cigarette smoke may decrease conductance, possibly by bronchoconstriction. The geometric mean provocation concentration of histamine required to decrease the specific airway conductance by 35% was found to be significantly lower in smokers. Nonspecific bronchial reactivity may be a factor in the development of airway obstruction in smokers (Garrard et al., 1980). Robertson et al. (1960) also reported that changes in airways conductance after smoking were significantly less when smoking a cigarette with an efficient filter. A study of 4 subjects showed that airways conductance returned rapidly to baseline after smoking. The results indicate that reactivity to cigarette smoke is decreased by increasing a cigarette filter's retention efficiency. Reactivity to cigar-tobacco smoke, if inhaled, was no less than reactivity to cigarette smoke.

However, when Clarke et al. (1970) compared the bronchoconstrictor effect due to three different cigarettes for 16 subjects, no significant difference between the response to the cigarette with a filter that removed vapor and the response to the cigarette with a filter that removed particles was detected. Rees et al. (1982) measured airways resistance in 6

male smokers and 6 male nonsmokers following a single puff and inhalation from 5 types of cigarettes and 1 type of cigar. Smallest volumes were taken from unfiltered and largest volumes from mildest filtered cigarettes (lowest nicotine, tar, and carbon monoxide). Greatest decreases in airways conductance were found in nonsmokers smoking unfiltered high tar cigarettes and in smokers smoking cigars.

Sterling (1967) studied the airway resistance and lung volume for 11 normal adults. Smoking produced a significant decrease in airway conductance that lasted 20-30 minutes. Conductance increased after injection of atropine. DaSilva and Hamosh (1973) studied respiratory functions of 21 subjects before and after smoking a nonfilter cigarette. Specific airways conductance and maximum expiratory flow at 50% of vital capacity decreased after smoking. A delayed bronchodilation of the small airways after smoking a low-nicotine cigarette might represent a response usually masked by other long-acting components in smoke (Da Silva and Hamosh, 1971). In a more extensive analysis, White and Froeg (1980) compared pulmonary function in 2,100 middle-aged subjects. Nonsmokers chronically exposed to tobacco smoke had significantly lower forced mid- and end-expiratory flow rates than nonsmokers not exposed. Spirometric values for passive smokers were not significantly different from those of light smokers and noninhaling smokers. The degree of pulmonary function abnormality was found to be associated with the extent

of smoker exposure. Nonsmokers in smoke-free work environments had the high test (most normal) spirometric values. Passive smokers, noninhaling smokers, light smokers, and heavy smokers had progressively and significantly lower (more abnormal) spirometric values.

Chiang and Wang (1970) studied the effect of acute cigarette smoke inhalation on multiple breath nitrogen washout, spirometric lung volumes, and forced expiratory flows in 7 nonsmokers (18-43 years old). Among the lung volume measurements, only an increase of residual volume was significantly different between the control and smoking conditions. None of the respiratory flow measures were significantly different between the two conditions. There also were no significant differences in all but one (nitrogen clearance delay) of the nitrogen washout measurements. The significant differences between the two conditions included nitrogen washout time, lung clearance index, fractional volume of slow compartment, and alveolar dilution factors. McCarthy et al. (1976) reported that intensive smoking was associated with a reduction in effort-dependent tests and with altered gas mixing in the lung. Resistance to air flow in the larger airways or reduction in effort and increased nonuniformity of intraregional distribution of ventilation was associated with acute intensive cigarette smoking. In subjects who stopped smoking, improvement in closing volume as a percentage of vital capacity and closing

capacity as a percentage of total lung capacity were found at 6 and 12 months (Buist et al., 1976). Respiratory symptoms decreased dramatically in those who stopped smoking, moderately in those who reduced consumption by at least 25%, and very little in those who did not modify consumption very much.

Tobin et al. (1982) reported that central respiratory drive (inferred from mean inspiratory flow) of smokers increased during smoking and decreased after smoking. Administration of the opiate antagonist naloxone before smoking had no effect on respiratory drive during smoking, but antagonized the respiratory drive depression following smoking.

C. METABOLIC EFFECTS

C. Metabolic Effects

- 1. Metabolism and Endocrine Functions**
- 2. Gastrointestinal Functions**

1. METABOLISM AND ENDOCRINE FUNCTIONS

Dill et al. (1934) studied a male subject who smoked six cigarettes in 2 hours following a light breakfast and who had a fasting glucose level of 95 mg/dl. The observations on blood sugar within this period ranged from 92 to 95 mg/dl. After smoking was discontinued and in the succeeding 1.5 hours, 5 of 6 blood glucose values ranged from 92 to 96 mg/dl. Smoking had no appreciable effect on blood glucose. While the metabolic rate after smoking remained unchanged in some subjects, in other subjects it increased 5%-15%. Smoking one cigarette produced no change in blood glucose, lactic acid or respiratory quotient. Szanto (1966) reported that 12 subjects showed no appreciable change after smoking, while 14 had an increase in blood glucose ranging from 8 to 22 mg/dl. After abstaining from smoking for 48 hours, their fasting blood glucose decreased and the hyperglycemic effect of two cigarettes increased. Bornemisza and Suciu (1980) showed that both diabetic and normal control showed an increase in blood glucose levels following smoking. Diabetics showed a greater increase. In 16 cases, the experiment was repeated, and an even higher increase of blood glucose was recorded. No increase in blood glucose was observed after smoking nicotine free cigarettes nor after smoking tobacco cigarettes without inhaling. The increase of blood glucose after smoking was assumed to be due to the secretion of catecholamines,

growth hormone, and cortisol. This reaction was greater in diabetics than in metabolically normal subjects. Coiro et al. (1984) tested the hypothesis that nicotine stimulates the secretion of growth hormone by interaction with an adrenergic pathway. Serum levels of growth hormone were studied following smoking and the oral administration of clonidine (0.15 mg), a specific alpha-adrenergic stimulant. Sixteen normal males (24-37 years old) who were chronic smokers abstained from smoking for 12 hours before receiving the single dose of clonidine. The subjects then smoked two non-filter cigarettes within 15 minutes of clonidine administration. Blood samples were taken at five 30-min intervals following drug administration. Clonidine increased growth hormone levels significantly. Together, nicotine and clonidine increased growth hormone levels higher than after either smoking or clonidine-induced increments alone. Results indicated that nicotine produced a significant increase in serum growth hormone within 30 minutes of smoking. These studies suggest that growth hormone secretion in man may be mediated by a neuroendocrine pathway that is sensitive to both nicotinic cholinergic and adrenergic stimulation.

Winternitz and Quillen (1977) reported a sharp increase in circulating cortisol after 2 cigarettes that was maintained through the second hour but decreased slowly after smoking.

Circulating growth hormone also began to increase after 2 cigarettes, peaked at 1 hour, and decreased to control levels while smoking continued. Urinary catecholamines increased more on smoking days than on nonsmoking days. In contrast, Cherek et al. (1982) reported that during an operant task a decrease in blood cortisol levels from the beginning to the end of smoking sessions occurred. Salivary cortisol levels were not affected by any of the conditions. Blood cortisol levels correlated highly with salivary cortisol levels. Seyler et al. (1984) investigated the relationships among changes in plasma nicotine, adrenocorticotrophic hormone (ACTH) and cortisol secretion after smoking. Ten male subjects smoked cigarettes containing 2.87 mg nicotine and 0.48 mg nicotine. Increases in cortisol and ACTH were not detected after smoking the lower nicotine cigarettes. Cortisol elevations were significant in 11 of 15 instances of smoking the higher nicotine cigarettes, but ACTH increased significantly in only 5 of these 11 cases. Each ACTH rise was accompanied by nausea, and subjects also appeared pale, sweaty and tachycardiac. Cortisol increases were significantly greater in nauseated than in non-nauseated smokers. The results suggest that such nausea stimulates cortisol release by stimulating ACTH secretion. Cortisol release in non-nauseated smokers appeared to occur through a non-ACTH mechanism. Kershbaum et al. (1968) studied the influence of tobacco smoking and nicotine on secretions of the adrenal cortex in nine humans and in animals.

