EFFECTS OF SOME TRANQUILIZING,
ANALEPTIC AND VASODILATING DRUGS
ON PHYSICAL WORK CAPACITY
AND ORTHOSTATIC TOLERANCE

R. V. GANSLEN
B. BALKE
F. J. NAGLE
E. E. PHILLIPS
Biodynamics Branch

FEDERAL AVIATION AGENCY
CIVIL AEROMEDICAL RESEARCH INSTITUTE
AERONAUTICAL CENTER
OKLAHOMA CITY, OKLAHOMA
DECEMBER 1963
EFFECTS OF SOME TRANQUILIZING, ANALEPTIC
AND VASODILATING DRUGS ON PHYSICAL WORK
CAPACITY AND ORTHOSTATIC TOLERANCE

*R. V. GANSLEN, Ph.D.
B. BALKE, M. D.
**E. E. PHILLIPS, Ph.D.
F. J. NAGLE, Ed.D.

For ages, man has attempted to induce changes of psychosomatic behavior by utilizing plants or plant products with stimulating or sedating properties. Some of these products have become such normal ingredients of daily life that most people are no longer aware of their addiction to the specific biological effects of such chemicals as caffeine, nicotine or alcohol. During the most recent years, drugs which had been developed for controlling psychosomatic disturbances of various types and origins have become almost as popular as coffee, tobacco, or alcohol. There can be no doubt, however, that under certain conditions the individual's sensory and functional capacity might become affected by such pharmacas in a way interfering with, or being detrimental to, an important working task.

This investigation was predicated on the basis: (a) that drugs used for general therapeutic purposes, such as the tranquilizers of the mebrobamate group, may affect the work capacity or efficiency of normal subjects; (b) that certain drugs, vaguely or specifically referred to as aids to heart function in persons evidencing cardiac insufficiency, may materially alter the maximal working capacity of normal healthy subjects; (c) that the biological effects of the drugs under investigation were of such a nature that their ingestion should be indicated or contra-indicated for persons in certain occupations such as pilots, motor vehicle operators, or for individuals who might be subjected to extensive physical demands.

Methods and Procedure

Five healthy male subjects in the range from 29 to 54 years participated in one or the other phase of the experimental investigations. Two different testing procedures were employed for studying the effects of various drugs on hemodynamic adjustments to stress: (a) a tilt table test, for the assessment of orthostatic tolerance, and (b) a treadmill test for the determination of the aerobic work capacity and of the quality of the functional adjustments.

Tilt Table Test

The subject assumed a supine position on a horizontal tilt table, with the feet firmly planted against a footboard. Straps were pulled across the hips and across the forelegs, the head was slightly raised on a cushion. After a state of complete relaxation was attained, measurements of blood pressure and heart rate were made twice during each of 5 minutes in the supine position, likewise during a period of 10 minutes (unless syncope intervened) tilted foothwards to a 60-degree angle, and during 3 minutes of supine recovery. The pulse rate count was obtained electronically, the blood pressure by the conventional ausculatory method.
**Treadmill Test**

The treadmill test consisted of walking at a speed of 91.5 m/min (3.4 m.p.h.) at a grade of 1 per cent during the first minute, at 2, 3, 4, etc., per cent during each of the following minutes. The cardio-vascular response to the increasing metabolic demands was monitored regularly by measuring heart rate and blood pressure by the conventional Korotkoff method during the second half of each minute.\(^{(1)}\)

The subjects taking part in this study were accustomed to the walking on the treadmill and to all the laboratory procedures. They were in such a state of training condition that repeated but sufficiently spaced control tests elicited the same functional responses. In order to study the effects of a particular drug when taken routinely in several single doses during a 1 - 2 day period, the work capacity tests were terminated at submaximal efforts, at pulse rates of 160 beats per minute. In that way, two or three tests per day were possible without ill effects on the physiological responses due to fatigue.

After satisfactory control patterns had been established, the drug of particular interest was administered orally. The re-test then, was performed after elapse of the time necessary for the drug to become effective. The following drugs were studied: (1) Caffeine and Metrazol (Pentamethylenetetrazol) separately, and combined in a tablet containing .2g Caffeine and .4g Metrazol; (2) Recordil (flavon-7-ethyl oxyacetate), an Italian vasodilator substance,\(^{(2)}\) in a single dose of 200 mg; (3) Equanil (Meprobamate), in the clinical dose of 5 x 400 mg/day, or in single dosages of varying amounts.

