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BY

DAVID M. SUMMERS

A dissertation submitted to the Graduate Faculty in Biomedical Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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ABSTRACT

CLINICAL ELECTROPHYSIOLOGICAL INVESTIGATION OF
A SLEEP DISORDER RELATED TO A SUSPECTED NEUROTOXIN:
A FIELD STUDY ON MICHIGAN RESIDENTS EXPOSED TO PBB

by

David M. Summers

Adviser: Professor Sidney P. Diamond

The sleep EEGs of twelve adult Michigan residents, who had been exposed to polybrominated biphenyls (PBBs) and who complained of hypersomnia, were recorded in order to determine objectively the character and extent of the reported sleep disturbance. In addition to this electrophysiological study, neuropsychological tests were administered to each of the subjects, and their serum PBB levels were measured.

Analysis of the sleep data revealed a greater number of awakenings, an increase in eye movement density of REM sleep, and a decrease in stage 4 sleep as compared to a normal population of the same age. The older subjects also showed a decrease in the amount of stage 3 sleep. The patterns of sleep were not consistent with the changes seen in pathological increases or decreases in the amount of sleep. To reconcile the observed sleep changes of the subjects with their subjective reports of hypersomnia, it is hypothesized that increased number of awakenings and decreased stage 4 may contribute to an inferior quality of sleep and to an increased time taken to complete a sleep cycle. This in turn might produce an increase in the time spent sleeping in order to achieve the presumed restorative effects of sleep.

The levels of PBB were found to correlate with the amount of stage 0, the average duration of an awakening, the duration of first REM period, and the eye movement density in that period. A significant negative correlation was found between PBB levels and total sleep time, sleep efficiency index, the number of slow wave sleep periods and the number of sleep cycles. A comparison of sleep profiles of this group with other classes of pathological sleep syndromes suggested closest resemblance to the changes seen in aging.

The negative correlation of performance on the Mattis-Kovner Memory Recognition Test and the Associate Learning Test with measurements of wakefulness, and the results of the Benton Revised Visual Retention Test suggest that subjects may have some degree of impairment of cognitive functioning similar to that seen in aging.

Since this study was not designed to determine the status of PBB as a neurotoxin, no statement can be made about its causal relation to the sleep disturbances observed in this subject population. However, the investigation does establish the value of sleep analysis as an objective technique in environmental medicine for characterizing sleep complaints and for recognizing a low degree of diffuse organic brain dysfunction. Furthermore, the correlations found between serum levels of PBB and changes in sleep patterns suggest that if significant sleep complaints persist in the exposed population, a controlled study should be done designed to evaluate a causal connection between PBB and central nervous system changes.

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For my parents

Joan Marie Summers

and

Merrill Smith Summers

with love

TABLE OF CONTENTS

TABLE OF CONTENTS (contd.)

LIST OF FIGURES

LIST OF FIGURES (contd.)

LIST OF TABLES

DEFINITION OF TERMS AND ABBREVIATIONS

PBB : Polybrominated Biphenyl

HBB_6 : 2,4,5,2',4',5'-Hexabromobiphenyl

E : 2,3,4,2',4',5'-Hexabromobiphenyl

F : 2,4,5,3',4',5'-Hexabromobiphenyl

HBB_7 : 2,3,4,5,2',4',5'-Hexabromobiphenyl

SLEEP ONSET: The onset of a period of stage 2 sleep which continued without interruption for five minutes.

TIME IN BED (TIB): The period of time between "lights off" and "lights on".

SLEEP PERIOD TIME (SPT): The period of time between sleep onset and final awakening.

TOTAL SLEEP TIME (TST): The period of time spent in stages 1, 2, 3, 4 and REM of sleep between sleep onset and final awakening; the sleep period time excluding time spent awake.

SLEEP EFFICIENCY INDEX (SEI): The total sleep time divided by the time in bed; TST/TIB.

AWAKENING: During the sleep period time, a period of wakefulness which consisted of at least twenty seconds of stage 0 and which included time spent in stage 1, if present, before a return to sleep which was defined as the occurrence of five minutes or more of continuous sleep, i.e. stage 2, 3, 4 or REM.

STAGE SHIFT: A change from one stage to another stage during the sleep period time.

SLEEP ONSET LATENCY: The period of time between "lights off" and the onset of sleep; also the latency to stage 2.

LATENCY TO STAGE 0, 1, 3, 4 OR REM: The period of time between sleep onset and the first appearance of stage 0, 1, 3, 4 or REM.

EPOCH: An interval of twenty seconds used to segment the sleep record for sleep scoring purposes.

EYE MOVEMENT (EM) DENSITY: The number of epochs of REM sleep which contained rapid eye movements divided by the total number of REM sleep epochs.

TWITCH: A body movement which continued for less than three seconds.

BODY MOVEMENT: A body movement which continued for three seconds or longer.

BODY MOVEMENT DENSITY (BMD): The sum of the number of total sleep time and movement time epochs which contained at least one body movement divided by the total sum of total sleep time and movement time epochs.

MOVEMENT DENSITY (MD): The sum of the number of total sleep time and movement time epochs which contained at least one twitch or one body movement divided by the total sum of total sleep time and movement time epochs.

SLOW WAVE SLEEP (SWS): Sleep scored stage 2, 3 or 4.

SLOW WAVE SLEEP PERIOD (SWSP): The amount of time spent in stages 2, 3 and 4 between the onset of sleep and the onset of the first REM period or between the end of a REM period and the beginning of the next REM period. A SWS period was complete if at least fifteen minutes in duration, but the final SWS period was complete if followed by at least five minutes of REM sleep.

RAPID EYE MOVEMENT PERIOD (REMP): The amount of time spent in REM sleep between two SWS periods. The first REM period had no minimum duration. Later REM periods were complete if at least five minutes in length. After the first REM period, episodes of REM sleep less than five minutes in duration were added to the preceding complete REM period. If less than fifteen minutes of continuous SWS occurred between two episodes of REM sleep, the episodes were summed to form one REM period with the SWS added to the previous complete SWS period. If fifteen minutes or more of continuous SWS occurred, the REM sleep episodes were considered to be two distinct REM periods if at least five minutes in duration. The final REM period was complete if followed by at least five minutes of SWS.

SLEEP CYCLE (SC): The amount of time composed of a SWS period and the following REM period. A cycle was complete, if the REM period was complete.

INTRODUCTION

In a clinical field survey performed in November, 1976 (Selikoff et al., 1976), a number of the Michigan dairy farm residents and direct consumers of farm products who were examined reported a marked increase in sleep requirement and in sleep time. It was suggested that the sleep complaint of hypersomnia might be related to the prior exposure to polybrominated biphenyls (PBBs) through ingestion of contaminated farm products.

The purpose of this research was to investigate the complaint, using electrophysiological sleep recording techniques to determine the type and extent of the clinically reported sleep disorder and to examine relationships among PBB, sleep and neuropsychological parameters. It was expected that the results of the study would provide neurophysiological data which would supplement previous research findings concerning the neurotoxicological consequences of human exposure to PBBs.

A brief history of the Michigan-PBB contamination incident will be given, followed by a review of the chemical and toxic characteristics of PBB with regard to animals and humans. The physiological basis of the electroencephalograph and the characterization of sleep using the electroencephalograph will be reviewed, before mentioning other sleep disorders associated with chemical intoxication. Finally, the assumptions, purposes and design of the present investigation will be outlined.

THE MICHIGAN-PBB INCIDENT

In 1973 the Michigan Chemical Corporation was manufacturing Nutrimaster®, which is magnesium oxide, and FireMaster FF-1®, which is a mixture of polybrominated biphenyls (PBBs). Non-toxic Nutrimaster was used as a dairy feed supplement to increase milk production, while toxic FireMaster FF-1, which physically resembled Nutrimaster, was utilized as a flame retardant for thermoplastics (Kay, 1977). The Michigan Chemical Corp. supplied Nutrimaster to the Farm Bureau Services, Inc. who added it to cattle feed and distributed the mixed feed (0.4% magnesium) to dairy farmers (Kay, 1977).

During the summer of 1973 the Michigan Chemical Corp. plant at St. Louis, Michigan shipped FireMaster FF-1, instead of Nutrimaster, to the Farm Bureau Services at Battle Creek, Michigan (Carter, 1976). At that time both products were packaged in plain brown bags with the trade name stencilled in black across the top (Cordle et al., 1978). In July the Farm Bureau Services mixed between 500-1,000 pounds of PBB into cattle feed and distributed the contaminated feed within the state of Michigan (Carter, 1976). Indirect contamination of other animal feeds occurred through the use of PBB contaminated feed mill equipment (Dunckel, 1975). Consequently, PBB exposure was extended from cattle to include all livestock.

In late September, 1973, Frank Halbert, a Michigan dairy farmer, was the first to report toxic effects from the use of PBB contaminated feed. His cattle exhibited anorexia, weight loss, decreased milk production, hematomas, abnormal hoof growth and hair loss; and in the next six months 5% of his herd of 400 cows died (Jackson and Halbert, 1974). Halbert persistently attempted to discover the feed contamin-

ant, and due to his efforts in April, 1974 Dr. George F. Fries by using gas chromatography and mass spectrometry at the U.S.D.A. laboratory at Beltsville, Maryland identified the contaminant as PBB (Carter, 1976).

Immediately following this discovery the Michigan Department of Agriculture began to investigate the PBB contamination problem. Michigan farm families and their neighbors as well as the general population, to a lesser extent, were exposed to PBB through ingestion of contaminated farm products such as milk, other dairy products, meat and eggs for at least the period from July, 1973 through May, 1974 (Carter, 1976). By the end of 1975, the Michigan Department of Agriculture had quarantined 500 farms, had destroyed 29,800 cows, 5,920 hogs, 1,470 sheep and 1.5 million chickens, and had buried 865 tons of feed, 17,990 pounds of cheese, 2,630 pounds of butter, 34,000 pounds of dry mild products and 5 million eggs (Carter, 1976).

The Michigan Chemical Corp. stopped manufacturing FireMaster FF-1 in 1974 as a consequence of the Michigan-PBB incident (Di Carlo et al., 1978) which has come to be considered the costliest contamination episode in the history of United States agriculture (Isleib and Whitehead, 1975).

FIREMASTER FF-1: POLYBROMINATED BIPHENYLS

FireMaster FF-1 is a combination of FireMaster BP-6® (Michigan Chemical Corp.) and 2% calcium polysilicate, an anticaking compound (Di Carlo et al., 1978). FireMaster FF-1 has a bromine content of 75% (Kay, 1977) and is chemically relatively inert (Getty et al., 1977). FireMaster BP-6 is a solid, softens at 72° C, decomposes above 300° C, is highly soluble in non-polar solvents and is virtually

insoluble in water (Di Carlo et al., 1978). Both FireMaster products exhibit nearly identical isomeric composition (Norström et al., 1976).

FireMaster BP-6 is a mixture of polybrominated biphenyls composed of 4% penta-, 63% hexa- and 33% heptabromobiphenyls (Hass et al., 1978). Twelve brominated biphenyl congeners have been determined through the use of gas chromatography: A) 2,4,5,2',5'-penta-, B) 2,4,5,3',4'-penta-, C) hexa-, D) 2,4,5,2',4',5'-hexa-, (HBB_6), E) 2,3,4,2',4',5'-hexa-, F) 2,4,5,3',4',5'-hexa-, G) hepta-, H) 2,3,4,5,2',4',5'-hepta-, (HBB_7), I) hepta-, J) hepta-, K) octa- and L) 2,3,4,5,2',3',4',5'-octabromobiphenyl (Moore and Aust, 1978; STRUCTURE IDENTIFICATION: A,B,E,F,L-Moore and Aust, 1978; D - Jacobs et al., 1976 and Sundström et al., 1976; H - Hass et al., 1978 and Moore et al., 1978b).

The major components of FireMaster BP-6 are HBB_6 (Figure 1, p.5) and HBB_7 which comprise 56 and 27 percent, respectively (Moore, 1978). Because HBB_6 is the major component of FireMaster BP-6 and the congener stored in the tissues in the highest concentration (e.g. rat- Ecobichon et al., 1979), the blood and tissue levels of HBB_6 have been determined by standard gas chromatographic technique and used as the biological indicators of PBB absorption. It is possible, however, that future research of FireMaster BP-6 will indicate a congener other than HBB_6 or a contaminant as the toxic substance of primary importance.

PBBs are easily absorbed in the gastro-intestinal system of most higher animals (Di Carlo et al., 1978). Cows absorbed eighty-five percent of the ingested FireMaster FF-1 (Robl et al., 1978), while rats absorbed ninety percent or more of the dose of HBB_6 (Matthews et al., 1977). Fries et al. (1976) found that during oral exposure to FireMaster BP-6 the heptabromobiphenyls and the octabromobiphenyls were

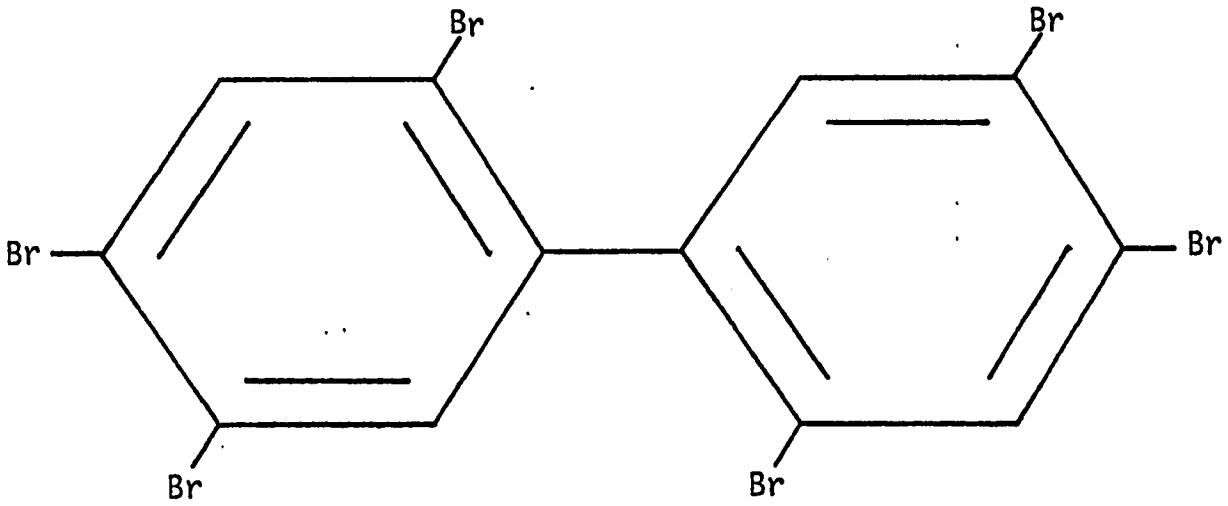


Figure 1: 2,4,5,2',4',5'-HEXABROMOBIPHENYL (HBB_6)

excreted in the feces of chickens in a greater proportion than HBB_6. HBB_7 was retained in fat in much lower relative concentrations as compared to HBB_6 in the rat (Kimbrough et al., 1978), cow (Fries, 1978) and chicken (Fries et al., 1976). Whether the more brominated congeners (seven bromines or more) are less easily absorbed in the gut or more readily eliminated through biliary excretion has not yet been determined.

After absorption PBB is distributed into the fat of the major tissues and organs of the body. In the rat HBB_6 was found to be distributed initially in the highest amounts in fatty tissue and in the highly blood-perfused liver and muscle and later to be redistributed out of the liver and muscle into adipose tissue (Matthews et al., 1977). Corbett et al. (1978a) reported that in mice the concentration of PBB in the brain initially was relatively high but later was much lower. After reaching a steady state, HBB_6 is distributed in the highest concentration in adipose tissue followed next by that in the liver in the rat (Harris et al., 1978a; Mc Cormack et al., 1979), cow (Gutenmann and Lisk, 1975; Fries et al., 1978; Robl et al., 1978), pig (Ku et al., 1978) and sheep (Gutenmann and Lisk, 1975). Matthews et al. (1977) found that the distribution of HBB_6 in the rat was the same for both oral and intraperitoneal exposure. Wolff and Selikoff (1979) reported that the distribution of the homologs of FireMaster FF-1 was the same in the fat as in the blood serum of the rat.

PBB has been found to concentrate in body tissue. The ratios of the diet to adipose tissue concentrations of HBB_6 were 1 to 4 or 1 to 3 for chickens (Fries et al., 1976; Polin and Ringer, 1978) and 1 to 50 for cows (Robl et al., 1978).

The bromobiphenyls of FireMaster BP-6 undergo very little meta-

bolic degredation. Kohli and Safe (1976) reported that after seven days only about one percent of an intraperitoneal dose of FireMaster BP-6 had been excreted in the urine and feces of a pig as pentabromobiphenylol acetate, which was thought to be a hydroxylated metabolite of one of the pentabromobiphenyl congeners. HBB_6 has been found not to be significantly metabolized in the rat (Matthews et al., 1977; Safe et al., 1978) or the dog (Matthews and Kato, 1979).

During oral exposure HBB_6 excretion occurs almost exclusively in the feces in the rat (Matthews et al., 1977), pig (Ku et al., 1978) and cow (Willett and Irving, 1976). The primary route of elimination of HBB_6 is through the milk of lactating cows (Cook et al., 1978) and through the eggs of laying hens (Fries et al., 1976). Once distributed HBB_6 has been found to be eliminated slowly and minimally in the chicken (Polin and Ringer, 1978), cow (Willett and Irving, 1976), dog (Matthews and Kato, 1979), pig (Kohli and Safe, 1976) and rat (Matthews et al., 1977). Matthews et al. (1977) estimated an infinite half-life for HBB_6 in the rat.

In studying the elimination rates of the congeners of FireMaster FF-1 in the rat, Wolff and Selikoff (1979) found that 2,4,5,2',5'-penta- and 2,4,5,3',4',5'-hexabromobiphenyl disappeared most quickly from blood, HBB_7 and 2,4,5,3',4'-pentabromobiphenyl left at a similar rate and 2,3,4,2',4',5'-hexabromobiphenyl remained at a fairly constant level over forty-two days.

Hill Top Research, Inc. (1970) conducted a study for the Michigan Chemical Corp. on the toxicity of FireMaster BP-6 and reported for the rat a relatively high acute oral LD_{50} of 21.5 g./kg. of body weight. It appears, however, that due to the biological persistence of PBB,

the chronic rather than the acute effects of exposure are of greater significance.

In animals one of the primary symptoms of exposure to PBB is anorexia. PBB intoxication produced decreased body weight or, in young animals, decreased weight gain in the pig (Ku et al., 1978), chicken (Ringer, 1978), cow (Durst et al., 1977; Mercer et al., 1978; Robl et al., 1978), monkey (Allen et al., 1978; Lambrecht et al., 1978) and rat (Garthoff et al., 1977; Luster et al., 1978; Mc Cormack et al., 1978a, 1978b, 1979). Decreased food intake was also noted in the pig (Ku et al., 1978), chicken (Polin and Ringer, 1978) and cow (Prewitt et al., 1975; Durst et al., 1977; Mercer et al., 1978).

The liver has been found to be one of the primary organs affected by exposure to PBB. An increased liver weight and/or an increased liver weight/body weight was reported to occur after exposure to FireMaster FF-1 or BP-6 in the pig (Ku et al., 1978), rabbit (Waritz et al., 1977), mouse (Corbett et al., 1975, 1978b; Dent et al., 1977) and rat (Corbett et al., 1975; Dent et al., 1976b; Sleight and Sanger, 1976; Babish and Stoewsand, 1977; Evers et al., 1977; Garthoff et al., 1977; Harris et al., 1978a; Kasza et al., 1978b; Mc Cormack et al., 1978a, 1979; Moore et al., 1978a; Cagen et al., 1979; Ecobichon et al., 1979). Hypertrophy of hepatocytes due to PBB has been noted in the monkey (Lambrecht et al., 1978), mouse (Corbett et al., 1978b) and rat (Sleight and Sanger, 1976; Harris et al., 1978a; Kasza et al., 1978b; Ecobichon et al., 1979). Other effects of FireMaster FF-1 or BP-6 on the liver were an increase in the smooth endoplasmic reticulum in the monkey (Lambrecht et al., 1978), mouse (Corbett et al., 1978b) and rat (Sleight and Sanger, 1976; Kasza et al., 1978b), an increase of abnormal mito-

chondria in the mouse (Corbett et al., 1978b) and rat (Garthoff et al., 1977; Kasza et al., 1978b), an increase of lipid in hepatocytes in the monkey (Lambrecht et al., 1978) and rat (Evers et al., 1977; Garthoff et al., 1977; Kasza et al., 1978b), a decrease of glycogen in the mouse (Corbett et al., 1978a) and rat (Harris et al., 1978a) and hyperplasia of bile ducts in the cow (Gutenmann and Lisk, 1975), monkey (Lambrecht et al., 1978) and rat (Kasza et al., 1978b). In considering the changes seen in the liver of the rat, Kasza et al. (1978b) suggested that PBB blocks the transport of lipid in hepatocytes.

PBB stimulates the mixed function oxidase (MFO) system in the liver, kidney, lung and mammary tissue. Phenobarbital exemplifies one of two main classes of MFO inducing agents and characteristically increases liver weight, microsomal protein, NADPH-cytochrome P-450 reductase, cytochrome P-450, biphenyl-4-hydroxylase (BP-4-OH), epoxide hydratase (EH) and aminopyrine demethylation (Moore et al., 1978a). The second class of inducing agents is exemplified by 3-methylcholanthrene, which typically increases cytochrome P_1-450, aryl hydrocarbon hydroxylase (AHH), biphenyl-2-hydroxylase (BP-2-OH) and UDP-glucuronyltransferase (UDP-GT) (Moore et al., 1978a). In the rat and mouse liver FireMaster BP-6 shares the induction characteristics of both phenobarbital and 3-methylcholanthrene and acts as a "mixed-type" inducer (Dent et al., 1976a, 1976b, 1977, 1978a, 1978b; Babish and Stoewsand, 1977; Ahotupa and Aitio, 1978; Mc Cormack et al., 1978a; Moore et al., 1978a). Dent et al. (1978a) reported that even though FireMaster BP-6 induced in a mixed-type fashion, the induction was different, and they suggested that PBB probably represents a new class of inducing agents. In comparison to FireMaster BP-6, HBB_6 and HBB_7 are phenobarbital-type

inducers in the liver of the rat (Moore et al., 1978a, 1978c), while 2,4,5,3',4',5'-hexabromobiphenyl is a mixed-type inducer (Dannan et al., 1978).

Mc Cormack et al. (1978a) found that in the kidney of the rat FireMaster BP-6 increased AHH, BP-4-OH and BP-2-OH and decreased EH and in mammary tissue and lung increased AHH. Dent et al. (1978b) reported an increase of AHH in the kidney and an increase of AHH and EH in the mammary tissue of rats exposed to FireMaster BP-6. Ahotupa and Aitio (1978) noted that in the mouse FireMaster BP-6 increased UDP-GT in the kidney.

Other organs of the body have been reported to be affected by exposure to PBB. In the pig an increased kidney weight/body weight was found (Ku et al., 1978), and in the cow enlarged kidneys with dilated collecting ducts and convoluted tubules were noted (Moorehead et al., 1977; Mercer et al., 1978). A decrease in thymus tissue occurred in the rat (Luster et al., 1978), chicken (Ringer, 1978) and cow (Moorehead et al., 1977). In the rat (Luster et al., 1978) and chicken (Ringer, 1978) decreased spleen weights were detected. Allen et al. (1978) reported that the most severe lesion in monkeys was hyperplastic gastroenteritis. Using the electron microscope, Kasza et al. (1978a) found cellular abnormalities in the rat thyroid which suggested that PBB interfered with the synthesis and secretion of thyroxine.

In calves Robl et al. (1978) noted an increase in serum glutamic-pyruvic transaminase (SGPT), blood urea nitrogen (BUN) and serum alkaline phosphatase. Lambrecht et al. (1978) found an increase in SGPT and a decrease in serum cholesterol in monkeys, while

in cows Moorehead et al. (1977) found an increase in serum glutamic-oxalacetic transaminase (SGOT), lactic dehydrogenase, serum bilirubin and BUN.

In studying the immunological system of the monkey, Allen et al. (1978) found altered T-cell function and decreased immunoglobins. Luster et al. (1978) noted in mice and rats a depressed T-cell function and in mice a depression of humoral immunity. In chickens Ringer (1978) found loss of splenic germinal centers and a decrease of lymphoid tissue.

Tilson and Cabe (1979) investigated the neurobehavioral effects of Fire Master BP-6 exposure in the rat. They noted a decrease in locomotor activity, forelimb grip strength, hindlimb extensor response and startle responsiveness.

Exposure to FireMaster FF-1 has been found to decrease production of eggs in laying hens (Polin and Ringer, 1978) and of milk in lactating cows (Prewitt et al., 1975).

In a comparison of the degree of toxicity of HBB_6 and FireMaster BP-6 or FF-1, HBB_6 was found to be less toxic with regard to egg hatchability in chickens (Polin et al., 1979) and to neurobehavioral changes in rats (Tilson and Cabe, 1979).

Transplacental transfer of HBB_6 was reported to occur in the mouse (Corbett et al., 1978b), cow (Detering et al., 1975), rat (Dent et al., 1978b; Rickert et al., 1978; Cagen et al., 1979) and monkey (Allen et al., 1978). Cagen et al. (1979) found that rats who were exposed prenatally to FireMaster BP-6 had increased liver weight/body weights. Dent et al. (1978b) noted that rats exposed prenatally to FireMaster BP-6 showed a mixed-type induction of liver enzymes. Fries et al.

(1978) calculated the concentrations of HBB_6 in maternal to fetal cow fat to be 1 to 0.36 and in blood to be 1 to 0.37.

Maternal exposure to FireMaster BP-6 or FF-1 caused an increase in fetal deaths in the monkey (Lambrecht et al., 1978), rat (Beaudoin, 1977), chicken (Polin and Ringer, 1978) and cow (Detering et al., 1975; Prewitt et al., 1975; Durst et al., 1977) and resulted in an increase in neonatal deaths in the chicken (Polin and Ringer, 1978) and cow (Detering et al., 1975; Prewitt et al., 1975).

FireMaster BP-6 or FF-1 fed to the mother produced decreased fetal weight in the monkey (Lambrecht et al., 1978), mouse (Corbett et al., 1975, 1978a) and rat (Corbett et al., 1975, 1978a; Beaudoin, 1977) and produced decreased neonatal growth rate in the monkey (Lambrecht et al., 1978), cow (Detering et al., 1975) and rat (Harris et al., 1978b).

Beaudoin (1977) reported that in the rat FireMaster BP-6 was teratogenic. However, studies in the mouse (Corbett et al., 1978a; Wertz and Ficsor, 1978) and in the rat (Garthoff et al., 1977) found it not to be teratogenic or mutagenic.

In summary, the lipophilic PBBs are easily absorbed and become distributed in the fat of the body and in the organs with high lipid content. Distribution of PBB occurs with the highest concentration being found in adipose tissue, the primary compartment of long term storage. The chemically stable PBBs undergo little metabolism and are excreted only minimally and very slowly. The toxic syndrome associated with exposure to PBB in animals consists principally of anorexia, hepatic hypertrophy, altered immunological functioning, "behavioral suppression", muscular weakness, induction of hepatic and extrahepatic microsomal enzymes, and fetotoxicity.

HUMAN HEALTH EFFECTS OF PBB EXPOSURE

The Michigan-PBB incident was the only major known episode of human exposure to PBB. The human health effects of PBB absorption have been investigated by studying Michigan residents who were exposed to PBB during the 1973-1974 contamination period.

Studies have indicated that the source of exposure to PBB was through ingestion of contaminated farm products. Higher serum PBB levels were found in Michigan residents associated with quarantined farms than in those associated with non-quarantined farms (Wolff et al., 1978a). A significant difference in the distribution of serum PBB concentrations was not found between residents of quarantined farms and consumers of their farm products or between residents of non-quarantined farms and their consumers (Lilis et al., 1978). PBB serum levels tended to cluster by families (Wolff et al., 1978b; Landrigan et al., 1979). From a general population study in Michigan the major source of PBB exposure was found to be through ingestion of contaminated milk (Selikoff and Anderson, 1979). The populations in decreasing order of exposure were: 1) the farm families whose farms had been contaminated with PBB, 2) the immediate customers of produce from contaminated farms and ultimately, 3) the general population as contaminated food entered the Michigan food chain (Selikoff et al., 1976).

In November, 1976 a group led by Dr. Irving J. Selikoff from the Environmental Sciences Laboratory of the Mount Sinai School of Medicine of The City University of New York conducted a clinical field survey in Grand Rapids to investigate the human health effects of PBB exposure in Michigan. Those examined were approximately 1,000 PBB-exposed Michigan residents, most of whom were members of farm families; in March, 1977,

228 Wisconsin farm residents who had no known exposure to PBB were also examined. The Michigan population studied in the November, 1976 survey will be referred to as the Michigan Farm Population (MFP), and the Wisconsin population will be referred to as the Wisconsin Farm Population (WFP).

Anderson et al. (1978a) compared the examination results of the adults of the WFP with those of an adult MFP subgroup, both groups having been procured through random invitational processes. The Michigan group had a significantly higher prevalence of reported neurological, musculoskeletal and skin symptoms. Significant symptoms and some manifest expressions of disability were found to be those in the neurological category. The major symptoms were: 1) marked tiredness and fatigue, 2) a significant increase in sleep requirement of up to eighteen hours per twenty-four hours, 3) a striking decrease in the physical and intellectual work capacity, 4) muscle weakness and sensory disturbances and 5) changes in mental and behavioral functions, including loss of memory. Tiredness and hypersomnia were often found to be associated with the gastrointestinal symptoms of loss of appetite and weight loss.

Diamond et al. (1977) performed clinical neurological examinations on a MFP subgroup who had been referred because of unexplained disorders of the nervous system. They reported finding mental and behavioral deficits, sensory disturbances, motor disabilities, headache and hypersomnia.

In analyzing the time course of the onset of symptoms in subgroups of the WFP and the MFP, Valciukas et al. (1978) found that neurological symptoms were likely to be the earliest manifestations of abnormalities

among the MFP. The Michigan group reported a significantly higher prevalence of the following symptoms, in decreasing order of significance: tiredness, nervousness, sleepiness, headaches, paraesthesia, dizziness, depression, vomiting, nail discoloration, loss of balance, blurred vision, drier skin, muscle weakness, prolonged healing, difficulty walking, perspiration and joint swelling (Valciukas et al., 1979).

In examining a cohort of 4,537 Michigan residents exposed to PBB, Landrigan et al. (1979) found fatigue, headaches, paraesthesias and joint problems to be the most frequently reported symptoms. Stross et al. (1979) discovered a high prevalence of sensory neuropathies, reactive depression and hepatomegaly in a group of forty-six PBB-exposed Michigan residents.

Certain abnormalities associated with PBB absorption have been indicated by laboratory findings. Anderson et al. (1979) reported that significantly more Michigan subjects, as compared to Wisconsin subjects, had abnormal SGPT and SGOT levels, and that an abnormal SGPT level was significantly associated with the reported symptoms of excessive fatigue and sleepiness. Bekesi et al. (1979) and Landrigan et al. (1979) found altered lymphocyte functioning in PBB-exposed Michigan residents.

Investigators have used HBB_6 to calculate serum levels of PBB in exposed individuals. The levels of HBB_7 and 2,4,5,2',5'-pentabromobiphenyl in the serum of farmers were found to be significantly lower, relative to HBB_6, as compared to levels in FireMaster BP-6 (Wolff and Aubrey, 1978). As the second major component of FireMaster BP-6, the marked scarcity of HBB_7 in blood serum suggests poor gastrointestinal absorption or rapid biliary excretion in humans. The low serum concentration of 2,4,5,2',5'-pentabromobiphenyl is most likely attributable

to a fast rate of elimination which was found to occur in rats (Wolff and Selikoff, 1979).

In a survey of the general population of Michigan for health effects of PBB exposure, Selikoff and Anderson (1979) found that at least seventy percent of the Michigan population had detectable (greater than 0.3 parts-per-billion) levels of PBB in serum, with the highest concentrations found in individuals who resided in the western part of the state. Landrigan et al. (1979) and Selikoff and Anderson (1979) found significantly higher levels of serum PBB in Michigan males than females and higher levels in children than adults. Because serum levels of PBB have not changed significantly with time (Humphrey and Hayner, 1975; Landrigan et al., 1979; Wolff et al., 1979), it is thought that PBB body distributions have reached equilibrium, and that Michigan residents have relatively permanent body burdens of PBB.

Landrigan et al. (1979) and Wolff et al. (1979) found the partition ratio for PBB concentrations in adipose tissue to blood serum to be 362.8 to 1.0 and 370 to 1, respectively. Breast milk to blood serum concentrations of PBB were reported by Landrigan et al. (1979) to be 122.0 to 1.0. Brilliant et al. (1978) in investigating the concentration of PBB in human breast milk found that ninety-six percent of the samples from the lower peninsula of Michigan and forty-three percent from the upper peninsula contained detectable levels of PBB. PBB was found to be transferred from mother to fetus through the placenta with an average ratio of PBB concentrations in maternal to cord blood serum of 7.04 to 1.0 (Landrigan et al., 1979).

Anderson et al. (1978a) and Landrigan et al. (1979) did not find any significant positive correlations between serum PBB levels and

reported symptoms. Bekesi et al. (1978) found no significant correlation between altered lymphocytes and serum concentrations of PBB. However, Selikoff and Anderson (1979) reported that a higher serum PBB among adults was statistically associated with increased infections. Anderson et al. (1979) discovered significant positive correlations between serum levels of PBB and levels of SGPT and (1978b) between plasma levels of carcinoembryonic antigen (CEA) and serum levels of concentrations of PBB greater than or equal to 10 parts-per-billion.

In summary, Michigan residents were exposed to PBB through ingestion of contaminated farm products, most notably milk, with dairy farm families and direct consumers of farm produce being the most heavily exposed. HBB_6 was used as the biological indicator of PBB absorption and was found in the blood serum, adipose tissue and breast milk of exposed individuals. Neurological symptoms were the most frequently reported indications of disability, with marked drowsiness and excessive sleeping being two of the major complaints. Laboratory findings indicated that abnormal liver and lymphocyte functioning were associated with exposure to PBB. Serum levels of PBB were found to be correlated to increased infections in adults, to the serum level of a liver function enzyme and to the serum level of CEA. A very high percentage of Michigan residents had detectable levels of PBB; fat tissue levels were found to be 370 times higher than serum concentrations. It has been hypothesized that the body burdens of PBB were relatively permanent.

SLEEP AS DEFINED BY EEG

One of the primary purposes of the present investigation was to

examine electrophysiologically the sleep of a group of Michigan residents and to compare their sleep with known pathological sleep syndromes. In order to evaluate sleep and its disorders, it will be necessary to review what is currently accepted as the physiological basis of the electroencephalograph (EEG). Finally, we will review the use of EEG in conert with other electrophysiological measures in characterizing normal sleep and in identifying disorders of sleep.

In electroencephalography, the electrical potentials recorded from the scalp are thought to be principally generated within the cerebral cortex. The post-synaptic potentials (PSPs) of vertically oriented cortical pyramidal cells have been suggested as the main generators of the EEG-waves. The extracellular potential field resulting from either depolarization or hyperpolarization of the pyramidal cell is thought to be similar to that produced by one or more dipoles. Thus, summation of dipole fields associated with vertically arranged pyramidal cells is thought to give rise to large population potentials (Creutzfeldt, 1974).

The actual form of the surface potential may be related both to the type of PSP and the location on the cell of the synaptic activity. Excitatory PSPs may produce a positive surface potential when the pyramidal cell's somatic or middle apical dendritic region is affected or a negative potential when the cell's distal apical dendritic region is excited. Surface potentials of the opposite polarity to those of excitatory PSPs would occur, when inhibitory PSPs affect the same corresponding locations.

Certain surface potentials of the EEG highly correlate with activity of single neurons of the cerebral cortex. The rhythmical

spindle waves of 7 to 10 waves/second noted in the EEG of cats are thought to be similar to the alpha waves of 8 to 12 waves/second seen in the human EEG. In cats, summated excitatory PSPs of pyramidal cells are closely related to individual spindle waves of the EEG; it is found that cellular depolarizations coincide with surface negative potentials. Although the EEG spindle waves are generated within the cortex, it is thought that the thalamus functions as a pacemaker for the rhythmical waves. It is suggested that the recurrent inhibitory mechanisms in specific thalamic relay nuclei transform the tonic, random input of the relay nuclei into excitatory-inhibitory cycles which result in synchronous bursts of thalamo-cortical fiber activity. This synchronous fiber activity would then generate rhythmical negative surface potentials, because the majority of the afferent fibers are thought to make excitatory synapse on the apical dendrites of cortical pyramidal cells.

Theta waves, 4 to 7 waves/second, and delta waves, 1 to 3 waves/second, have also been found to have cellular depolarizations associated with surface negative waves. However, it has been found that the phase relationship between neuronal events and alpha waves or theta waves is more consistant than that found for delta waves.

The desynchronized EEG seen during wakefulness and rapid eye movement sleep (v.i.) is thought to correspond to an absence of synchronization of discharges among cortical neurons due to a non-synchronized, random synaptic input. The ascending reticular activating system (Moruzzi and Magoun, 1949) may produce cortical desynchronization by inhibiting the thalamic recurrent inhibitory mechanism which, as previously mentioned, may be involved in the generation of synchronized neuronal activity in the cerebral cortex.

In the past thirty years researchers have described normal human sleep in quantitative terms using such measurable parameters as spontaneous and evoked brain waves, slow and rapid eye movements, somatic muscular activity, heart rate and respiratory rhythm (Aserinsky and Kleitman, 1953, 1955; Dement and Kleitman, 1957a, 1957b; Feinberg, 1974; Williams et al., 1974). Since the discovery by Loomis et al. (1937) that sleep measured electrophysiologically is not a steady state, different stages of sleep have been characterized. The criteria of Dement and Kleitman (1957a) for classifying or scoring sleep stages became those most widely employed and provided the basis for the standardization of sleep scoring by Rechtschaffen and Kales in 1968.

The principal parameters used to define sleep stages are those measured by the EEG, electrooculograph (EOG) and electromyograph (EMG). The polygraphic sleep record is divided into fixed time intervals or epochs and scored in an epoch-by-epoch manner. An epoch may be scored as one of the following: stage 0, 1, 2, 3, 4 or REM or movement time. Movement time epochs are those epochs in which the polygraph record is obscured by artifact produced by movements of the subject. A stage 0 epoch has an EEG containing alpha waves, 8 to 12 waves/second, and/or low voltage, mixed frequency activity and refers to the behavioral state of wakefulness. Stage 1 epochs consist of a relatively low voltage, mixed frequency EEG and are without rapid eye movements. Stage 1 is associated with the drowsy state usually occurring between full wakefulness and the onset of sleep. Many researchers employ stage 2 to designate the onset of sleep, although stage 1 sometimes is assigned that function. An epoch of stage 2 sleep is distinguished by the presence of sleep spindles (sigma waves), a spindle shaped

group of 12 to 14 waves/second sinusoidal waves, by K-complexes, a wave form of an initial negative deflection followed by a positive deflection, and by a background of relatively low voltage, mixed frequency EEG activity. Also, a stage 2 epoch must contain less than twenty percent delta waves. Delta waves are characterized by a frequency of less than 3 waves/second and an amplitude of greater than 50 μV. An epoch having twenty to fifty percent delta is scored stage 3 and one containing more than fifty percent is scored stage 4. Thus, stages 3 and 4 constitute what is called delta sleep. Stages 2, 3 and 4 are referred to as slow wave sleep (SWS). A stage REM epoch is characterized by a relatively low voltage, mixed frequency EEG, by episodic rapid eye movements (REMs) and by a low amplitude EMG. REM sleep has been highly correlated with dreaming (Aserinsky and Kleitman, 1953; Dement, 1955; Dement and Kleitman, 1957b; Foulkes, 1962; Goodenough et al., 1965).

Stages 2, 3, 4 and REM indicate the typical sequence of occurrence at the beginning of a night's sleep (Dement and Kleitman, 1957a). They usually occur in a cyclic pattern during sleep with a period of SWS and one of REM sleep composing a sleep cycle. Several sleep cycles normally occur during a night's sleep. However, sleep cycles of the first hours of sleep have relatively greater amounts of stages 3 and 4 and less of stage REM as compared to later cycles, while the amount of stage 2 per sleep cycle remains relatively constant (Williams et al., 1964).

The above criteria have been employed for approximately thirty years to characterize sleep, and sleep scoring has been found to be reasonably reliable with both within and across scoring having high reproducebility.

SLEEP DISORDERS RELATED TO TOXIC CHEMICALS

Patients who have been occupationally or accidentally exposed to a toxic chemical have frequently reported a sleep disorder as part of a symptom complex. Insomnia, sometimes accompanied by daytime somnolence, has often been the complaint, while hypersomnia has rarely been reported as a problem.

Patients have complained of insomnia after intoxication from bismuth (Buge et al., 1977; Ferrey-Hanin and Ferrey, 1977), carbon disulfide (Braceland, 1942; Bruederl and Benini, 1974; Lilis, 1974; Seppäläinen, 1974), lead (Cassells and Dodds, 1946; Korolenko and Piven, 1971), mercury (Korolenko et al., 1971; Antonyuzhenko et al., 1976) and organophosphate compounds (Conyers and Goldsmith, 1971; Viyevskaya, 1973). Exposure to chlorinated hydrocarbons (Sukhotina et al., 1973) or manganese (Mena et al., 1967; Smith, 1972; Cook et al., 1974) has produced in patients nighttime insomnia with daytime somnolence. Sleepiness, frequently overwhelming, was reported to occur in cases of occupational exposure to carbon disulfide (Lilis, 1974).

Clinically reported sleep disorders resulting from chemical intoxication have been studied with electrophysiological techniques by a few investigators. In examining the sleep of patients with bismuth poisoning, Ferrey-Hanin and Ferrey (1977) found a uniform EEG throughout the night which resulted in the use of non-EEG polygraphic criteria to identify sleep stages. They reported a decreased amount of sleep which was thought to be caused by abnormal movements occurring just prior to awakenings.

Antonyuzhenko et al. (1976) analyzed the night sleep of patients

who had chronic occupational mercury or methylmethacrylate and unsaturated hydrocarbons poisoning. Mercury intoxication was characterized by disorganization of the cyclic structure of sleep, an increased sleep onset latency, an increased amount of wakefulness and an increased number of awakenings during the night. Poisoning with methylmethacrylate and unsaturated hydrocarbons was associated with two syndromes, one of decreased total sleep time with disorganization of the cyclic structure of sleep and the other of a decreased number of sleep cycles.

In examining patients with organophosphate poisoning, Metcalf and Holmes (1969) and Taneda and Murasaki (1976) observed sleep onset REM periods at night and somnolence during the day. Duffy et al. (1979) studied patients who had been occupationally exposed to the organophosphate compound, sarin. The sleep of the patients showed an increase in both the percent and absolute amount of REM sleep.

Hypersomnia, associated with chemical intoxication, has not been investigated using modern sleep recording techniques prior to the present study.

THE PRESENT INVESTIGATION

Hypersomnia was one of the major neurological symptoms reported by Michigan residents exposed to PBB (Diamond et al., 1977; Anderson et al., 1978a; Valciukas et al., 1979). In order to further elucidate one of the primary human health effects associated with PBB, the electroencephalograph (EEG) was to be used to examine objectively the sleep complaint.

With the use of the EEG the sleep of the Michigan subjects was to be characterized in terms of normal sleep parameters. Quantification

of the sleep of the subjects was to enable the extent of the abnormality to be delineated. The sleep disorder was to be examined and compared with other classes of pathological sleep. Such analysis could suggest possible treatment for the sleep problem and could provide insight into the effect of PBB on the central nervous system. Correlations among sleep parameters and medical and biochemical data were to provide additional information about exposure to PBB.

One of three results was expected to be found when the reported complaint of hypersomnia was investigated using electrophysiological sleep recording techniques. First, the sleep of the subjects could be found to be relatively normal. In this case the explanation would be either that the subjects had inaccurately reported the symptom of increased sleep requirement or that the sleep of the subjects had been abnormal when the hypersomnia complaint was reported but was normal when tested. The latter explanation is supported by the finding that the incidence of symptoms associated with exposure to PBB was at its highest during 1974 (Anderson et al., 1979). A lack of sleep abnormality in 1979 could be explained by a recovery of sleep functions mediated by the central nervous system during the intervening five years.

Second, the majority of the subjects could exhibit normal sleep, while a few could show relatively minor sleep abnormalities. Since subjects with the most severe sleep complaints had been examined, this finding would suggest that, as determined with present sleep recording techniques, PBB affects the normal functioning of sleep minimally at most, and that a sleep disorder associated with exposure to PBB would not be a significant health concern for the general population.

Third, one or more abnormalities in the sleep of most of the subjects could be discovered. The alterations in sleep measures seen in chronic hypersomnia, narcolepsey, the neutral state syndrome, hypothyroidism, the fibrositis syndrome, aging, depression and the sleep apnea syndrome suggest certain abnormalities which could be found in the sleep of subjects exposed to PBB.

Individuals with chronic hypersomnia have an increase in total sleep time (Roth et al., 1972); a similar finding for the subjects would correspond to the reported increase in sleep requirement.

A disruption in the normal sequence of the sleep stages, perhaps similar to that seen in narcolepsy, could be observed. The symptoms of narcolepsy are excessive daytime sleepiness, sleep episodes and cataplexy (Guilleminault and Dement, 1977); it is characterized electrophysiologically by the occurrence of nocturnal sleep onset REM periods (Rechtschaffen et al., 1963; Cadilhac et al., 1966; Suzuki, 1966; Hishikawa et al., 1976).

A decrease or increase in the absolute amount or percent of the sleep period time of one or more of the sleep stages would indicate sleep pathology. Individuals with the neutral state syndrome, characterized by excessive daytime sleepiness and frequent daytime occurrences of microsleep episodes, show a decreased amount of stage 3 and stage 4 and an increased amount of stage 2 in their nocturnal sleep (Guilleminault et al., 1975). Sleepiness is one of the characteristic symptoms of hypothyroidism. The night sleep of hypothyroid adults shows increased stage 2 and decreased stage 4 (young adults) or decreased stage 3 (elderly adults) (Kales et al., 1967a).

The fibrositis syndrome is characterized by the primary symptoms

of sleep disturbance, chronic fatigue, decreased work tolerance, muscular aching and stiffness, poor appetite, depression and irritability (Moldofsky et al., 1975). The sleep of individuals having the fibrositis syndrome consists of increased wakefulness, alpha-contaminated slow wave sleep (SWS) and frequently absent stage 4 and absent or decreased stage 3. Moldofsky et al. (1975) suggested that an internal arousal system competes with the SWS system and impairs the presumed restorative function of SWS. Their results indicated that a disturbance of SWS, namely stage 4 deprivation, would be associated with the appearance of musculoskeletal and mood symptoms. An increased wakefulness and decreased stage 4 might be expected to characterize the sleep of the subjects, since marked fatigue, decreased work capacity, depression, muscular weakness, joint problems and poor appetite had been reported by Michigan residents as major complaints (Anderson et al., 1978a; Valciukas et al., 1978; Landrigan et al., 1979).

The symptoms of fatigue, decreased physical and mental work capacity and loss of memory reported by Michigan residents (Anderson et al., 1978a) suggest a possible "premature aging" effect of PBB on the central nervous system. If this were the case, the sleep of the subjects could be found to be "older" than would be expected from their chronological ages. With increasing age, total sleep time, REM sleep and stage 4 sleep decrease (Kales et al., 1967b; Williams et al., 1974). Other changes in sleep parameters seen with increasing age are the shortening of the first NREM period (Feinberg, 1974), a decrease in the sleep efficiency index (Williams et al., 1974), an increase in the number of awakenings per night (Kales et al., 1967b; Feinberg, 1974; Williams et al., 1974) and an increase in the average duration

of an awakening (Feinberg et al., 1967; Feinberg, 1974).

Depression was one of the significant symptoms reported by Michigan residents (Valciukas et al., 1979). If the sleep disorder of the subjects is related to depression, then changes similar to those seen in the sleep of depressives might be found. Unipolar depressives have the secondary symptom of an insomnia-type sleep disturbance which consists of an increased sleep onset latency, an increased number of awakenings, an increased stage 0, an increased time spent awake in the early morning, a decreased total sleep time and a decreased stage 4 (Mendels and Hawkins, 1967a). Depressives characteristically show a decreased latency to the first REM period (Synder et al., 1968; Kupfer and Foster, 1972; Weiss et al., 1974; Kupfer, 1976; Kane et al., 1977); the degree of measured depression has been negatively correlated with the latency to the first REM period (Kupfer and Foster, 1972; Fink et al., 1977).

The subjects could show changes in respiratory drive which would explain their reports of hypersomnia. The sleep of individuals with the sleep apnea syndrome shows respiratory pauses which are associated with arousal from one sleep stage to another and which produce daytime sleepiness with overwhelming and unrefreshing sleep attacks (Guilleminault et al., 1976).

Of the three possible results, it was expected that the study would establish the sleep of most subjects to be abnormal. It was further hypothesized that if central nervous system functions of the subjects had been altered by exposure to PBB, this alteration would be expressed, at least in part, by changes in their sleep patterns. In this case the subjects' sleep might resemble the sleep of individuals chronologically older than the study population. If alterations in

normal brain function of subjects were demonstrated to be related to PBB levels, then the possible causal connection could be either by primary involvement of the central nervous system substrate or by reflection of some intermediate systemic pathology, e.g. toxic metabolic changes due to hepatic disease.

Examining the sleep of the subjects was considered to be medically appropriate, because a sleep disorder usually has a rather pervasive detrimental effect on the quality of the life of an individual, and because methods of objectively characterizing and delineating sleep problems were available which might lead to effective treatment. In addition, if sleep recording could be shown to be useful in this study, it might be employed in future epidemiological studies of possible neurotoxins.

Thus, using electrophysiological recording techniques, the present investigation examined the sleep of Michigan residents who had been exposed to PBB and who had reported a marked increase in sleep requirement and in sleep time. In addition to sleep evaluation, neuropsychological tests were administered to each of the subjects, and their serum PBB levels were measured. These additional procedures were performed to allow for a survey of relationships among PBB, sleep and neuropsychological parameters.

METHODS

SUBJECTS

Subjects were selected from the one hundred and twenty participants in the November, 1976 Michigan PBB Health Survey (Selikoff et al., 1976) who had reported in a physician-administered special PBB questionnaire experiencing "tiredness" and "sleepiness" during part or all of the period beginning in 1973 and ending in 1976. Males who had also reported sleeplessness (n=10) on the questionnaire and all females (n=46) were excluded. Forty-seven of the remaining participants were interviewed by phone using a Sleep Questionnaire to determine: 1) if the original sleep complaint of hypersomnia persisted and if so, to characterize its present state and 2) if the individual was interested in the proposed sleep examination.

Subjects were selected for the following characteristics: 1) the presence of a reported hypersomniac sleep problem, 2) the absence of the use of sleep-altering medication, 3) an age under 60 years and 4) a willingness to participate in the sleep examination study. Sixteen subjects were selected and scheduled for sleep examination; ultimately three did not participate, while another took part for only the first night. Therefore, twelve males who ranged in age from 23.1 to 57.5 years with a mean of 41.8 $\pm$ 11.5 and a median of 45.0 years participated in the study. All subjects lived in the lower peninsula of Michigan. At the time of the 1976 study, six had been residents of quarantined farms, four of non-quarantined farms and two had been consumers of products from quarantined farms. Nine of the men were dairy farmers, two were manual laborers and one was a veterinarian.

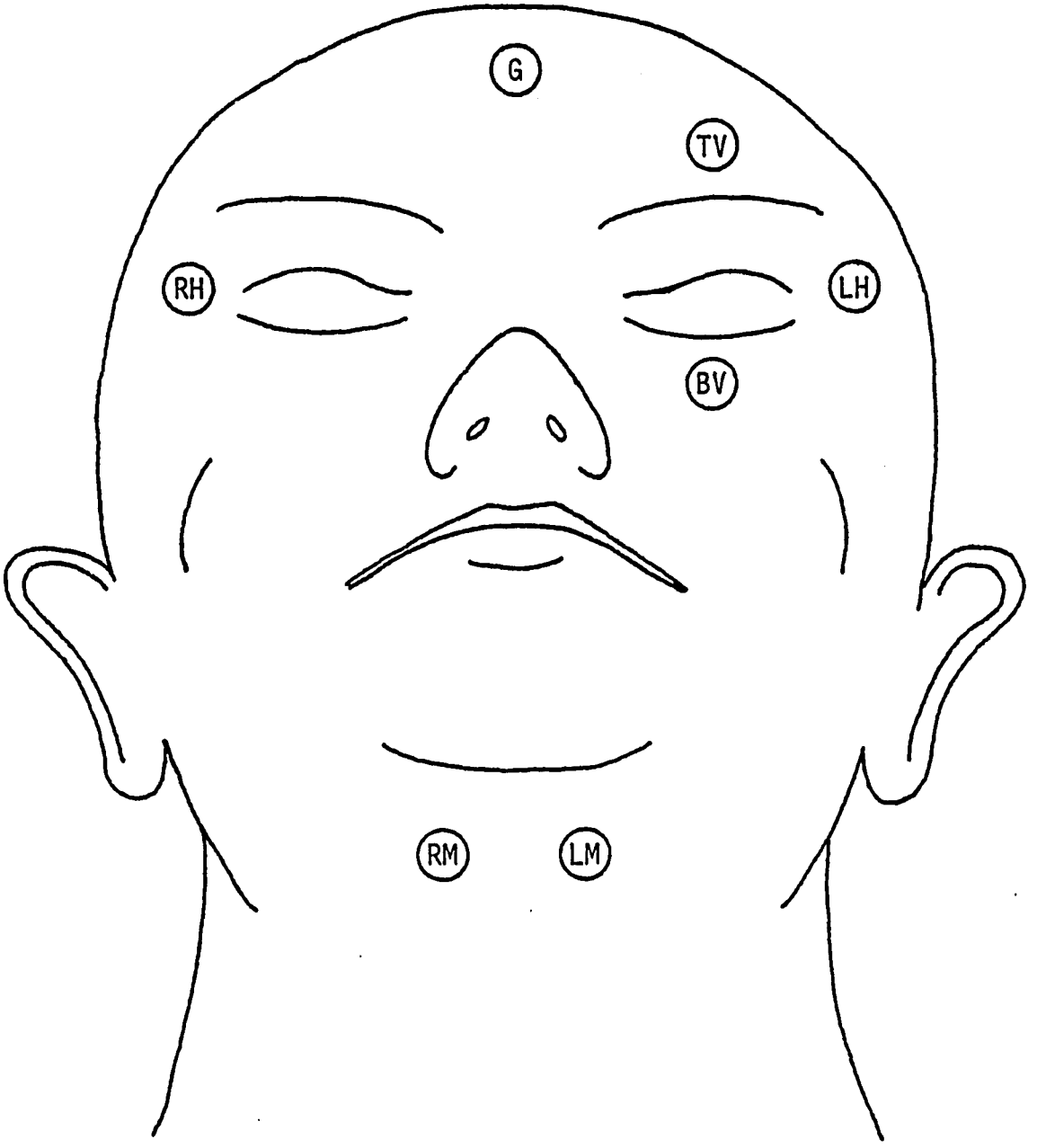
APPARATUS

A 16 Channel Grass Electroencephalograph (Model #8-16B) provided a continuous paper record at 15 mm/sec. of electrooculogram (EOG), electromyogram (EMG), electroencephalogram (EEG), heart rate and respiratory rate. These physiological measures were assigned to seven channels for each subject in the following manner.

Channels 1 and 2 recorded horizontal and vertical eye movement potentials respectively. The third channel monitored the tonic and phasic activities of the digastric muscles. Channels 4 and 5 recorded the EEG by utilizing the differential pairs of electrodes C_3 - A_2 and O_1 - A_2 respectively or rarely C_4 - A_1 and O_2 - A_1. The sixth channel monitored heart rate using the differential pair of electrodes right digastric muscle - A_2. Channel 7 recorded the respiratory rate.

The EOG electrodes were positioned as follows (Figure 2, p.31): horizontal - an electrode was located at the outer canthus of each eye, and vertical - an electrode was attached above and below the left eye. The two EMG electrodes were positioned on the left and right sides under the chin over the anterior bellies of the left and right digastric muscles, respectively (Figure 2, p.31). The EOG and EMG electrodes were Beckman silver-silver chloride disc electrodes, attached by adhesive collars, as was a ground electrode which was placed on the center of the forehead.

The EEG electrodes were Grass E5GH gold-plated cup electrodes with holes, secured with collodion. The International 10-20 Electrode System for electrode placement (Jaspers, 1958) was utilized except for the occipitals which were located 3 cm. more anteriorly. The left and right ear electrodes, A_1 and A_2, were located over the



RH = Right Horizontal

LH = Left Horizontal

TV = Top Vertical

BV = Bottom Vertical

RM = Right Muscle

LM = Left Muscle

G = Ground

Figure 2: PLACEMENT OF EOG, EMG AND GROUND ELECTRODES

left and right mastoid processes, respectively.

Beckman electrolyte gel was used to interface all electrodes with scalp or skin, and electrode resistance was less than 5,000 ohms.

The respiratory rate was recorded by measuring thoracic movements with a strain gauge connected through a 1,000 ohms bridge circuit to a direct coupled input of the electroencephalograph amplifier.

The frequency response of the amplifiers was set to give a pass band from 0.5 Hz (t.c.= 0.12 sec.) - 90 Hz for EOG and EEG and 2.5 Hz (t.c.= 0.035 sec.) - 90 Hz for EMG. Both pass bands are 6 db. down in voltage at the endpoints.

A time code was recorded on channel 16. Wireless intercoms were used for subject - technician communication.

PROCEDURE

Each subject slept for three consecutive nights at the Kent Community Hospital in Grand Rapids, Michigan. Subjects had been instructed by phone: 1) not to take any naps during the day starting from the first day prior to sleep recording and continuing throughout the study and 2) not to drink any coffee, tea, soft drinks or alcohol or take any psycho-active drugs from 12:00 noon on the first day prior to sleep recording and continuing throughout the study. Subjects arrived in the evening of the first night and were again given the above instructions. They were also instructed that during the study they could leave the hospital during the day but should confine their activities to the general Grand Rapids area and should not do any activites which were unusual, extreme or out of the ordinary in any way.

Each subject slept alone in a double bed-sized hospital room with westward-facing windows which were covered by thick cardboard and curtains. The rooms of the subjects and the equipment room were located on an unused floor of the hospital. Each night before the light was turned off, subjects were told to sleep until awakened by the technician, and time pieces were not available to them. Subjects completed the sleep examination study at approximately 12:00 noon on the day following the third night's recording.

The bioelectric parameters were recorded for eight hours on the first two nights and for twelve hours on the third night of three consecutive nights. The recording was done in pairs for eight subjects and individually for four.

For each recording session subjects completed a Pre-Sleep Questionnaire just prior to "lights off" and a Post-Sleep Questionnaire immediately following "lights on". After arriving for the first night's recording, subjects completed the Zung Self-Rating Depression Scale (Zung, 1965) which they were told was a general questionnaire. Subjects were administered a Memory Test on the second evening of the study before the application of electrodes.

Using vacutainer tubes, peripheral blood (20 ml.) was taken by venipuncture from each subject on the third morning, after he had completed a Post-Sleep Questionnaire and before electrode removal. After one hour the blood was centrifuged, and the serum removed and stored frozen in glass bottles with Teflon-lined caps. The bottles had been pre-washed with detergent and water and rinsed in succession with tap water, distilled water, acetone and hexane. At the completion of the study the frozen serum was refrigerated in dry ice and transported

directly to the Mount Sinai Environment Sciences Laboratory for determination of serum levels of PBBs.

The sleep examination study commenced on March 13, 1979 and ended on April 9, 1979.

DATA ANALYSIS

Visual sleep scoring using generally accepted methods (Rechtschaffen and Kales, 1968) was carried out on the records of all three study nights for each subject. Delta wave amplitude was defined to be at least 50 μV peak-to-peak, according to Feinberg (1974). The sleep terminology (cf. Definitions of Terms and Abbreviations, pp.xiii-xiv) was that used by Feinberg et al. (1967), Williams et al. (1974) and Feinberg and Floyd (1979). Sleep stages, rapid eye movement densities and body movement were determined with subject blindness and night number blindness for seventy-six percent of the records.

The questions for the Sleep, Pre-Sleep and Post-Sleep Questionnaires were designed using as a model a sleep questionnaire of Dr. Irwin Feinberg (V.A. Hospital, San Fransisco, CA.). The scoring of questions was similar to the method used by Zung (1965). The Sleep Questionnaire (Appendix A, p.106) was used to interview potential participants in the sleep study. The answers to nine out of seventeen of the sleep history questions were scored one, two or three points each. A Sleep Index which ranged from 0.33 to 1.00 was obtained by dividing the highest possible score, 27, into the actual score. A high index value indicated a reported hypersomniac sleep problem.

The Pre-Sleep Questionnaire (Appendix B, p.109) monitored a sub-

ject's compliance with his instructions; six of the questions also quantified the probability of a rapid onset of restful sleep. Each of the six questions had five possible answers which were scored sequentially one through five points. A Pre-Sleep Index which ranged from 0.20 to 1.00 was obtained by dividing the highest possible score, 30, into the actual score. A high index value indicated a high probability of a rapid sleep onset followed by restful sleep.

The Post-Sleep Questionnaire (Appendix C, p.112) quantified a subject's self-evaluation of the quality of the previous night's sleep. Ten questions each with five possible answers which were scored sequentially one through five points dealt with the periods of falling asleep, sleep during the night and final awakening. A Post-Sleep Index which ranged from 0.20 to 1.00 was obtained by dividing the highest possible score, 50, into the actual score. A high index value indicated a subjectively good night's sleep. For all three questionnaires, one-half of the scored questions had answers which were increasingly positive symptomatically from left to right while the other half of the questions had answers which were oppositely sequenced.

The Zung Self-Rating Depression Scale (Zung, 1965; Appendix D, p.115) was designed to aid in the diagnosis of depression. Twenty questions, ten worded to be symptomatically positive and ten negative, each with four possible answers which were scored sequentially one through four points asked a subject to evaluate various aspects of his life. A Depression Index ranging from 0.25 to 1.00 was obtained by dividing the highest possible score, 80, into the actual score. A high index value suggested the diagnosis of primary depression.

The Memory Test (Appendix E, p.117) was compiled by Drs. Sidney P.

Diamond, Brenda Eskenazi and Steven Mattis and was used in a 1978 Michigan general population study of the health effects of PBB (Selikoff and Anderson, 1979). The test lasted thirty minutes and was composed of: 1) the Mattis Sentence, 2) the Benton Revised Visual Retention Test, 3) the Mattis-Kovner Memory Recognition Test and 4) the Associate Learning Test.

The Mattis Sentence, which measured verbal recall, was part of the Dementia Rating Scale of Dr. Mattis (personal communication) but for this study was modified from a recall duration of one minute to one of thirty minutes. While showing to the subject a sheet of paper on which was the sentence, "The boy has a brown dog.", the tester said, "I want you to read this sentence out loud. Remember the sentence, because I am going to ask you to repeat it later." The subject then read the sentence out loud. After the completion of the Associate Learning Test, the tester said to the subject, "What was the sentence I told you to remember?" The response of the subject was recorded and was scored in the following manner. For the correct complete sentence, four points were given; if the word "boy", "brown" or "dog" was missing, one point was subtracted from the score; if "the" or "has" was missing, one-half a point was subtracted; if an insertion was made (e.g. "little" boy), one-half a point was subtracted; if the context was incorrect, one-half a point was subtracted; and if the entire sentence was not remembered, no points were given.

The Benton Revised Visual Retention Test was designed to assess visual perception, visual memory and visuo-constructive abilities (Benton, 1974). In this study "Administration A" and "Form D" were used. The tester showed to the subject ten sheets of paper, one at a

time, on each of which were one or more geometric figures. The subject studied a sheet for ten seconds, the sheet was removed, and then the subject was allowed an unlimited amount of time to draw on a blank sheet what he had seen. The test was scored for: 1) the number of correct reproductions (Correct Score) which was a measure of the general efficiency of performance and 2) the number of errors (Error Score). For the Correct Score, one point on an all-or-none basis was given for each correctly reproduced design with ten points as a perfect score. For all incorrect designs, one or more types of errors were made and given one point each. The Error Score was the total number of all errors.

The Mattis-Kovner Memory Recognition Test (personal communication) measured recognition of names of animals and examined the change in performance over repeated trials of random verbal presentations. The tester read to the subject a list of twenty animal names (the original list). The subject repeated each name after it was given and tried to remember as many names as he could. Then the tester read a list (first trial list) of forty animal names, twenty of which were from the original list and twenty of which were new. If the name was from the original list, the subject said, "Yes"; if it was not, he said, "No". The tester recorded the answers of the subject and provided immediate feedback regarding their correctness (e.g hit, correct rejection, miss or false alarm). A total of four trial lists were used. For each list the number of hits and the number of false alarms were used to calculate d' for each of the four trials.

The Associate Learning Test was used in this study to measure recall of pairs of associated words (Wechsler and Stone, 1974). The tester said to the subject, "I am going to read pairs of words to you.

I want you to try to remember the words that go together." After reading ten pairs of words from a presentation list, the tester read in a different order the first word of each pair, while the subject attempted to respond with the associated word. Six of the paired words were designated "easy" to associate, and four were termed "hard". Three presentation lists were read, each having the same paired words, but in a different order. The test score was obtained by dividing by two the total number of correctly paired "easy" associations for all three presentation lists and adding that number to the total number of correctly paired "hard" associations for all three presentation lists. The test score for perfect recall was 21.0.

Dr. Mary S. Wolff of the Mount Sinai Environmental Sciences Laboratory determined serum levels of PBBs for all subjects using gas chromatography with electron capture detection. The complete method for analysis of serum PBB used by her laboratory has been reported (Wolff et al., 1978a).

For statistical analysis and presentation of data, "N1" and "N2" will label data from the first and second night sleep recordings, respectively. "N3a" will refer to the data from the first eight hours of sleep recording on the third night, while "N3b" will correspond to data from the entire twelve hours of sleep recording.

The number (n) used for statistical analysis involving data from N1 and N2 was 12. The third night sleep of two subjects was unavoidably interrupted by the ringing of a fire alarm. Therefore, the "n" used for most data from N3a and N3b was 10.

Two-tailed tests of significance were used for all testing with $p \leq .05$ considered as the level of significance.

The sleep of the subjects of this study was compared to the sleep of normal subjects using the values of Williams et al. (1974), Feinberg et al. (1967) and Feinberg (1974). Data from N2 and N3a were used for the comparison. The subjects were divided into a Young Group (YG) and an Old Group (OG) to correspond to the age groups of the normative data (Table 1, p.40). The means of the sleep variables of the YG were compared to those of the Twenties Men, Thirties Men, Young Normals and Group Four, while the means of the OG were compared to those of the Forties Men, Fifties Men, Aged Normals and Group Five. Two normal age groups from Williams et al. (1974) were used for comparison with each of the subject groups because of the mean ages of the YG and OG. Unpaired t-tests were utilized to test for differences in mean values between groups (Chao, 1974).

It is noted that each of the four groups of Dr. Feinberg include both men and women, whereas the two subject groups consist only of men. Williams et al. (1974) reported the significant differences in sleep parameter values between men and women for several age groups. The pertinent differences concerning the present comparison of the sleep values of the subjects with those of the four groups are lower percents of stage 3 and stage 4 of the sleep period time for men as compared to women in the seventies age group. These differences may be relevant to the sleep data of the Aged Normals because of the age similarity. However, the Aged Normals Group consists of one and one-half times as many men as women, and, therefore, the effect of the inclusion of women in this group on the stage 3 and stage 4 values would be expected to be relatively moderate. Consequently, a comparison between the OG and the Aged Normals Group was considered reasonable.

TABLE 1: DESCRIPTIVE DATA OF THE AGE GROUPS USED IN THE NORMAL SLEEP COMPARISON

AGE GROUP		NUMBER TOTAL	MEN	WOMEN	AGE (years) MEAN	±SD	RANGE
Young [1]	N2+N3a	5	5	0	29.9	4.9	23.1-35.4
Old [1]	N2	7	7	0	50.2	5.0	44.6-57.5
	N3	5	5	0	52.3	4.2	46.8-57.5
Twenties Men [2]		11	11	0	25.	-	20-29
Thirties Men [2]		10	10	0	35.	-	30-39
Forties Men [2]		10	10	0	45.	-	40-49
Fifties Men [2]		12	12	0	55.	-	50-59
Young Normals [3]		15	9	6	26.6	-	19-39
Aged Normals [3]		15	9	6	77.0	-	65-96
Group Four [4]		13	8	5	31.5	5.5	26.2-43.3
Group Five [4]		8	2	6	55.3	8.1	45.9-64.8

[1] Subjects of present study

[2] Williams et al., 1974

[3] Feinberg et al., 1967

[4] Feinberg, 1974

A consideration concerning the use of the sleep values of Feinberg et al. (1967) is that the average time in bed (TIB) for the Young Normals was only 7.01 ± .45 (mean ± SD) hours as compared to the TIB of eight hours for the subjects. With less time in bed a decrease in the total sleep time (TST) would probably occur. Because stage 3 and stage 4 occur in higher percents of the TST in the first hours of sleep (Williams et al., 1964), a decreased TIB situation could cause an increase in the percents of the TST of stage 3 and stage 4. However, this possibility is not a major concern, because the comparisons involving the values of the Young Normals Group are similar to those involving the other normal groups as reported in the results section.

Conversely, the Aged Normals Group had an average TIB of 7.82 ± .64 (mean ± SD) hours which corresponds closely to the TIB of the subjects, while the average TIB of Groups Four and Five of Feinberg (1974) are of no major significance, because the data of those groups are reported in terms of sleep cycles.

Williams et al. (1974) scored sleep records using one minute epochs, used stage 1 or stage 2 for the sleep onset marker, and had the TIB terminated when a subject naturally awakened in the morning and wished to arise. These procedures differed from those of the present study, but only the TIB difference was considered to be possibly significant in reference to the use of the data in comparisons with the data of the subjects of this study. The means ± SD of the TIB for the Twenties, Thirties, Forties and Fifties Men were 7.37 ± .20, 7.24 ± .34, 7.15 ± .65 and 7.04 ± .75 hours, respectively. Because the TIB was not shortened prematurely by the experimenter but rather was terminated by the subject in a natural manner, the sleep efficiency index and the percents

of the stages of the sleep period time were thought to be representative of normal values and, therefore, of use in a comparison with the values of the YG and OG.

To discover during what stages of sleep awakenings occurred, the number of awakenings occurring during stages 2, 3, 4 and REM were calculated in terms of percents of awakenings for each stage for N1, N2, N3a and N3b. Paired t-tests were used to test for the differences between the mean values.

The first night of laboratory sleep has been considered an adaptation night, because the sleep of normal subjects on the first night as compared with later nights has been found to be different. Specifically the first night of sleep has: 1) an increased number of awakenings, 2) an increased amount of wakefulness, 3) an increased latency to the first REM period, 4) a decreased amount and/or percent of stage REM and 5) an increased latency to stage 3 (Rechtschaffen and Verdone, 1964: 1,4; Agnew et al., 1966: 1,3,4; Gulevich et al., 1967: 4; Mendels and Hawkins, 1967b: 2,3,5; Schmidt and Kaelbling, 1971: 1,2,4, 5; Cobbe et al., 1974: 3). Schmidt and Kaelbling (1971) also reported an increased sleep onset latency, a decreased total sleep time, a decreased amount of stage 2, an increased number of stage shifts and a decreased number of REM periods for the sleep of the first night.

In contrast to normal subjects, insomniacs, depressives and schizophrenics do not exhibit typical first night sleep adaptation effects. Karacan et al. (1971) reported that insomniacs showed a decreased sleep efficiency and an increased latency of arising, while the control subjects did not. Depressives (Mendels and Hawkins, 1967b; Kupfer et al., 1974) and schizophrenics (Gulevich et al., 1967; Kupfer

et al., 1974) show few, if any, first night sleep adaptation effects.

The first night sleep adaptation effects of the subjects were investigated by testing for the differences between the mean values of the sleep variables of N1 and N2, and N1 and N3a using paired t-tests (Chao, 1974).

The Depression Indices of the subjects were compared to the Depression Indices of the three groups reported by Zung (1965) (Table 6, p.73). For the depression analysis subjects were divided into the following three subgroups: 1) all of the subjects, 2) subjects with relatively low Depression Indices and 3) subjects with relatively high Depression Indices. The three Zung groups consisted of: 1) normal subjects who were free of observable symptoms of depression and who had no history of recent depressive illnesses, 2) individuals who were diagnosed as having depressive disorders and 3) individuals who were initially diagnosed as having depressive disorders but who were later diagnosed as having other psychiatric disorders consisting mainly of anxiety reactions, personality disturbances and psychophysiological disturbances. Unpaired t-tests were used to test for differences in mean Depression Indices between the subject groups and the Zung groups (Chao, 1974).

The results of the Benton Revised Visual Retention Test of the subjects were evaluated for indications of acquired impairment of cognitive functioning. The normative data furnished by Benton (1974) were employed with the premorbid intelligence quotient of each of the subjects estimated to be average, i.e. 95-109 for the correct score and 95-104 for the error score.

The mean scores for the Associate Learning Test of the YG and OG

were compared to the mean scores of two normal groups reported by Wechsler and Stone (1974) using unpaired t-tests (Table 7, p.73). The YG was compared to the Twenties Group which consisted of men and women with an age range of 20-29 years and an intelligence quotient of 102.9 ± 5.46 (mean ± SD). The OG was compared to the Forties Group which consisted of men and women with an age range of 40-49 years and an intelligence quotient of 102.0 ± 6.58 (mean ± SD).

Correlation coefficients were computed using sleep parameters, age, PBB serum level, PBB fat level, Depression Index, Memory Test scores, and Sleep, Pre-Sleep and Post-Sleep Questionnaire Indices. The t-test was used to determine significant correlations (Chao, 1974).

Calculations for all tests were performed on a Texas Instruments (TI-55) electronic calculator.

RESULTS

The results of the study will be presented in four sections: 1) Normal Sleep Comparison, 2) First Night Sleep Adaptation Effects, 3) Neuropsychological Data and 4) Correlation Data.

NORMAL SLEEP COMPARISON

The descriptive data of the groups used in the normal sleep comparison can be found in Table 1, p.40. The means and standard deviations for N2 and N3a sleep variables of the Young Group (YG) and of the Old Group (OG) are reported in Table 2, pp.46-48, and Table 3, pp.49-51, respectively. The N2 and N3a mean values of the YG and OG for sleep efficiency index and percents of the sleep period time (SPT) of stages 0, 1, 2, 3, 4, REM and 3+4 were compared to the values of normal subjects given by Williams et al. (1974). Significant results of the analysis are listed in Table 4, p.52. The mean percents $\pm$ standard deviations of stage 3 and stage 4 of the groups are displayed respectively in Figures 3 and 4, pp.54,55. The principal findings were: 1) the sleep efficiency indices of the YG and OG were not significantly different from those of the normal groups and 2) the percent of stage 4 of the YG was decreased as compared to that of the Thirties Men.

The N2 and N3a mean values of the YG and OG for sleep onset latency, latency to the first REM period, percents of the total sleep time (TST) of stages 3, 4 and REM (TST data not presented), number of stage 3 and stage 4 epochs and eye movement (EM) density were compared to the values of normal subjects reported by Feinberg et al. (1967). Table 4, p.52, indicates the results. The YG, as compared to the Young Normals,

TABLE 2: MEANS AND THEIR STANDARD DEVIATIONS FOR N2 AND N3a SLEEP VARIABLES OF THE YOUNG GROUP

SLEEP VARIABLE		N2 (n=5) MEAN	±SD	N3a (n=5) MEAN	±SD
Sleep Period Time (min.)		466.4	9.2	472.6	2.7
Total Sleep Time (min.)		458.0	9.1	455.8	9.6
Sleep Efficiency Index		.95	.02	.95	.02
Sleep Onset Latency (min.)		8.1	5.4	6.8	3.0
% of SPT	Stage 0	1.8	1.3	3.5	1.8
	1	4.1	1.9	4.8	1.5
	2	58.9	4.3	59.2	3.8
	3	8.1	4.9	6.7	4.2
	4	.2	.4	:2	.5
	REM	26.9	2.8	25.6	4.3
	3+4	8.3	4.9	6.9	4.2
Latency (min.):	Stage 0	113.7	49.1	82.7	66.5
	1	69.0	43.9	61.5	34.0
	3	16.8[W]	5.4	17.3	5.1
	REM	75.3	33.9	64.2	9.8
Movement Density		.14	.03	.19	.05
Body Movement Density		.04	.02	.03	.01
Number of Stage Shifts		79.8	27.0	106.2	37.3
Number of SWS Periods		4.4	1.1	4.4	.9
Number of Sleep Cycles		4.0	1.2	4.0	.7

[W] n=4

TABLE 2 (contd.)

SLEEP VARIABLE		N2 (n=5) MEAN	±SD	N3a (n=5) MEAN	±SD
No. of Stage 3 Epochs (20 sec.)	Cycle 1	66.2	54.3	65.0	50.4
	2	43.6	41.3	28.0	25.3
	3	0.	0.	1.8	4.0
	4	0. [W]	0.	0.	0.
	Entire Night	112.6	68.0	94.8	59.8
No. of Stage 4 Epochs (20 sec.)	Cycle 1	2.4	5.4	0.	0.
	2	0.	0.	3.0	6.7
	3	0.	0.	0.	0.
	4	0. [W]	0.	0. [W]	0.
	Entire Night	2.4	5.4	3.0	6.7
No. of Awakenings (≥40 sec.)	Cycle 1	.600	1.342	.800	1.095
	2	2.000	1.225	3.400	1.817
	3	2.000	1.581	3.600	1.140
	4	1.750[W]	.500	3.250[W]	2.062
	Entire Night	9.000	4.183	15.200	5.630
Average Duration of an Awakening (≥40sec.)(min.)	Cycle 1	.42	.94	.53	.74
	2	1.37	1.12	1.54	.67
	3	1.08	.81	2.37	2.03
	4	2.05[W]	.58	2.57[W]	1.07
	Entire Night	1.92	.80	2.33	.39

[W] n=4

TABLE 2 (contd.)

SLEEP VARIABLE		N2 (n=5) MEAN	±SD	N3a (n=5) MEAN	±SD
Eye Movement Density	Cycle 1	.622	.104	.530	.209
	2	.666	.069	.714	.098
	3	.694	.119	.738	.109
	4	.653[V]	.115	.668[W]	.179
	Entire Night	.680	.059	.702	.073
Duration of a SWS Period (min.)	Cycle 1	74.2	33.6	65.1	13.1
	2	84.1	29.5	80.0	8.6
	3	65.8	12.1	72.7	15.9
	4	53.6[W]	8.7	47.1[W]	7.6
	Night Average	68.4	13.8	66.1	9.6
Duration of a REM Period (min.)	Cycle 1	18.4	10.4	17.3	7.4
	2	33.6	20.2	28.7	11.3
	3	38.1	11.0	31.3	28.2
	4	34.1[V]	12.1	37.8[W]	12.7
	Night Average	31.5	5.6	28.9	9.5
Duration of a Sleep Cycle (min.)	Cycle 1	92.6	39.5	82.4	8.1
	2	117.7	42.2	108.7	11.1
	3	103.1	19.3	104.0	40.5
	4	90.7[V]	11.6	84.9[W]	7.7
	Night Average	103.3	21.9	96.7	18.1

[V] n=3 [W] n=4

TABLE 3: MEANS AND THEIR STANDARD DEVIATIONS FOR N2 AND N3a SLEEP VARIABLES OF THE OLD GROUP

SLEEP VARIABLE		N2 (n=7) MEAN	±SD	N3a (n=5) MEAN	±SD
Sleep Period Time (min.)		456.1	11.4	456.0	16.3
Total Sleep Time (min.)		427.1	26.4	417.4	43.8
Sleep Efficiency Index		.89	.05	.87	.09
Sleep Onset Latency (min.)		14.3	13.4	13.3[z]	7.2
% of SPT	Stage 0	6.4	5.0	8.5	7.8
	1	8.9	3.8	7.5	3.4
	2	61.2	7.4	63.4	8.0
	3	1.9	3.2	2.3	5.0
	4	0.	0.	0.	0.
	REM	21.6	5.0	18.3	3.7
	3+4	1.9	3.2	2.3	5.0
Latency (min.):	Stage 0	155.7	158.9	65.1	30.0
	1	53.5	37.7	40.3	32.2
	3	24.3[v]	1.9	21.5[u]	1.2
	REM	68.8	19.6	66.0	9.4
Movement Density		.16	.05	.15	.06
Body Movement Density		.04	.02	.04	.03
Number of Stage Shifts		101.1	41.0	118.2	43.0
Number of SWS Periods		4.3	1.0	4.6	1.1
Number of Sleep Cycles		3.9	.9	4.2	.8

[u] n=2 [v] n=3 [z] n=7

TABLE 3 (contd.)

SLEEP VARIABLE		N2 (n=7) MEAN	±SD	N3a (n=5) MEAN	±SD
No. of Stage 3 Epochs (20 sec.)	Cycle 1	18.9	36.0	12.6	28.2
	2	5.6	14.7	17.0	38.0
	3	2.3	6.1	0.	0.
	4	0. [X]	0.	0. [W]	0.
	Entire Night	26.7	44.7	29.6	66.2
No. of Stage 4 Epochs (20 sec.)	Cycle 1	0.	0.	0.	0.
	2	0.	0.	0.	0.
	3	0.	0.	0.	0.
	4	0. [X]	0.	0. [W]	0.
	Entire Night	0.	0.	0.	0.
No. of Awakenings (≥40 sec.)	Cycle 1	.714	1.113	.200	.447
	2	2.286	2.059	2.800	.837
	3	1.429	1.718	2.800	1.643
	4	2.400[X]	2.302	3.500[W]	1.732
	Entire Night	8.571	5.094	11.800	3.271
Average Duration of an Awakening (≥40 sec.)(min.)	Cycle 1	1.16	1.54	1.20	2.68
	2	5.21	7.94	3.00	2.24
	3	3.36	3.21	9.42	16.48
	4	1.78[X]	1.64	2.77[W]	1.49
	Entire Night	6.10	3.25	6.75	5.65

[W] n=4 [X] n=5

TABLE 3 (contd.)

SLEEP VARIABLE		N2 (n=7) MEAN	±SD	N3a (n=5) MEAN	±SD
Eye Movement Density	Cycle 1	.559	.159	.584	.103
	2	.773	.051	.712	.158
	3	.670	.107	.776	.086
	4	.795[W]	.157	.915[W]	.044
	Entire Night	.707	.048	.760	.046
Duration of a SWS Period (min.)	Cycle 1	68.8	16.6	64.8	9.8
	2	85.3	29.8	84.3	21.3
	3	67.4	20.3	62.1	14.7
	4	48.3[X]	10.2	54.0[W]	13.8
	Night Average	67.4	14.9	63.8	11.2
Duration of a REM Period (min.)	Cycle 1	18.7	11.1	17.8	10.4
	2	26.5	14.3	13.7	4.7
	3	23.5	11.8	20.5	10.5
	4	21.1[W]	12.3	23.4[W]	4.0
	Night Average	24.0	8.5	18.7	5.3
Duration of a Sleep Cycle (min.)	Cycle 1	87.4	15.9	82.6	18.5
	2	111.8	41.9	97.9	22.6
	3	90.9	27.9	82.6	21.4
	4	69.5[W]	20.0	77.4[W]	11.3
	Night Average	94.1	22.2	83.9	13.6

[W] n=4 [X] n=5

TABLE 4: RESULTS OF COMPARISONS BETWEEN MEAN SLEEP VALUES OF PATIENT GROUPS AND NORMAL GROUPS

SOURCE OF NORMAL GROUP	SLEEP VARIABLE		YOUNG GROUP N2	YOUNG GROUP N3a	OLD GROUP N2	OLD GROUP N3a
Williams et al. (1974)	% Stage 0	a		↑ **		
	% Stage 2	a	↑ θθ	↑ θθ		
	% Stage 3	c			↓ *	
	% Stage 4	a	↓ θθ	↓ θθ		
	% Stage 3+4	a	↓ θθ	↓ θθ	c ↓ *	
	% Stage 4	b	↓ *	↓ *		
Feinberg et al. (1967)	% Stage 3				↓ θθ	↓ θ
	% Stage 4		↓ θθ	↓ θθ	↓ *	↓ *
	Epochs Stage 3				↓ θθ	↓ θ
	Epochs Stage 4		↓ θθ	↓ θθ	↓ *	↓ *
	EM Density			↑ *	↑ θθ	↑ θθ

[a] vs. Twenties Men [b] vs. Thirties Men [c] vs. Forties Men

* $p \leq .05$ ** $p \leq .01$ θ $p \leq .005$ θθ $p \leq .001$

TABLE 4 (contd.)

SOURCE OF NORMAL GROUP	SLEEP VARIABLE		YOUNG GROUP N2	YOUNG GROUP N3a	OLD GROUP N2	OLD GROUP N3a
Feinberg (1974)	Epochs Stage 3	C_1				↓ *
		C_2			↓ θθ	
		C_3	↓ θθ	↓ θ	↓ **	↓ *
	Epochs Stage 4	C_1	↓ **	↓ θ	↓ θ	↓ *
		C_2	↓ *	↓ *	↓ θ	↓ *
	EM Density	C_1	↑ *			
		C_2		↑ *	↑ θ	↑ *
		C_3		↑ *	↑ *	↑ θθ
		C_4			↑ **	↑ θθ
	No. Awakenings	C_2	↑ *	↑ θθ		↑ θθ
		C_3	↑ *	↑ θθ		↑ *
		C_4	↑ *	↑ θ	↑ *	↑ θθ
	A.D.A.	C_1	↓ *	↓ *		
	REMP Duration	C_2				↓ **
		C_3	↑ *			

* $p \leq .05$ ** $p \leq .01$ θ $p \leq .005$ θθ $p \leq .001$

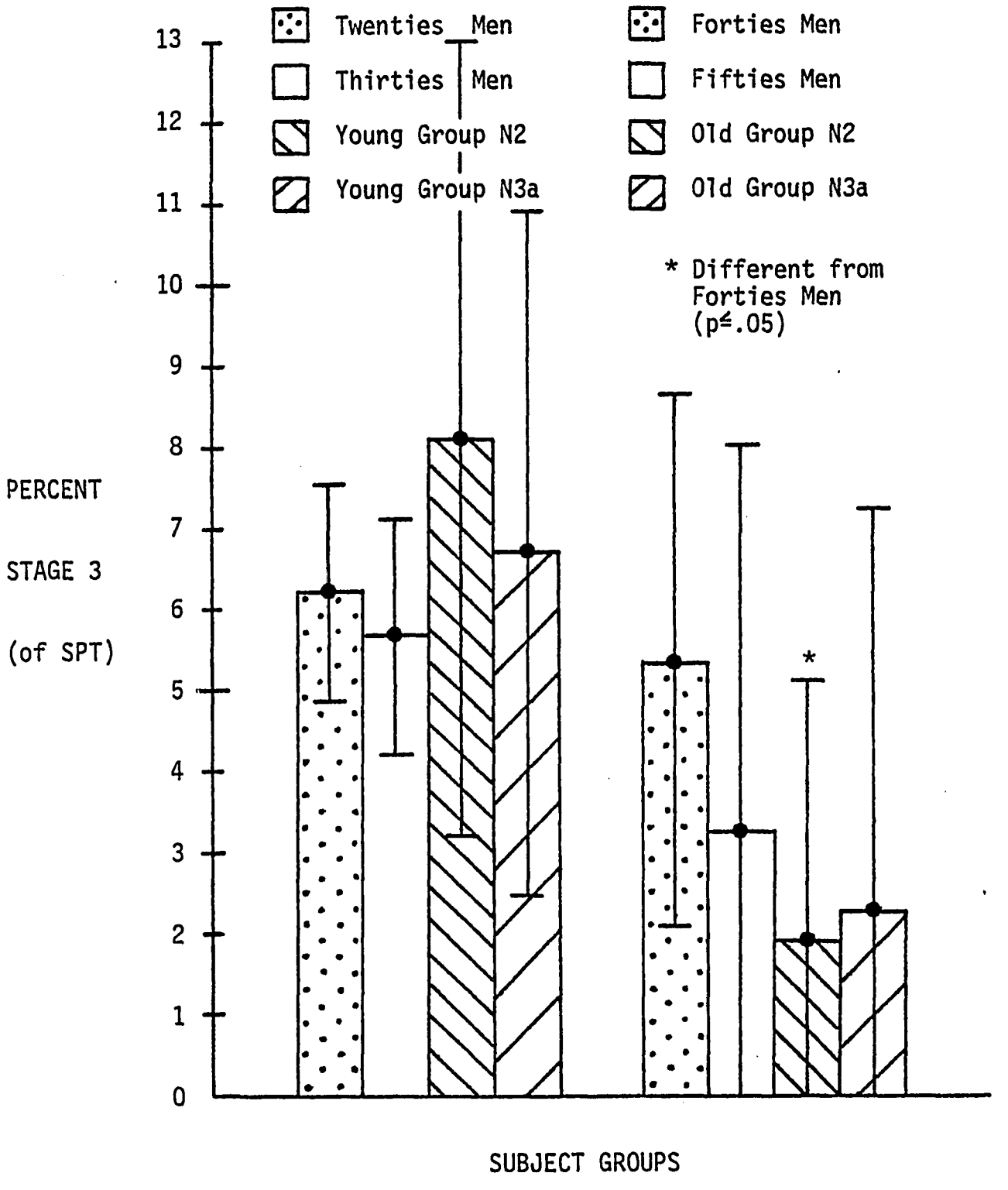


Figure 3: MEAN PERCENT STAGE 3 OF TWENTIES MEN, THIRTIES MEN, YOUNG GROUP, FORTIES MEN, FIFTIES MEN AND OLD GROUP (± standard deviation)

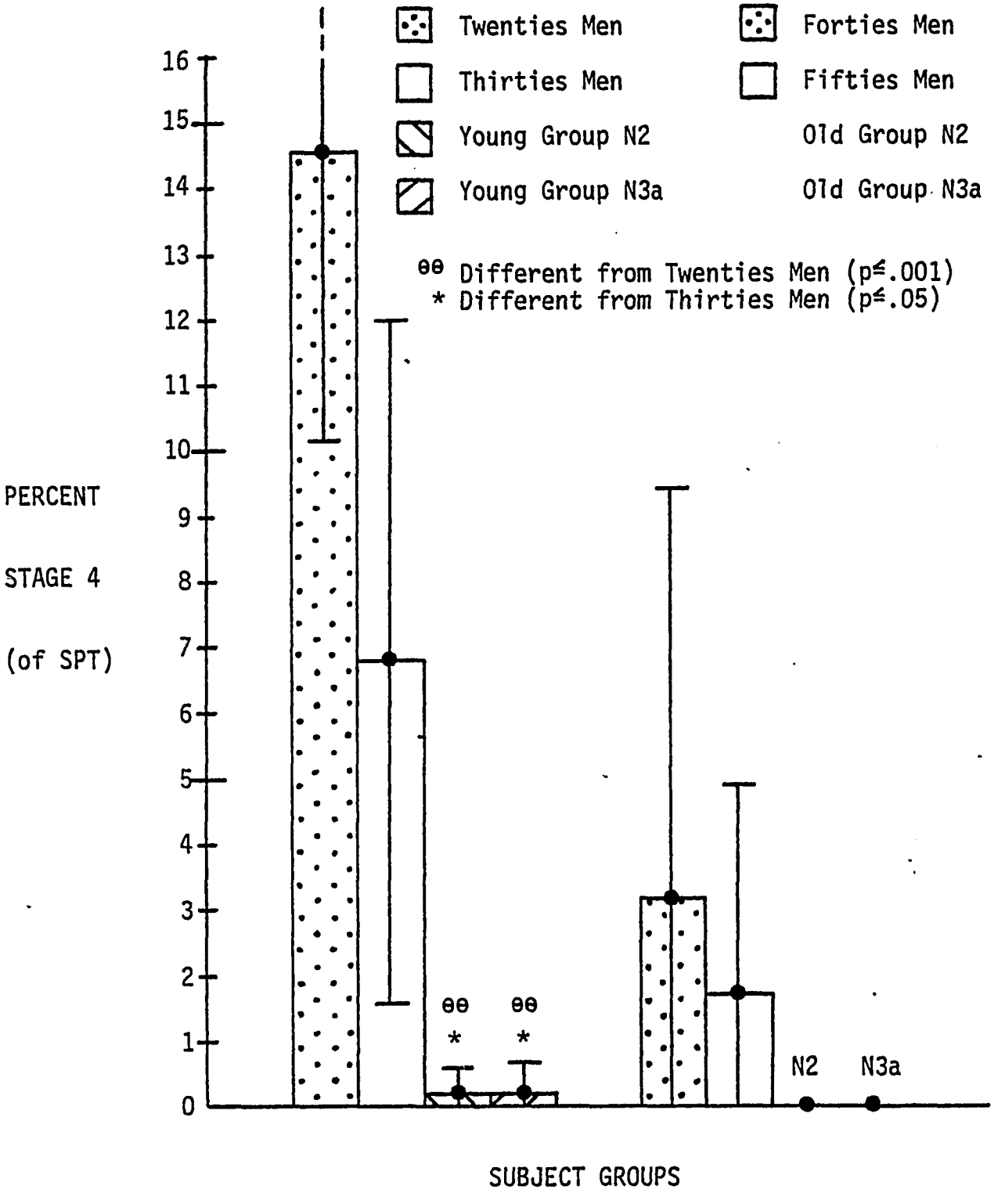


Figure 4: MEAN PERCENT STAGE 4 OF TWENTIES MEN, THIRTIES MEN, YOUNG GROUP, FORTIES MEN, FIFTIES MEN AND OLD GROUP (± standard deviation)

showed a decreased amount and percent of stage 4 and an increased EM density. The OG, as compared to the Aged Normals, had decreased amounts and percents of both stage 3 and stage 4 and an increased EM density. The mean percents ± standard deviations of stage 3 and stage 4 and the mean EM density ± standard deviation of the groups are displayed respectively in Figures 5, 6 and 7, pp.57-59.

The N2 and N3a sleep cycle mean values of the YG and OG for number of stage 3 and stage 4 epochs (cycles 1-3), number of awakenings (cycles 1-4), average duration of an awakening (A.D.A.) (cycles 1-4), EM density (cycles 1-4), slow wave sleep (SWS) period duration (cycles 1-4) and REM period duration (REMP D.) (cycles 1-4) were compared to the values of the normal subjects given by Feinberg (1974). Only completed sleep cycles were used in the analysis. The results are listed in Table 4, p.53. The YG, as compared to Group 4, had decreased amounts of stage 3 for the third sleep cycle (SC_3) of N2 and N3a and stage 4 for SC_2 and SC_3 of N2 and N3a, and an increased EM density for SC_1 of N2 and SC_2 and SC_3 of N3a, an increased number of awakenings for SC_2, SC_3 and SC_4 of N2 and N3a, an increased REM period duration for SC_3 if N2 and a decreased average duration of an awakening for SC_1 of N2 and N3a. The OG, as compared to Group 5, showed decreased amounts of stage 3 for SC_1 of N3a, SC_2 of N2 and SC_3 of N2 and N3a and stage 4 for SC_1 and SC_2 of N2 and N3a, and an increased EM density for SC_2, SC_3 and SC_4 of N2 and N3a, an increased number of awakenings for SC_2 and SC_3 of N3a and SC_4 of N2 and N3a, and a decreased REM period duration for $SC_2$of N3a. Figures 8-15, pp.60-67, display the comparisons of the sleep cycle mean values ± standard deviations of the YG with Group 4 and the OG with Group 5 for number of stage 3 epochs and

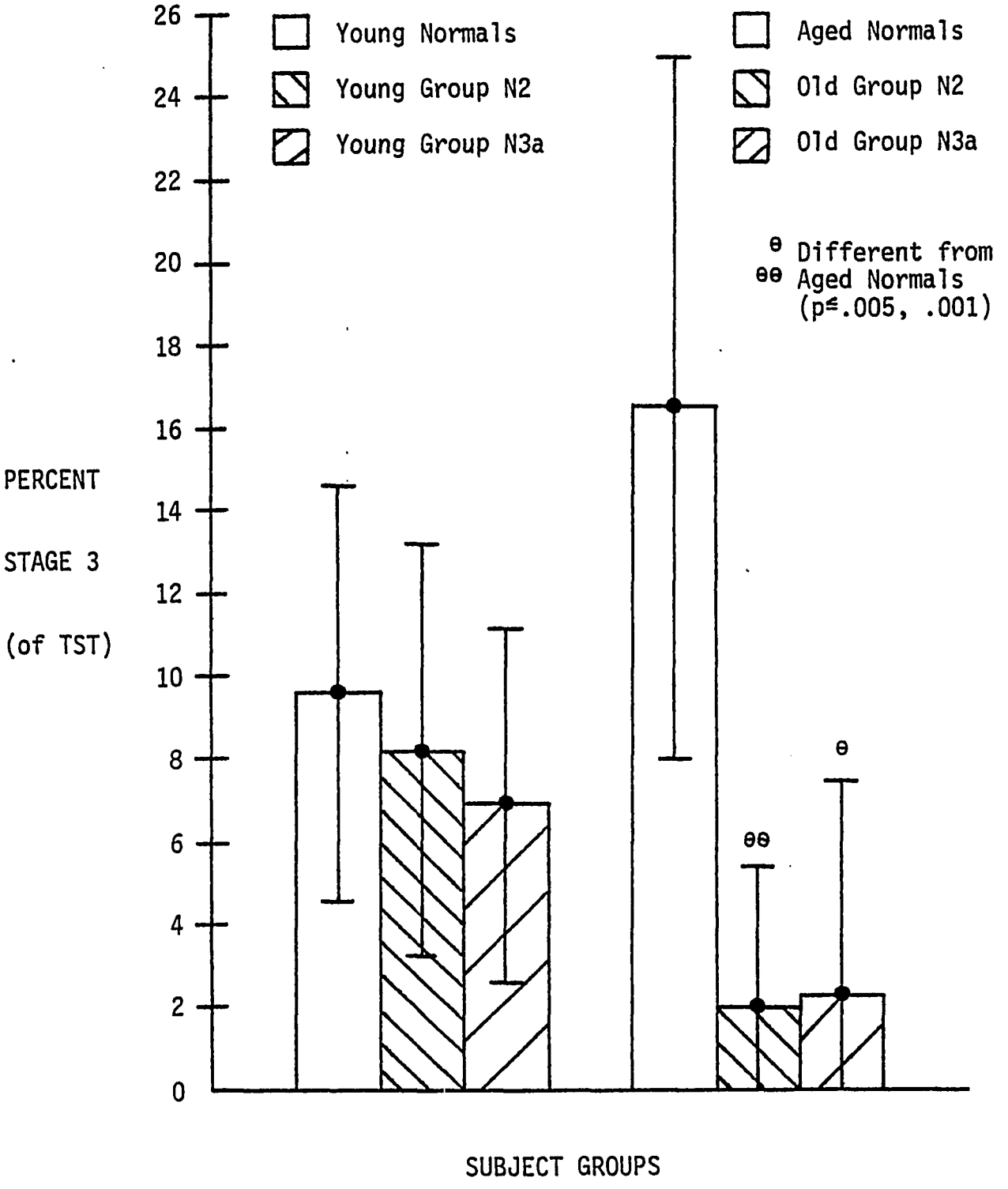


Figure 5: MEAN PERCENT STAGE 3 OF THE YOUNG NORMALS, YOUNG GROUP, AGED NORMALS AND OLD GROUP (± standard deviation)

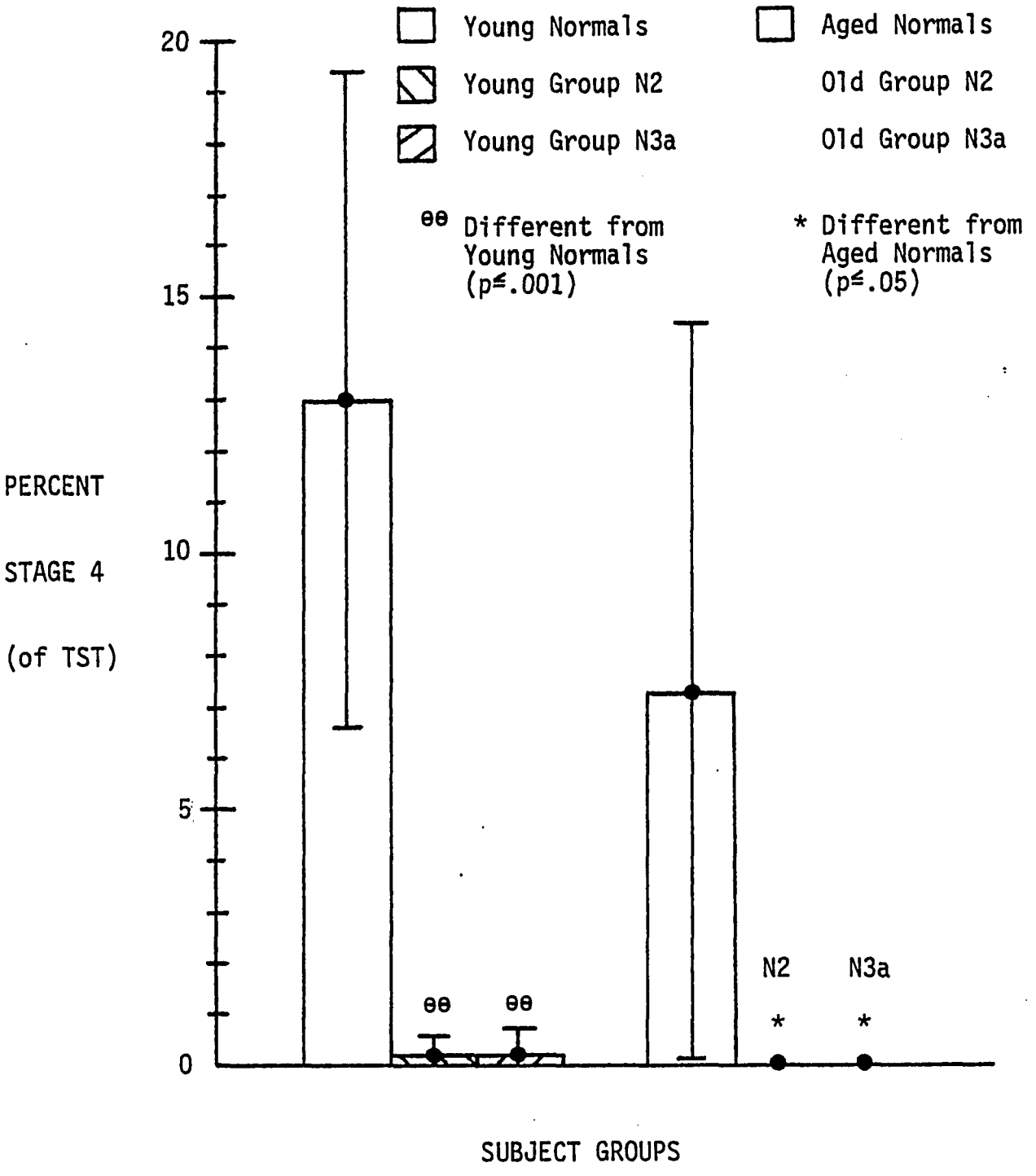


Figure 6: MEAN PERCENT STAGE 4 OF THE YOUNG NORMALS, YOUNG GROUP, AGED NORMALS AND OLD GROUP (± standard deviation)

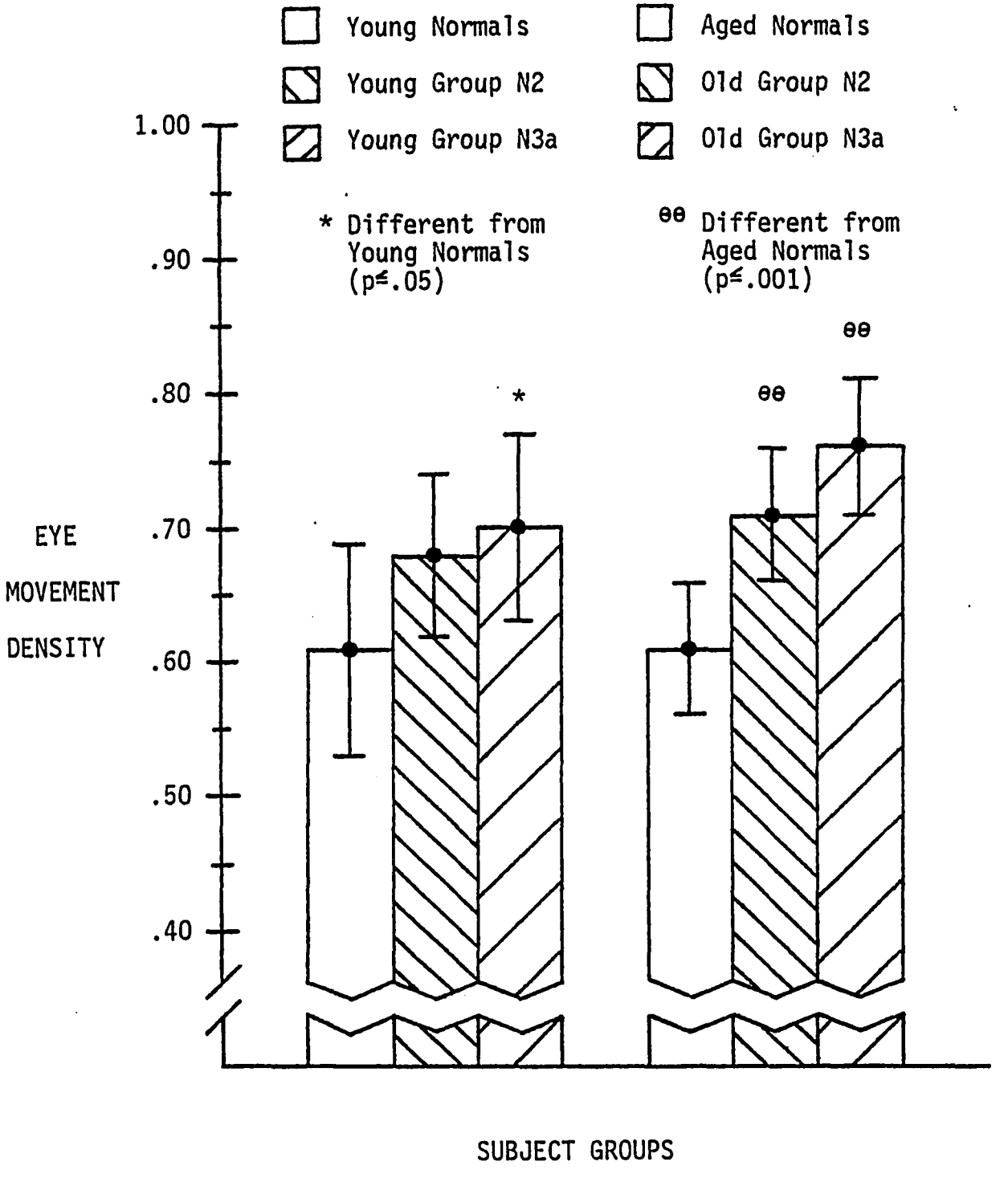


Figure 7: MEAN EYE MOVEMENT DENSITY OF THE YOUNG NORMALS, YOUNG GROUP, AGED NORMALS AND OLD GROUP (± standard deviation)

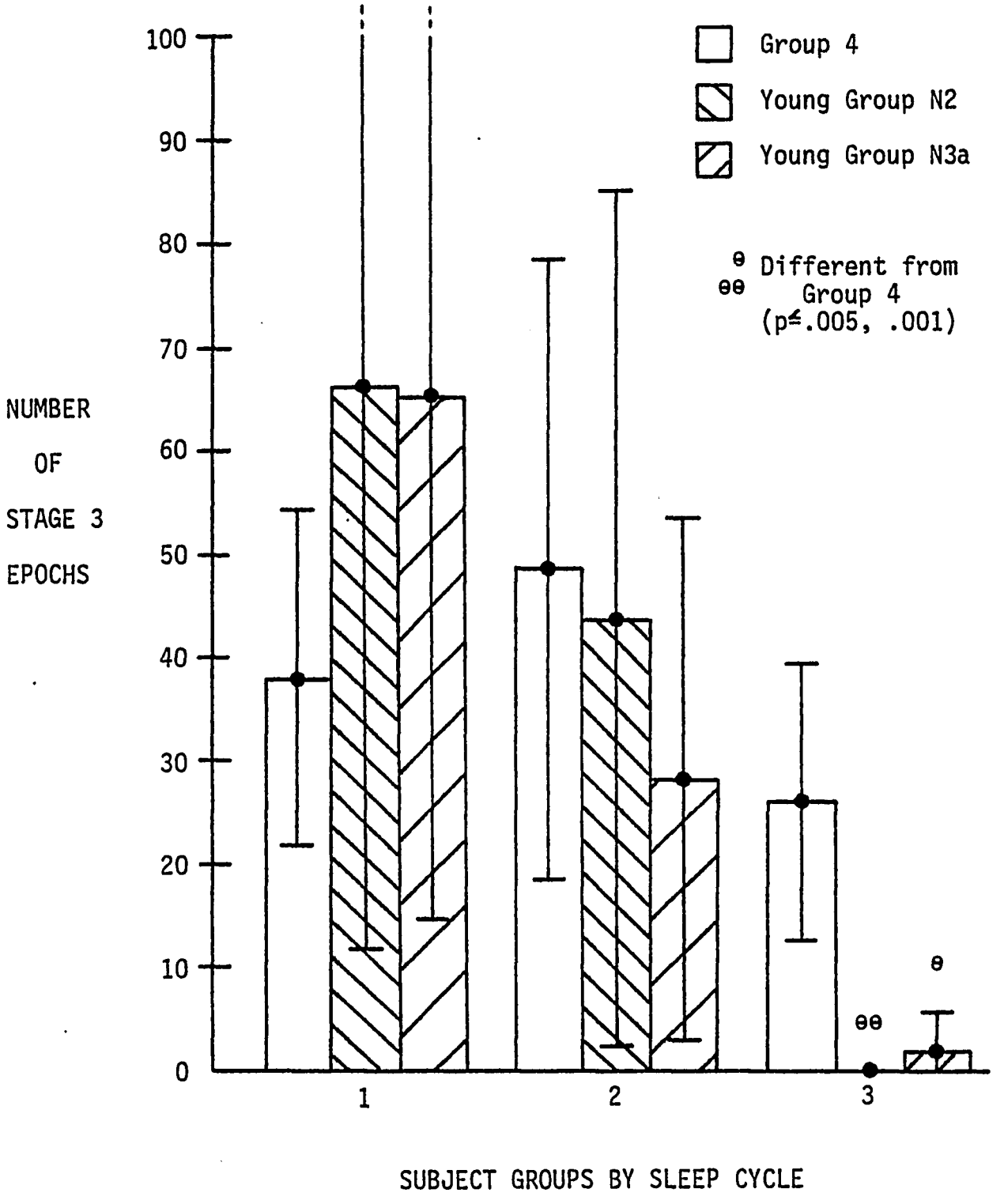


Figure 8: MEAN NUMBER OF STAGE 3 EPOCHS OF GROUP 4 AND YOUNG GROUP BY SLEEP CYCLE (± standard deviation)

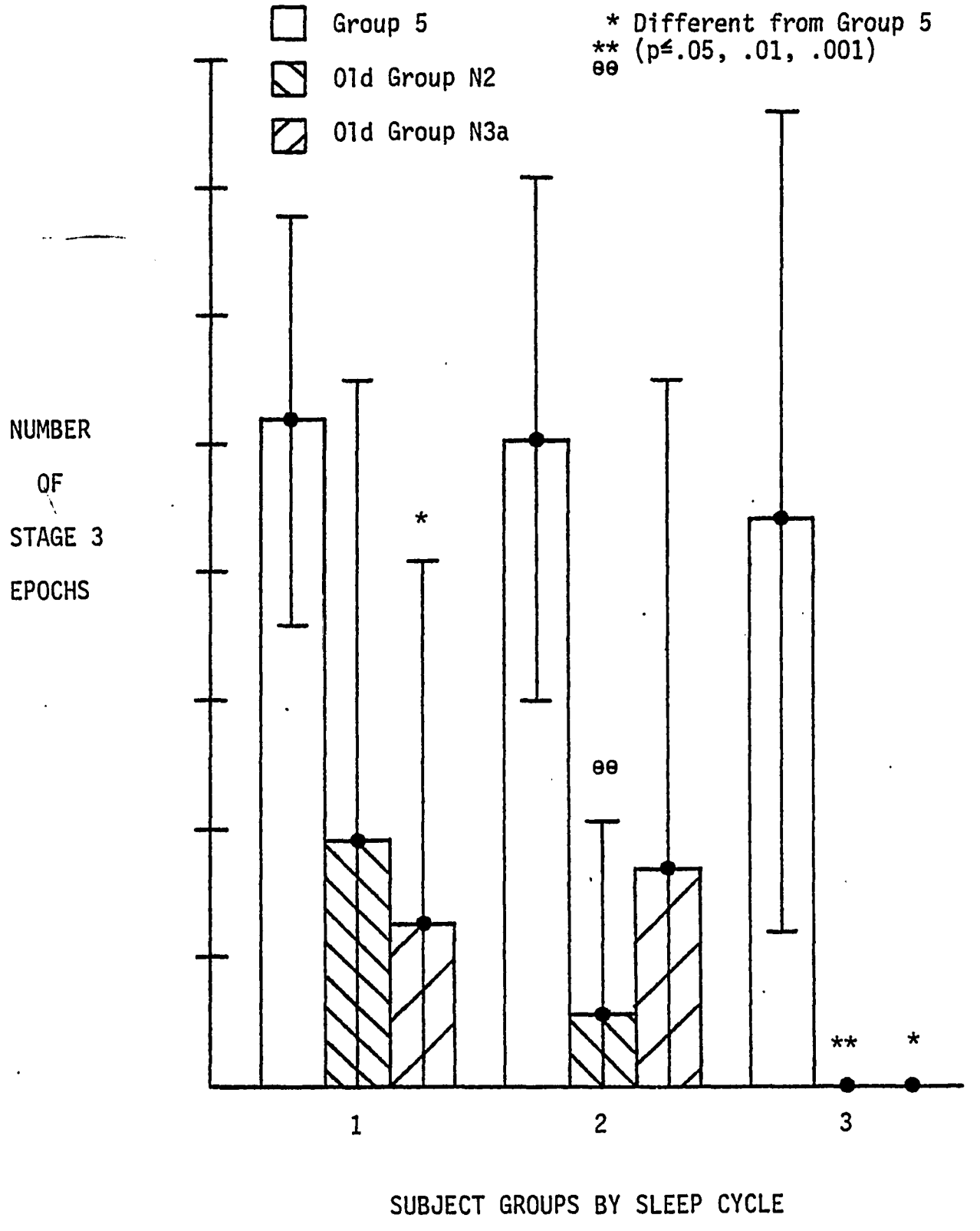


Figure 9: MEAN NUMBER OF STAGE 3 EPOCHS OF GROUP 5 AND OLD GROUP BY SLEEP CYCLE (± standard deviation)

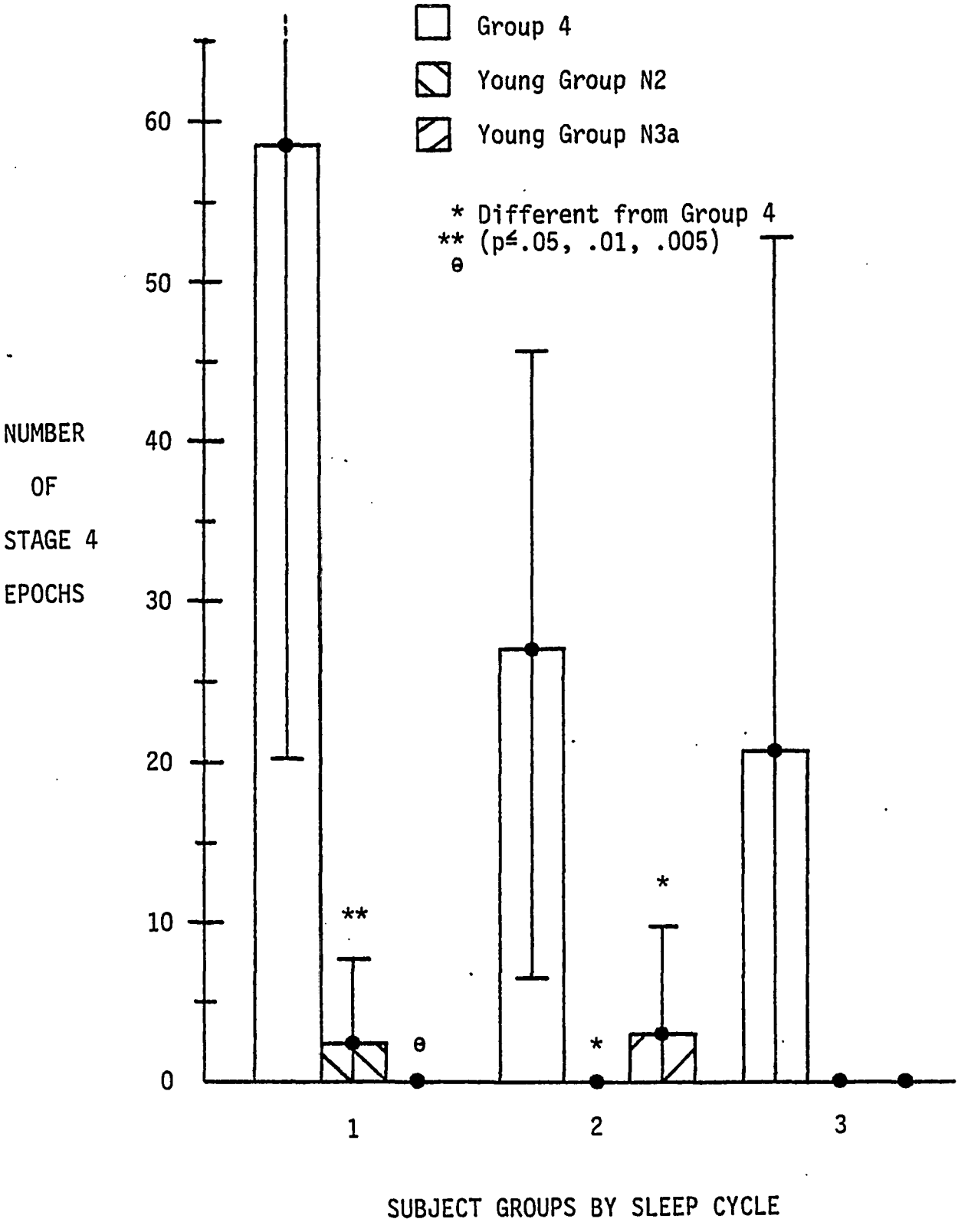


Figure 10: MEAN NUMBER OF STAGE 4 EPOCHS OF GROUP 4 AND YOUNG GROUP BY SLEEP CYCLE (± standard deviation)

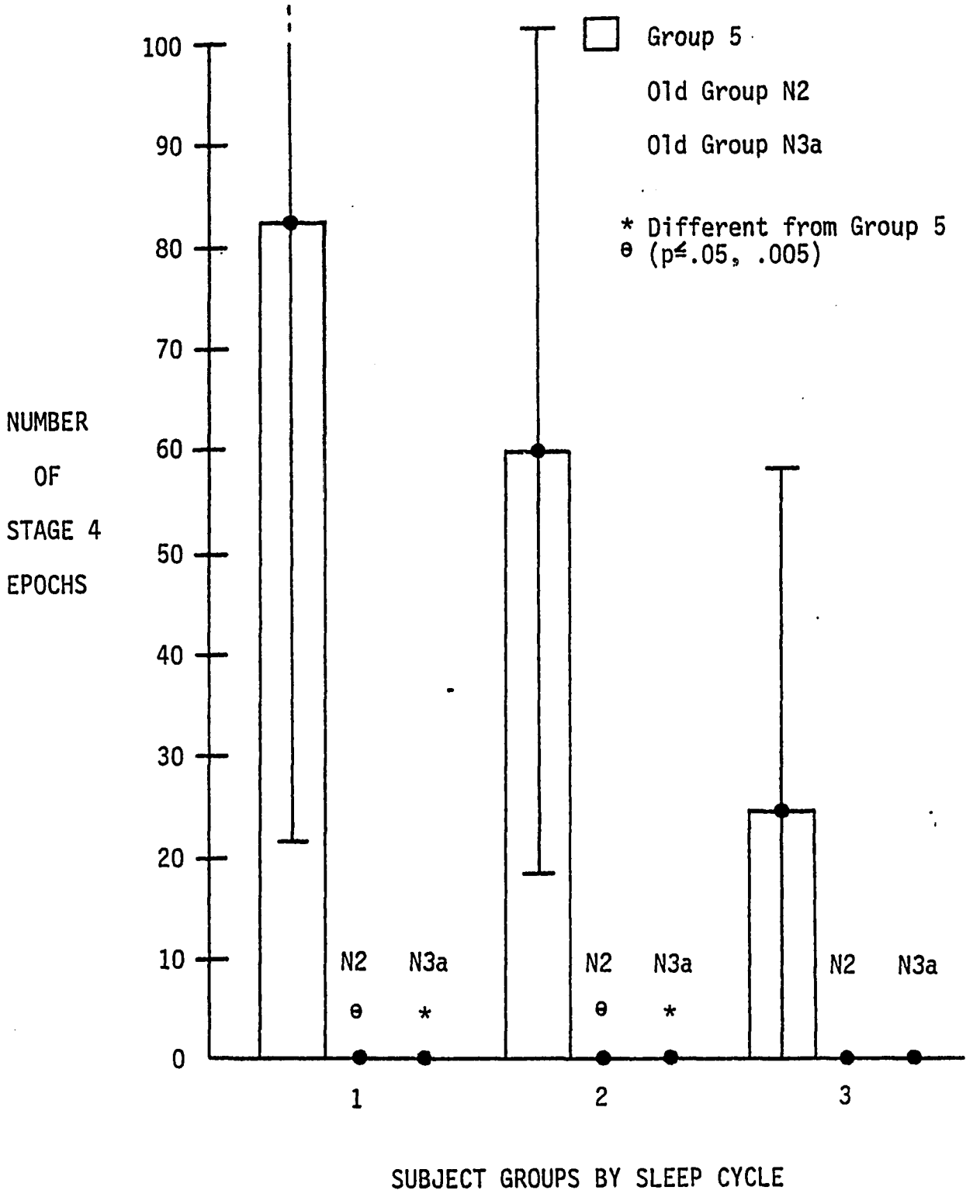


Figure 11: MEAN NUMBER OF STAGE 4 EPOCHS OF GROUP 5 AND OLD GROUP BY SLEEP CYCLE (± standard deviation)

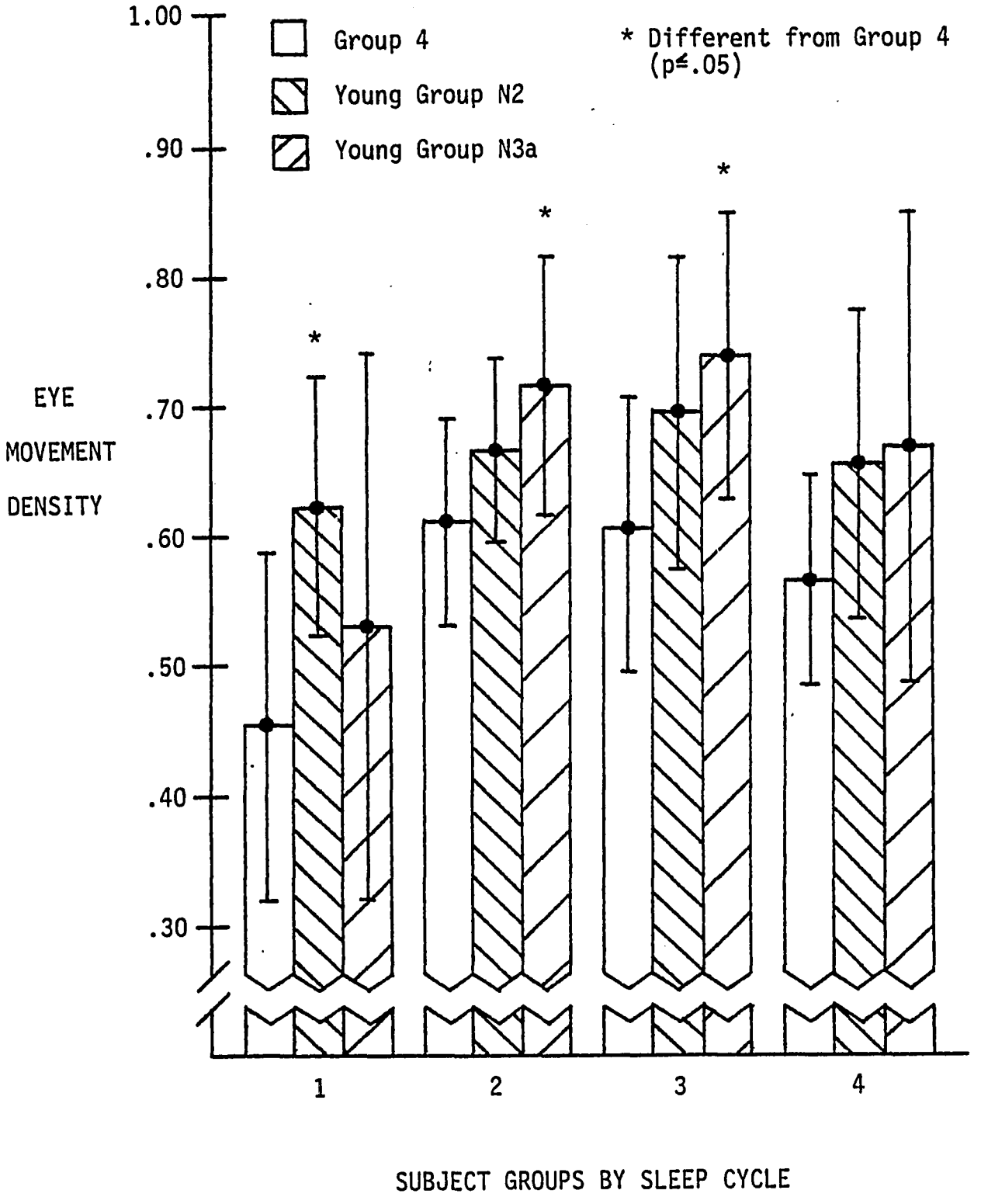


Figure 12: MEAN EYE MOVEMENT DENSITY OF GROUP 4 AND YOUNG GROUP BY SLEEP CYCLE (± standard deviation)

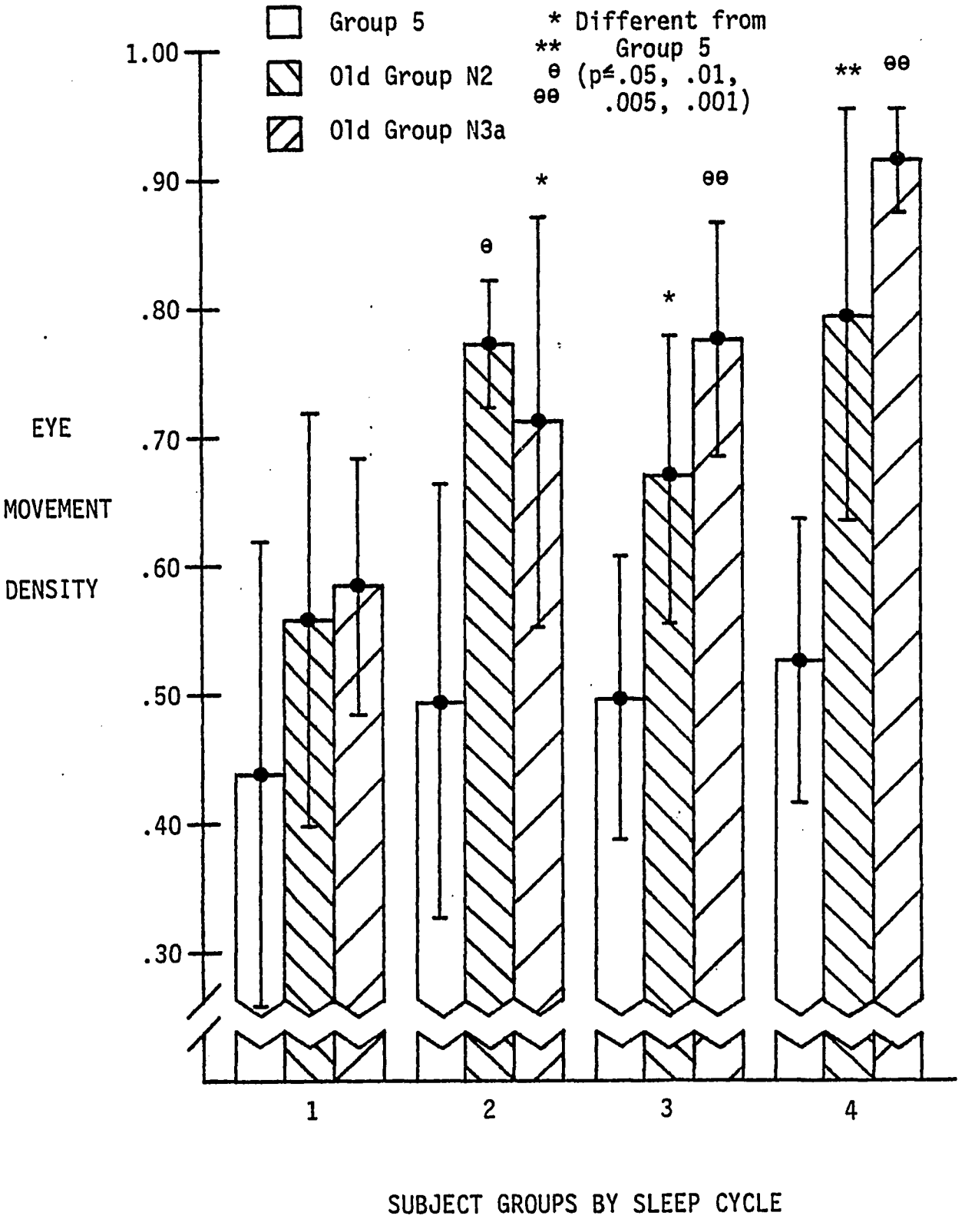


Figure 13: MEAN EYE MOVEMENT DENSITY OF GROUP 5 AND OLD GROUP BY SLEEP CYCLE (± standard deviation)

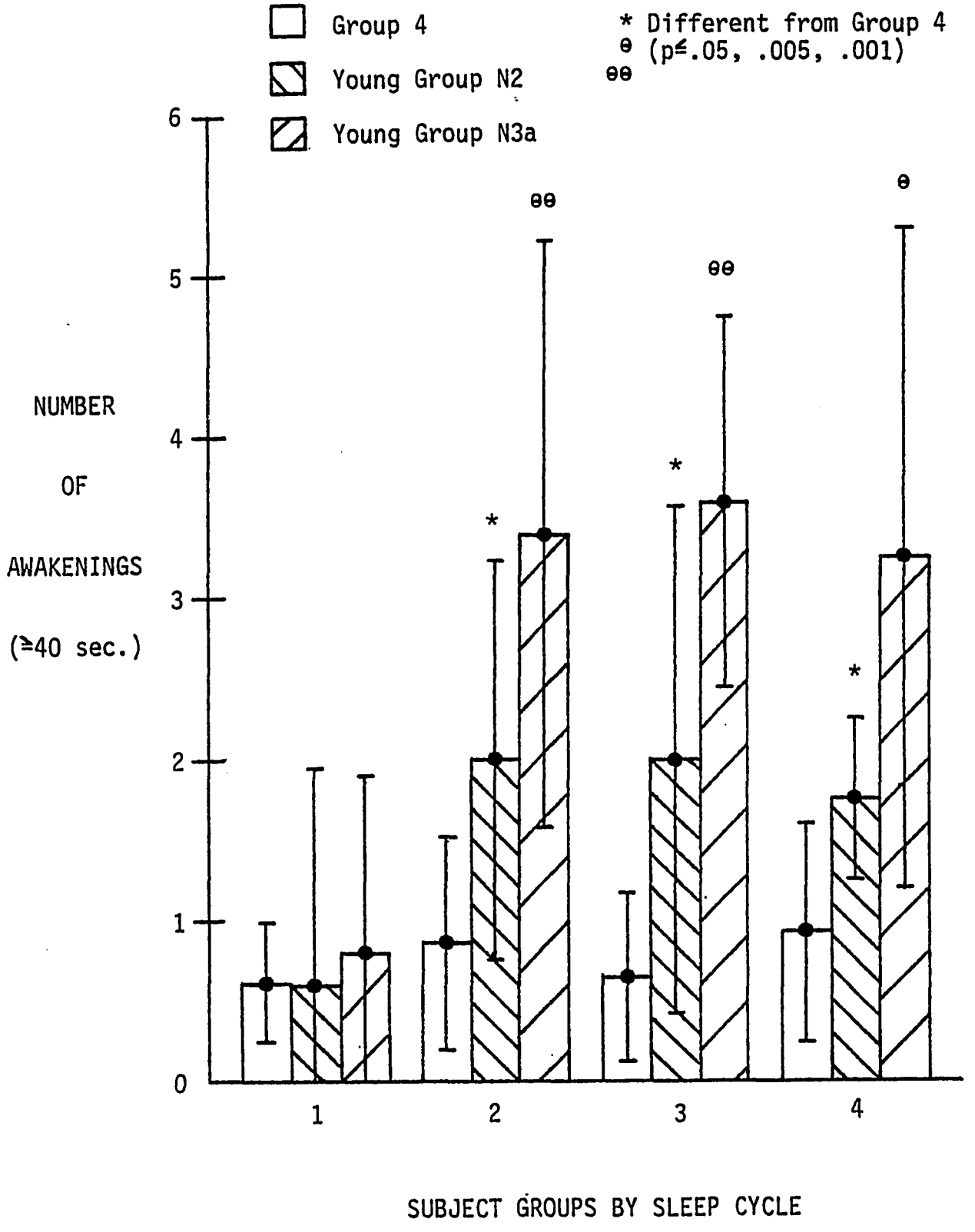


Figure 14: MEAN NUMBER OF AWAKENINGS OF GROUP 4 AND YOUNG GROUP BY SLEEP CYCLE (± standard deviation)

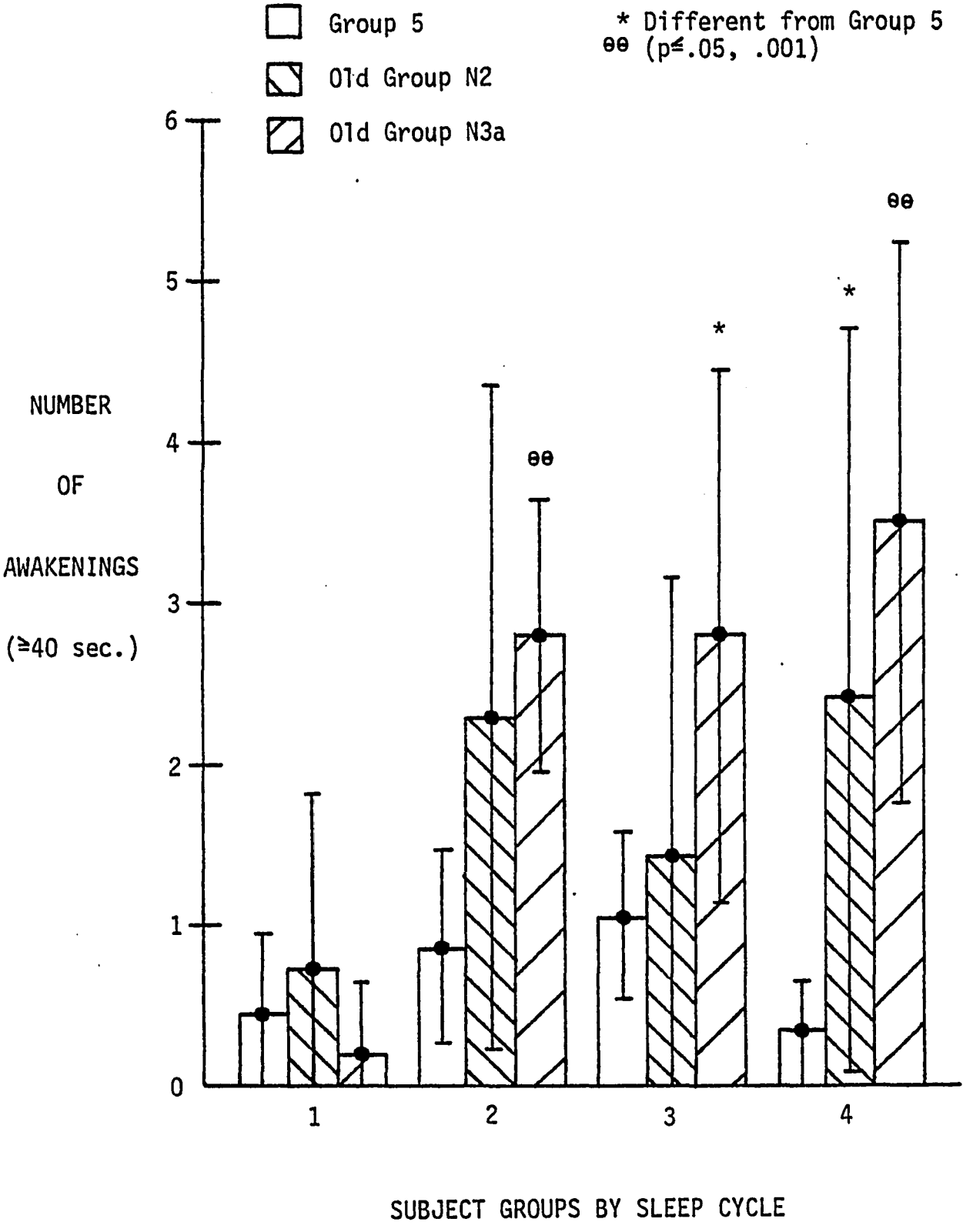


Figure 15: MEAN NUMBER OF AWAKENINGS OF GROUP 5 AND OLD GROUP BY SLEEP CYCLE (± standard deviation)

stage 4 epochs, EM density and number of awakenings.

Awakenings during the SPT were analyzed and were found to occur almost exclusively during stage 2 and stage REM as compared to stage 3 and stage 4 (data not presented). For the YG and OG the one significant difference between the mean percents of awakenings for stage 2 and stage REM for N1, N2, N3a and N3b was a higher percent of awakenings for stage 2 on N3b ($p \leq .05$) for the YG.

Sleep abnormalities associated with narcolepsy or the sleep apnea syndrome were not discovered. Subjects did not exhibit any abnormal sequencing of sleep stages; sleep onset REM periods were not observed for any of the thirty-six sleep records. Sleep apnea episodes were not demonstrated for any subjects by the respiration records.

As revealed by the comparison with normal sleep, the sleep profile of the subjects consisted primarily of an increase in number of awakenings and EM density of REM sleep and a decrease in amount and percent of stage 4 and, for older subjects, in amount and percent of stage 3.

FIRST NIGHT SLEEP ADAPTATION EFFECTS

The sleep variables employed to investigate the first night sleep adaptation effects are listed in Table 5, pp.69-70, and are accompanied by the testing results. No significant differences between the mean values of any sleep variable for N1-N2 or N1-N3a comparisons were found.

NEUROPSYCHOLOGICAL DATA

The distribution of the Depression Indices of the subjects was bimodal as is shown in Figure 16, p.71. Because of the bimodality, the subject group was divided into subgroups of low and high Depression In-

TABLE 5: RESULTS OF TESTING FOR FIRST NIGHT SLEEP ADAPTATION EFFECTS

SLEEP VARIABLE		T-VALUE[o] N1-N2 (df=11)	N1-N3a (df=9)
Total Sleep Time		-1.052	- .893
Sleep Efficiency Index		-1.048	- .814
Sleep Onset Latency		.512	1.302[s]
% of SPT:	Stage 0	1.198	.708
	1	- .236	.049
	2	- .137	- .397
	3	-1.178	- .385
	REM	-1.248	- .622
	3+4	- .184	- .094
Minutes:	Stage 0	1.184	.738
	1	- .251	- .019
	2	- .121	- .466
	3	-1.145	- .393
	REM	-1.208	- .719
	3+4	.170	.109
Latency:	Stage 0	-1.537	- .686
	1	-1.812	- .332
	3	.822[r]	.838[r]
	REM	.849	1.743

[o] $t_{(11,.05)} = \pm 2.201$ $t_{(9,.05)} = \pm 2.262$ $t_{(6,.05)} = \pm 2.447$

[r] df=6 [s] df=11

TABLE 5 (contd.)

SLEEP VARIABLE	T-VALUE[o] N1-N2 (df=11)	N1-N3a (df=9)
Movement Density	.602	- .701
Body Movement Density	-1.281	-1.032
Number of Stage Shifts	.328	- .521
Number of Awakenings (≥20 sec.)	.918	- .619
Ave. Dur. of an Awakening (≥20 sec.)	.446	- .197
Eye Movement Density	- .603	-1.333
Ave. Duration of a SWS Period	-1.549	- .617
Ave. Duration of a REM Period	-1.534	- .535
Ave. Duration of a Sleep Cycle	-1.934	- .475
Number of SWS Periods	.770	0.
Number of Sleep Cycles	.600	0.
Pre-Sleep Index	.838	1.451[s]
Post-Sleep Index	-1.258	-1.534

[o] $t_{(11,.05)} = \pm 2.201$ $t_{(9,.05)} = \pm 2.262$

[s] df=11

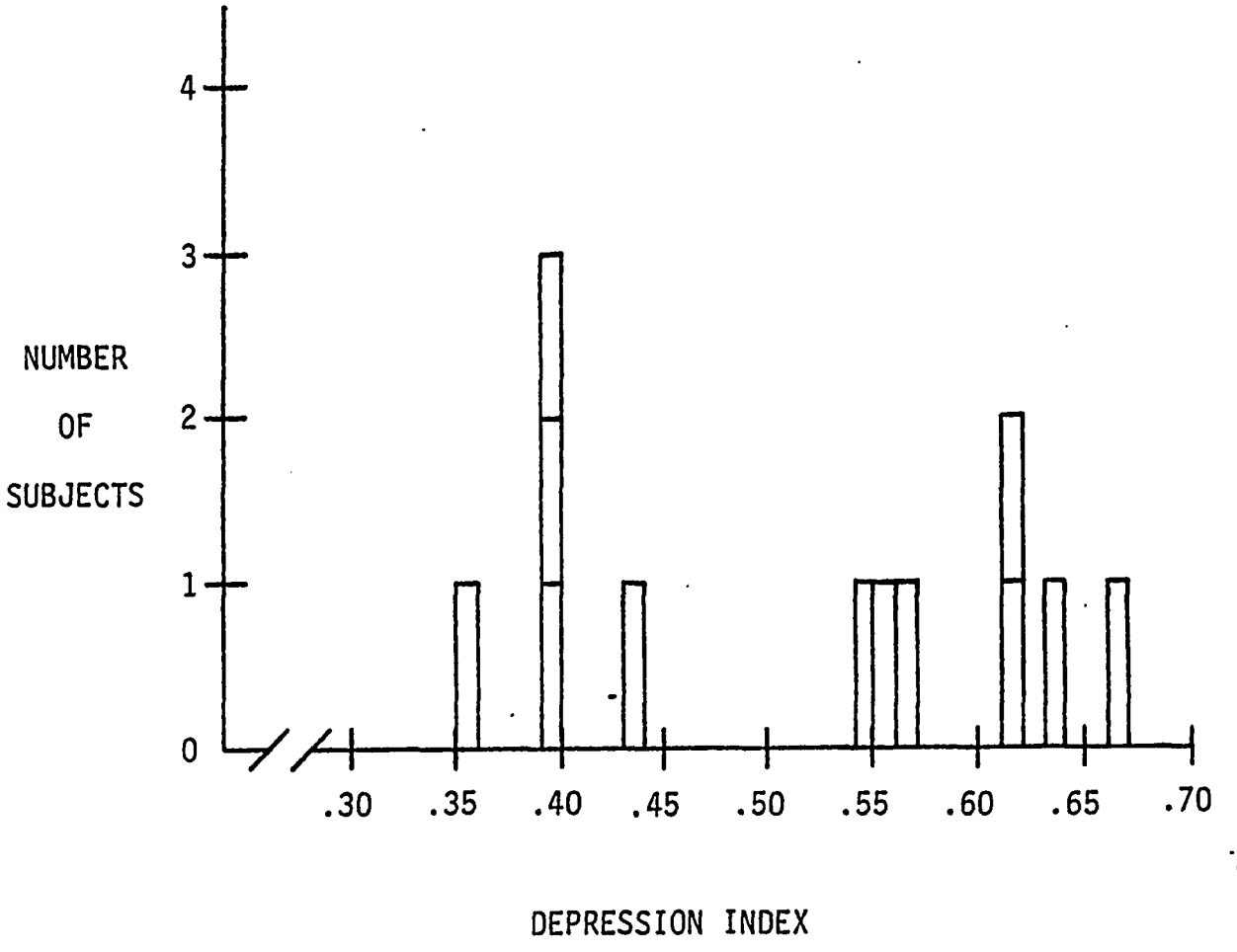


Figure 16: DISTRIBUTION OF THE DEPRESSION INDICES OF THE SUBJECTS

dices. The means and standard deviations for the Depression Indices of the groups used in the depression analysis are listed in Table 6, p.73. The results of the depression analysis comparing the mean Depression Indices between subject groups and Zung groups are as follows. The mean index of the All Subjects Group was significantly higher than that of the Normals ($p \leq .001$), lower than that of the Depressives ($p \leq .001$) and not different from that of the Others. The mean index of the Low Depression Index Subjects Group was significantly higher than that of the Normals ($p \leq .01$) and lower than that of the Depressives ($p \leq .001$), Others ($p \leq .001$) and High Depression Index Subjects Group ($p \leq .001$). The mean index of the High Depression Index Subjects Group was significantly higher than that of the Normals ($p \leq .001$), lower than that of the Depressives ($p \leq .001$) and not different from that of the Others.

The correct and error scores for the Benton Revised Visual Retention Test of the subjects are listed in Table 9, p.76. Three subjects (#5,8,10) showed a "strong indication" of, one (#12) showed a "suggestion" of and one (#4) had the "question raised" of acquired impairment of cognitive functioning as indicated by both their correct and error scores. Three other subjects had the "question raised" of acquired impairment based for two (#3,6) on their correct scores and for one (#11) on his error score. A total of eight out of the twelve subjects, sixty-seven percent, showed some indication of acquired impairment of cognitive functioning.

The mean Associate Learning Test scores of the YG and OG were compared to the Twenties Group and Forties Group, respectively (Table 7, p.73). For both comparisons no significant difference between the means were found.

TABLE 6: MEANS AND THEIR STANDARD DEVIATIONS FOR DEPRESSION INDICES OF SUBJECT GROUPS AND ZUNG GROUPS

GROUP		TOTAL NUMBER	DEPRESSION INDEX MEAN	±SD
All Subjects	[1]	12	.51	.11
Low Depression Index Subjects	[1]	5	.39	.03
High Depression Index Subjects	[1]	7	.59	.05
Normals	[2]	100	.33	.05
Depressives	[2]	31	.74	.08
Others	[2]	25	.53	.08

[1] Subjects of present study

[2] Zung, 1965

TABLE 7: MEANS AND THEIR STANDARD DEVIATIONS FOR ASSOCIATE LEARNING TEST SCORES OF SUBJECT GROUPS AND WECHSLER AND STONE GROUPS

GROUP		TOTAL NUMBER	ASSOC. LEARN. SCORE MEAN	±SD
Young	[1]	5	15.30	4.19
Old	[1]	7	13.00	3.95
Twenties	[2]	50	15.72	2.81
Forties	[2]	46	13.91	3.12

[1] Subjects of present study

[2] Wechsler and Stone, 1974

CORRELATION DATA

Tables 8 and 9, pp.75,76, present the subjects' age, fat and serum levels of PBBs, Sleep Index, Depression Index and Memory Test scores. The fat HBB_6 ('76) and serum HBB_6 ('76) levels are from the November, 1976 Michigan PBB Health Survey (Selikoff et al., 1976), while the serum HBB_6 ('79), serum 2,3,4,2',4',5'-hexabromobiphenyl (E) and serum 2,4,5,3',4',5'-hexabromobiphenyl (F) levels are from the present study. The serum HBB_6 ('79) levels of the subjects ranged from 0.4 to 32.4 parts-per-billion (ppb) with a mean ± standard deviation of 6.2 ± 8.7 ppb and a median of 4.3 ppb.

The serum HBB_6 ('79) levels, fat HBB_6 ('76) levels, ages, Sleep Indices and Depression Indices were tested for correlation with the levels of all PBBs, all sleep variables (data not presented), ages, Sleep Indices, Depression Indices, Memory Test scores, and Pre-Sleep and Post-Sleep Indices (data not presented). The levels of serum HBB_6 ('76), serum E and serum F were tested for correlation with the variables listed above with the exception of some of the sleep variables. The Pre-Sleep and Post-Sleep Indices were tested for correlation with all sleep variables using N1-N1, N2-N2 and N3-N3a and N3b correlation tests. The Memory Test scores were tested for correlation with the amount and percent of stage 0 and the number of awakenings.

Table 10, pp.77-78, lists the correlations between the levels of PBBs and the sleep study variables. The levels of fat HBB_6 ('76), serum HBB_6 ('76), serum HBB_6 ('79), serum E and serum F were all intercorrelated ($p \leq .001$). The correlations for serum HBB_6 ('79) will be reported in the text but for the correlations for the other PBBs see Table 10.

TABLE 8: AGES, PBB LEVELS, AND SLEEP AND DEPRESSION INDICES OF THE SUBJECTS

SUBJECT NUMBER	AGE (years)	1976 LEVEL[1] FAT HBB_6 (ppm)	1976 LEVEL[1] SERUM HBB_6 (ppb)	1979 LEVEL SERUM HBB_6 (ppb)	1979 LEVEL SERUM E^2 (ppb)	1979 LEVEL SERUM F^3 (ppb)	SLEEP INDEX	DEPRESS. INDEX
1	23.1	2.25	17.7	8.4	1.4	.7	.81	.56
2	28.1	tnp	1.0	1.1	.4	.1	.70	.39
3	29.3	tnp	1.1	.4	0.	0.	.81	.61
4	33.8	1.63	5.1	5.3	1.3	.8	.81	.63
5	35.4	tnp	13.3	5.7	1.3	1.1	.74	.39
6	44.6	tnp	4.2	3.3	.4	.5	.78	.35
7	45.3	.69	2.9	2.9	.5	.3	.78	.55
8	46.8	.33	2.5	1.4	.7	.4	.78	.61
9	49.6	2.54	7.8	6.3	.7	.6	.74	.39
10	53.1	1.60	6.8	6.8	1.7	.4	.85	.54
11	54.6	.11	.6	.7	0.	0.	.89	.66
12	57.5	8.44	28.8	32.4	4.5	1.6	.85	.43

[1] Selikoff et al., 1976
[2] E = 2,3,4,2',4',5'-Hexabromobiphenyl
[3] F = 2,4,5,3',4',5'-Hexabromobiphenyl

tnp = test not performed

TABLE 9: MATTIS SENTENCE, BENTON, ASSOCIATE LEARNING AND MATTIS-KOVNER VALUES OF THE SUBJECTS

SUBJECT NUMBER	MATTIS SENT. SCORE	BENTON CORRECT SCORE	BENTON ERROR SCORE	ASSOC. LEARN. SCORE	MATTIS-KOVNER d' TRIAL ONE	TWO	THREE	FOUR
1	3.0	9	1	20.5	2.486	1.348	1.226	1.161
2	4.0	8	5	18.5	3.241	1.877	1.682	1.710
3	4.0	6	4	13.5	2.317	2.345	2.801	2.634
4	2.0	6	6	10.0	1.805	1.421	.911	1.048
5	2.5	3	9	14.0	3.605	1.028	.128	.250
6	3.5	5	6	20.0	2.996	1.710	1.365	2.169
7	4.0	6	6	14.0	2.484	2.085	1.281	1.710
8	0.	0	17	12.0	2.562	2.317	1.877	2.122
9	0.	6	6	11.5	2.486	1.710	.260	2.085
10	2.5	2	10	10.0	1.198	1.560	1.710	1.048
11	4.0	5	8	15.5	2.562	2.681	2.317	2.122
12	3.5	3	9	8.0	1.515	1.198	2.030	.909

TABLE 10: CORRELATION COEFFICIENTS FOR PBB LEVELS AND SLEEP STUDY VARIABLES OF THE SUBJECTS

SLEEP STUDY VARIABLE		1976 LEVEL FAT[a] HBB_6	1976 LEVEL SERUM[b] HBB_6	1979 LEVEL SERUM[b] HBB_6	1979 LEVEL SERUM[b] E	1979 LEVEL SERUM[b] F
Serum HBB_6 ('76)		$.930^{\theta\theta}$	--	--	--	--
Serum HBB_6 ('79)		$.992^{\theta\theta}$	$.915^{\theta\theta}$	--	--	--
Serum E		$.950^{\theta\theta}$	$.904^{\theta\theta}$	$.967^{\theta\theta}$	--	--
Serum F		$.937^{\theta\theta}$	$.881^{\theta\theta}$	$.828^{\theta\theta}$	$.870^{\theta\theta}$	--
SPT	N1	-.806*	-.625*	-.715**	-.736**	$-.797^{\theta}$
	N3b	-.898**	$-.826^{\theta\theta}$	-.778**	-.765*	$-.909^{\theta\theta}$
TST	N2	-.769*	-.494	-.704*	-.656*	-.547
	N3a	-.851*	-.682*	$-.880^{\theta\theta}$	$-.843^{\theta}$	-.679*
	N3b	$-.965^{\theta\theta}$	$-.921^{\theta\theta}$	$-.925^{\theta\theta}$	$-.939^{\theta\theta}$	$-.958^{\theta\theta}$
SEI	N2	-.754*	-.489	-.698*	-.651*	-.553
	N3a	-.853*	-.679*	$-.876^{\theta\theta}$	$-.842^{\theta}$	-.683*
	N3b	$-.962^{\theta\theta}$	$-.921^{\theta\theta}$	$-.926^{\theta\theta}$	$-.942^{\theta\theta}$	$-.956^{\theta\theta}$
% Stage 0	N1	.424	.422	.330	.461	.687*
	N2	.755*	.610*	$.775^{\theta}$	$.758^{\theta}$	.618*
	N3a	$.931^{\theta}$	.732*	$.933^{\theta\theta}$	$.895^{\theta\theta}$	.717*
	N3b	.799*	.618	.778**	$.816^{\theta}$	.496
Min. Stage 0	N1	.378	.401	.306	.440	.667*
	N2	.724*	.607*	$.769^{\theta}$	$.756^{\theta}$	.616*
	N3a	$.928^{\theta}$	.726*	$.928^{\theta\theta}$	$.892^{\theta\theta}$	.715*
Min. Stage 2	N3b	-.697	-.770**	-.635*	-.613	$-.808^{\theta}$

* $p \leq .05$ ** $p \leq .01$ $^{\theta}$ $p \leq .005$ $^{\theta\theta}$ $p \leq .001$

[a] For N1, N2 and non-sleep data: df=6; for N3a and N3b: df=5

[b] For N1, N2 and non-sleep data: df=10; for N3a and N3b: df=8

TABLE 10 (contd.)

SLEEP STUDY VARIABLE		1976 LEVEL FAT[a] HBB_6	1976 LEVEL SERUM[b] HBB_6	1979 LEVEL SERUM[b] HBB_6	1979 LEVEL SERUM[b] E	1979 LEVEL SERUM[b] F
#Awak. (≥20sec.)	N3b	-.766*	-.813$^{\theta}$	-.793**	-.742*	-.564
(≥40sec.)	N3b	-.736	-.749*	-.738*	-.702*	-.499
(≥1 min.)	N3b	-.732	-.806$^{\theta}$	-.737*	-.709*	-.549
A.D.A. (≥20sec.)	N3a	.904$^{\theta}$	.744*	.933$^{\theta\theta}$	.858$^{\theta}$	.673*
	N3b	.918$^{\theta}$	.766**	.897$^{\theta\theta}$	.837$^{\theta}$	.544
(≥40sec.)	N3a	.934$^{\theta}$	.728*	.926$^{\theta\theta}$	.855$^{\theta}$	.658*
	N3b	.882**	.693*	.851$^{\theta}$	.816$^{\theta}$	.481
(≥1 min.)	N3a	.938$^{\theta}$	.744*	.934$^{\theta\theta}$	.863$^{\theta}$	.669*
	N3b	.894**	.754*	.866$^{\theta}$	.824$^{\theta}$	.507
#Sleep Cycles	N3a	-.745	-.841$^{\theta}$	-.721*	-.738*	-.709*
	N3b	-.825*	-.860$^{\theta}$	-.815$^{\theta}$	-.870$^{\theta}$	-.783**
#SWS Periods	N1	-.570	-.651*	-.573	-.655*	-.672*
	N3a	-.651	-.755*	-.703*	-.712*	-.557
	N3b	-.741	-.818$^{\theta}$	-.752*	-.820$^{\theta}$	-.703**
EM Density C_1	N2	.814*	.422	.471	.480	.283
Dur. REMP C_1	N1	.774*	.434	.630*	.619*	.500
Pre-Sl. Index	N2	.640*	.459	.634*	.673*	.328
Post-Sl. Index	N3b	-.151	.456	.556	.689*	.669*
M.-K. d' Trial 2		-.687	-.735**	-.577*	-.669*	-.832$^{\theta\theta}$
Trial 4		-.572	-.637*	-.486	-.639*	-.747**

* $p \leq .05$ ** $p \leq .01$ $^{\theta}$ $p \leq .005$ $^{\theta\theta}$ $p \leq .001$

[a] For N1, N2 and non-sleep data: df=6; for N3a and N3b: df=5

[b] For N1, N2 and non-sleep data: df=10; for N3a and N3b: df=8

The level of serum HBB_6 ('79) correlated positively with amount (N2, N3a) and percent of (N2,N3a,N3b) stage 0, average duration of an awakening (ADA) (N3a,N3b), duration of the first REM period (N1) and Pre-Sleep Index (N2); the level correlated negatively with sleep period time (N1,N3b), total sleep time (TST) (N2,N3a,N3b), sleep efficiency index (SEI) (N2,N3a,N3b), amount of stage 2 (N3b), number of awakenings (N3b), number of SWS periods (N3a,N3b), number of sleep cycles (N3a, N3b) and d' for the second trial of the Mattis-Kovner Memory Recognition Test. Summarizing the major correlations, we found that the level of PBB correlated positively with stage 0 and ADA and negatively with TST, SEI, number of SWS periods and sleep cycles and performance of the Mattis-Kovner Memory Test. Figures 17-22, pp.80-85, display respectively the TST, SEI, percent of stage 0, ADA, number of sleep cycles and Mattis-Kovner d' for trial 2 as a function of the serum HBB_6 ('79) level.

In addition to the correlations listed in Table 10, the fat HBB_6 ('76) level was also negatively correlated with latency to stage 3 for N3a ($df=2$, $r= -.977$, $p \leq .05$) and latency to stage 4 for N1 ($df=1$, $r= -.999$, $p \leq .05$). Both of these correlations had low "n" values because of the low "n" value for fat HBB_6 ('76) level (max.: n=8) and the absence of latency measures for subjects whose sleep was without stage 3 or stage 4. The number of subjects showing stage 3 and stage 4 were respectively 8 and 4 on N1, 7 and 1 on N2, and 6 and 1 on N3a.

To further analyze possible correlations with stage 4, the levels of the PBBs were tested for correlation with the amount and percent of stage 4 of subjects who showed stage 4. The fat HBB_6 ('76) level correlated positively with amount ($df=1$, $r= 1.000$, $p \leq .001$) and percent of

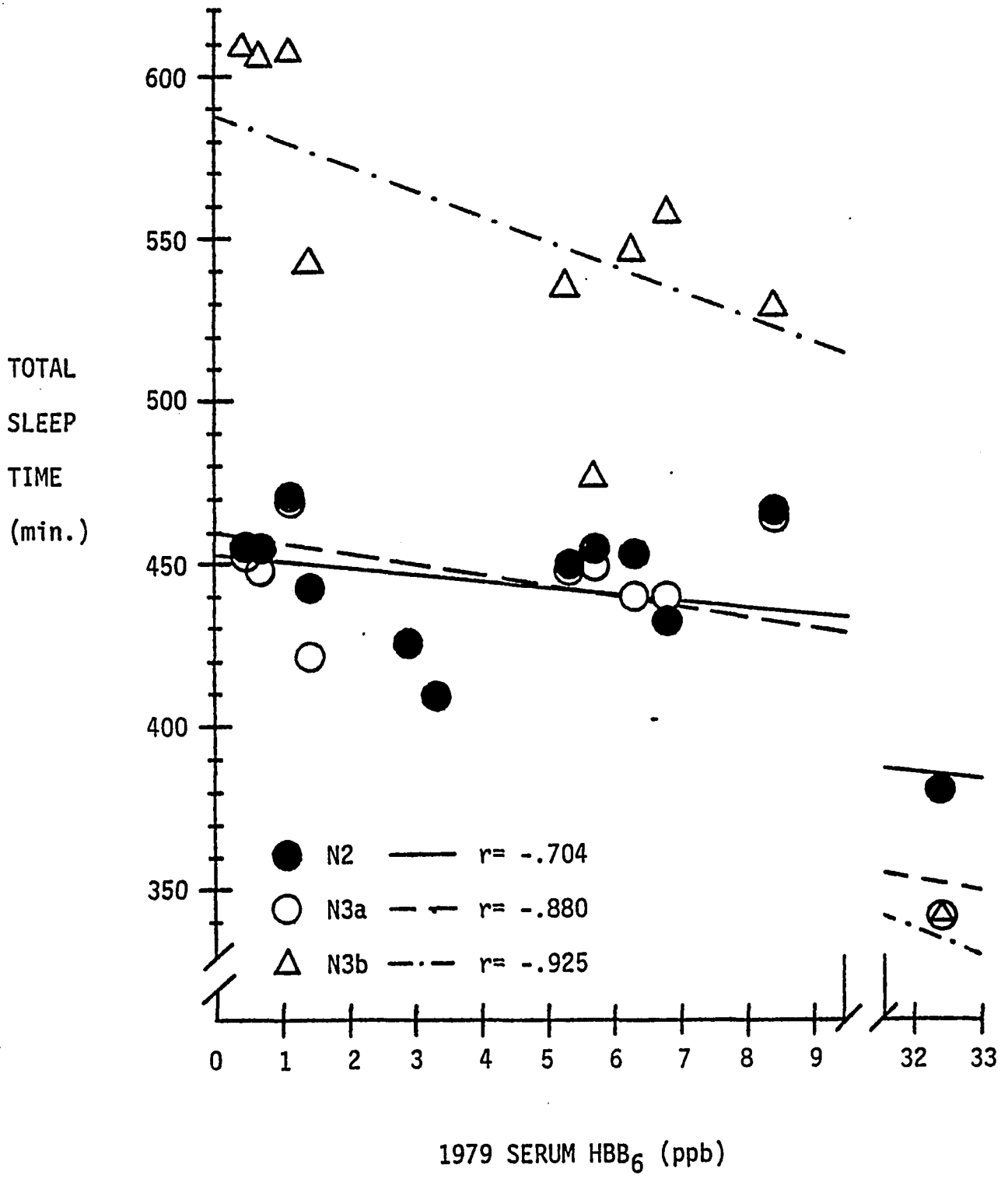


Figure 17: TOTAL SLEEP TIME AS A FUNCTION OF 1979 SERUM HBB_6 LEVEL

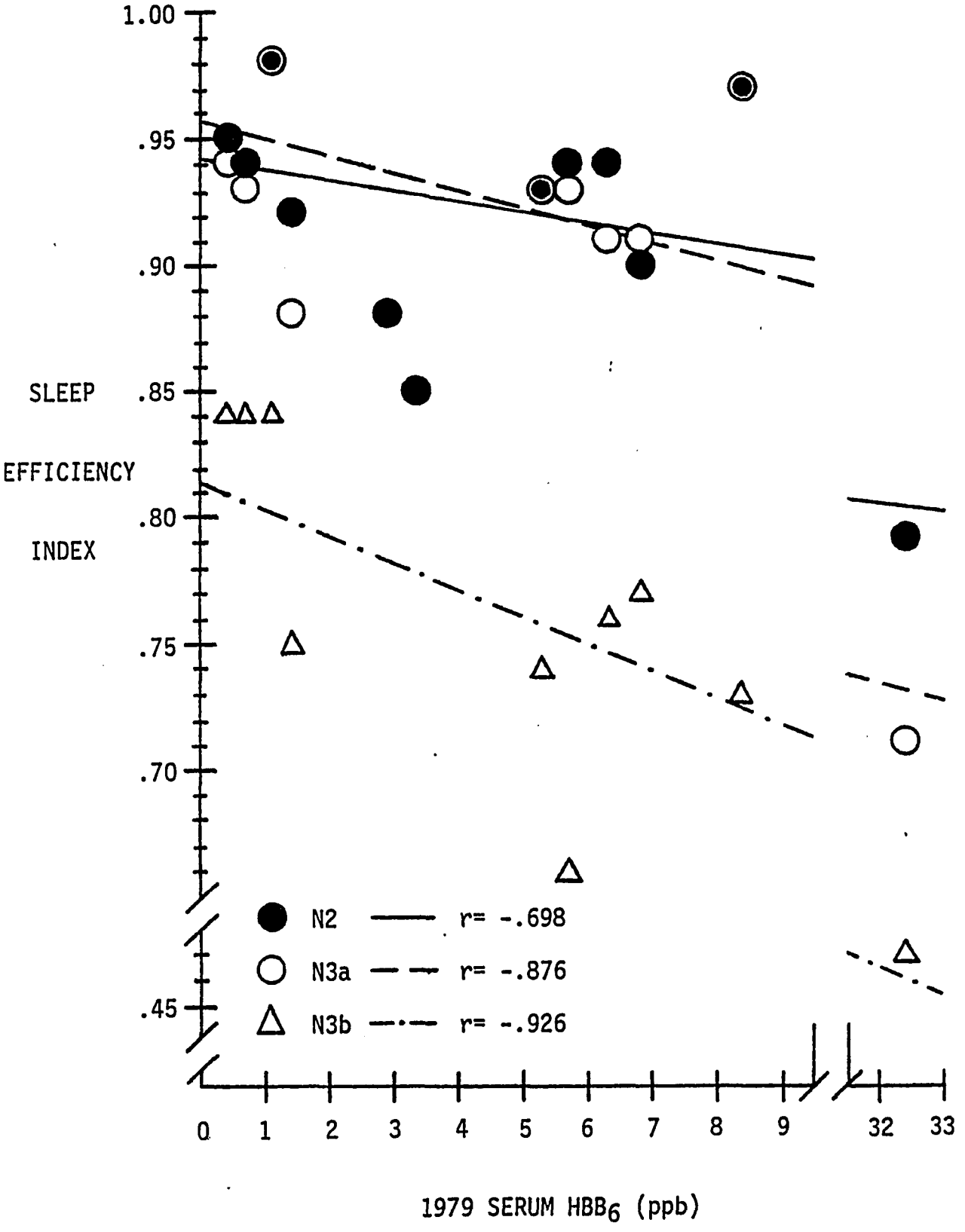


Figure 18: SLEEP EFFICIENCY INDEX AS A FUNCTION OF 1979 SERUM HBB_6 LEVEL

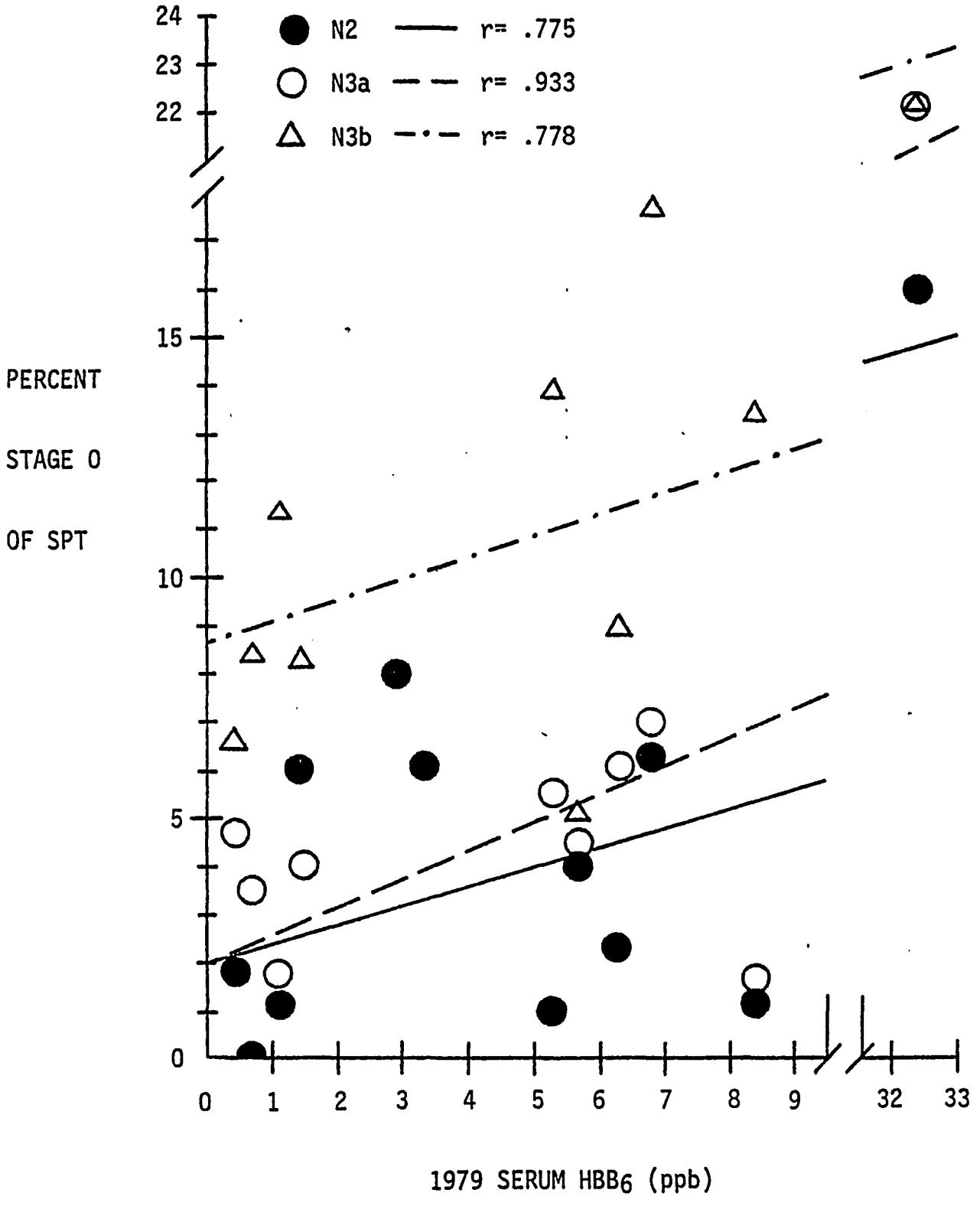


Figure 19: PERCENT OF STAGE 0 AS A FUNCTION OF 1979 SERUM HBB_6 LEVEL

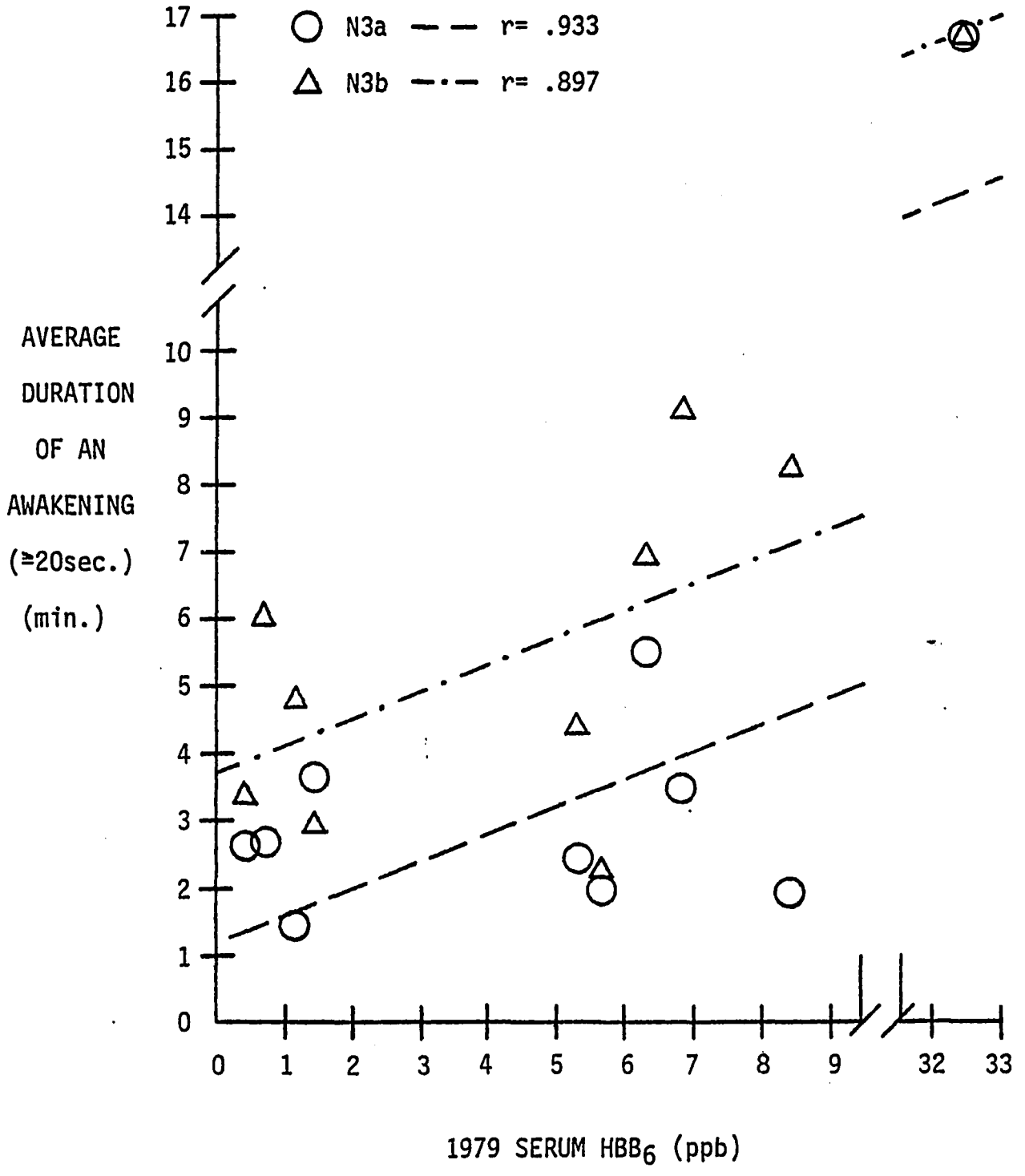


Figure 20: AVERAGE DURATION OF AN AWAKENING AS A FUNCTION OF 1979 SERUM HBB_6 LEVEL

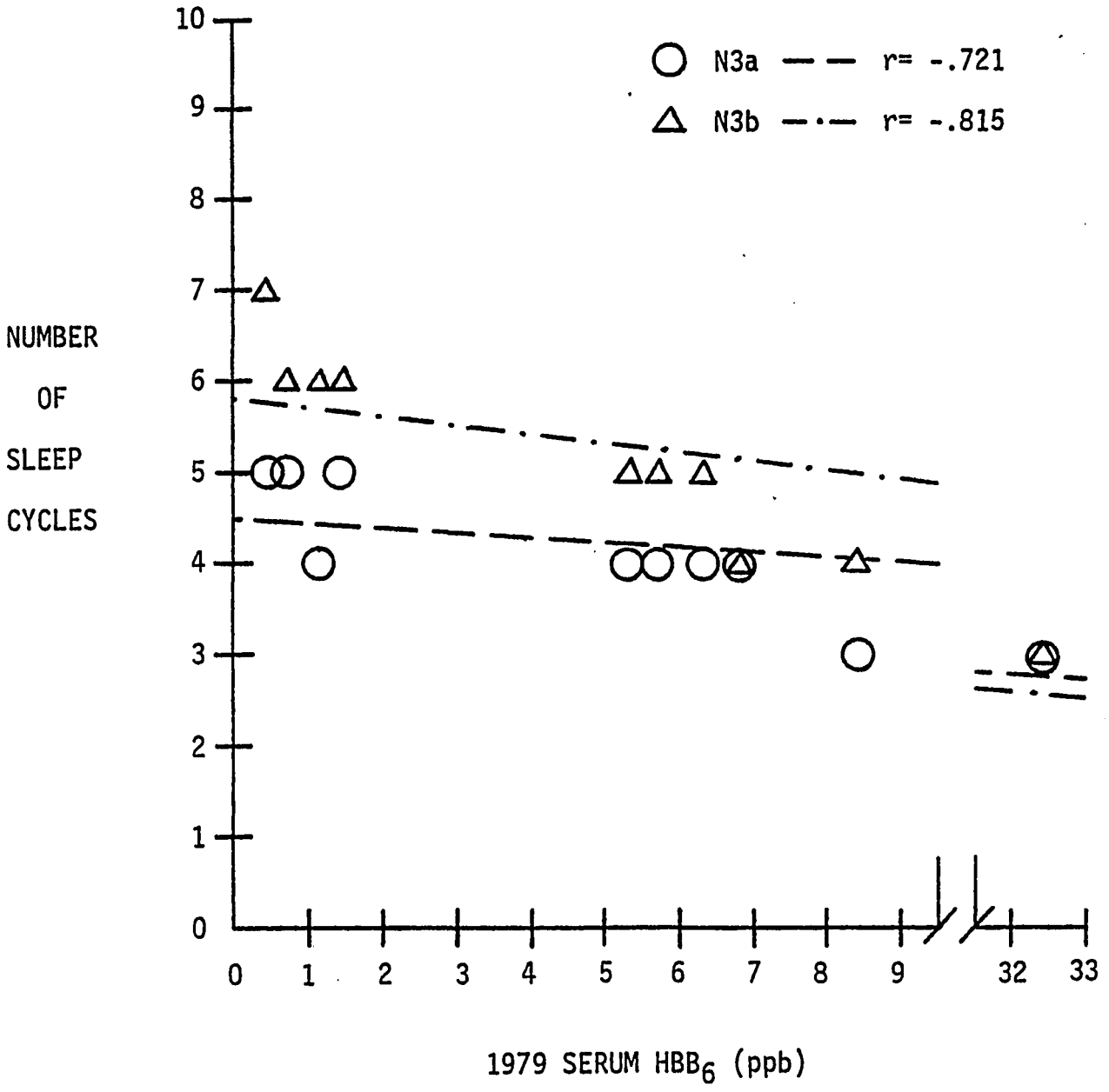


Figure 21: NUMBER OF SLEEP CYCLES AS A FUNCTION OF 1979 SERUM HBB_6 LEVEL

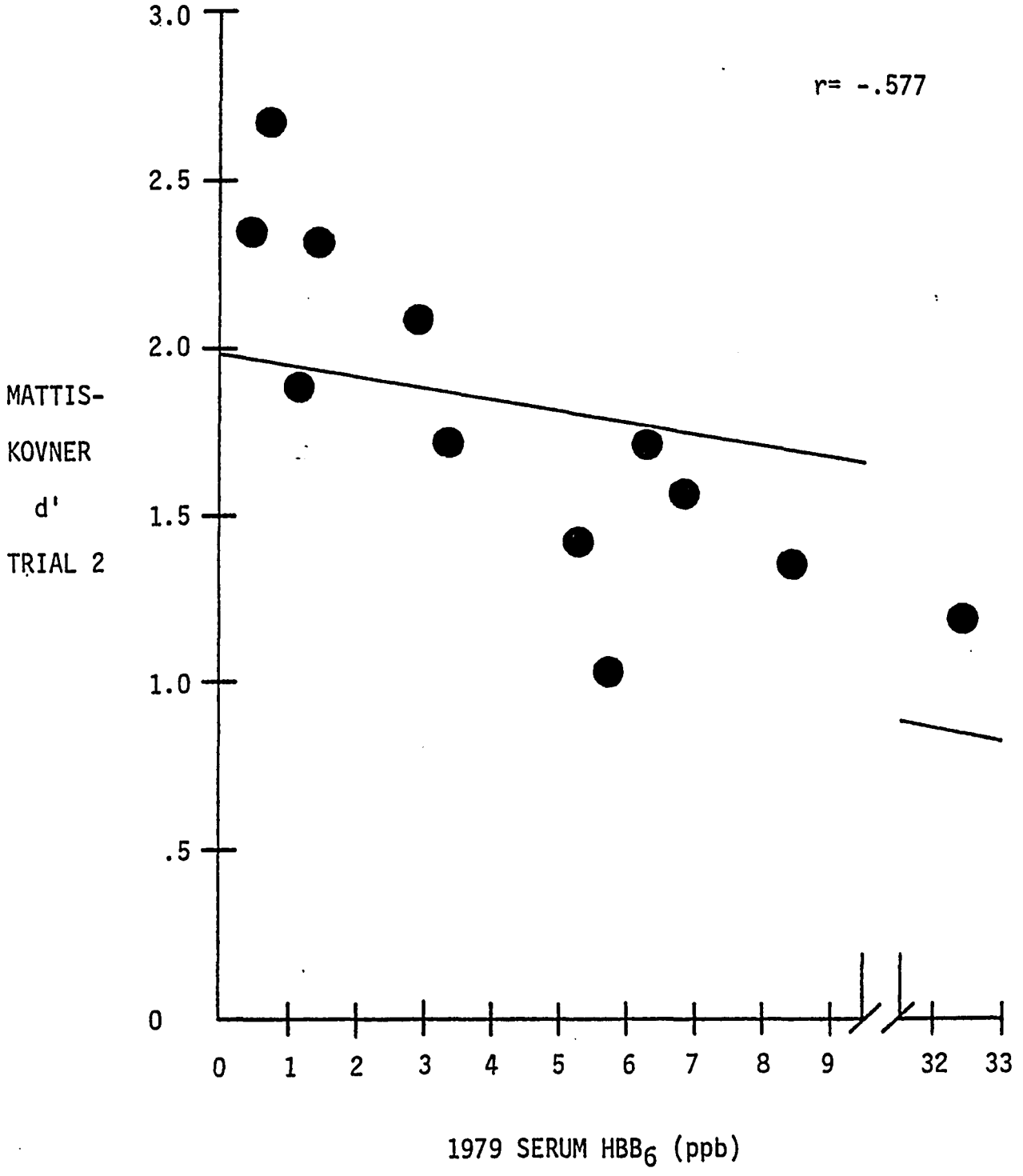


Figure 22: MATTIS-KOVNER d' FOR TRIAL 2 AS A FUNCTION OF 1979 SERUM HBB_6 LEVEL

(df=1, r= .999, $p \leq .01$) stage 4 for N1.

A further analysis of the correlation between the Mattis-Kovner d' and the serum HBB_6 ('79) level was made by excluding the d' value of the patient (#12) with a relatively high serum HBB_6 ('79) level (32.4 ppb), as compared to the other subjects. The serum HBB_6 ('79) level (n=11) was then negatively correlated with Mattis-Kovner d' for trial 2 (r= -.823, $p \leq .005$), trial 3 (r= -.685, $p \leq .05$) and trial 4 (r= -.671, $p \leq .05$).

The correlations for age are presented in Table 11, p.87. Age correlated positively with amount and percent of stage 0 (N2), percent of stage 2 (N3b), number of awakenings (N2), ADA (N2), EM density for SC_2 (N2), Pre-Sleep Index (N1) and error score of the Benton Revised Visual Retention Test. Age was negatively correlated with TST (N2, N3a), SEI (N2,N3a), amount and percent of stage 3 (N1,N2,N3a,N3b), stage 4 (N1), stage REM (N2,N3a,N3b) and stage 3+4 (N1,N2,N3a,N3b) and duration of the REM period for SC_2 (N3a), average duration of the REM period (N3b) and correct score of the Benton Test. Summarizing the major correlations, we found that age correlated positively with stage 0, number of awakenings, ADA and Benton error score and negatively with TST, SEI, stages 3, 4, REM and 3+4 and Benton correct score.

Table 12, p.88, reports the correlations for the Sleep, Depression, Pre-Sleep and Post-Sleep Indices. The Sleep Index correlated positively with duration of the SWS period for SC_2 (N1) and Depression Index and negatively with amount (N2,N3a,N3b) and percent (N3a,N3b) of stage REM, latency to stage 3 (N1), movement density (N3a,N3b), number of sleep cycles (N2) and Mattis-Kovner d' for trial 1.

The Depression Index correlated with duration of the SWS period

TABLE 11: CORRELATION COEFFICIENTS FOR AGE AND SLEEP STUDY VARIABLES OF THE SUBJECTS[a]

SLEEP STUDY VARIABLE		AGE
TST	N2	-.655*
	N3a	-.661*
SEI	N2	-.669*
	N3a	-.677*
% Stage 0	N2	.578*
Min. Stage 0	N2	.577*
% Stage 2	N3b	.636*
% Stage 3	N1	-.652*
	N2	-.615*
	N3a	-.641*
	N3b	-.649*
Min. Stage 3	N1	-.652*
	N2	-.616*
	N3a	-.665*
	N3b	-.665*
% Stage 4	N1	-.610*
Min. Stage 4	N1	-.610*
% Stage REM	N2	-.667*
	N3a	-.834$^{\theta}$
	N3b	-.766**

SLEEP STUDY VARIABLE		AGE
Min. Stage REM	N2	-.693*
	N3a	-.835$^{\theta}$
	N3b	-.785**
% Stage 3+4	N1	-.711**
	N2	-.616*
	N3a	-.647*
	N3b	-.652*
Min. Stage 3+4	N1	-.711*
	N2	-.617*
	N3a	-.671*
	N3b	-.671*
#Awak.(≥5 min.)	N2	.626*
A.D.A.(≥20sec.)	N2	.592*
EM Density C_2	N2	.583*
Dur.REMP C_2	N3a	-.801**
Dur.REMP Ave.	N3b	-.682*
Pre-Sl. Index	N1	.605*
Benton Correct score		-.634*
Error Score		.579*

* $p \leq .05$ ** $p \leq .01$ $^{\theta}$ $p \leq .005$ $^{\theta\theta}$ $p \leq .001$

[a] For N1, N2 and non-sleep data: df=10; for N3a and N3b: df=8

TABLE 12: CORRELATION COEFFICIENTS FOR SLEEP, DEPRESSION, PRE-SLEEP AND POST-SLEEP INDICES AND SLEEP STUDY VARIABLES OF THE SUBJECTS[a]

SLEEP STUDY VARIABLE		SLEEP INDEX	DEPRESSION INDEX	PRE-SLEEP INDEX	POST-SLEEP INDEX
TST	N3b	-.142	.403	.322	-.656*
SEI	N3b	-.149	.394	.315	-.655*
% Stage REM	N2	-.572	-.387	-.622*	-.041
	N3a	-.693*	-.355	.023	-.402
	N3b	-.837$^{\theta}$	-.492	.061	-.300
Min. Stage REM	N2	-.598*	-.366	-.587*	-.033
	N3a	-.672*	-.338	.007	-.415
	N3b	-.718*	-.257	.189	-.463
Latency Stage 3	N1 [c]	-.870$^{\theta}$	-.921$^{\theta}$	-.361	.328
Movement Dens.	N3a	-.680*	-.536	-.413	-.218
	N3b	-.689*	-.451	-.331	-.274
#Sleep Cycles	N2	-.657*	-.344	-.103	-.234
Dur. SWSP C_2	N1	.715**	.808$^{\theta}$	.557	-.028
Ave.	N3a	.490	.067	-.641*	.079
Ave.	N3b	.497	.002	-.681*	.195
Dur. REMP C_1	N3a	-.248	-.654*	-.224	.494
Dur.Sl.C. Ave.	N3b	.135	-.202	-.637*	.105
M.-K. d' Trial 1		-.674*	-.413		
Depression Index		.616*	--		

* $p \leq .05$ ** $p \leq .01$ $^{\theta}$ $p \leq .005$

[a] For N1, N2 and non-sleep data: df=10; for N3a and N3b: df=8

[c] df=6

for SC_2 (N1) and Sleep Index and negatively with latency to stage 3 (N1) and duration of the REM period for SC_1 (N3a).

The Pre-Sleep Index was negatively correlated with amount and percent of stage REM (N2), average duration of the SWS period (N3a,N3b) and average duration of the sleep cycle (N3b). The Post-Sleep Index was negatively correlated with TST (N3b) and SEI (N3b).

Table 13, p.90, lists the correlations for Associate Learning score, Mattis-Kovner d' value and sleep study variables. The Associate Learning score correlated negatively with amount and percent of stage 0 (N3a). The Mattis-Kovner d' values of trial 1 (N3b) and trials 2, 3 and 4 (N1) were negatively correlated with amount and percent of stage 0, and the d' value of trial 4 correlated negatively with number of awakenings (N1).

TABLE 13: CORRELATION COEFFICIENTS FOR ASSOCIATE LEARNING SCORE, MATTIS-KOVNER d' VALUE AND SLEEP STUDY VARIABLES OF THE SUBJECTS[a]

SLEEP STUDY VARIABLE		ASSOCIATE LEARNING SCORE	MATTIS-KOVNER d' TRIAL ONE	TWO	THREE	FOUR
% Stage 0	N1	-.488	-.081	-.733**	-.648*	-.867$^{\theta\theta}$
	N3a	-.697*	-.556	-.375	.148	-.295
	N3b	-.404	-.769**	-.439	.167	-.389
Min. Stage 0	N1	-.486	-.084	-.726**	-.663*	-.805$^{\theta}$
	N3a	-.718*	-.567	-.381	.140	-.298
	N3b	-.249	-.775**	-.230	.182	-.287
#Awak.(≥20sec.)	N1	.016	.053	-.512	-.275	-.689*

* $p \leq .05$ ** $p \leq .01$ $^{\theta}$ $p \leq .005$ $^{\theta\theta}$ $p \leq .001$

[a] For N1, N2: df=10; for N3a and N3b: df=8

DISCUSSION

In this discussion the subjects' complaint of hypersomnia will be analyzed using information from the Sleep and Post-Sleep Questionnaires. The sleep changes observed in our subjects will be classified as to the type of disorder, and an hypothesis will be stated to explain the apparent discrepency between the subjective reports and the objective findings. The sleep changes of the subjects will be compared to known pathological sleep syndromes with correlation data providing additional delineation of similarities. Further analysis of correlation and neuropsychological data will be made in relation to the sleep data and the status of central nervous system functioning. Finally, we will consider the effect of exposure to PBB with regard to the results of this investigation and then discuss management of the sleep disorder.

It will be recalled that our subjects were selected for participation in this study on the basis of having a complaint of hypersomnia. In order to determine the subjective factors which may be responsible for the complaint, it will be of help to analyze the information previded by the subjects in the Sleep and Post-Sleep Questionnaires.

The data from the Sleep Questionnaires indicate that at home most subjects regularly slept for more than eight hours per night with one-third of them spending as much as ten to twelve hours asleep. In addition to their nighttime sleep, most subjects reported additional daytime naps. Falling asleep at night was not a problem, and, to their knowledge, awakenings during the night occurred rarely or only occassionally. Upon awakening in the morning most subjects felt tired with one-half also reporting mental dullness. Thus, an absence of frequent distur-

bances by awakenings at night and the presence of an increase in sleep time combined with tiredness even after a night's sleep were clearly incorporated into their reports of excessive sleep.

The data derived from Post-Sleep Questionnaires indicate that in the laboratory most subjects fell asleep with relative ease. Because of the different sleep times and conditions of the three study nights, it is not clear whether the number of awakenings was higher or lower than they typically experienced at home. A certain degree of night-to-night and subject-to-subject variability for reports of the depth of sleep at night and state of mind and body upon awakening made analysis of this data difficult. However, on the average, subjects reported medium depth of sleep (between light and deep), medium mind (between alert and dull) and average to tired body. These Post-Sleep findings can be said to be relatively similar to those of the pre-study Sleep Questionnaires and certainly do not alter in any significant way the subjective sleep profile of the subjects. Therefore, from the subjective reports provided in the questionnaires it appears that the subjects believe they experience a sleep problem which might be symptomatically classified as hypersomnia. The objective validation of the complaint by quantitative analysis of various sleep parameters was one of the principal purposes of the present investigation.

The results of this quantitative, physiological study indicate that the sleep of the subjects is characterized by an increase in number of awakenings and in eye movement density of REM sleep and a decrease in stage 4 sleep. In addition, older subjects show a decrease in stage 3 sleep. These observed changes in sleep patterns are not typical of any specific sleep disorder, but can be seen in varying circumstances in a

number of pathological sleep syndromes. For example, an increase in number of awakenings is found in narcolepsy (Hishikawa et al., 1976), while decreases in stage 4 and/or stage 3 are observed in the neutral-state syndrome (Guilleminault et al., 1975), hypothyroidism (Kales et al., 1967a) and the fibrositis syndrome (Moldofsky et al., 1975). Moreover, in aging (Feinberg et al., 1967; Kales et al., 1967b; Williams et al., 1974) and in depression (Mendels and Hawkins, 1967a) a decrease in stage 4 and an increase in number of awakenings are seen.

Initially we note that the patterns of sleep disturbance we recorded do not support a classification of either a hypersomnia or an insomnia sleep disorder. Although hypersomnia was the uniform complaint of the subjects in this study, our data reveal that they do not have an abnormally increased total sleep time (TST) in relation to the amount of time spent in bed. This is in contrast to what was found in the chronic hypersomniacs reported by Roth et al. (1972). Narcoleptics, who typically complain of hypersomnia, also fail to show increases in TST as compared to normals (Hishikawa et al., 1976). Certain narcoleptics, namely those with auxiliary symptoms, experience an increase in number of awakenings (Hishikawa et al., 1976), as do our subjects. However, unlike the narcoleptics, subjects in this study showed no decrease in REM sleep onset latency over a three nights study period. From these considerations we must conclude that our subjects cannot be said to suffer from an abnormal enhancement of sleep.

The sleep of insomniacs is characterized by a decrease in TST (Carskadon et al., 1975; Frankel et al., 1976) and depending on the type of insomnia (Frankel et al., 1976) may include an increase in sleep onset latency (Kales, 1969; Karacan et al., 1971; Carskadon et

al., 1975; Frankel et al., 1976), an increase in early morning awakening and a decrease in sleep efficiency (Karacan et al., 1971; Frankel et al., 1976). Our subjects do show an increase in number of awakenings, but their adjusted TST is not significantly diminished. Furthermore, they do not complain of wakefulness, unlike insomniacs, who have been found to overestimate the amount of sleeplessness (Frankel et al., 1976). It is concluded then that although the sleep of the subjects is disturbed, it is clearly not diminished and therefore cannot be categorized as insomnia. In view of the foregoing analysis, the sleep disorder of the subjects is best characterized as a disturbance of sleep rather than a change in the amount of sleep, either enhancement or diminution.

Since the objective findings do not support classification of the sleep disorder as hypersomnia and are not therefore in accord with subjective reports, it is of interest to explore the relationship between these findings and reports. In other words, how can the changes found in the sleep of the subjects be reconciled with their reports of excessive sleep?

The altered slow wave sleep (SWS) of the subjects as indicated by an increased number of awakenings and a decreased stage 4 may suggest why the subjects would remain sleeping in bed longer than usual and yet feel tired, as they report. Feinberg (1974) suggests that stage 4 acts to reverse the catabolic effects of wakefulness with stage 2 and stage 3 qualitatively similar to but less intense than stage 4. The duration of the SWS periods declines through the night with stage 4 and stage 3, the more intense stages, predominating in the early periods and with stage 2, the least intense stage, predominating in the later ones.

When the final SWS periods consisting of stage 2 approach in duration the REM periods with which they alternate, the effects of wakefulness have been reversed and morning waking occurs. The function of REM sleep is to maximize the occurrence of SWS.

The SWS of the subjects may be functionally less efficient or less "intense" in comparison with normal SWS because of a decrease in stage 4 and an increase in number of awakenings. In addition, due to excessive interruptions by wakefulness, the SWS periods of the subjects may be continuing for a longer than usual duration before alternating with REM sleep, at least in terms of clock time, as was found to be the case in a study of normal subjects by Březinová (1974). If the durations of the SWS periods of the patients were extended, fewer SWS periods and sleep cycles would occur in a night. If the SWS of the subjects is functionally less intense and the SWS periods are also extended, the subjects may be sleeping in bed longer than normally, trying to complete enough sleep cycles to achieve the restorative effects of sleep. However, if the disturbed sleep of the subjects did not produce full restoration even with an extended time spent sleeping in bed, then the subjects should feel fatigued and sleepy during the day. This combination of low quality sleep, extended sleep time and daytime somnolence could readily account for the subjective complaint of hypersomnia reported by our experimental group.

In the foregoing discussion the sleep changes observed in our subjects have been considered in relation to the patterns seen in hypersomnia and insomnia and were found to be at variance with these disorders. It remains now to compare in some detail the subjects' sleep characteristics with the sleep changes seen in the neutral-state

syndrome, hypothyroidism, the fibrositis syndrome, depression and aging.

The decrease in stage 4 of the subjects and decrease in stage 3 of older subjects resemble the changes in sleep seen in both the neutral-state syndrome (Guilleminault et al., 1975) and hypothyroidism (Kales et al., 1967a). However, the sleep disorder of the subjects more closely resembles the disturbed sleep associated with the fibrositis syndrome, since both types of sleep are deficient in stage 4 and interrupted by wakefulness. Moreover, Moldofsky et al. (1975) suggest that the sleep disorder associated with the fibrositis syndrome is a non-restorative sleep syndrome which, as has been discussed, may describe the type of sleep disorder of the subjects.

Unipolar depressives have the secondary symptom of an insomnia-type sleep disturbance consisting of an increase in sleep onset latency, number of awakenings, stage 0 and time spent awake in the early morning and a decrease in stage 4 and TST (Mendels and Hawkins, 1967a). It has been discussed that insomnia is not the complaint or problem of the subjects, but a decrease in stage 4 and an increase in number of awakenings are sleep changes which are similar for both subjects and depressives. Depressives characteristically show a decreased latency to the first REM period (Kupfer and Foster, 1972). It was not possible to compare the latency to the first REM period of the subjects with normal subjects. However, by utilizing the results of a study which showed that the REM latency was shorter for a group of primary depressives as compared to a group of medical depressives (Fink et al., 1977), it appears by inspection that the mean latency to the first REM period of the subjects (pp.46,49) is more similar in duration to that of the medical depressives (71.2 min.) than to that of the primary depressives

(38.3 min.). These results and other data of this study to be discussed later suggest that the sleep disorder of the subjects is similar to that associated with primary depression in some respects but that the changes in sleep patterns are probably not secondary symptomatic expressions of primary unipolar depression.

The sleep of elderly adults as compared to that of young normal adults shows an increase in: 1) number of awakenings, 2) average duration of an awakening (ADA), 3) stage 0, 4) duration of the first REM period and 5) eye movement density for the first REM period and a decrease in: 6) TST, 7) sleep efficiency index (SEI), 8) stage 4 and 9) REM sleep (Feinberg et al., 1967: 1,2,3,4,8,9; Kales et al., 1967b:1, 6,8,9; Feinberg, 1974: 1,2,4,5,8,9; Williams et al., 1974: 1,3,6,7,8, 9; Březinová, 1975: 3,6,9, 1976: 6). The subjects' sleep resembles older sleep by having an increased number of awakenings and a decreased stage 4. Furthermore, older normal adults show a decreased ability to sustain sleep without frequent interruptions by wakefulness (Feinberg et al., 1967; Březinová, 1975) but achieve approximately the same TST as younger adults by remaining in bed for a longer period (Feinberg et al., 1967). Similarly, it has been suggested that the SWS of the subjects is less efficient than normal SWS because of an increased number of awakenings and a decreased stage 4, and that the abnormal SWS causes them to remain sleeping in bed longer than normally in an attempt to achieve the restorative effects of sleep.

In comparing the sleep patterns of the subjects with those of the class of disorders considered above, we observe that the sleep abnormalities seen in the fibrositis syndrome, depression and aging resemble most closely those seen in the subjects. Further distinctions can be

provided from analysis of PBB correlations and neuropsychological data.

Our data show that levels of PBB correlate significantly with a number of sleep variables. This correlation is positive with stage 0, ADA and duration of and eye movement density for the first REM period and negative with TST, SEI and number of SWS periods and sleep cycles. These correlation data suggest that the sleep changes in our subjects correspond to a greater extent with the patterns observed in aging than with those observed in depression. Subjects with higher levels of PBB have sleep which resembles "older" sleep more than it does depressive sleep. Furthermore, the Depression Index of the subjects (v.i.) is uncorrelated with the latency to the first REM period and is negatively correlated with the duration of the first REM period. This is in contrast to the results found for primary depressives who have the degree of measured depression negatively correlated with the latency to the first REM period (Kupfer and Foster, 1972) and who have a longer mean duration of the first REM period than medical depressives have (Fink et al., 1977). In addition, the negative correlations of levels of PBB with number of SWS periods and sleep cycles lend support to the hypothesis that our subjects may be sleeping in bed longer than normally, as do elderly normal subjects, in an attempt to complete enough sleep cycles. Thus, it appears that the sleep of this population resembles sleep more characteristic of individuals older than the chronological ages of our subjects.

Since depression was one of the significant symptoms reported by Michigan residents in the 1976 health survey (Valciukas et al., 1979), it was necessary to determine whether our subjects should be considered primary depressives with their disturbed sleep a secondary symptom of

that disorder. To provide quantitative assessment of the disorder of depression in our subjects, we employed the Zung Self-Rating Depression Scale (Zung, 1965). The mean Depression Index of the subjects is .51 (SD: .11) which is significantly lower than the .74 (SD: .08) of the group of primary depressives reported by Zung, while also being significantly higher than the .33 (SD: .05) of his group of normal subjects. Thus, our subjects cannnot be classified as depressives. This finding combined with the differences observed in comparing the sleep patterns of depressives with those of our subjects make it unlikely that the altered sleep of the subjects is an expression of primary depression.

Although not thought to be primary depressives, our subjects cannot be considered normal with regard to depression. Not only is their mean Depression Index significantly higher than that of the normal group, it is also not significantly different from the .53 (SD: .08) of Zung's group of persons who were initially diagnosed as having depressive disorders but who were later found to have disorders such as psychophysiological disturbances, anxiety reactions and personality disturbances. If the subjects are more depressed than normal subjects, then their depression may be related to their altered SWS. Increased depression is found in persons with insomnia (Kales, 1969; Kales et al., 1973; Coursey et al., 1975), the fibrositis syndrome (Moldofsky et al., 1975) and, of course, primary depression. Decreased stage 4 and/or delta sleep is reported for insomniacs (Frankel et al., 1976), individuals having the fibrositis syndrome (Moldofsky et al., 1975), depressives (Mendels and Hawkins, 1967a) and schizophrenics (Caldwell, 1969; Feinberg et al., 1969). Furthermore, the level of depression is negatively correlated with the amount of stage 4 in schizophrenics (Reich

et al., 1975), and the symptom of depression is thought to be a result of deprivation of stage 4 in persons with the fibrositis syndrome (Moldofsky et al., 1975). Thus, any noted depression in the subjects might be symptomatic of their disturbed sleep patterns rather than suggestive of primary depression.

In 1976, two-thirds of our subjects reported memory loss of from one to three years duration (Selikoff et al., 1976). To investigate this complaint and to provide additional measurement of central nervous system functioning, we administered a memory test designed to assess recall, recognition and learning.

The results of the Benton Revised Visual Retention Test reveal that for sixty-seven percent of the subjects there is an indication of acquired impairment of cognitive functioning with twenty-five percent showing a strong indication. In addition, performance correlates negatively with age but does not correlate with levels of PBB. In normal subjects performance correlates positively with intelligence level and, beginning in the fourth decade, negatively with chronological age (Benton, 1974). We could not compare the results of our subjects on the Mattis-Kovner Memory Test with those of normal subjects, but their performance correlates negatively with levels of PBB, stage 0 and number of awakenings. The mean scores of the Associate Learning Test are not significantly different from those of normal subjects, but the scores correlate negatively with stage 0. Performance on this test in normal subjects correlates with age and intelligence level (Wechsler and Stone, 1974).

Of the results of the Memory Test, only those of the Benton Revised Visual Retention Test clearly suggest that some of our subjects

may have a certain degree of memory impairment; however, the degree of impairment does not correlate with levels of PBB. It is of interest to note that an exact match-up does not exist between those subjects who had reported memory loss in 1976 and those who now present that sign. On the other hand, the negative correlations of performance on the Mattis-Kovner Memory Recognition Test and the Associate Learning Test with measurements of wakefulness are similar to those observed in the normally and pathologically aged. Feinberg et al. (1967) reported that scores on the Progressive Matrices Test in the elderly and performance on the Wechsler Adult Intelligence Scale (WAIS) in persons with the chronic brain syndrome (CBS) were correlated negatively with the percent of stage 0 of the time spent in bed. Moreover, individuals with the CBS had scores on the Wechsler Memory Scale and the verbal section of the WAIS which were negatively correlated with the number of awakenings. From these findings Feinberg et al. (1967) hypothesized that the symptom of sleep with chronic and frequent interruptions by wakefulness indicates an impairment of brain functioning. In view of the foregoing analysis, the sleep data and memory correlation data of this study suggest that our subjects may have an impairment of cognitive functioning similar to that seen in aging.

The sleep, neuropsychological and correlation data suggest that certain functions of the central nervous systems of the subjects appear older than would be expected from their chronological ages. