Effects of Inspiration, Expiration, and Apnea upon Pacemaking and Block in Atrial Fibrillation

By John R. Urbach, M.D., Jacob J. Grauman, E.E.B.S., and Sandor H. Straus, M.A.

SUMMARY
The effects of inspiration, expiration, and apnea on A-V transmission system block and on A-V junctional and idioventricular pacemakers were studied in 53 examinations on 29 patients with atrial fibrillation. The severity of block and the location, prevalence, and firing frequency of subsidiary pacemakers were measured separately in each phase of respiration and compared by quantitative methods. In most patients, apnea increased the severity of A-V block, the prevalence of A-V junctional escape and ventricular automaticity but reduced the prevalence of A-V junctional tachycardia. The firing frequency of the subsidiary pacemakers was not affected. Occasionally apnea shortened the coupling interval of premature ventricular contractions. Cheyne-Stokes respiration markedly accentuated the effects of apnea and often produced bursts of ventricular tachycardia in patients who had only isolated ventricular ectopic beats during regular respiration. The data indicate that intermittent respiration has deleterious effects upon cardiac activity and should be corrected whenever possible.

Additional Indexing Words:
A-V block, Periodic respiration, Apnea, Respiration

Atrial fibrillation

In the course of our studies on the behavior of subsidiary pacemakers in atrial fibrillation,1 we noted that ventricular contractions arising from A-V junctional and idioventricular pacemakers during atrial fibrillation often appeared in bursts which coincided with the apneic phase of Cheyne-Stokes respiration.

This observation differs markedly from previous reports of sino-atrial node depression, A-V block, A-V junctional and idioventricular arrhythmias, and even cardiac arrest during the hyperpneic phase of Cheyne-Stokes respiration.2-10 The work to be reported was undertaken to confirm the validity of our observation, to investigate its clinical significance, and to examine in detail the effects of all phases of regular and intermittent respiration upon pacemaking and block in atrial fibrillation.

The literature contains few reports of respiratory influence on the behavior of the heart in atrial fibrillation. Kilgore11 reported that inspiration and expiration altered the ventricular beat-to-beat interval duration in this arrhythmia but that the effects differed from patient to patient. He assumed that this pulse rate variation resulted from varying

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Supported by National Institutes of Health Project Grant HE-08855 and Regional Computer Resource Grant FR-15. Computation was also supported by a Computation Grant from the Phoebe Waterman Foundation, Philadelphia.

Some portions of this work have been presented at the 39th and 40th Scientific Sessions of the American Heart Association.

Received September 29, 1969; revision accepted for publication April 21, 1970.
Table 1

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not digitalized</td>
<td>13</td>
</tr>
<tr>
<td>Digitalized</td>
<td>11</td>
</tr>
<tr>
<td>Over digitalized</td>
<td>7</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3</td>
</tr>
<tr>
<td>Myocardialis</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolization</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>1</td>
</tr>
<tr>
<td>Interatrial septal defect</td>
<td>1</td>
</tr>
</tbody>
</table>

*The sum of the numbers listed is greater than the number of patients in the study because patients suffering from multiple abnormalities were listed more than once.

degrees of vagal stimulation of the A-V junction. Hoff and Geddes, working with dogs under morphine and pentobarbital anesthesia with atrial fibrillation induced by repetitive electrical stimuli, concluded that the ventricular rate accelerated during inspiration and at the end of expiration but slowed in midexpiration and during prolonged apnea. On occasion these investigators observed idioventricular escape beats during marked bradycardia. They also found that the atrial waves of the atrial electrogram slowed with inspiration and accelerated with expiration. However, they concluded that the observed variation in ventricular response resulted primarily from varying degrees of A-V junctional block caused by direct vagal and sympathetic stimulation of the A-V node. Roth, Flandin and co-workers, and Hamburger and associates reported several cases of atrial fibrillation and Cheyne-Stokes respiration in which the ventricular rate accelerated with apnea and slowed during hyperpnea. These authors did not attempt to identify the effects of inspiration or expiration.

Our observations confirm that the phases of respiration significantly alter impulse transmission in the A-V junction and demonstrate that they also affect impulse generation in the A-V junction and the ventricles. Using quantitative technics, we demonstrated that high-grade A-V block and ectopic rhythms appear primarily during apnea. The observations indicate that intermittent respiration is a surprisingly common disorder even in ambulatory, apparently well-controlled patients with heart disease, and that it has deleterious effects upon cardiac activity.

Methods

Patient Population

Twenty-nine patients were studied in 53 examinations. They were selected if they had atrial fibrillation and one or more of the clinical conditions listed in table 1. Fourteen patients were ambulatory; 20 had periods of Cheyne-Stokes respiration during at least one examination (table 2).

Data Collection

For each examination the electrocardiogram and respiratory chest excursion were recorded simultaneously on paper and magnetic tape together with a calibrated 400 Hz sine wave until 7,000 to 15,000 heart beats were collected. In some patients several recordings were made, for example, during and after therapeutic digitalization, when digitalis toxicity had cleared, or during and after other crucial events in the subject's illness.

Data Analysis

The procedure used to detect and identify nonfibrillatory pacemakers in atrial fibrillation was validated and reported in detail in a previous

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Cheyne-Stokes resp.</th>
<th>No Cheyne-Stokes resp.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recordings</td>
<td>Patients</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Not ambulatory</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

*The number of patients listed in this table is greater than the total number of experimental subjects because patients who became ambulatory or who discontinued Cheyne-Stokes respiration after the initial recording were listed in both columns or rows.

Circulation, Volume XLII, August 1970
Effects of Respiration on Pacemaking

Interval histograms of a patient with atrial fibrillation and A-V junctional escape rhythm (JE). Each bar represents by its height the fraction of intervals in the recording with a duration designated by the position of the bar on the abscissa. The 5,595 intervals that terminated during inspiration or expiration are displayed on the left, and the 1,841 intervals that terminated during apnea, on the right. The peak composed of intervals 1,565 to 1,760 msec long (JE) is caused by A-V junctional escape (see "Methods"). It is significantly taller (P < 0.001) during apnea than during respiration. The bars representing intervals which are short are generally smaller, and the bars representing intervals which are long are generally larger in apnea than in respiration; this demonstrates general slowing of the pulse rate during apnea (table 3).

Publication. It consists of recording the electrocardiogram on paper and magnetic tape, reducing the contained information to certain displays, and testing statistically the hypotheses suggested by them. The displays employed are (1) a plot of the duration or the reciprocal of the duration of successive electrocardiographic R-R intervals against elapsed time (tachogram); (2) a plot of the number of R-R intervals in the recording within each duration class against the duration of the class (interval histogram, figs. 1 to 3); (3) a plot of the number of beat-to-beat interval sequences composed of intervals with equal durations, successively diminishing durations, and durations representing multiples of a common time segment, against the duration of the identifying interval of each sequence (sequence histogram); and (4) a graphic presentation of the averaged electrocardiographic presystolic potential. The R-R intervals in the recording were labeled "inspiratory" if they terminated during chest expansion, "expiratory" if they terminated during chest contraction, and "apneic" if they terminated while the chest moved but slightly.

Sequences of intervals were designated by the label of their first interval. For example, a sequence of 10 equal intervals was labeled "inspiratory" if the first of the series terminated during inspiration, even if other intervals terminated during expiration and apnea. Interval and sequence histograms were cast separately for all intervals, for only inspiratory, only expiratory, and only apneic intervals. The mean and standard deviation of interval duration were calculated for each of these histograms, and the values were compared with each other by means of t and chi square tests. If a class of intervals was found to contain A-V junctional tachycardia, A-V junctional escape, or ectopic beats of ventricular origin, the number of inspiratory, expiratory, and apneic intervals and sequences in that class were compared by t tests. Rigorous definitions of the sequence types and derivations of the statistical formulae used in this work are contained in the "Appendix" which may be obtained from the
authors* upon request. Computer programs for all calculations are available from the DECUS Program Library.†

Because most expirations followed by apnea of significant duration decline exponentially, there is no sharp point of division between expiration and apnea. We utilized this finding to measure the duration of the average R-R interval of early and late expiration. In six patients the average interval duration in expiration and apnea was calculated twice from the same recording: first with the amplitude of the respiration signal large, and then with this amplitude reduced. This maneuver changed the location of the “dividing point” used by the computer to distinguish expiration from apnea. In the first calculation, the intervals of early and later expiration are averaged and compared to those terminating only in complete apnea. In the second calculation, the intervals terminating in late expiration and apnea are averaged and compared to those terminating in early expiration.

Results

Respiratory Variation of the Ventricular Responses to Atrial Fibrillation (Table 3)

In 17 recordings on 13 patients fewer than 500 intervals were recorded during apnea; in these only inspiration and expiration were compared. In 36 recordings on 15 patients respiration produced significant changes in the ventricular response. In general, the differences between inspiration and expiration were small compared to differences between apnea and either of the other phases of respiration.

The average R-R interval was usually shorter, and the pulse rate faster, early in expiration than later in expiration or in inspiration. During apnea the average R-R interval was usually much longer, and the pulse rate slower, than in either inspiraton or expiration. The presence of Cheyne-Stokes respiration usually increased the number of intervals recorded during apnea and prolonged the duration of the average apneic R-R interval.

The variability of interval duration was generally far more pronounced during apnea than in inspiration or expiration, and slightly

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†DECUS Program Library, Maynard, Massachusetts 01754.

Figure 3

Interval histograms of a patient with atrial fibrillation and coupled premature ventricular contractions (PVC). Each bar represents its height the fraction of intervals in the recording with a duration designated by the position of the bar on the abscissa. The 6,675 intervals that terminated during inspiration or expiration are displayed on the left and the 1,657 intervals that terminated during apnea, on the right. Intervals longer than 2,020 msec are not shown on the plot. The peak composed of intervals 460 to 590 msec long (PVC) is caused by premature ventricular contractions and is significantly (P < 0.001) taller in apnea than in respiration.

less pronounced early than late in expiration or inspiration. Differences in variability of interval duration between inspiration and expiration were small compared to changes in the interval duration resulting from apnea. Variability in interval duration closely paralleled the course of interval duration, variability increasing with duration (see also table 1B in reference 1).

Effect of Inspiration, Expiration, and Apnea on A-V Junctional Pacemakers (Table 4)

A-V junctional escape rhythm was observed in nine recordings on six patients. Apnea markedly increased, and the other phases of respiration decreased the prevalence of A-V junctional escape rhythm in five recordings on three patients (fig. 1). In the remaining recordings containing this rhythm too few intervals were registered during apnea to permit quantitative comparison. In most patients there was no difference in the prevalence of escape rhythm between inspiration and expiration. Neither inspiration, expiration, nor apnea altered the firing rate of the pacemaker.

Circulation, Volume XLII, August 1970
A-V junctional tachycardia was observed in five recordings on five patients. In two of these the A-V junctional focus captured the ventricle less frequently during apnea than during respiration but neither inspiration, expiration nor apnea did not alter the discharge rate of the A-V pacemaker. Both patients had an average pulse rate which slowed during apnea and accelerated with breathing. The other three patients with A-V junctional tachycardia who registered no respiratory changes in ventricular capture by the A-V pacemaker also manifested no respiratory change in the intervals between ventricular beats arising from fibrillatory stimuli. A-V junctional transmission system block of atrial fibrillatory stimuli, therefore, paralleled the block of stimuli arising from the A-V junctional accelerated pacemaker. In one of the patients, the decrease in ventricular beats arising from the accelerated A-V junctional pacemaker during apnea coincided with the appearance of a separate A-V junctional escape pacemaker which was discernible only during apnea (fig. 2).

**Effect of Inspiration, Expiration, and Apnea on Ventricular Pacemakers**

(Tables 4 and 5)

Ventricular premature contractions and paroxysms of ventricular tachycardia in sufficient number for quantitative comparison were observed in 15 recordings on 11 patients. Among these, prevalence of ventricular automaticity increased markedly during apnea in nine recordings on seven patients (fig. 3) and did not change with any phase of respiration in six recordings on four patients. Apnea decreased the coupling interval of ventricular premature contractions in some of the 11 affected patients. There was no difference in

---

**Table 3**

*Effects of Inspiration, Expiration, and Apnea on Average R-R Interval Duration, and Variability of R-R Interval Duration*

<table>
<thead>
<tr>
<th>Difference is:</th>
<th>A Average R-R interval duration</th>
<th>B Variability of R-R interval duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recordings</td>
<td>Patients</td>
</tr>
<tr>
<td><strong>Comparison inspiration and expiration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not significant</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In inspir. &gt; in exp.</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>In exp. &gt; in inspir.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total†</td>
<td>49</td>
<td>25</td>
</tr>
<tr>
<td><strong>Comparison inspiration and apnea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not significant</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In apnea &gt; in inspir.</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>In inspir. &gt; in apnea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total†</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td><strong>Comparison expiration and apnea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not significant</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In apnea &gt; in exp.</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>In exp. &gt; in apnea</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total†</td>
<td>32</td>
<td>18</td>
</tr>
</tbody>
</table>

*In 17 recordings on 13 patients fewer than 500 intervals were recorded during apnea; these were not included in the comparisons of inspiration to apnea and of expiration to apnea.

†The total number of patients used in the comparisons does not equal the sum of the numbers of patients listed in each column because when successive recordings in the same patient produced different results, the same patient had to be listed in more than one row.

Abbreviations: Exp. = expiration; inspir. = inspiration.
The Effect of Respiration and Apnea upon the Relative Number of Ventricular Beats Arising from the Ectopic Pacemakers During A-V Junctional Tachycardia, A-V Junctional Escape, and Idioventricular Rhythms*

<table>
<thead>
<tr>
<th>Difference between respiration and apnea</th>
<th>A-V junctional tachycardia</th>
<th>A-V junctional escape</th>
<th>Ventricular premature contractions or ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recordings</td>
<td>Patients</td>
<td>Recordings</td>
</tr>
<tr>
<td>Not significant</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More ectopic activity during respiration than apnea</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>More ectopic activity during apnea than respiration</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No. used in comparison</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*The number of recordings and patients with A-V junctional escape and ventricular ectopic rhythms used in these comparisons does not equal the total number observed in the course of this work because the small number of apneic intervals in some recordings precluded meaningful statistical analysis.

The Effects of Respiration and Apnea on Ventricular Automaticity and A-V Block in Patients With and Without Cheyne-Stokes Respiration*

<table>
<thead>
<tr>
<th>Ventricular automaticity</th>
<th>Cheyne-Stokes respiration</th>
<th>No Cheyne-Stokes respiration</th>
<th>No. used in the comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recordings</td>
<td>Patients</td>
<td>Recordings</td>
</tr>
<tr>
<td>More frequent during:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea than respiration</td>
<td>9</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Respiration than apnea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A-V junctional block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More pronounced during:</td>
<td>14</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Apnea than respiration</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Respiration than apnea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No. used in the comparisons</td>
<td>27</td>
<td>19</td>
<td>7</td>
</tr>
</tbody>
</table>

*When respiration significantly altered ventricular automaticity and A-V junctional block, or when successive recordings in the same patient demonstrated different respiratory rhythms, recordings and patients were listed more than once. Thus, the number of recordings and patients used in the comparisons does not equal the sum of the numbers listed. Meaningful comparisons could be made of only a few patients without Cheyne-Stokes respiration because the small number of apneic intervals recorded precluded statistical analysis.

the prevalence of ventricular premature contractions between inspiration and expiration, although coupling intervals were sometimes shorter in inspiration than expiration. In the ventricular tachycardias observed in the course of this study, we found no respiratory variation of the pacemaker firing rate. Ventricular tachycardia was more frequent during apnea than during inspiration or expiration and occurred much more frequently in patients with Cheyne-Stokes respiration than in others (tables 4 to 6).

Discussion
These observations indicate that apnea increases A-V junctional transmission system block in most patients with atrial fibrillation. As a result the average pulse rate slows. The peak in the interval histogram produced by ventricular beats arising from A-V
EFFECTS OF RESPIRATION ON PACEMAKING

Table 6

Effect of Cheyne-Stokes Respiration on the Occurrence of A-V Junctional and Ventricular Ectopic Pacemakers in Atrial Fibrillation*

<table>
<thead>
<tr>
<th></th>
<th>Cheyne-Stokes respiration</th>
<th>No Cheyne-Stokes respiration</th>
<th>No. used in the comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recordings</td>
<td>Patients</td>
<td>Recordings</td>
</tr>
<tr>
<td>Ventricular automaticity</td>
<td>21</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>A-V junctional tachycardia</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>A-V junctional escape</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No nonatrial pacemaking</td>
<td>8</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>No. used in the comparisons</td>
<td>32</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

*The number of recordings and patients used in the comparisons does not equal the sums of the numbers listed in same rows and columns because many recordings contained more than one arrhythmia and successive observations on the same patient often contained different respiratory rhythms.

...junctional tachycardia (JT, fig. 2) shrinks with apnea, demonstrating that block between this pacemaker and ventricle increases with apnea. However, the location of the peak on the histogram does not change. Therefore, the phases of respiration do not affect the discharge rate of this focus. The peak in the interval histogram produced by ventricular beats arising from the A-V junctional escape focus increases with apnea (JE, fig. 1). At the same time sequences of intervals denoting second degree block between the junctional escape focus and the ventricle, such as Wenckebach periods and sequences of intervals which are multiples of the pacemaker's discharge interval, diminish or remain the same with apnea. These facts denote that block between the escape pacemaker and ventricle does not increase and sometimes diminishes during apnea. It appears, therefore, that in our patients the A-V block which waxes and wanes with respiration is located above the A-V escape focus but below the A-V accelerated focus. The location of the peak in the interval histogram produced by ventricular beats arising from the A-V junctional escape focus does not change with apnea. Therefore, the phases of respiration do not affect the discharge rate of this pacemaker either.

We have previously reported two patients for whom recordings with and without A-V junctional escape were available for comparison. In both many intervals longer than that of the escape focus were seen in the histograms containing no escape. Furthermore, eight other patients had many ventricular beat-to-beat intervals 1.5 sec long or longer without any evidence of escape beating. These observations suggest that A-V junctional escape does not result from high-grade A-V block of the transmission system alone, but that apnea or the slow pulse rate resulting therefrom enhances a regional block within the A-V junction which prevents depolarization of the escape focus by atrial stimuli.

Apnea increases the prevalence of ventricular premature contractions and bursts of ventricular tachycardia. The former phenomenon may be the direct result of the slower pulse rate produced by apnea ("the rule of bigeminy")10. The latter phenomenon may be due to the fact that apnea occasionally also shortens the coupling interval so that a premature beat is more likely to fall into the vulnerable period of the preceding repolarization. Cheyne-Stokes respiration intensifies these effects of apnea, but also increases ventricular automaticity in the other phases of respiration (tables 5 and 6). In view of these observations Cheyne-Stokes respiration should be eliminated whenever possible, particularly in the many patients with this respiratory arrhythmia who are clinically well and ambulatory (table 2) and therefore not within reach of help when a dangerous cardiac arrhythmia supervenes.

Most previous reports detailing the effects of Cheyne-Stokes respiration upon cardiac behavior indicate that in the absence of increased intracranial pressure A-V block and ventricular ectopic rhythms appear during...
hyperpnea and disappear during apnea. Comeau demonstrated that the grade 1 and 2 A-V block presented by his patient during hyperpnea was mediated by the vagus since it was abolished by atropine. Steele and Anthony and Klein suggested that the cardiac arrhythmias of intermittent respiration are caused by deficient gas exchange and reported that in their patients hypoxia and hypercarbia were most severe during hyperpnea. We cannot account for the difference in timing of the arrhythmias between these reports and ours. We can only call attention to the fact that our report is based on measurements of thousands of intervals during thousands of respiratory cycles, whereas older observations made with manual measurement techniques must be based on a much smaller number of events. There is an apparent but not real discrepancy between our report of the changes in average pulse rate with inspiration, expiration, and apnea and that of Hoff and Geddes. We find beat-to-beat intervals slightly longer in inspiration than in expiration, whereas Hoff and Geddes state that pulse rate accelerates in inspiration. The difference results from two factors: (1) Hoff and Geddes do not differentiate between beats occurring in expiration and apnea, and label them all "expiratory," including the very slow ones of apnea. The average duration of their expiratory intervals is, therefore, much longer than ours. (2) We designate intervals "inspiratory" if they terminate in inspiration, even if most of their life is spent in apnea. This tends to prolong our average inspiratory interval. At any rate, we found differences between events in inspiration and expiration to be of little clinical interest. The important changes took place during apnea.

Acknowledgment

The authors gratefully acknowledge the indispensable technical assistance and creative advice of Messrs. Jimmie M. Williams, James P. Berneski, and Alan F. Peters, engineers of the Bioengineering Research Laboratory of the Woman's Medical College of Pennsylvania; the generous cooperation of Dr. David Garfinkel, Mr. Anthony Straccholini, and Miss Linda Schaeffer of the NIH Computing Resource, University of Pennsylvania; and the help and encouragement of Dr. Leonard S. Dreifus of Hahnemann Medical College. Mrs. Seretta Berlin reviewed the manuscript. Messrs. Alan F. Peters and Bennet Palmer of our laboratory, and Paul Shrager and David Greenblatt of the University of Pennsylvania wrote the Linc-8 programs. Miss Lee Tanen of the Philadelphia College of Physicians conducted the MEDLARS literature search. All computer programs may be obtained through DECUS Program Library. The "Appendix," which contains the derivations of the algorithms used in this work is available from the authors upon request.

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Paradigms in Research

A paradigm [in scientific research] is defined as a shared and consensually agreed upon system of assumptions, acceptable operations, standards for evidence, and rules of conduct for a scientific endeavor that are dominant at a particular time in a field of investigation and is expressed in the form of model problems and solutions.—From A. J. MANDELL, and C. E. SPOONER: Psychochemical Research Studies in Man. Science 162: 1442, 1968.
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Circulation. 1970;42:261-269
doi: 10.1161/01.CIR.42.2.261
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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