DEPARTMENT OF THE ARMY
US ARMY RESEARCH, DEVELOPMENT AND ENGINEERING COMMAND
5183 BLACKHAWK ROAD
ABERDEEN PROVING GROUND MD 21010-5424

REPLY TO ATTENTION OF:

August 26, 2009

Office of the Chief Counsel

Mr. John Greenewald, Jr.
[redacted]

Dear Mr. Greenewald:

This is the final response to your FOIA request dated June 18, 2009 and assigned **RDECOM FOIA #FA-09-0036** where you sought copies of the following records:

a. "Long Term Followup of Medical Volunteers", Accession Number AD-519540, dated March 1972 (enclosed).

b. "Physiological Action of BZ on Men Subjected to High Temperatures and Exercise", Accession Number AD-347911, dated February 1964 (enclosed).

c. "The Search for Toxic Chemical Agents", Accession Number AD-507852, dated November 1969 (exempt from release).

The redacted records were subject to FOIA exemptions (b)(3) and (b)(6).

a. FOIA exemption (b)(3) covers matters that a statute specifically exempts from disclosure. Specifically, "The Search for Toxic Chemical Agents" contains data on hundreds of compounds that could be used as potential chemical agents. Therefore, "The Search for Toxic Chemical Agents" is exempt from release, in accordance with 10 U.S.C. § 130, which protects the release of technical data that could be used in a military setting and is subject to the Arms Export Control Act.

b. FOIA Exemption (b)(6) along with a Department of Defense policy allows for the withholding of government employee names, email addresses, and other personal information.

If you consider this response to be an adverse action, you may administratively appeal, in writing, to the Secretary of the Army. However, prior to appealing directly to the Secretary of the Army, the Initial Denial Authority, (Mr. Patrick R. Sheldon), must review the appeal. Therefore, any such appeal should be addressed to this office. We will review your appeal and forward your appeal to the Army Office of General Counsel, the designated Army Freedom of Information Act appellate authority.

Additionally, if you choose to appeal, the appeal must be received by the appellant authority (Army General Counsel), no later than **60 days** following receipt of this letter. Please send correspondence to the following address:

Brian A. May
RDECOM, ATTN AMSRD-CCF
5183 Blackhawk Road, E4435
Aberdeen Proving Ground, MD 21010-5424

Should you have any questions or concerns regarding your request I can be reached at (410) 436-2289 or brian.may3@us.army.mil

Sincerely,

//SIGNED - BAM//
Brian A. May
FOIA Officer, HQ RDECOM

Enclosure

PHYSIOLOGICAL ACTION OF BZ ON MEN SUBJECTED TO HIGH TEMPERATURES AND EXERCISE

CHEMICAL RESEARCH AND DEVELOPMENT LABS EDGEWOOD ...

FEB 1964

Atch 3

AD NUMBER

AD347911

CLASSIFICATION CHANGES

TO

unclassified

FROM

confidential

AUTHORITY

USAEA notice, 19 Mar 1969

[redacted]

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[redacted]

UNCLASSIFIED

U. S. Army
Chemical Research and Development Laboratories
Technical Report

[redacted]

Physiological Action of BZ on Men Subjected to High Temperatures and Exercise (U)

(b)(6)

February 1964

EDGEWOOD ARSENAL, MD
Group 4

Downgraded at 3 Year Intervals;
Declassified After 12 Years.

[redacted]

February 1964

CRDLR 3199

PHYSIOLOGICAL ACTION OF BZ ON MEN SUBJECTED TO HIGH TEMPERATURES AND EXERCISE (U)

by

(b)(6)

Physiology Division

Recommending Approval:

(b)(6)

Director of Medical Research

Approved:

(b)(6)

for Technical Director

U. S. Army Edgewood Arsenal
CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES
Edgewood Arsenal, Maryland

[redacted]AL

(U)

FOREWORD

These tests were authorized under Project 4C08-02-023, CW Biological Science Research (U). The observations were made between October 1961 and April 1962.

Acknowledgments

The authors are indebted to (b)(6) Ph. D., for supplying the agent used in these tests and to (b)(6) M. D., for medical care of the subjects. Valuable technical assistance was supplied by (b)(6) of the Applied Physiology Branch. We also thank the Human Investigations Facility, in particular (b)(6) for the cooperation received in supplying volunteers for these tests.

Notices

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(C)

DIGEST

Fourteen Medical Research Division Volunteers were given BZ in a 4- or 5-μg/kg oral dose and exercised for 6 hr in various environments, from 85° to 115°F. Incapacitation occurred in 5 of the 14 men. Four men were unable to complete the walking or running exercises and exhibited ataxia, general weakness, tachycardia, and elevated body temperature. One man was removed from the test situation because of an elevated rectal temperature.

In the average case, BZ reduced sweating by approximately 30% of control levels from the end of the second hour to the end of the sixth hour of testing. The reduction ranged from 45% to 0%. Average skin temperatures after BZ were 2° to 3°F higher than control values; average body temperatures rose 0.5° to 0.7°F above control values. Six hours after BZ, one man had a rectal temperature above 103°F, three men above 102°F, and two above 101°F. The four men who did not finish the 6-hr test also exhibited overheating. BZ increased heart rates during walking by 20%.

The following conclusions were reached:

The effects of exercise and heat do not seem to potentiate the central-nervous-system effects of BZ in an oral dose of 5 μg/kg. Additional incapacitation from heat exhaustion can be expected, however, in about one-fifth of the individuals receiving this dose when exercise is performed in hot environments. Even at 85°F some heat casualties may occur. In resting men, heat regulation is maintained for at least 6 hr in the environments tested.

The parasympatholytic effects of the oral dose of BZ are similar to and slightly less in severity than those of a 2-mg intramuscular dose of atropine tartrate, but they persist for a much longer time.

(U)

CONTENTS

(C) PHYSIOLOGICAL ACTION OF BZ ON MEN SUBJECTED TO HIGH TEMPERATURES AND EXERCISE (U)

I. (C) INTRODUCTION.

(C) The purpose of this experiment was to determine the physiological action of BZ (EA 2277) on men subjected to the stresses of high environmental temperature and exercise. This is a functional approach to drug action and represents an intermediate research stage between clinical testing and field application of an agent.