Blood samples from the human subjects showed a 27% to 77% increase in plasma 11-hydroxycorticosteroid concentrations after heavy cigarette smoking, compared to a normal daytime decrease during control observations with no smoking. In dogs, intravenous doses of nicotine resulted in a 64% rise in plasma corticosteroids, and in rats a 58% increase. It is suggested that this increase in adrenocortical activity is due to enhanced corticotropin release resulting from a nicotine-induced increase in sympathetic and catecholamine activity. Because of these results and the known relationship of smoking to atherosclerotic vascular disease, further investigation should be done to determine whether the adrenocortical effect of smoking may be related to atherogenesis.

Wilkins et al. (1982) reported that blood growth hormone, prolactin and heart rate increased for a nicotine exposed group (2 mg). Growth hormone and prolactin increases were associated with a 25% increase of heart rate at 10 minutes; heart rate and plasma nicotine levels were maximal at 10 minutes and decreased linearly over 60 minute experimental elevated. At 60 minutes, heart rate approached baseline, but plasma nicotine remained elevated.

Bosse et al. (1980) studied smoking behavior and weight change over five years for 1,749 men. Ex-smokers generally gained more weight than men in other smoker categories, yet

nearly 36% of the ex-smokers either lost weight or maintained the same weight after quitting. Younger quitters tended to gain weight; whereas, older quitters tended to lose weight. Lean men tended to gain weight; whereas, stout men tended to lose weight. Subjects who received high doses of tar tended to gain weight; whereas, those who consumed less tar tended to lose weight. Subjects with low clinical anxiety tended to lose weight. Garvey et al. (1974) studied a cohort of 870 male veterans aged 20-69 years during a 5-year period to determine the effects of age and change in smoking status on body weight. Age at the beginning of the study was divided into 6 groups: 20-34, 35-39, 40-44, 45-49, 50-54 and 55 and older. Smoking behavior was divided into four categories: recent ex-cigarette smokers, continuing cigarette smokers, never smokers, and former smokers. The dependent variable was weight change from time 1 (beginning of study) to time 2 (5 years later) in pounds. Regardless of age, the former cigarette smokers gained more weight than did other men. The increase in weight was greatest for quitters between the ages of 40 and 54. Chronological age accounted for 5.1% of the variance of weight change and smoking behavior accounted for 2.4%. The importance of other factors in explaining the weight change is stressed.

Brozek and Keys (1957) calculated average weights for years 1 and 2 (before test subjects stopped smoking) and for years 3 and 4 (after test subjects stopped smoking). A weight change of +1.18 kg was reported for the control group and of +5.65 kg for the group who quit smoking cigarettes. The weight change for subjects who quit smoking showed the effect of body weight on smoking cessation.

Kershbaum (1966) reported that there was a greater increase in blood free fatty acid (FFA) concentration with cigarette than with cigar smoking. Inhaling caused a greater FFA response than no inhaling with both cigars and cigarettes. With tobacco containing glucose labelled with C-14, there was a greater absorption of C-14 with cigarette smoking. The greater output was attributable to differences in smoke inhalation and nicotine absorption.

Aziz et al. (1978) found that resting urinary level of total catecholamines was slightly higher in a smoker group than in a nonsmoker group. Smoking 20 cigarettes increased urinary catecholamine output in all subjects. The increase was largest in hypertensive smokers, in normoreactive smokers and nonsmokers. Smoking 2 cigarettes increased the number of hyperreactors among hypertensives by 60% and the number of hyperreactors among normotensives by about 20%.

Rowe et al. (1980) reported that intravenous administration of nicotine resulted in no effect on plasma vasopressin, a transient increase in mean blood pressure and heart rate associated with symptoms of light-headedness. Low and high nicotine cigarettes increased plasma vasopressin (high nicotine cigarettes had a greater increase). Symptoms of light headedness after high nicotine cigarettes and nausea after low nicotine cigarettes were reported. All 3 intravenous doses of nicotine yielded transiently increased blood pressure and heart rate of similar magnitudes. Smoking both cigarettes was followed by a transient increase in blood pressure. The increase above basal plasma vasopressin is greater after high nicotine cigarettes than low nicotine cigarettes. These results confirm that smoking in the absence of nausea, vomiting or decreases in blood pressure induces vasopressin secretion. This effect may be mediated by an airway-specific mechanism.

Burn et al. (1945) reported that six out of seven subjects experienced inhibition of diuresis for two to three hours after smoking one, two or three cigarettes, dependent on individual sensitivity. An experiment with two subjects showed the same effect after intravenous injection of nicotine in the amount equal to the amount that produced the effect after smoking. Walker (1948) also showed that 1 or 2 cigarettes produced

antidiuresis. Smoking 2 cigarettes increased secretion of antidiuretic hormone (Burn and Grewal, 1951). Nicotine was found to be a stimulus for both vasopressin and neurophysin secretion in some normal individuals, and the release mechanisms for these two peptides may be closely linked (Husan et al., 1975).

In 34 of 60 habitual smokers, in vitro thrombus formation time was found to be decreased following smoking; in 23 subjects the time was unchanged; and in 3 subjects the time was increased (Engleberg, 1965). However, when blood was repeatedly drawn over a period of several hours, there was variability of thrombosis time. The disparity seen between thrombus formation times and clotting times after smoking emphasized that thrombosis and coagulation are different processes. Increased thrombotic tendency may be mediated via the nicotine-induced secretion of epinephrine. This hyperthrombotic state may be a major etiological factor in the increased incidence of acute myocardial infarction in smokers.

Tanzen and Nilssen (1975) reported that after 12 hours abstention from tobacco, smokers had the same fibrinolytic activity as nonsmokers. Of 71 heavy smokers, 31 refrained from smoking during 8-9 weeks. Neither in those who abstained nor in controls did the fibrinolytic activity differ from that initially recorded. The smoking of six cigarettes was associated with increased fibrinolytic in superficial hand veins.

Sogani and Joshi (1965) studied whole blood clotting time, recalcified plasma clotting time, prothrombin time, platelet adhesiveness, fibrinogen content, and fibrinolytic activity. Changes before and after tobacco consumption were seen in all tests performed, but only the effect on platelet adhesiveness and fibrinolytic activity were significant. An increased tendency to coagulation and decreased fibrinolytic activity were evident in all the tests performed and with three modes of tobacco consumption.

Levine (1976) reported that in 11 smokers, no platelet aggregation responses were measured 10 and 20 minutes before and after smoking a lettuce-leaf cigarette. Before and after smoking a standard cigarette compared to the change in aggregation after lettuce-leaf cigarette smoking, the increases in aggregation were maximal at 10 and 20 minutes and at or near baseline by 30 minutes. None of the 11 subjects developed an increase in blood FFA after the lettuce-leaf cigarette. After the standard cigarette, all 11 subjects had increased FFA. The time of maximal FFA increase was 30 minutes after smoking. In three subjects, the increase in FFA occurred only after the increase in platelet aggregation was noted. The data suggest a possible direct casual link between cigarette smoking and arterial thrombotic disease.

Hart et al. (1976) reported that the mean antipyrine half-life was lower in smokers than in nonsmokers. Cigarette smoking significantly enhanced antipyrine disappearance rate; smoking contributed to the large variation in rates of drug metabolism observed in these subjects.

Smith and Landau (1978) concluded that carbon monoxide exposure from cigar or cigarette smoke was a frequent cause of an increased erythrocyte volume and/or a decreased plasma volume detected in smokers.

Warren et al. (1982) studied the effect of smoking on the immune system. The relationship between smoking and serum IgE levels was investigated. Skin tests, total serum IgE levels, and a respiratory questionnaire were used with 1,768 subjects, including smokers and nonsmokers. For subjects who had no skin test reactions or history of asthma or hayfever, the geometric mean total IgE levels were 14.8 U/ml for men and 11.9 U/ml for women. IgE levels among nonsmokers, former smokers, and current smokers varied significantly when skin reactivity and smoking history were considered. The percentage of subjects with elevated total IgE was significantly higher in smokers than in nonsmokers regardless of skin reactivity. Although the IgE levels were significantly higher in smokers than nonsmokers, there was no relationship between intensity of smoking and IgE

levels; these results confirm the association between smoking and elevated levels of serum IgE. Ferson et al. (1979) reported that low natural killer cell activity and immunoglobulin levels in smokers may be related. Miller et al. (1982) showed that cigarette smoking causes reversible changes in immunoregulatory T cells. Corberand et al. (1979) investigated the effect of smoking on the functions of polymorphonuclear leukocytes in 68 subjects including smokers and nonsmokers. Phagocytosis, oxygen consumption, and bactericidal activity were normal in smokers. Myeloperoxidase and neutrophil alkaline phosphatase activities were not changed. Nitroblue tetrazolium reduction and serum lysozyme levels were slightly increased in smokers. However, the capillary tube random migration was depressed and this was further aggravated by intensive smoking. Tobacco smoke may act directly on one or more unidentified target sites of polymorphonuclear leukocytes, which probably plays a role in the development of bronchopulmonary disease in heavy smokers. Rasp and Clawson (1978) studied the reversibility of the adherence of alveolar macrophages from smokers in 33 smokers and nonsmokers using a standardized nylon fiber assay and scanning electron microscope. The adherence of alveolar macrophages from cigarette smokers was uniformly decreased. However, after 2 months abstinence the defect was not found, which was not attributable to factors in lavage fluids and was not apparent in polymorphonuclear leukocytes. The surface of alveolar macro-

phages from smokers showed marked alterations that could affect the ability to adhere. Alveolar macrophages from smokers had a defect in structure and adherence that may influence their function and may account for the increased yield of alveolar macrophage from cigarette smokers.

To evaluate the role of oxidants from alveolar macrophages on the development of emphysema, alterations in the oxidative metabolism of alveolar macrophages were studied in 51 nonsmokers and 32 smokers (Hoidal et al., 1981). The superoxide anion produced in smokers was greater than that from nonsmokers. This also occurred before and after stimulation by bacteria or phorbol myristate acetate. However, oxygen uptake and glucose oxidation by unstimulated and stimulated alveolar macrophages from smokers were the same as that from nonsmokers. Because intracellular superoxide dismutase was increased in alveolar macrophages from smokers, the increase of superoxide anion did probably not result from lack of anion scavenging agent in the cells. The lysis of fibroblasts by alveolar macrophages from nonsmokers was completely prevented by addition of intracellular superoxide dismutase and catalase, confirming the importance of superoxide anion release. The elastase and lysozyme activities in alveolar macrophages were studied in 27 smokers and nonsmokers (Hinman et al., 1980). Macrophages, particularly those in smokers, were found to synthesize a calcium-dependent activity against synthetic

substrate which was distinct from polymorphonuclear leukocyte elastase. This activity was enhanced in smokers. Smokers' macrophages contained serine-proteinase activity that had an inhibitor profile similar to that of polymorphonuclear leukocyte elastase. The macrophages from smokers secreted 5 times more lysozyme and contained more lactate dehydrogenase activity than those of nonsmokers. These data show that polymorphonuclear elastase can become associated with the alveolar macrophage, which could assume a protective role against unrestrained elastinolysis. Martin (1973) studied alveolar macrophages from 11 smokers and 13 nonsmokers for altered morphology and increased acid hydrolase content. Crystalloid, refractile cytoplasmic inclusions of autofluorescent material were found in fewer than 5% of macrophages from nonsmokers while 30 to 95% from smokers contained this material. Multinucleated giant cells were found in the lavage of 3 smokers. The macrophages from smokers had acid hydrolase concentrations that were increased as much as 6 times normal. These increases correlated with the amount of daily cigarette consumption. The increased acid hydrolase concentrations in the cells from smokers indicate a mechanism by which chronic pulmonary disease may be related to smoking.

Finley and Ladman studied pulmonary surfactant layers taken from the lungs of smokers and nonsmokers by making an analysis of lipids. When compared with nonsmokers, endobronchial lavage of

smokers showed a deficit in surface active material. The volume of surfactant rapidly returned to the same levels as those of nonsmokers when the subject stopped smoking. There was no qualitative difference in the lipid analysis of surfactant from smokers and nonsmokers. However, the total lipid content, especially lecithin, was seven times less in smokers than nonsmokers.

2. GASTROINTESTINAL

Schnedorf and Ivy (1938) studied the effects of nicotine on gastrointestinal activities in smoking and nonsmoking normal human subjects, patients with peptic ulcer, and dogs. Results indicated that smoking, but not subcutaneously injected nicotine (0.4 mg), stimulates salivation in most smoking and nonsmoking subjects. Hunger contractions of the stomach in human subjects tended to decrease for 15-60 minutes following smoking one cigarette. While subcutaneous nicotine injection (1 mg) did not inhibit such contractions in dogs, inhalation of cigarette smoke inhibited the gastric motility promptly. Inhibition was blocked by sectioning of the vagi above the diaphragm in dogs, indicating reflex control of these contractions via vagal motor pathways. In normal smokers, there was no significant effect of smoking on emptying time. However, gastric acidity was significantly decreased. Neither gastric emptying time nor acidity were significantly affected by smoking in the ulcer group. Subcutaneous injection of 1 mg nicotine decreased acid secretion in one of three dogs. Subcutaneous nicotine injection (0.2, 0.4 or 1 mg) or smoking two cigarettes in dogs had no effect or decreased acid secretion during fasting. Smoking one to two cigarettes and subcutaneous or intravenous injections of 0.2 to 1 mg of nicotine had no effect on bile or pancreatic secretion in dogs, except when marked changes in blood pressure were produced by nicotine.

In both smokers and nonsmokers, smoking increased colon motility. Following smoking, significant increases in gastric retention (emptying rate), gastric acidity, untoward cardiovascular effects (fainting after smoking on an empty stomach) and increase in colon motility were observed.

Ivey and Triggs (1978) reported that nicotine was well absorbed in 15 minutes during intragastric administration at pH 9.8. Absorption was accompanied by untoward effects of nausea and vomiting, and delay in gastric emptying. Rapid cigarette smoking and i.v. nicotine decreased gastric acid secretion. Neither oral administration, i.v. infusion (4 mg/hr of nicotine base), nor smoking 3-5 cigarettes per hour significantly altered the gastric mucosal barrier (as measured by gastric ionic fluxes and potential differences). Grines and Goddard (1978) reported that smoking a cigarette increased the rate at which liquid left the stomach, suggesting that the rate of acidification of the duodenum after a meal might be correspondingly more rapid. Solid did not accompany the liquid and did not buffer the excess leaving the stomach. Pathogenesis of duodenal ulcer and delay in healing may be associated with cigarette smoking. Piper and Raine (1959) studied the maximum secretory response to histamine estimated during the 2nd hour after smoking 4-6 filter cigarettes. Secretion in the 2nd (smoking) hour showed an increase over the basal hour of over 100% in free acid and total

acid output as well as an increase in volume and in chloride output. A study of 4 subjects showed that smoking stimulated both the parietal-cell and non-parietal-cell components of gastric secretion.

Murthy et al. (1977) reported that smoking resulted in a transient increase in basal acid secretion, but was significant only for ulcer subjects. This increase was followed by a nonsignificant decrease for both groups. Fluid and bicarbonate secretion were inhibited during the smoking period, but returned to control levels within 30-60 minutes in the ulcer groups and within 60-90 minutes in the nonulcer group. There was no difference between the two groups in the degree of pancreatic secretion inhibition during smoking. Basal pancreatic secretion inhibition correlated with plasma nicotine concentrations. Plasma levels of secretion and gastrin were not altered by smoking. Debas et al. (1971) found that the mean plateau output of acid was 4.56 millimoles/15 minutes or 42% of the maximum response. Stimulation of acid secretion occurred following the smoking hour. Pepsin response reached 180% of the control value. It seems unlikely that smoking may exert a harmful effect on the normal human stomach, but that conclusion may not apply to the ulcer patient. This was confirmed by Rack and Sonnenberg (1983) who found that during fasting, gastric juice, and, during infusion of pentagastrin, the gastric concentration and output of

bound N-acetylneuraminic acid (NANA) were similar in smokers and in nonsmokers. Acute nicotine administered intravenously or by smoking had no effect on gastric NANA. This study suggests that neither chronic nor acute consumption of nicotine may affect gastric turnover or adherence of mucus to the mucosa. Whitecross et al. (1974) studied the effect of cigarette smoking on gastric secretion in 13 control subjects and 8 subjects with chronic peptic ulcers. Gastric juices were collected from each subject after smoking 4 cigarettes in 1 hour. The output of acid, pepsin and mucus was not significantly different in either group or between the two, and was not influenced by the tar and nicotine content of the cigarettes. In the control subjects biliary reflux was more marked in the hour that the subject smoked. Consequently, smoking does not seem to influence gastric secretions or ulcer healing. Sonnenberg and Husmert (1982) investigated the effects of nicotine on gastric mucosal blood flow and acid secretion in 13 males. Doses were administered via intravenous nicotine infusion and cigarette smoking, with blood flow measured by gastric neutral red clearances. Nicotine reduced volume secretion, acid secretion and neutral red clearance in a dose-dependent manner. Smoking five cigarettes elicited an effect similar to an intravenous dose of 5 ug/kg/hr of nicotine. Results seem to show that nicotine increases blood supply to the gastric mucosa relative to the reduced gastric secretion. Nicotine may exert its ulcerogenic action via other mechanisms than change in acid secretion and gastric mucosal blood flow.

Wilkinson and Johnson (1971) reported that in control pentagastrin infusions in which 9 normal subjects and 5 duodenal ulcer patients simulated smoking, gastric acid secretion, heart rate, and blood pressure all remained constant. Cigarette smoking produced inhibition of pentagastrin-stimulated gastric acid secretion in normal subjects and in patients with duodenal or peptic ulcers. In 11 normal subjects, acid secretion decreased by a mean of 38%; in 10 patients with duodenal ulcers, by a mean of 21%; in 4 patients with gastric ulcers, by a mean of 18%. Acid output decreased after smoking in 25 subjects. Inhibition produced by 2 cigarettes was not greater than inhibition produced by 1 cigarette. Inhibition was as great in smokers as in nonsmokers. No significant change in acid secretion was observed during constant pentagastrin infusion in normal subjects and in patients with peptic ulcers who puffed on non-nicotine cigarettes. Acid concentration decreased by a mean of 12% in 11 normal subjects; by 14% in 10 duodenal ulcer patients; and by 17% in 4 gastric ulcer patients. Mean pepsin secretion decreased by 31.0% in 11 normal subjects and by 44.9% in 10 duodenal ulcer patients. Smoking 1 cigarette elicited decreased acid secretion of 2%, 78% and 42% in subjects who received nicotine acid tartrate (1, 3, and 4 mg). Acid secretion decreases after infusion of nicotine (3 mg) similarly to the decrease produced by cigarette smoking.

D. WITHDRAWAL EFFECTS

Cessation of smoking produces a set of signs and symptoms that have been termed the tobacco withdrawal syndrome. An increasing number of investigations have linked many of these objective and subjective effects of decreases in accustomed nicotine intake, or nicotine withdrawal. The onset of the syndrome appears to be rapid, with changes in mood (Schechter and Rand, 1974) and performance (Myrsten et al., 1972) evident as early as two hours after withdrawal. A wide variety of unpleasant side effects are reported by habitual smokers who stop smoking, including craving for tobacco, irritability, restlessness, dullness, sleep disturbances, gastrointestinal disturbances, anxiety, and impaired concentration, judgment, and psychomotor performance. The onset of symptoms may occur within hours or days of quitting and may persist for a few days to several months. Additional objective signs include decreases in heart rate and blood pressure, increased rapid eye movement (REM) sleep, and decreased frequency of EEG activity.

This section focuses primarily on the acute effects of nicotine withdrawal, although some long-term effects are cited when relevant.

D. WITHDRAWAL EFFECTS

D. Withdrawal Effects

1. Physiological Changes
2. Mood
3. Psychomotor Performance
4. Cortical Arousal
5. Eating Behavior and Weight Control

1. Physiological Changes

A range of physiological changes occurs upon nicotine withdrawal. Physiological signs of smoking cessation that have been reported consistently in several studies include decreased heart rate, increased skin temperature as a result of peripheral vasodilatation, increased predominance of EEG slow-wave activity, decreased excretion of epinephrine, and decreased blood glucose concentration 30 minutes after an oral glucose load as late as one month after cessation (West, 1984; Myrsten et al., 1977). Abstaining smokers or those who switched from high-nicotine to low-nicotine brands exhibited decreased heart rate and blood pressure. A decrease of around 60 percent in blood nicotine levels was found to be associated with relatively mild withdrawal effects (West, 1984). Elgerot (1978) reported that abstinence was accompanied by a decreased arousal, indicated by decreases in both epinephrine and norepinephrine excretion, with these decreases paralleled by increased emotional irritability. Puddey et al. (1984) reported on 66 smokers divided into two groups to study the effect of smoking on blood pressure. The experimental group was asked to stop smoking on entry into a six-week withdrawal program. The control group continued their normal smoking habit during this time before entering a similar program. Laboratory assessment at baseline and at the end of the study included a cold pressor test and assays for epinephrine, norepinephrine, cortisol, and prolactin. During the study blood

pressure and weight were measured every two weeks. Questionnaires were given to detect changes in physical activity, diet, and anxiety. The experimental group showed an increased anxiety level. Both groups had significantly lower norepinephrine levels after the study than at the beginning.

2. Mood

Smoking withdrawal phenomena can often be detected within hours of the last cigarette. As little as 90 minutes of abstinence may increase emotional irritability (Schechter and Rand, 1974). Hutchinson and Emley (1973) measured jaw clenching in smokers attending a withdrawal clinic at weekly intervals after subjects stopped smoking, and reported an increase in the frequency of spontaneous jaw contractions after smoking cessation, which was correlated with verbal reports of irritability. Switching to an ultra-low nicotine cigarette may induce the subjective and physiological effects of nicotine withdrawal. In a study of these effects over a 10-day interval, West et al. (1984a) found that the plasma nicotine concentration decreased by 60% after switching. Switching to a low-nicotine cigarette was accompanied by a significant increase in hunger, a decrease in mean heart rate of slightly more than 6 beats per minute, and a significant increase in skin temperature of 1.8 degrees C. Mean epinephrine concentration tended to be decreased (not statistically significant), but other common cigarette

withdrawal symptoms such as irritability, depression, and inability to concentrate, were not observed. The major subjective effect of lower nicotine concentration was increased hunger.

Several studies have shown that nicotine deprivation plays a major role in the cigarette withdrawal syndrome and that relatively low levels of nicotine replacement aid in amelioration. In a study of the effect of nicotine gum on withdrawal symptoms, West et al. (1984b) found that following a 24-hour abstinence from cigarettes, with nicotine supplied as 0.5 or 2 mg in chewing gum, the low nicotine gum group was significantly different in measures of depression, irritability, and sociability than the high nicotine group. There were no significant differences in measures of restlessness, dizziness, ability to concentrate, and hunger. The 2 mg gum group had significantly less increase in irritability and depression and significantly less decrease in sociability than the 0.5 mg gum group. The 2 mg gum group also exhibited a significant increase in hunger and decrease in ability to concentrate, compared to the changes in the 0.5 mg group. The average decrease in heart rate was 14.4 beats per minute in the 0.5 mg gum group but only 9.7 beats per minute in the 2 mg group. There was a slight but nonsignificant increase in skin temperature in the 0.5 mg gum group. Subjects in the 0.5 mg gum group rated themselves as having become increasingly

irritable, restless, dizzy, and hungry after 2 hrs of abstinence from cigarettes. They also reported they were less social and less able to concentrate. The 2 mg gum helped to alleviate some of these effects of depression, irritability, and problems in socializing. The 0.5 mg gum group exhibited a decrease in heart rate and excreted epinephrine; the 2 mg gum produced a smaller decrease in heart rate, but did not ameliorate the decrease in epinephrine excretion. The onset of hunger and absence of detectable increases in emotional irritability are consistent with the results of previous studies on the effects of nicotine chewing gum in decreasing withdrawal symptoms. Although the gum alleviates irritability and depression it does not seem to prevent a short term increase in hunger. A small dose of nicotine may prevent an increase in irritability but a higher intake may be required to prevent an increase in hunger.

Schneider and Jarvik (1984) studied the time course of smoking withdrawal symptoms in relation to nicotine replacement by nicotine chewing gum and compared subjects receiving either nicotine or placebo gum. Signs and symptoms of withdrawal were measured on a scale consisting of the following items: irritability, hostility, anxiety, depression, frustration, restlessness, annoyance, disorientation, insomnia, mental concentration, alienation, fluctuations in mood, concern about weight, and craving for cigarettes. All subjects reported an

initial increase in these symptoms during the first day of abstinence. Significant increases in symptoms were reported in the evening for the placebo group in comparison to morning and afternoon responses and in contrast to the nicotine gum group. Nicotine gum appeared to have ameliorated withdrawal symptoms compared to a continuing increase in symptoms in placebo subjects.

Shiffman and Jarvik (1980) studied participants in a smoking cessation clinic during the first two weeks of abstinence. Results showed a strong diurnal variation in craving for cigarettes, with craving lowest early in the morning and rising to a peak around 7:00 PM. Many symptoms appeared within two hours of withdrawal. Severity of all symptoms decreased the first week, followed by leveling off or increase in the second week. Two groups, totally abstinent smokers and partially abstinent smokers who decreased their cigarette consumption by an average of 60%, reported similar levels of symptom severity. The totally abstinent group experienced a notable decrease in symptoms during the first week; whereas, the partially abstinent group maintained withdrawal symptoms.

A preliminary study of three subjects suggested that the tobacco withdrawal syndrome is reliable and can be studied using within-subject designs (Hughes et al., 1984). The majority of

the signs and symptoms of tobacco withdrawal occurred during abstinence, returned to baseline when smoking resumed, and then recurred during a second abstinence period. Variables such as setting, expectancy, and method of cessation may have influenced the syndrome, but these variables were held relatively constant. In comparing baseline and abstinence conditions, there were consistent decreases in heart rate and consistent increases in insomnia, caloric intake, irritability, restlessness, and drowsiness. The 4 signs and symptoms that did not occur consistently were orthostatic hypotension, craving, and difficulty concentrating in one subject each and anxiety in two subjects. Two total discomfort measures indicated that intensity of withdrawal discomfort was similar across trials.

3. Psychomotor Performance

Several studies of complex performance have shown significant adverse effects of smoking withdrawal on visual tracking; there is additional evidence that short-term withdrawal from smoking can produce decrements in attention and vigilance, choice reaction time, and selective attention (Mertens et al., 1983). Mertens et al. (1983) studied the effects of smoking withdrawal during a four hour interval on the performance of healthy smokers in flight related tasks at a simulated cabin altitude of 6,500 ft. Each experimental session consisted of six 30 minute tasks separated by 10 minute intermissions. During the test session

for the smoking condition, subjects smoked one cigarette during the 10 minutes immediately prior to the first half hour period and one cigarette during each 10 minute break thereafter. During the nonsmoking condition, subjects smoked one cigarette prior to the first performance task but did not smoke again for the four hour session. Visual tracking was the only task component showing a statistically significant decrease in the smoking withdrawal condition, although there was a tendency for performance in monitoring red lights to decrease during withdrawal over the first three half hour periods; vigilance performance in monitoring red lights tended to increase with time in the smoking condition. In tracking performance, the adverse effect of smoking withdrawal was independent of a trend toward decreased performance with time, which occurred in both smoking and nonsmoking conditions. Performance in monitoring red lights and arithmetic tasks increased with time in the smoking condition. Subjective ratings of attentiveness were significantly higher when subjects smoked. Arousal was not significantly affected by either smoking or time of testing but smoking tended to increase arousal and withdrawal to decrease arousal over the course of the session. Levels of tiredness, tension, boredom, and irritation were higher at the ends of the sessions than before but were unaffected by smoking withdrawal. The higher heart rates and higher attentiveness scores obtained when subjects smoked suggest that decreased arousal in the absence of smoking may be a mechanism for detrimental effects of smoking withdrawal in habitual smokers.

Heimstra et al. (1977) examined the effects of smoking on driving performance by comparing ad lib smokers, abstaining smokers, and nonsmokers in a 6 hour simulated driving test. On a variety of measures of tracking and vigilance, there were no significant differences between the performance of nonabstaining smokers and nonsmokers, but abstaining smokers exhibited decreased tracking and vigilance performance. Myrsten et al. (1977) found that verbal learning was essentially unaffected over five days of smoking abstinence.

4. Cortical Arousal

Herning et al. (1983) studied effects of acute tobacco withdrawal of 10-17 hours on EEG changes. Cigarettes were smoked at 30 minute intervals either freely (Group 1) or at the rate of one puff per minute (Group 2). The time course of EEG spectral changes after smoking a single cigarette was followed by a one day experimental session. The effects of repeated nicotine cigarette smoking on EEG and the duration of nicotine effects after switching to placebo cigarettes were tested in a two-day session. Theta and alpha power increased significantly following tobacco abstinence and were decreased by nicotine cigarette smoking but not by placebo smoking. The peak alpha frequency was decreased more after abstention than after smoking a nicotine cigarette. Decreases were not always significant. The increased theta power during abstention may correlate with drowsiness and a

mild version of stimulant withdrawal syndrome. Changes in alpha activity have been attributed to characteristic differences in arousal or cognitive processing of smokers; changes in alpha power and peak frequency may be simply secondary to the theta power changes. The dominant alpha frequency in abstaining smokers was decreased compared to the smoking of a nicotine cigarette, but decreases were not always statistically significant.

Soldatos et al. (1980) monitored the sleep patterns of five male smokers for five days of abstinence and found that sleep latency and time awake after sleep onset decreased. The improvement in sleep efficiency may have resulted from decreased catecholamine concentrations after withdrawal from smoking.

5. Eating Behavior and Weight Control

Population studies have shown that smokers tend to weigh less than nonsmokers (Blitzer et al., 1977). Changes in eating behavior and weight gain following cessation of cigarette smoking are two of the most widely studied effects of nicotine withdrawal. Weight gain is well documented, but whether it results from increased appetite and food intake or metabolic changes, or a combination of both, has not been precisely determined. Glauser et al. (1970) studied metabolic changes associated with smoking cessation in seven men at the time of and

one month after smoking cessation. Six of the subjects gained weight during the month after smoking cessation; mean weight increased from 83.29 kg to 87.33 kg. The subject whose weight remained constant markedly increased his activity levels. Significant decreases in heart rate, 30 minute postprandial blood glucose level, protein bound iodine, oxygen consumption, and serum calcium were observed. These results indicate that the metabolic changes associated with cessation of smoking involve decreased basal oxygen consumption. With no change in caloric intake or physical activity, these metabolic changes would produce weight gain. A study of 300 normal, middle-aged men showed a significant 9.3 lb (4.23 kg) gain over a 5 year interval in those who voluntarily stopped smoking in comparison with a control group who did not stop smoking (Brozek and Keys, 1957). Smoking tended to decrease the perceived need for food. This interpretation was based on experimental observations of the inhibition of gastric hunger contractions on smoking and the increased tobacco consumption by individuals on low-calorie diets. A longitudinal analysis of 57,032 women confirms the weight changes found in longitudinal studies of men and indicates the weight gain associated with smoking cessation is permanent (Blitzer et al., 1977). Light smokers, who smoke one-half pack a day, may expect to gain about 5 pounds if they stop; moderate smokers may expect to gain 15 pounds. Heavy smokers, consuming two or more packs per day, gained about 30 pounds. Cross-sectional analysis showed that former smokers were 3.2 to 3.9 pounds heavier than current smokers.

E. SUMMARY AND EFFECTS ON SOLDIER READINESS

E. Summary and Effects on Soldier Readiness

- 1. Soldier Readiness**
- 2. Summary**
- 3. Recommendations**

E. SUMMARY AND EFFECTS ON SOLDIER READINESS

1. Soldier Readiness

The concept of soldier readiness is defined as the ability to perform any specialized and/or routine military duty. There is a wide range of tasks that may be required to be performed in preparation for and during combat. Therefore, the effects of nicotinic stimulation and withdrawal on combat readiness and performance review the major findings of the present report on (a) central nervous and psychological; (b) cardiopulmonary and musculoskeletal; and (c) metabolic and gastrointestinal functions.

2. Summary

a. Central Nervous and Psychological Functions

Smoking nicotine produces a transient stimulation followed by depression of both sympathetic and central nervous structures. Circulating epinephrine and vasopressin secreted from the adrenal medulla and neurohypophysis augment sympathetic and central nervous stimulation. Increased blood glucose level that may be secondary to epinephrine secretion could contribute to the mood elevation, although epinephrine may also act directly on the central nervous system to produce positive affect. Negative affect is associated with nicotine withdrawal. Although the etiology is complex and has not been systematically investigated, there is evidence that decreased blood epinephrine and excretion,

decreased heart rate, and decreased arterial blood pressure accompany withdrawal. Relaxation and feelings of tranquility have been associated with smoking, while increased aggression has been found during withdrawal. Relaxation by smoking has also been associated with decreased skeletal muscle tension at rest, but increased resting muscle tension has also been detected. Effects of nicotinic stimulation and withdrawal on decision-making and manual dexterity have been addressed in experiments measuring simple choice reaction times, response time, and arithmetic and letter cancellation tasks. Smoking decreased inhibition associated with key tapping, an effect that may have implications for reaction time testing. Both smoking and nicotine withdrawal decrease hand steadiness, a motor effect that may decrease both reaction/response times and manual dexterity. Increased errors have been reported by arithmetic and letter cancellation tests under both conditions of smoking and withdrawal.

Learning and recall reflect the complex interaction of information acquisition, storage, and retrieval. Both smoking and withdrawal have produced mixed results. Under some conditions, learning and recall is enhanced and under other conditions, they are impaired. State dependent learning occurs wherein information learned under the effects of nicotine is recalled better while smoking than while abstaining.

Attentiveness and rapid information processing have been studied in combination with visual and auditory stimuli, requiring motor responses of subjects. Some components of attention and rapid information processing have been associated with increased speed and accuracy, while others have produced performance decrements. During monotonous tasks, vigilance has been increased and the normal decremental performance observed over a prolonged time course has been ameliorated by nicotine and smoking. There is evidence that after three hours, the blood nicotine level is decreased virtually to zero, and testing over prolonged time may, therefore, provide information on performance during withdrawal.

Effects of nicotine and smoking that increase CNS arousal and withdrawal effects that decrease CNS arousal may also affect abilities to remain alert during monotonous, prolonged tasks and to learn new tasks. It has been shown that interindividual variations in performance during smoking may be related to smoking under high arousal versus low arousal conditions. Indeed, personality differences among smokers and measures of extroversion and neuroticism have been correlated with regulation of CNS arousal by nicotine and smoking.

Smoking and nicotine effects on attentiveness and alertness have produced mixed effects on learning tasks. Smoking subjects have demonstrated selectivity of memory processing to information that is perceived to be irrelevant more than relevant and to information presented in the peripheral more than the central visual fields.

Decreased visual acuity from smoking has been associated with decreased size of visual fields, widening of retinal angioscotomata, decreased light sensitivity of both rods and cones, and speeding of dark adaptation. In contrast, rapid visual information processing may be enhanced by smoking. The frequency at which flickering light forms a single image (flicker fusion frequency) is increased in some and decreased in other smokers, and decreases in flicker fusion frequency have been correlated with other visual defects. Flicker fusion frequency may increase with CNS arousal and both increases and decreases have been reported with passive smoking. Movement detection, temporal judgments and estimation of velocity and distance of moving targets have been impaired under some conditions and improved under other conditions. When performing complex visual and auditory monitoring tasks simultaneously, only the auditory task was impaired by nicotine and smoking.

b. Cardiopulmonary and Musculoskeletal Function

Blood flow to cutaneous structures is compromised by smoking, resulting in decreased skin temperature, which may impair thermoregulation in hot and decrease comfort in cold environments. Peripheral cutaneous vasoconstriction has been associated with regional differences, increased skeletal muscle flow, and may be undetectable in most human retinas.

Although there are numerous reports of increased heart rate and blood pressure associated with testing of smoking subjects, some studies have shown minimal or no effects under normal everyday conditions. In most cases, withdrawal and abstinence are associated with decreased blood pressure and heart rate. Smoking associated with exercise testing has decreased blood carbon monoxide levels, endurance, and performance on tests of high strenuousness. Exercise time until angina, maximal oxygen uptake, and grip strength have also been reported. Maximal heart rate and recovery from skeletal muscle fatigue have been increased by smoking with exercise.

Respiratory effects of smoking have resulted in bronchoconstriction and increased airways resistance that increases the work of breathing and decreases pulmonary airflow. Pulmonary symptoms and increased airways resistance have been ameliorated by cessation of smoking. Passive smokers experience respiratory

discomfort and decreased pulmonary function under some conditions, and filtering of tobacco smoke has been used to effectively decrease pulmonary impairment. Recently, central respiratory drive has been shown to be decreased by smoking. These effects probably limit tolerance for physical exercise in synergism with cardiovascular factors.

c. Metabolic and Gastrointestinal Functions

Smoking may increase the fasting blood glucose level in normal and especially in diabetic subjects. Increased circulating catecholamines, growth hormone, cortisol, and prolactin concentration may both mediate and exacerbate this hyperglycemic diabetogenic effect. These hormones may increase the blood free fatty acid concentration and produce adipokinesis in smokers. Mobilization of fat from body adipose tissue depots may decrease the fat body mass and contribute to the lower total body weight of groups of smokers versus groups of nonsmokers, although this has not been systematically studied. However, decreased threshold for bitter and increased threshold for sweet tastes associated with smoking may contribute to decreased caloric intake and control of body weight. Nicotine withdrawal seems to increase body weight, supporting the theory that an important reason for smoking is weight control in some individuals.

Anxiety, age, and anthropometric classification may be important determinants of inter-individual variations in body weight changes associated with withdrawal from smoking. Increased blood vasopressin (antidiuretic hormone, ADH) levels associated with smoking may act synergistically with catecholamines contributing to systemic hypertension. This may be especially significant for increased peripheral vascular resistance because of the cutaneous vasoconstriction associated with smoking. The antidiuretic action of vasopressin concentrates urinary solutes, increases specific gravity, and may contribute to increased circulatory blood volume and hypertension.

Increased fibrinolysis and platelet aggregation produces a hyperthrombotic state that may contribute to the increased incidence of myocardial infarctions and other arterial thrombotic diseases associated with smoking.

Decreased immunological responsiveness associated with smoking may increase susceptibility to both acute infections (especially respiratory tract) and cancer. Smoking and nicotine may induce hepatic drug metabolizing enzymes that have been associated with increased antipyrine disappearance indicative of increased drug metabolism; thus, greater doses of drugs may be required to produce a therapeutic effect in smokers.

3. Recommendations

The database described herein is composed of human research on the effects of smoking and nicotine on soldier performance and readiness for combat. Some studies were designed to determine whether cigarette smoking or nicotine affected performance; others were designed to determine what aspect of smoking affected performance. Thus, the majority of studies were not based upon any particular theoretical framework, and the database reflects an accumulation of fragmentary evidence acquired from unrelated studies using different, nonstandardized methodologies. Such a structure makes it difficult to make meaningful comparisons between studies because of the large data gaps identified. Some of these gaps may be filled by animal studies; there is a large body of information from experimental animals in the literature. Experimental animal data has been excluded from the present database by design, and its inclusion would contribute significantly to the analysis of the effects of smoking and nicotine on human performance.

In the human studies described herein, most experimental populations were heterogeneous with respect to age, sex and anthropometric variables. Such designs contributed to the great inter-individual variations reported. Multivariate statistical analysis was performed infrequently, but when performed, confirmed that future studies should use homogeneous subject populations to decrease variability.

Similarly, there was considerable variability in experimental conditions; diurnal changes associated with peak cigarette consumption at a particular time of day, diet and eating behavior, compliance of subjects with protocol, dose of nicotine, and amount of smoke inhalation were generally not controlled. Testing was often performed after smoking intervals when the blood nicotine level had peaked. Therefore, performance may have been evaluated when the blood nicotine level might have decreased by as much as 50% within 10 minutes. From a pharmacological viewpoint, future studies should be performed before, during, immediately after, and even further after the last puff of the cigarette concomitantly with blood nicotine analyses. It may take 3 hours for the blood nicotine level to decrease to zero following smoking; therefore, less than 3 hours abstinence may compound results by the effects of residual nicotine. Conversely, studies performed after 3 hours abstinence may be interpreted as data derived from smokers during nicotine withdrawal.

Smoking and nicotine effects on learning and memory have been especially difficult to interpret because of the complex process of learning that has usually not been addressed in study protocols. Memory is usually inferred from the persistence of the effects of experience until the time of a recall test. Memory impairment has four stages: (1) information input; (2)

information storage and consolidation; (3) information maintenance and retention; and (4) information retrieval and recall. Using preacquisition doses of nicotine, it may not necessarily be concluded that nicotine had modified learning unless a companion study rules out changes in sensory processing, motivation, and motor output. A partial solution may involve administration of nicotine or cigarettes prior to acquisition, but to test recall after nicotine has been excreted would not affect motor/sensory performance at the time of recall. Postacquisition doses of nicotine may not affect information input, but rather information retrieval and storage.

Future studies of cigarette smoking should be designed to study the effects of carbon monoxide independently of nicotine on the same subjects. Carbon monoxide is a colorless and odorless gas produced by the incomplete combustion of organic matter. The smoke from one cigarette can contain up to 21.4 mg of carbon monoxide. Cigarettes have concentrations ranging from 0.1-2.5 mg nicotine. In the database described herein, there are few examples of studies so designed, but when performed, parallelism and synergism between the effects of carbon monoxide and nicotine have been demonstrated.

Systematic measurements of performance that directly relate to combat and soldier readiness have generally not been performed. Therefore, future experiments should involve careful analysis of tasks necessary to soldier readiness and studies designed to simulate appropriate conditions. In selection of tasks to be studied, it should be emphasized that physiological systems are inherently efficient; there is usually considerably less opportunity for improvement than for impairment of performance. Detection of improvement may be difficult unless situations are designed to be somewhat stressful in order to impair performance under control conditions. Therefore, the ideal task designed to study performance may be one that is capable of showing both improvements and impairments in performance. Use of frequent control measurements and training intervals prior to testing may decrease the possibility of training effects confounding performance data derived from smoking subjects.

APPENDIX A: CODING INSTRUCTIONS

APPENDIX A: CODING INSTRUCTIONS

Performance Record

ACC: Enter number 1-999 stamped on document.

LOC: Leave blank.

AU: Enter last name followed by space followed by first initial followed by space followed by middle initial, without punctuation (each AU not to exceed 60 characters, up to a limit of 6 AU).

TI: Enter title of document on 3 lines (each line not to exceed 60 characters). Numbers are acceptable.

SO: Enter journal name, or book title without punctuation in combinations of numbers and letters (not to exceed 70 characters); source of report may be name of government agency or DTIC TECHNICAL REPORT. Abbreviations are not acceptable.

VOL: Enter volume number of combination of numbers and letters not to exceed 8 characters to indicate source collection series; leave blank if source is a book or report without volume indicated.

SPACE: Enter the first page number of the hit document (not to exceed 4 digits).

LPAGE: Enter the last page number of the hit document (not to exceed 4 digits).

PUBYR: Enter the year of publication (not to exceed 4 digits).

ISSUE: Enter the issue of the source as either a number or combination of numbers and letters indicating a date (not to exceed 15 characters, e.g., 15 MAR 1978).

PUBLISHER: Enter the name of the publishing company or government agency if source is either a book or a report, in combinations of letters and numbers if necessary without punctuation (not to exceed 48 characters); if source is journal, leave blank.

LANG: Enter "ENG".

STAT: Enter strings of 2-letter codes indicating statistical parameters (each code separated by space) from the list of statistical codes).

STATRAT: Enter a number in the range 1-5 indicating the complexity of statistical analysis (Appendix B).

DOCTYPE: Enter a single letter (J, B, or R) indicating whether the source is a book, journal, or report.

COND: Enter a single letter (e.g., G, F, or P) indicating whether the condition (readability) of the AGI copy of the hit document is good, fair, or poor.

CAT: Enter a combination of a letter followed by a period and a string of numbers each separated by a period (e.g., C.1.3.5) not to exceed 12 characters including periods from the list of category codes.

PERFN: Enter the name of each performance variable not to exceed 48 characters each (limit 10 performance variables).

SUBJNO: Enter the number 0-999 indicating the total number of subjects.

MALENO: Enter a number 0-999 indicating total number of male subjects.

FEMALENO: Enter a number 0-999 indicating total number of female subjects.

AGE: Enter a number 0-4 indicating the age range of subjects.

SUBJTYPE: Enter a 1-letter code indicating whether the subjects were smokers (S), nonsmokers (N), light smokers (L), medium smokers (M), heavy smokers (H), combination of L, H, or M = X, combination of S and N = Y.

ASPER: Enter the pre-experimental abstinence interval in hours as numbers only (limit 4 digits).

DISCAT: Enter the disease category (not to exceed 10 characters) ascribed to subjects that are not normal healthy subjects; if normal and healthy enter "NORMAL".

SPECIES: Enter "HUMAN".

DRNO: Enter the number 1-10 indicating the number of drugs studied; if more than one dose or form of drug, enter each dose and/or form as a separate drug.

DRUG: For each drug number enter under the field DRNO, enter the scientific names of the drugs (generic) as specifically as possible in combinations of letters and numbers if necessary (not to exceed 36 characters); name the organic moiety first (e.g., nicotine); all records will have at least one drug as some form of NICOTINE (and possibly CARBON MONOXIDE).

Index Record

ACC: Enter number 1-999 stamped on "hit" document.

ITNO: Enter number 0-50, indicating the number of index terms assigned to hit document (limit 50 index terms).

ITERM: Enter each descriptive index term as combination of letters and numbers if necessary (not to exceed 55 characters); the number of ITERM entries must be exactly equal to the number indicated by ITNO entry.

Annotation Record

ACC: Enter number 1-999 stamped on "hit" document.

ABSNO: Enter the number 1-100 indicating the number of 70 character lines required to print the abstract (annotation).

ABSTRACT: Enter the annotation giving the bibliographic citation first, then skipping a line and entering the abstract as a single paragraph.

Enter the bibliographic citation in the following format:

Line #1 --

Enter the author's last name followed by first initial followed by middle initial for all authors; separate each author by comma (e.g., Vogel J A, Minner D F, Speight Y).

Line #2 --

Enter the title of "hit" document capitalizing the first letter of the first word only; followed by period (The effects of nicotine on human performance.).

Line #3 --

Enter the full name of source, followed by volume, followed by issue number in parentheses (), followed by colon (:), followed by page range, followed by comma, followed by publication year, followed by period (e.g., Proceedings of the Society for Experimental Biology and Medicine, 88(3):888-898, 1978).

When no issue number given (e.g., 88:888-898, 1978).

Line #4 --

Leave blank.

Line #5 --

Enter 70 character text (not to exceed 100).

APPENDIX B: STATISTICAL RATING SCALE

APPENDIX B

STATISTICAL RATING SCALE

The computerized database includes a quantifying statistical rating scale (STATRAT field) assigned by the principal investigator, that is indicative of the quantitation of results described in each source document. Values range from 1 to 5 evaluated by the following criteria:

1. Quantitative description of data is lacking.
2. Basic statistical methods and parameters are lacking, but the data have been described quantitatively by measurement average values, distribution, sample size, and number of controls. Statistical analysis of variance has neither been described nor given.
3. Detailed description of statistical method is lacking, but statistical analysis appears to have been performed. Standard error of the mean, chi square (with degrees of freedom), correlation coefficients, or P-values for levels of statistical significance have been appended to results.

4. Routine simple statistical procedures including descriptions of control and experimental samples, analysis of variance, t-test, probit analysis, regression analysis, sample distributions, and P-values for statistical significance have been described and used.
5. Exceptionally sophisticated statistical methods including multivariate analysis, curvilinear plots, nonparametric tests, or complex statistical procedures have been used.

APPENDIX C: COMPUTERIZED DATABASE USER INSTRUCTIONS

I. INTRODUCTION

The Performance Database is a collection of on-line bibliographic citations and abstracts housed on the USAMRDC Computer Center's VAX 11/780 at Frederick, Maryland. The Database covers all published literature regarding the effects of selected chemical agents on human performance.

At present, the database deals with the agent nicotine, and contains 453 records representing the most current and authoritative literature and non-public literature (e.g., DTIC) concerning the effects of nicotine. The literature search from which these 453 items were selected covered over 1,100 pieces of the most up-to-date information on the subject, including journal articles, private research notes, and research reports.

The literature search was conducted during the period October 1985-January 1986, so the database may be considered to reflect the state-of-the-science through mid-1986. (At that time, update searching would be needed to confirm the currency of the nicotine data.)

II. THE PERFORMANCE DATABASE RECORD

The Performance Database uses the VAX DATATRIEVE Database Management System (TM). Technically, the database consists of three linked subdatabases -- Performance, Index, and Annote --

whose fields can be merged and mingled freely. This arrangement permits the database to add new fields at a later date, and also gives the Performance Record certain options and special features it would not otherwise have.

The fields in the database are:

<u>Subdatabase</u>	<u>Field Contents</u>	<u>Field Name (for Searching)</u>
Performance	Accession	ACC
"	Author (1-n)	AUTHOR
"	Title	TITLE
"	Source Title	SO
"	Start Page (0-n)	SPAGE
"	Last Page (1-n)	LPAGE
"	Publication Year	PUBYR
"	Issue Number	ISSUE
"	Publisher	PUBL
"	Language	LANG
"	Statistical Rating	STAT
"	Document Type	DOCTYPE
"	Document Condition	COND
"	Category Code	CAT
"	Performance Variables (1-n)	PERF_VAR
"	Number of Subjects	SUBJNO
"	Number of Males	MNO

"	Number of Females	FNO
"	Age of Subjects	AGE
"	Subject Type	SUBJTYPE
"	Abstinence Period (from Nicotine)	ABSPER
"	Disease Category	DISCAT
"	Species	SPECIES
"	Drugs (includes all subfields)	DRUGS
"	Drug Name	DRUG
"	Dose	DOSE
"	Route	ROUTE
"	Form of Drug	DFORM
"	Level of Exposure	LEVEL
Index	Number of Index Terms	ITNO
"	Index Terms (0-50 Terms)	ITERM
Annote	Abstract (0-100 lines)	ABSTRACT

All fields in the Performance Database are searchable.

III. GAINING ACCESS TO THE PERFORMANCE DATABASE

The database is stored on one volume of 160-bpi magnetic tape at the USAMRDC Computer Center in Frederick, Maryland. To access the Frederick data you must first have authorized access to that VAX. Then you must call the computer center to request three things:

- o That the Performance Database tape be copied into your directory. This transfers raw data to you. (You can do this yourself if you call the computer center to obtain the tape number and if you know the commands for mounting and dismounting tapes.)
- o That the computer center modify your "LOGIN.COM" file to permit you to use Datatrieve. (You can amend your LOGIN.COM yourself by adding the following two lines:

```
$DTR32="SYS$SYSTEM:DTR32.EXE"
$ASSIGN/PROCESS "CDD$TOP.DTR$USERS.
[Your Username]"CDD$DEFAULT
```

Note that your own VAX Username must be used for the underscored text (not brackets) above.

- o That the Computer Center copy the Performance Database record formats into the VAX Common Data Dictionary. Specify whether you want all users to have access, or only yourself. This permits you to use (and modify) the data copied earlier.

If you wish to access the Database from a computer nearer your terminal than Frederick, MD, you can:

- o Download the above files to disk or tape on your local VAX, or
- o Request the Frederick Computer Center to copy the files to tape and ship the tape to you.

Please observe that the Performance Database is proprietary software of USAMRDC. No copying of, downloading to, or sharing of access to the database is authorized without written USMRDC content.

IV. LOGGING ON AND OFF THE PERFORMANCE DATABASE

To access the Database:

- o Log on the proper VAX.
- o At the operating system ("\$") prompt, type "DTR32"
\$DTR32

(Underscored text indicates your input.)

The system will open Datatrieve as follows:

```
VAX Datatrieve V3.0
DEC Query $ Report System
Type HELP for help.
```

DTR>

The "DTR>" prompt means that you are ready to use Datatrieve.

To exit Datatrieve, type "Exit."

DTR> Exit

This will return you to the operating system. To abort any commands or activities you wish Datatrieve to interrupt, type CTRL-Y.

To obtain help, simply type "Help Error" after an error message. The system will give you an analysis of what you did wrong. You can also obtain help messages by typing "Help." The system will give you a menu of help messages to choose from.

V. ACCESSING THE DATABASE

To read and search records, you must first "ready" the database as follows:

```
DTR> Ready Performance
```

```
DTR> Ready Index
```

```
DTR> Ready Annote
```

This matches up each data file with the formatting codes to permit searching and output.

VI. SEARCHING THE DATABASE

Below are some sample searches to illustrate the use of the Performance Database:

Search #1 Find all records where the Performance Variable (PERF_VAR) studied was "reaction time." Print the bibliographic citation and abstract

```
DTR> FIND PERFORMANCE WITH PERF_VAR="REACTION TIME"
```

```
[4 records found]
```

```
DTR> PRINT ACC OF CURRENT
```

```
DTR> PRINT ANNOTE WITH ACC=324 OR ACC=533 OR  
CONT> ACC=546 OR ACC=585
```

Note: "Current" designates the set created by your most recent "FIND" command.)

Search #2 Find all records with the author Ashton. Print the bibliographic citation and abstract.

DTR> FIND PERFORMANCE WITH AUTHOR GE "ASHTON" AND
CONT> AUTHOR LT "B"

[11 records found]

DTR> PRINT ACC OF CURRENT

DTR> PRINT ANNOTE WITH ACC=34 OR ACC=59

Note that text parameters you input (e.g.,
Performance="reaction time" are enclosed in quotes.
Numeric parameters (e.g., ACC=324) do not need
quotes.

Note too that operators LT, LE, GT, GE can be used
with either alpha or numeric fields, a capability
that permits searching of non-indexed records.

Search #3 Find all records with author Ashton where the performance variable was reaction time. Print the bibliographic citation and abstract.

DTR> FIND PERFORMANCE WITH PERF_VAR="REACTION TIME"
CONT> AND (AUTHOR GE "ASHTON" AND AUTHOR LT "B")

(Note: "CONT" is how the system prompts you for a
continuation line on an incomplete command.)

The basic syntax for searching, thus, is:

COMMAND } DATABASE "WITH" } FIELDNAME } OPERATOR }
PARAMETER(S)

or

FIND ... [Subdatabase] ... WITH ... [Fieldname] ...
AND/OR/GT/GE/LT

LE ... [Parameter]

You may print any search this way.

Search #4 Print the entire database.

You may do this with Annote or Index with the command form:

DTR> PRINT ANNOTE WITH ACC GE 0

You may not do this with the subdatabase Performance because it requires a special report format for proper display of data. See your database administrator to request this. Should you request a "dump" of the Performance subdatabase, you may see the data with uncontrolled wrapping.

(Use CTRL-Y if you inadvertently request this or any other unwanted and lengthy search.)

For reasons that are clear, it is always better to search the database first before printing your data. At times, doing this may require that you skim or scan a set before printing. This is described in Search #5.

Search #5 Print only part of a search set, so you can skim its contents to see if these are the records you want.

DTR> FIND PERFORMANCE WITH PERF_VAR
CONT> "REACTION TIME"

[14 records found]

DTR> SELECT 1
DTR> PRINT AUTHOR
DTR> SELECT 2
DTR> PRINT AUTHOR

Note that skimming simple fields such as ACC can be done with PRINT ACC OF CURRENT. Subfields such as Author require that you select records one at a time.

Search #6 Print the authors and all performance variables for accession #4.

1) DTR> FIND PERFORMANCE WITH ACC=4
 DTR> PRINT ACC,AUTHOR,PERF_VAR

or

2) DTR> PRINT ACC, AUTHOR, PERF_VAR
 CONT> OF PERFORMANCE WITH ACC=4

Note that to print more than one field at a time, you must link the fieldnames with commas, and place them with the word "of" before the subdatabase you are searching. In addition, you must request the ACC as your first field to display.

When requesting multiple fields in the performance subdatabase, Datatrieve will automatically format your output in columnar fashion.

If you request fields that cannot fit the 80-character line-length on your CRT, you will receive an error message or inappropriate wrapping. To correct this, request an output format from your database administrator.

VII. FURTHER ACTIVITIES WITH THE PERFORMANCE DATABASE

The Performance Database is a powerful and flexible application of Datatrieve. It is best to practice and experiment with it to get a real feel for the many ways to incorporate it into your work.

There are a variety of other functions Datatrieve permits that are not covered here:

- 1) Adding new records to the database.
- 2) Modifying records in the database (either in your own personal collection of them or in the entire database).
- 3) Generating polished output formats and tables.

To obtain further information about these features, see your database administrator to request Datatrieve documentation and training materials.