**RESULTS**

**Caffeine-Metrazol:** Preliminary experimentation with either one of the substances taken by a well-trained subject did not reveal any change in work capacity or in the cardiovascular response pattern to the test work. The combination of both drugs in a single tablet, when absorbed sublingually, had the effect as shown in Figure 1: for any given load during the gradually increasing test work the heart rate was 4 - 8

![Figure 1: Effects of caffeine-metrazol on cardiovascular response to gradually increased energy expenditure.](image)
beats per minute lower than in the control test, the systolic pressure about 6–10 mm Hg higher. Work capacity, under the effect of the drug, was improved: the oxygen intake at the crest load was 57.7 ml/kg/min against 54.4 ml/kg in the control test. In both cases the maximum pulse rate was 188 beats per minute, the maximum systolic pressure, however, was 235 mm Hg in the drug experiment compared to 225 mm Hg in the control test.

**RECORDIL**

**Work Capacity Test:** Four hours after ingestion of a single dose of 200 mg Recordil the two participants in this study reached a higher peak load with an unusual subjective ease and with an uncommon lack of straining symptoms. Both subjects exceeded their maximum pulse rate of 162 beats per minute attained in the control tests, one reaching a final rate of 172, the other a rate of 174 beats per minute. In contrast to the previously reported experiment (caffeine-metrazol), in which pulse rate was lower and systolic pressure higher throughout the drug-test, in this series the heart rate was slightly higher most of the time, but both the systolic and diastolic pressure were substantially lower than in the control test (see Figure 2).

![Graph](image)

**Figure 2:** Effects of Recordil (flavon-7-ethyl-oxyacetate) on cardio-vascular response to the standard treadmill test.
**Tilt Table Test:** A general vasodilating effect of the drug was not only observed during the exercise but also in the supine as well as in the tilted position on the tilt table. In one of the subjects tilting caused syncope although the control tests before and 30 hours after drug administration had shown "normal" response pattern (see Figure 3).

Subjectively, the drug made the subjects feel "keyed up" for about 12 hours after ingestion. Approximately 24 hours later both individuals experienced faint anginal sensations of short duration.

**EQUANIL**

**Work Capacity Test:** The cardiovascular responses to the treadmill test work was practically unaffected by doses of up to 800 mg. The slight variations observed were similar to those seen in repeatedly performed control tests. However, with dosages above 1200 mg, either in single or accumulated doses, a typical response pattern appeared to become evident in all subjects: at each given work load the systolic blood pressure was 10 - 20 mm Hg lower than in the controls while the diastolic blood pressure as well as the heart rate remained essentially unchanged. These responses are illustrated in Figure 4 which shows the relative changes of systolic pressure and heart rate from the control resting values (systolic Bl. Pr. = 112, Heart Rate = 42 beats/min.) for the course of the work capacity test. The product of these relative systolic pressure and pulse rate changes, serving as an indicator of relative changes in cardiac output during exercise (9), appears to disclose a depressing effect of the drug on the cardiac output. Equanil also caused a slight reduction of the systolic blood pressure during

---

**Figure 3:** Effects of Recordil on cardiovascular response to passive changes of body position (tilting footwards to 60°).
relaxed resting conditions accompanied by a slight rise in heart rate while diastolic pressure, on the average, did not change (Table 1). The effect of tilting on blood pressure and heart rate was similar in both the control experiments and when different doses of the drug were ingested. As schematically indicated in Table 2, tilting did not result in a uniform change of the systolic blood pressure, but in almost all cases a rise of the diastolic pressure and pulse rate did occur. Only after administration of a large single dose of 1200 mg the already lowered resting systolic pressure dropped furthermore upon tilting in the three subjects tested; no syncope was observed.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Systolic Bl. Pr. mm Hg</th>
<th>Diastolic Bl. Pr. mm Hg</th>
<th>Heart Rate per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B  G  P  R</td>
<td>B  G  P  R</td>
<td>B  G  P  R</td>
</tr>
<tr>
<td>Control 1</td>
<td>122 110 120 135</td>
<td>74 77 75 71</td>
<td>56 54 48 62</td>
</tr>
<tr>
<td>Control 2</td>
<td>120 116 122 125</td>
<td>80 73 75 75</td>
<td>54 58 40 66</td>
</tr>
<tr>
<td>Average</td>
<td>121 113 121 130</td>
<td>77 75 75 73</td>
<td>55 56 44 64</td>
</tr>
<tr>
<td>Equanil:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x 400 mg</td>
<td>110 108 115 114</td>
<td>84 86 60 75</td>
<td>58 61 48 66</td>
</tr>
<tr>
<td>4.5 x 400 mg</td>
<td>110 107 115 124</td>
<td>72 72 72 80</td>
<td>57 60 40 60</td>
</tr>
<tr>
<td>1 x 1200 mg</td>
<td>— 111 102 121</td>
<td>— 75 70 80</td>
<td>— 60 48 62</td>
</tr>
</tbody>
</table>

Table 1: The effect of Equanil on blood pressure and heart rate in the supine resting state.
**DISCUSSION**

Hartwich (5) reported beneficial effects from the ingestion of metrazol (cardiazol, pentamethylene tetrazol) on the work capacity of man during the German Himalayan Expedition (1931). According to Graf (6), this drug stimulates circulation in states of severe physical fatigue but has no effect on performance under normal conditions. In other experiments in which psychomotor performance was tested, improvement resulted in both cases when a combination of metrazol and caffeine (dose: .2g + .1g) was given. This combination of drugs also had the advantage of not producing the “sagging” after-effects frequently observed after administration of caffeine only.

The increase of aerobic work capacity in the experiment described in Figure 1 must have been the result of improved cardiac dynamics. Since oxygen intakes had remained the same at given work loads, cardiac output was assumed to have remained unchanged too. Therefore, the lowering in heart rate had to be compensated for by an increase in stroke volume. The increase in systolic blood pressure — relatively in the same order of magnitude as the decrease in heart rate — appeared to substantiate such postulation. The increase of the maximum oxygen intake capacity (about 6 per cent above the control test) was a consequence of the greater maximum cardiac output derived from a larger systolic blood volume at the maximum heart rate.

Atzler, Lehmann and Szakall(8) have reported on the role of caffeine in carbohydrate and protein metabolism. Undoubtedly, the caffeine-metrazol combination assists in mobilizing energy from the body stores as was also observed in a field experiment simulating an emergency situation: one of the author’s covered in 13 hours a distance of approximately 55 miles in the mountains with a vertical ascent totaling 10,000 feet. This performance required an energy expenditure of about 9,000 kilocalories, of which only 1,000 kcal were supplied by external food intake after 3 hours of work. Since in a well-trained athlete about 400 g of glycogen (~ 1,600 kcal) are available as energy source(8) 7,400 kcal of energy must have been supplied from mobilized fat and/or protein stores. Normally, even the trained organism is not capable of working at a very high rate of energy expenditure for a period much longer than 2-3 hours without brief “refueling.” In this case, caffeine-metrazol (.2g + .2g) was administered sublingually whenever symptoms of approaching exhaustion called for a slowing down. Then, after awhile the pace picked up again and the improved work capacity lasted from 120 to 60 minutes, decreasing in duration with the accumulation of working time. In repeat dosages a total of 1.0 g caffeine and 1.0 g metrazol was consumed. Despite the deficit in caloric balances and general fatigue recovery was excellent and mountaineering was resumed after an eight-hour rest period.

Flavon-7-Ethyl-oxyacetate (Recordil), when used for the perfusion of the isolated rabbit heart by Setnikar and Zanolini (8), caused a marked dilatation of the coronary vessels without changes in amplitude or frequency of the beats. Tartara and Corbetta (9) were the first...

---

**Table 2:**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Systolic Bl. Pr.</th>
<th>Diast. Bl. Pr.</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B G P R</td>
<td>B G P R</td>
<td>B G P R</td>
</tr>
<tr>
<td>Control 1</td>
<td>- - - -</td>
<td>+ + + +</td>
<td>+ + + +</td>
</tr>
<tr>
<td>Control 2</td>
<td>+ - - +</td>
<td>+ + + +</td>
<td>+ + + +</td>
</tr>
<tr>
<td>Eguanil:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x 400 mg</td>
<td>- = + -</td>
<td>= + + +</td>
<td>+ + + +</td>
</tr>
<tr>
<td>5 x 400 mg</td>
<td>- = = +</td>
<td>= + + +</td>
<td>+ + + -</td>
</tr>
<tr>
<td>1 x 1200 mg</td>
<td>- - -</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
</tbody>
</table>

*Effects of Eguanil on orthostatic tolerance. The direction of changes in blood pressure and heart rate from supine to the tilted position is indicated by — (drop), + (increase), = (no change).*
to use this drug with cardiac patients and found
an attenuation of symptoms in four out of five
cases of recent myocardial infarct. Strausak,
Cuttier and Schmid(14) used Recordil in twenty
anginal patients to determine their tolerance to
walking on level ground and ascending steps.
60 to 90 mg were given daily for periods up to
16 months with considerable success. Star-
cich(15) prescribed Recordil for more than 25
cardiac patients and emphasized the lack of sig-
nificant changes in blood pressure and pulse
frequency. Epstein(16) administered Recordil to
medical students and faculty members for peri-
ods up to 30 days with dosages ranging from
30 - 660 mg daily. He noted slight lowering of
hemoglobin levels with large dosages.

The results of this investigation, using a
rather large dose of Recordil, indicates that the
systolic and diastolic blood pressure were sig-
nificantly altered during moderate to strenuous
physical exercise. Ischemic pains, usually expe-
erienced during the later stages of the tread-
mill test, were less conspicuous in both subjects.
The syncope of subject R.G. during tilting points
to a marked peripheral vasodilation at rest as
well as during work. Mild anginal pain was ob-
served by both subjects about 24 hours after
completion of the exercise test. One might specu-
late that the syndrome arose as an over-compen-
satory reaction of the coronary vessels after the
drug effect had worn off.

The meprobamate drugs, whose general ef-
fects have been extensively discussed in the
literature(17), are known to be excellent muscle
relaxants, create drowsiness, result in some
ataxia, depress certain portions of the EEG re-
cords (particularly those nuclei associated with
the thalamus). In very tense patients with mark-
ed muscle spasms, the drugs have proven quite
useful.

The marked drop in the blood pressure after
administration of Equanil may only have been
the consequence of general muscular relaxation
in the resting state, but the persistency of lower
blood pressures during work of identical inten-
sity on the treadmill suggests an involvement of
the central nervous system. It is not improbable,
in light of the generally observed effects of the
meprobamate drugs, that the stimuli or lack of
stimuli, which became evident in the blood pres-
sure disturbances, had a thalamic-medullary
component of interest. The atypical cardiody-
namic response was the result of some obscure
effect on the vasomotor center. This could con-
ceivably have arisen at some higher level in the
central nervous system. There also seemed to be
a lack of coordination in the response to sensory
input stimuli arising in the muscles under identical working conditions. All subjects re-
ported some motor instability during the early
stages of the treadmill test and were, at the out-
set, disinclined to work. The extent of the vas-
omotor system depression is perhaps best empha-
sized by the fact that the "activity", even at the
most strenuous level, did not alter the blood
pressure response to work. Relatively low blood
pressure during work was persistent.

Summary and Conclusions

Using standardized tests on the treadmill and
on the tilt table the effects of the following
anaesthetic and tranquilizing drugs on physical
working capacity and on orthostatic tolerance
were investigated: Caffeine-Metrazol: A
combination of this drug (in combined dosages
of .1g or .2g each) appeared to have potency as
antifatiguing medication and ergogenic aid,
accomplishing an improvement in cardiac eco-
nomy by increasing the stroke volume at a low-
ered heart rate and augmenting maximum car-
diac output as well as maximum oxygen intake.
Further investigations of this drug are war-
ranted.

Recordil: (Flavon-7-ethyl-oxyacetate): The
physical working capacity of the subjects was
materially benefited by a dose of 200 mg of
this drug taken 4 hours before the exercise test.
The absence of localized fatigue and leg pain
supports the thesis that peripheral vasodilation
is present and effective. The psychic-excitatory
effect of Recordil could not be explained except
on the basis of some conceivable increased cere-
bral blood flow mechanism for which there is
no evidence at this time.

Equanil: One must not associate disinclina-
tion to exertion (a common effect of meproba-
mates) with potential working capacity of the
individual. Although the latter was actually not
altered even under massive doses of Equanil,
disturbances of the vasomotor system became
evident. A real hazard seemed to exist with the
tendency of blood pressures to be depressed, particularly with subjects who naturally possessed low blood pressure. These vasomotor disturbances suggested central nervous system depression, especially of thalamic origin.

The psychic energizing effects of benzedrine and amphetamine compounds are well known but the improvements in working capacity with these substances are more often the result of motivational factors than physiological improvement. Substances which enhance capacity without noticeable psychological side effects are of great value. One must be concerned, however, with the question of "real" improvements in efficacy since these artificial means of unlocking the individual's reserve energy stores may not be subject to the will.

One strongly questions the safety of people engaged in the operation of aircraft or motor vehicles when "sedated" by such drugs as the meprobamates. Blood pressure depressions, as observed, would be aggravated by sudden changes in posture and increased "g" forces during aircraft maneuvers. Serious incidents and fatal accidents may be precipitated by the emotional indifference to suddenly arising problems or as a consequence of delayed circulatory responses during flight maneuvers.

REFERENCES