(U) Similar studies were done with atropine by Craig[1] and Robinson.[2] Atropine and BZ are parasympatholytic in effect. Atropine and related compounds, at appropriate doses, accelerate the heart and decrease sweating at high environmental temperatures. As the result of decreased sweat production in the heat, body temperature rises. In field tests at a dry-bulb temperature of 83°F, 2-mg doses of atropine could incapacitate working men by heat exhaustion after 2 hr.[2]

(C) The report of the original tests[3] with EA 2277 describes the psychotropic effects and general symptoms related to dose. The psychological and clinical effects[4] and the effect on skilled performance in simulated flight[5] have been investigated intensively. Tachycardia and depression of the T-wave of the ECG's of humans[3] and dogs[6] caused by this drug were reported earlier. The pnysiological effect upon exercising dogs has also been described.[6]

(C) Because of safety requirements in the use of a new compound in a new situation, the doses of BZ were limited to 4 or 5 µg/kg orally.

II. (C) METHODS AND MATERIALS.

A. (U) Subjects.

All humans used in these tests were selected from Medical Research Division volunteers. These men, except subject (b)(6) were selected by the same set of physical and psychological standards (table 1, appendix). They were required to be in good physical and mental condition and free from any abnormalities. They were a carefully selected group and not a random sample. The physical characteristics of this group are shown in table 2, appendix. The decision on the suitability of personnel was made by the medical staff of the Human Investigations Facility.

The environments within which the subjects exercised are given in table 3, appendix, and were selected to produce varying degrees of heat stress. The men wore only shorts in all but one test, when they wore the fatigue uniform (undershorts, T shirt, fatigue shirt and trousers, socks, and combat boots). Air movement was minimal. The relation between air and wall temperatures for this room has been described.[7]

B. (U) Exercise Schedule.

The exercise was distributed over 6 hr in three repetitive cycles, each cycle lasting 2 hr. A complete cycle progressed as shown in table 4, appendix.

To alleviate boredom, a radio was played for the men and they were allowed to read. They ate lunch between 12:00 and 1:00 during a resting phase of a cycle, usually at the beginning of cycle 2.

C. (U) Measurements.

Sweating rate was estimated from loss of body weight. Body weight was measured on a platform balance (Buffalo) of over 200-kg capacity and sensitive to ±5 gm. Heart rates were recorded continuously during the beginning of exercise and every 5 min thereafter. Blevins salt-bridge electrodes[7] were used to obtain the ECG signal for estimating the heart rate, which was recorded through a Sanborn ECG amplifier. Thermocouples fastened by elastic webbing over the chest, back, hips, and thigh sensed skin temperatures, which were recorded on a Leeds & Northrop Speedomax recorder. Rectal temperature, measured by a thermocouple inserted 7 cm into the rectum, was recorded beside the skin temperatures. Average body temperature was calculated by weighting rectal temperature doubly and averaging this with the average skin temperature.

Standard ECG leads were employed on the men while they were resting after exercise at hourly intervals. During exercise, end-tidal carbon dioxide was measured at 5-min intervals using a continually sampling Liston-Becker carbon dioxide meter, the output of which was recorded by a Sanborn galvanometer.

D. (C) Administration of BZ.

(C) BZ was obtained in hydrochloride form from (b)(6) these Laboratories. The original commercial sample was used in all tests except the last one, in which analytical sample 1210 was used. Samples,

1 mg, were weighed on a torsion balance and diluted to 100 ml with distilled water, giving a concentration of 10 μg/ml. Dilutions were made 2 hr before the tests to ensure complete solution. Individual doses of 4 or 5 μg/kg of body weight were measured from this solution, diluted to 250 ml with water, and administered orally.

(C) Two analyses of the stock solutions were made by the Physiological Chemistry Branch to check concentrations. These analyses yielded concentrations of 9.8 and 10.1 μg/ml, confirming the original estimates.

(U) The agent was given at zero time of the first test cycle (table 4, appendix). Men were instructed to fast before the test, but there was no direct control over this.

E. (U) Tests With Atropine.

To compare the effect of atropine with that of BZ, two men were given 2 mg of atropine tartrate intramuscularly. They then completed the three exercise cycles in a 100°F environment.

F. (U) Medical Care.

A Medical Officer was present while the tests were being conducted. The men were examined during the control and experimental periods. After the test the men were returned to the Human Investigations Facility, where their recovery was supervised.

III. (C) RESULTS.

A. (C) General Responses of Subjects.

Responses to the 3-μg/kg dose of BZ varied widely, ranging from little effect to hallucinations and inability to stand. Most subjects were ataxic and held onto the railing of the treadmill with one hand while walking; they were instructed to use both hands while running. Dryness of the mouth and a tired feeling in the limbs were the first subjective symptoms noticed by the subjects. These symptoms appeared in some men about 90 min after oral drug administration and were present to some degree in all subjects at 3 hr. In the hot environment, the face, shoulders, and arms of most subjects appeared red and flushed. This was associated with the measured reduction in sweating. Some men had slightly swollen hands, but this was also occasionally found during control experiments in the heat.

The general reaction in 11 of the 14 men receiving BZ in the 4- to 5-μg/kg dose was fatigue, involving a lack of motivation. They did not wish to exercise and preferred to lie with closed eyes on the cot provided. Their movements appeared slower, and they were unsteady while standing. Two men (b)(6) showed subjective recovery from these symptoms after 5 min of the walking schedule and claimed they felt better when exercising than when sitting or lying. After the walk they sat; the feeling of lassitude returned after about 5 min.

Two men, (b)(6), who were most severely affected developed uncontrollable movements of the limbs during the third hour. Intermittently, while they were lying down, their legs and arms would flex or extend in a rapid, jerky fashion, and they would change their position frequently.

The ECG's of two men, (b)(6), showed T-wave depression and, later, T-wave inversion (figure 1), attributed to the drug. T-wave flattening developed during the fourth hour after drug ingestion, and clinically indicates cardiac ischemia. Atropine, however, has been shown to increase coronary blood flow.[8] This T-wave flattening may be a result of change in heart position,[9] or it may be related to an irritation of the pericardial membranes. A more detailed analysis of the ECG records of all the men will be the subject of a later report.

Subject (b)(6), was hyperventilating in the hot room while under the influence of heat and BZ. This hyperventilation disappeared after he was removed from the room and had rested. Equipment was not set up at the time to measure respiratory parameters, but his respiratory rate was counted. Hyperventilation developed during the last 5 min of the 3-mph walking period. After 30 min of rest, his respiratory rate was extremely variable, ranging from 33 to 12 breaths/min 20 min later and then rising to 28 breaths/min 5 min later.

Subject (b)(6) also began to hyperventilate during the last 5 min of walking. He showed a lowering in end-tidal carbon dioxide and an increase in minute volume.

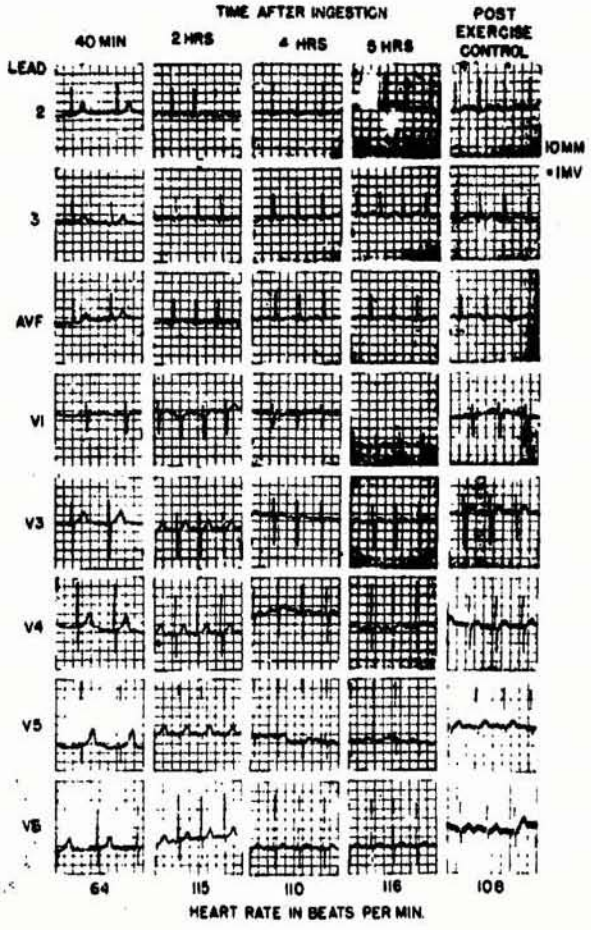

FIGURE 1

ELECTROCARDIOGRAMS OF SUBJECT C. B. AT VARIOUS TIMES AFTER INGESTION OF BZ (U)

Leads were selected that illustrated most marked change in record after BZ. Precordial leads V4, V5, and V6 illustrate T-wave depression 4 and 5 hr after BZ ingestion that was not present in postexercise control record. Postexercise control record was taken at 4 hr and 45 min of test and 3 min after 9-mph run. Temperature of test chamber was 100°F.

Incapacitation, defined as inability to continue physical work, occurred in 7 of the 14 subjects and was attributed to several conditions. One man exhibited a bradykinesia of the lower extremities when attempting to run at 9 mph, and therefore was unable to run. Three men reached the point where they were unable to walk or run because of ataxia and general weakness, associated with a tachycardia and elevated body temperature. One man did not have difficulty with the work but was taken out of the hot room at 5 hr and 40 min because of an elevated rectal temperature. For two men, (b)(6) there was an interval between onset of the first symptoms and incapacitation, whereas (b)(6) showed a rapid deterioration, becoming incapacitated almost simultaneously with the appearance of symptoms.

The hallucinations of (b)(6) lasted for 3 days. He began to lose contact with reality after about 6 hr and believed he was directing a field problem until his recovery 3 days later. Subject (b)(6) had mild auditory hallucinations at 5 hr. He thought he heard voices whispering, but had the capacity to realize that this could not be so. He also showed some disorganization in answering simple questions such as, "How are you?" The next day his I. Q. score was in the 60 to 70 group, whereas his pretest scores were well above average. He suffered some loss of memory but otherwise appeared normal physically and was able to engage in normal conversation.

The preceding material is summarized in table 5, appendix.

B. (C) Effect on Sweating.

Figure 2 illustrates the reduction in sweating as measured by hourly weight loss in the different environments. The hourly variation represents the hourly differences in physical activity, according to the test schedule (table 4, appendix). High sweating rates were observed in the 3-mph walk because of the long duration of exercise. Tabular data for weight loss during walking are shown in table 6, appendix, and for the rest-run session in table 7, appendix.

The highest sweat rates were obtained in the 115°F heat and the lowest at 85°F. Men with clothes sweated more at 100°F than those without. As can be seen from figure 2, the percent reduction in sweating is fairly constant for all environments and averages about 35% of the control values. There appears to be a reduction in sweat rate even during the first hour after ingestion of BZ. It seems improbable that BZ is exerting this effect, because one would not expect such rapid absorption from the gut and because heart rate does not become affected until 1-1/2 hr after ingestion.

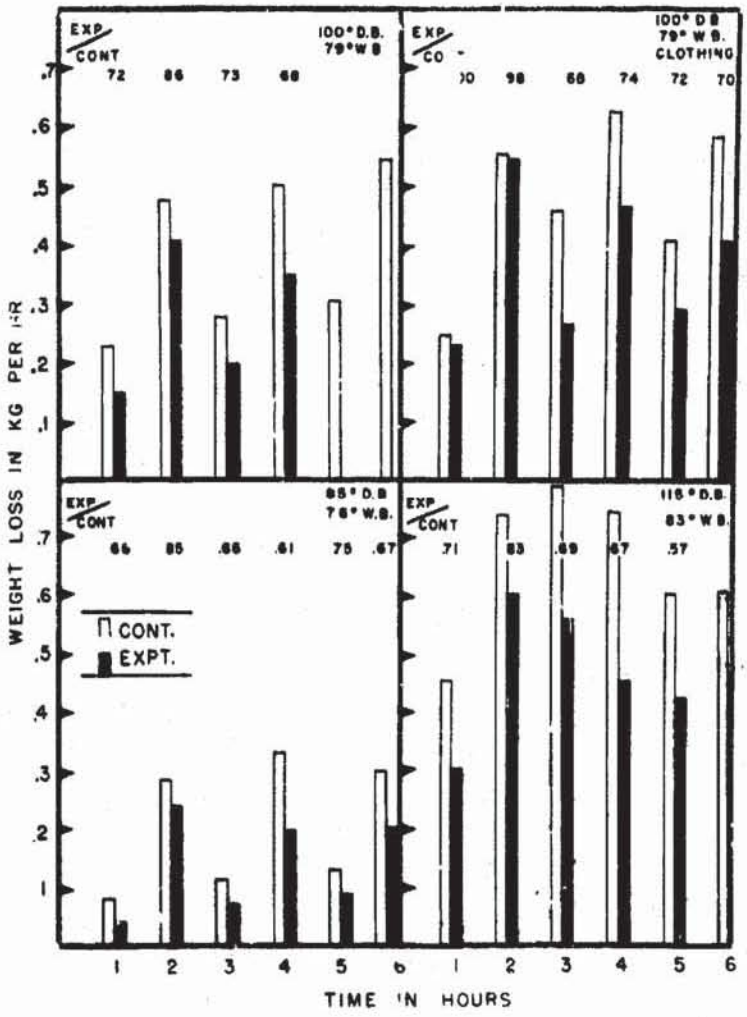

FIGURE 2

REDUCTION IN SWEATING CAUSED BY BZ, AS MEASURED BY HOURLY WEIGHT LOSS IN DIFFERENT ENVIRONMENTS

C. (C) Effect on Heart Rate.

(C) The effect of BZ on heart rate during the walking exercise is shown in table 8, appendix. A tachycardia is apparent in of 14 subjects after 2 to 2-1/2 hr; a slight increase in heart rate may appear after only 1-1/2 hr. This tachycardia appeared when at rest, when standing, and when walking. The effect of heat on heart rate may be noticed in the control series; the rising values with time are associated with a rise in body temperature.

(U) Heart rates obtained at the end of the 1-min 9-mph run are shown in table 9, appendix. These results for BZ are very similar to the control values. The rates are not maximum nor steady-state rates, which would have been obtained it the heavy exercise had been carried on for longer periods of time.

D. (C) Effect on Body Temperature.

The rise in rectal temperature that developed while subjects were walking at 3 mph is shown in table 10, appendix. At 100°F with clothing the additional heat storage is particularly apparent. After the men completed the walks and while they rested, regulation of body temperature seemed to become relatively efficient. Rectal temperature did not rise during resting and frequently dropped. The temperatures of those subjects who were very mildly affected by the drug remained much like their control values. Other subjects, who were more severely affected, exhibited rectal temperatures above 103°F.

The effect on mean body temperature, which is a weighted average of rectal and skin temperatures, is shown in table 11, appendix. After BZ, there was an increase in body temperature, most apparent in the two men at 115°F. As with atropine, there is a rise in the skin temperature (table 12, appendix). The increase in heat storage is most apparent in body temperature when one compares temperatures during the third cycle of the control and experimental tests. In each case, the temperature rise is greater after BZ. At 85°F, the control and drug values for skin temperature do not differ much except for subject (b)(6)

E. (C) Effect on Blood Pressure.

(C) No systematic measurements of blood pressure were taken, however, the Medical Officer did record blood pressure in subjects (b)(6) and (b)(6) and noted a postural hypotension. While the men were sitting, the systolic pressure was in the 115- to 120-mm-Hg range. When they stood up,

the systolic pressure dropped to the 90- to 100-mm-Hg range, but after approximately 2 min returned to the 115- to 120-mm-Hg range.

(U) The blood pressures of two subjects given atropine injections in 100°F heat were also taken. In one of these men, postural hypotension of the same magnitude as above (which lasted for 1 min after he stood up) was also noted.

F. (U) Tests With Atropine.

For comparison with the BZ series, two men were given 2 mg of atropine intramusculary and performed the exercise cycles in a 100°F environment. Two other men were given the same amount of atropine in a 65°F environment. Atropine reduced sweating to 60% to 50% of the control levels during the first hour (table 13, appendix). This effect began to disappear during the second hour and was almost gone by the third hour, as indicated by the experimental-to-control ratios.

Atropine caused a rapid rise in rectal temperature during the first hour, which resulted from the reduction in sweat rate. At the end of the third hour, rectal temperatures were roughly comparable with those of the controls and had decreased from levels reached at the end of the first hour.

Acceleration of the heart rate produced by atropine was most apparent during the second and third hours and began to diminish during the fourth hour of the test (table 14, appendix). Heart rates during the fifth hour were similar to the control values.

Examination of the heart rate at the beginning of exercise in the heat and after atropine showed that the heart may slow down for approximately 30 sec when exercise is started. This held true only when the standing heart rates were elevated by atropine or heat. In one man, the rate slowed by 40 bpm and returned to the standing level after 35 sec. In other subjects, this effect was not so pronounced. Details of these tests have been published elsewhere.[10]

IV. (C) DISCUSSION.

Incapacitation is the main tactical objective of the use of BZ. Some parasympatholytic compounds, such as atropine, can produce incapacitation in warm environments by interfering with heat regulation, others, such as Artane,

may incapacitate by inducing mental confusion.[2] Potentially, BZ can incapacitate by both methods, but the usual concept of use emphasizes the disorganization of normal central-nervous-system controls.

In these tests, incapacitation for physical work was most apparent in men exercising in the 100°F environment. Three of these four men exhibited central-nervous-system effects of dizziness and ataxia, and the ECG's of two of the four men showed evidence of coronary disturbance; i.e., T-wave flattening. Three of these men, had they continued, would have become overheated. Contrasted to these reactions, the 10 men exercising in other environments showed much milder symptoms. Since the men performed fairly well in other environments that included conditions more stressful (clothing, 115°F) than an ambient temperature of 100°F, it appears that heat and work in themselves do not enhance the effects of BZ on the central nervous system. Lack of adaptation to heat may be a factor in the marked effect of BZ found at the 100°F temperature, because the subjects for these tests were acclimatized to wintery temperatures when the tests were performed (October to April). One man of the group was atypical in that he was older than the others (42 yr) and did not receive an EEG. His hallucination was the most severe one experienced by any of the subjects.

The men in the 115°F environment received only 4 μg/kg of BZ, because at the time of these experiments orders restricting the dosage to this level were in effect. Even at this dose, however, one man was severely affected by the heat. It appears from this case and the others that BZ can produce casualties in hot environments by its effects on sweating, even though it may not produce a toxic delirium.

In the heat, the general feeling of lassitude induced by BZ may reduce the effectiveness of individuals in performing their mission when both physical and mental exercise are required. After 4 hr, most subjects fell asleep when given the opportunity and did not respond rapidly to directions for continuing exercise. They showed some aggression at being disturbed; this tendency was not present in the control tests.

The time to onset of physiological signs (decreased sweating and elevated heart rate) after the oral dose was about 2 or 3 hr. Incapacitation because of ataxia and lassitude did not occur until 4 hr after the oral dose.

Incapacitation occurred in men who maintained heat regulation; three men (b)(6) stopped exercise at 100°F because of ataxia and dizziness. Additional incapacitation occurred because of impaired heat regulation; two men (b)(6) during the last hour at 100°F with clothing and one man (b)(6) at 115°F stopped walking, with symptoms associated with high rectal temperatures. Some men were potential heat casualties but were not incapacitated during the test (b)(6) at 100°F and (b)(6) at 85°F).

There was no design in these tests for measuring a graded physiological response to increased doses of BZ. The central-nervous-system response to the drug is thought to be in the form of a plateau; i.e., the individual has either mild symptoms or hallucinations. The 5-μg/kg oral dose appears to be the threshold for the hallucinogenic effect. In this group of 14, 2 men had hallucinations. The range of physiological response exhibited by the subjects could illustrate the possibility of a graded response to dose for sweating and heart rate. Subjects receiving the 5-μg/kg dose showed a wide range of graded physiological responses on heart rate and sweating. The response was not an all-or-none type of response at the dose level used.

This wide range in response is typical for substances administered orally. Most subjects fasted or consumed only coffee on the day on which BZ was administered. One subject, (b)(6) was tested after he had eaten a hearty breakfast; he exhibited no symptoms that could be attributed to BZ, which perhaps indicates that food reduces the oral effectiveness of BZ. There appeared to be no correlation between the smoking habits of personnel and the effect of BZ. Some individuals smoked about 1 hr before receiving BZ and suffered only light effects.

A. Effect on Heart Rate.

Acceleration of the heart rate by BZ was most clearly seen in the walking experiments. The increment in rate increased during the experimental period to an average of 28 bpm at the end of the sixth hour at 85°F and to an average of 27 bpm at the end of the fourth hour at 100°F.

The results with atropine are not strictly comparable since atropine was injected intramuscularly and BZ was given orally. At 100°F the increments caused by atropine during walking averaged 45, 21, and 1 bpm,

respectively, at the end of the second, fourth, and sixth hours. In a previous study on three men, an intramuscular dose of 2 mg of atropine produced an average increment of about 37 bpm while resting and walking at environmental temperatures of 70° and 85°F over a 2-hr period. Progressively larger increments in heart rate were not produced by doses of atropine above 2 mg in a cool environment, where independent effects of body temperature on the heart rate secondary to inhibition of sweating were avoided.[2] Hence, this dose of atropine is thought to block the vagal control of the heart completely. The oral dose of BZ employed here appeared to produce only a partial block.

In a more detailed consideration of the atropine results, when the heart rate in the standing position was high because of exposure to heat or atropine or both, the initial acceleration of the heart in running at 9 mph was less than that seen ordinarily.[10] BZ produced similar although less well-defined effects.

B. Effect on Temperature Regulation.

There appears to be no chance of excess storage of heat at the 5-μg/kg dose of BZ in experimental situations where the subject does not perform heavy exercise. Some men participating in field tests with BZ may exhibit rectal temperatures of 103°F after 2 or 3 hr if both moderate exercise and heat are involved. As subject (b)(6) shows, it is possible to store heat under the influence of BZ without suffering the central-nervous-system effects. It is more probable that men exposed to BZ and feeling the accompanying effects of ataxia and tiredness would stop exercising, at least in the early stages of their BZ experience, before the onset of heat exhaustion.

In these tests, men frequently had higher initial rectal temperatures on the control days, which preceded those on which the agent was given. These higher temperatures should result in higher first-hour control sweating rates, which were observed. Since the control experiment was each subject's initial experience with the test situation, apprehension may have been a cause of the elevated rectal temperatures. Apprehension, however, was not apparent in the heart rates. The men were supposed to fast before the experiments, but there was no control over this variable. An increased blood supply to the gut, as in a man who had eaten breakfast, might also result in slightly elevated rectal temperatures, but reliable information was not available either to substantiate or to refute this possibility.

The reduction in sweating caused by the 5-μg/kg dose of BZ was less than that caused by a total dose of 2 mg of atropine tartrate (about 30 μg/kg). If proposed field tests of BZ are attempted, particularly in hot environments, the agent's prolonged action to reduce sweating should be considered from a safety aspect and body temperatures should be monitored. Diminished sweating may continue for as long as pupillary dilation and elevated heart rate. Men who receive higher doses of BZ than those used here may exhibit greater reductions in the rate of sweating than any of our subjects. These results with oral BZ may not indicate the correct time course of the physiological response if the agent is given by another route.

V. (C) CONCLUSIONS.

The following conclusions were reached:

The effects of exercise and heat do not seem to potentiate the central-nervous-system effects of BZ in an oral dose of 5 μg/kg. Additional incapacitation from heat exhaustion can be expected, however, in about one-fifth of the individuals receiving this dose when exercise is performed in hot environments. Even at 85°F some heat casualties may occur. In resting men, heat regulation is maintained for at least 6 hr in the environments tested.

The parasympatholytic effects of the oral dose of BZ are similar to and slightly less in severity than those of a 2-mg intramuscular dose of atropine tartrate, but they persist for a much longer time.

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(C) # APPENDIX

TABLES (")

(U) ### TABLE 1

CLINICAL TESTS USED IN SELECTING SUBJECTS FOR BZ EXPERIMENTATION

Test	Standard
Personal and medical history	No major illness within past 2 yr
Physical examination	Within normal limits
Chest X-ray	Within normal limits
Hematology, including white-blood-cell differential count	Within normal limits
Urine analysis	Within normal limits
Liver function	Within normal limits
Electrocardiogram	Within normal limits
Electroencephalogram	Within normal limits
Minnesota multiphasic personality inventory	Within normal limits (scale below 70)
Psychiatric interview	Above-average standards

(U)

TABLE 2

PHYSICAL CHARACTERISTICS OF SUBJECTS

Initials	Age	Height	Weight	Ethnic group	Physical conditioning	Occupation	Dates*
	yr	cm	kg				
(b)(6)	19	170	62	Caucasian	Fair	Cook	12/14/60 12/16/60
	19	180	75	Negro	Fair	Signal man	12/19/60C 12/21/60E 12/29/60C
	20	167	60	Caucasian	Fair	Mechanic	1/24/61 2/1/61
	42	191	91	Negro	Good	Infantry sergeant	2/14/61 2/16/61
	25	183	73	Caucasian	Good	Maintenance man	2/26/61 2/28/61
	24	178	68	Caucasian	Good	Gas handler	3/20/61 3/22/61
	18	176	76	Caucasian	Fair	Clerk	5/11/61 5/16/61
	19	185	78	Caucasian	Fair	Mechanic	5/18/61 5/23/61
	22	175	75	Caucasian	Good	Medic	6/15/61 6/20/61
	20	180	78	Negro	Fair	Teletypist	6/22/61
	24	191	96	Caucasian	Good	Truck driver	6/27/61 6/28/61
	30	178	73	Caucasian	Good	Paratrooper	9/20/61 9/25/61

* First date = control tests; second date = BZ test.

(U) TABLE 2 (contd)

Initials	Age	Height	Weight	Ethnic group	Physical conditioning	Occupation	Dates*
	yr	cm	kg				
(b)(6)	30	173	78	Caucasian	Fair	Medic	9/21/61 9/27/61
	22	175	69	Caucasian	Good	Tank crewman	8/10/61 8/14/61
	24	175	69	Caucasian	Good	Clerk	8/17/61 8/22/61
	19	175	57	Caucasian	Fair	Medic	1/11/62C 1/17/62E 1/30/62C
	21	185	89	Caucasian	Good	Medic	1/18/62C 1/24/62E 1/29/62C

* First date = control tests; second date = BZ test.

(U) TABLE 3

CONDITIONS OF TESTS

Environment				Clothing
Dry bulb	Wet bulb	Vapor pressure	Relative humidity	
°F		mm Hg	%	
100	79	20	40	Shorts
100	79	20	40	Fatigue uniform
85	75	20	62	Shorts
115	83	20	28	Shorts

(U) TABLE 4

SEQUENCE OF EVENTS IN EXERCISE CYCLE*

Minutes	Activity
0	Weigh subject
5	Rest supine or sitting on cot
36	Stand
37	Run 9 mph on treadmill
38	Stop run and rest
60	Weigh
67	Stand
68	Walk 3 mph on treadmill
110	Stop walk and rest
120	End cycle resting

* Three consecutive cycles were run on each test day.

(C)

TABLE 5

GENERAL CHARACTERISTICS OF RESPONSE TO BZ (U)

Subject	Incapacitation onset time	Total time	Symptoms exhibited
(b)(6)		A. 100°F, 5 μg/Kg of BZ	
	4 hr, 18 min	6 hr	Slightly ataxic, tired, unable to run
	2 hr, 16 min	6 hr	Ataxic, dizzy, tired, unable to walk or run, hyperventilation, T-wave inversion in ECG, muscle spasms
	5 hr	5 hr	Ataxic, dizzy, bradykinesia, tired and weak, sleepy, T-wave inversion, hyperventilation, unable to walk or run
	4 hr	4 hr	Ataxic, dizzy, bradykinesia, tired and sleepy, hallucinations, unable to walk or run, restlessness, muscle spasms
		B. 100°F, Clothed, 5 μg/Kg of BZ	
	5 hr, 40 min	5 hr, 40 min	Mildly ataxic, tired, sleepy, high rectal temperature
		6 hr	No symptoms
	5 hr, 40 min	5 hr, 40 min	Mildly ataxic, weak, tired, sleepy, bradykinesia, high rectal temperature, nausea
		6 hr	Ataxic, postural hypotension
		C. 115°F, 4 μg/Kg of BZ	
		6 hr	Sleepy
	4 hr	4 hr	Ataxic, postural hypotension, elevated heart rate, high rectal temperature
		D. 85°F, 5 μg/Kg of BZ	
		6 hr	Mildly ataxic, tired, sleepy
		6 hr	Mildly ataxic
		6 hr	Mildly ataxic, hallucinations (slight)
		6 hr	No symptoms

(C)

TABLE 6

WEIGHT LOSS DURING WALKING CYCLE (U)

Subject	Environment	Control weight loss			Experimental weight loss			Experimental/control ratio		
		2 hr	4 hr	6 hr	2 hr	4 hr	6 hr	2 hr	4 hr	6 hr
	°F	gm								
(b)(6)	100	462	458	488	440	376	416	0.95	0.82	0.85
	100	420	452	471	388	—*	—*	0.92	—*	—*
	100	425	451	434	272	309	—*	0.64	0.69	—*
	100	535	487	622	485	317	—*	0.91	0.54	—*
	Mean	460	487	529	396	334	—	0.86	0.68	—
	100 plus clothes	619	699	589	474	362	330	0.77	0.52	0.56
	100 plus clothes	590	693	749	799	693	590	1.35	1.00	0.79
	100 plus clothes	551	516	468	478	401	300	0.87	0.78	0.64
	100 plus clothes	480	611	514	450	418	420	0.94	0.68	0.82
	Mean	560	629	580	550	469	410	0.98	0.74	0.70
	115	805	799	649	544	347	243	0.68	0.43	0.37
	115	684	685	550	670	560	—*	0.98	0.82	—*
	Mean	744	742	599	607	453	—	0.83	0.62	—
	85	250	294	271	242	216	168	0.97	0.73	0.62
	85	301	313	318	216	236	269	0.72	0.72	0.85
	85	322	392	341	245	118	170	0.76	0.30	0.50
	85	289	346	283	274	237	204	0.95	0.69	0.72
	Mean	291	336	303	244	202	203	0.85	0.61	0.67

* (U) Not completed.

(C)

TABLE 7

WEIGHT LOSS DURING REST-...JN CYCLE "J)

Subject	Environment	Control weight loss			Experimental weight loss			Experimental/ control ratio		
		1 hr	3 hr	5 hr	1 hr	3 hr	5 hr	1 hr	3 hr	5 hr
	°F	gm								
(b)(6)	100	293	293	236	154	223	244	0.53	0.76	1.03
	100	128	274	276	50	171	—*	0.39	0.62	—*
	100	351	169	288	200	189	—*	0.57	1.12	—*
	100	101	348	362	142	147	—*	1.40	0.42	—*
	Mean	218	271	291	137	183	—	0.72	0.71	—
	100 plus clothes	287	434	411	258	222	226	0.90	0.51	0.55
	100 plus clothes	206	558	593	349	471	418	1.69	0.84	0.70
	100 plus clothes	249	425	296	220	278	244	0.88	0.65	0.82
	100 plus clothes	227	422	360	125	307	284	0.56	0.73	0.79
	Mean	241	460	415	238	269	293	1.00	0.68	0.72
	115	581	1,089	736	288	695	427	0.50	0.64	0.57
	115	339	576	471	316	417	—*	0.93	0.74	—*
	Mean	460	827	603	302	556	—	0.71	0.74	—
	85	65	97	147	70	95	98	1.08	0.98	0.67
	85	48	119	87	24	77	68	0.50	0.65	0.70
	85	164	141	149	34	57	123	0.21	0.40	0.83
	85	77	118	150	66	71	109	0.86	0.60	0.73
	Mean	89	119	133	49	75	96	0.66	0.66	0.75

* (U) Not completed.

(C)

TABLE 8

HEART RATE AT END OF 3-MPH WALK...G CYCLE (U)

Subject	Environment	Control rate			Experimental rate			Experimental/ control ratio		
		2 hr	4 hr	6 hr	2 hr	4 hr	6 hr	2 hr	4 hr	6 hr
(b)(6)	°F	bpm								
	100	120	125	123	131	156	166	1.09	1.21	1.35
	100	141	155	158	161	169	-*	1.14	1.09	-*
	100	129	139	151	136	175	-*	1.05	1.26	-*
	100	121	124	114	129	157	-*	1.07	1.26	-*
	Mean	128	136	137	139	163	-	1.09	1.21	-
	100 plus clothes	130	128	135	150	167	161	1.15	1.30	1.19
	100 plus clothes	128	135	139	119	131	139	0.93	0.97	1.00
	100 plus clothes	108	104	104	116	160	156	1.07	1.54	1.50
	100 plus clothes	114	127	139	126	148	142	1.10	1.17	1.02
	Mean	121	124	129	128	151	149	1.06	1.25	1.18
	115	128	135	142	110	134	138	0.86	0.99	0.97
	115	139	148	158	138	167	-*	0.99	1.12	-*
	Mean	133	141	150	124	150	-	0.93	1.06	-
	85	104	107	103	101	116	127	0.97	1.08	1.23
	85	112	115	115	112	122	130	1.00	1.06	1.13
	85	113	125	120	148	177	174	1.31	1.42	1.45
	85	113	112	107	110	118	113	0.98	1.05	1.06
	Mean	111	115	111	118	133	139	1.07	1.15	1.22

* (U) Not completed.

(C)

TABLE 9

PEAK HEART RATE AT END OF 9-MPH RUN (U)

Subject	Environment	Control rate			Experimental rate		
		1 hr	3 hr	5 hr	1 hr	3 hr	5 hr
	°F	bpm					
(b)(6)	100	174	171	170	158	-*	-*
	100	178	190	189	166	-*	-*
	100	167	175	176	162	171	-*
	100	156	160	154	152	158	-*
	Mean	169	174	172	159	-*	-*
	100 plus clothes	171	171	172	169	177	
	100 plus clothes	167	-**	179	160	-**	174
	100 plus clothes	153	-**	151	146	157	174
	100 plus clothes	157	158	162	140	153	155
	Mean	162	-	166	154	-*	-
	115	176	176	182	167	172	172
	115	182	188	185	174	179	-*
	Mean	179	182	184	171	176	-
	85	162	162	164	154	160	167
	85	164	174	176	164	176	190
	85	-**	-**	176	172	179	190
	85	164	158	158	152	160	156
	Mean	163	165	169	161	169	176

* (U) Not completed.

** (U) Data missing.

(C)

TABLE 10

RECTAL TEMPERATURE AT END OF WALK (U)

Subject	Environment	Control temperature			Experimental temperature		
		Cycle					
		1	2	3	1	2	3
(b)(6)	°F	°F					
	100	99.8	100.6	101.4	100.5	100.8	101.3
	100	101.4	101.9	102.1	100.3	101.5*	–
	100	101.2	101.3	101.6	99.5	101.1**	–
	100	100.7	100.5	100.6	100.0	102.4	–
	Mean	100.8	101.1	101.4	100.1	101.5	–
	100 plus clothes	100.4	100.2	100.0	99.9	102.4	103.1**
	100 plus clothes	100.4	101.0	100.4	99.7	99.6	100.1
	100 plus clothes	100.7	100.6	100.0	100.0	101.5	102.1**
	100 plus clothes	100.4	100.6	101.6	99.3	100.7	102.3
	Mean	100.6	100.6	100.5	99.8	101.1	101.9
	115	101.4	101.5	102.2	99.9	100.5	101.7
	115	100.6	100.6	101.7	100.7	102.6	–
	Mean	101.0	101.1	101.9	100.3	101.6	101.7
	85	99.9	100.1	99.8	100.0	99.8	100.4
	85	100.0	100.0	99.9	99.5	99.3	99.4
	85	100.5	100.9	100.4	99.6	101.7	102.4
	85	100.4	100.3	99.8	100.2	99.9	99.3
	Mean	100.2	100.4	99.9	99.8	100.2	100.3

* (U) After 90 min of 110-min cycle.

** (U) After 100 min of 110-min cycle.

(C)

TABLE II

RISE IN MEAN BODY TEMPERATURE DURING WALKING (U)

Subject	Environment	Control temperature			Experimental temperature		
		Cycle					
		1	2	3	1	2	3
	°F	°F					
(b)(6)	100	0.5	1.0	0.9	0.6	0.5	0.4
	100	0.9	1.3	1.7	1.2	1.6*	–
	100	1.0	1.6	1.4	0.5	1.7**	–
	100	1.0	0.0	0.0	-0.3	1.7	–
	Mean	0.9	1.0	1.0	0.5	1.1	–
	100 plus clothes	0.3	0.3	-0.2	0.6	1.4	0.3
	100 plus clothes	0.1	0.1	-0.5	0.1	0.0	0.4
	100 plus clothes	0.8	-0.1	0.0	0.5	1.2	0.7
	100 plus clothes	0.9	0.2	0.3	-0.1	0.3	1.4
	Mean	0.5	0.1	-0.1	0.3	0.7	0.7
	115	0.5	0.3	0.7	0.1	0.8	1.5
	115	0.2	0.3	0.7	0.4	1.6	1.5
	Mean	0.4	0.3	0.7	0.3	1.2	1.5
	85	0.4	0.1	-0.8	0.2	-0.2	0.2
	85	0.0	-0.1	0.2	0.4	0.0	0.2
	85	0.5	1.2	0.3	0.4	2.1	1.2
	85	-0.3	0.2	0.1	0.3	0.8	0.2
	Mean	0.2	0.4	-0.1	0.3	0.6	0.5

* (U) After 90 min of 110-min cycle.

** (U) After 100 min of 110-min cycle.

(C)

TABLE 12

AVERAGE SKIN TEMPERATURE AT END OF WALK (U)

Subject	Environment	Control temperature			Experimental temperature		
		Cycle					
		1	2	3	1	2	3
(b)(6)	°F	°F					
	100	95.2	96.7	98.4	95.4	96.2	96.8
	100	97.5	97.2	97.1	97.6	99.4	—*
	100	97.2	97.9	98.2	96.3	99.3	—*
	100	94.1	93.9	93.7	94.1	97.7	—*
	Mean	96.0	96.4	96.9	95.9	98.2	—*
	100 plus clothes	95.4	94.3	94.2	95.8	98.4	99.3
	100 plus clothes	95.4	96.1	96.2	95.8	94.8	96.9
	100 plus clothes	96.8	96.2	96.0	95.2	96.7	98.5
	100 plus clothes	96.8	96.2	96.8	94.7	95.5	98.9
	Mean	96.1	95.7	95.8	95.4	96.4	98.4
	115	98.4	97.4	97.2	95.8	97.3	97.0
	115	97.0	96.9	97.5	97.6	98.9	—*
	Mean	97.7	97.2	97.4	96.7	98.1	—*
	85	92.0	92.2	91.0	93.6	93.0	92.9
	85	93.7	92.7	93.2	93.3	93.4	93.7
	85	93.7	92.6	—	93.8	97.7	97.5
	85	93.4	93.3	93.0	93.3	94.5	94.4
	Mean	93.2	92.7	92.4	93.5	94.7	94.6

* (U) Cycle not completed.

(C)

TABLE 13

EFFECT OF INTRAMUSCULAR DOSE OF 2 MG ATROPINE TARTRATE ON WEIGHT LOSS AND RECTAL TEMPERATURE OF MEN EXERCISING AT 100°F (U)

Effect	Subject	Cycle 1						Cycle 2					
		1 Hr			2 Hr			3 Hr			4 Hr		
		Control	Experimental	Experimental/control ratio	Control	Experimental	Experimental/control ratio	Control	Experimental	Experimental/control ratio	Control	Experimental	Experimental/control ratio
		kg			kg			kg			kg		
Weight loss	(b)(6)	0.133	0.091	0.47	0.383	0.311	0.81	0.239	0.218	0.91	0.439	0.339	0.7
		0.179	0.073	0.41	0.517	0.500	0.97	0.318	0.333	1.05	0.535	0.548	1.
Rectal temperature, °F		100.	102.0					100.4	100.9				
		100.1	100.1					100.2	100.4				
Change in rectal temperature		+0.5	+2.2					-0.2	-1.3				
		+1.6	+1.8					+0.1	+0.3				

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(U)

TABLE 14

EFFECT OF 2 MG ATROPINE TARTRATE ON HEART RATE OF MEN EXERCISING AT 100°F

Subject	Heart rate					
	Control		Experimental		Control walk	Experimental walk
	Run	Rest	Run	Rest		
	bpm					
A. Cycle 1						
	1 hr				2 hr	
(b)(6)	165	86	167	111	100	160
	182	83	176	100	133	162
B. Cycle 2						
	3 hr				4 hr	
	155	86	171	150	100	133
	171	86	194	111	138	147
C. Cycle 3						
	5 hr				6 hr	
	156	79	158	83	118	115
	179	103	188	95	143	148

UNCLASSIFIED

ABSTRACT

1. Originating Activity

Physiology Division
U. S. Army Chemical Research and Development Laboratories
Edgewood Arsenal, Maryland

2a. Report Security Classification

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2b. Group (for DDC use only)

3. Report Title: PHYSIOLOGICAL ACTION OF BZ ON MEN SUBJECTED TO HIGH TEMPERATURES AND EXERCISE (U)

4. Descriptive Notes: Observations were made between October 1961 and April 1962

5. Authors: (b)(6)

6. Publication Date: February 1964

7. Total No. of Pages: 34

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10. Other Report Nos.

11. Supplementary Notes (for DDC use only)

12. Release Statements (for DDC use only)

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13. Author's Key Terms - Unclassified Only

Human estimates	BZ
Heart rate	Sweat rate
Body temperature	Toxic[illegible]
Incapacitation	ECG
Oral route	Casualties
Environmental tests	Intramuscular route
Parasympatholytic effects	Atropine tartrate
Temperature effects	High temperature effects

14. DDC Descriptors (for DDC use only)

15. Identifiers - Unclassified Only

16. Body of Abstract

(U) The effects of exercise and high environmental temperatures on the physiological action of BZ are presented. Measurements were made on men after oral doses of BZ were given, to determine the effects upon the heart and sweat rates, ECG's and body temperatures with exercise at four different environmental conditions. Some comparisons with atropine are also presented. The effects of exercise and heat do not seem to potentiate the central nervous system effects of BZ in a specific oral dose; however, additional incapacitation from heat exhaustion can be expected in some people receiving this dose when exercise is performed in hot environments. Even at moderate temperatures some heat casualties may occur. In resting men, heat regulations are maintained for at least 6 hr in the environments tested.

17. Indexing Annotation

A determination of physiological action of BZ on men subjected to high environmental temperatures and exercise.

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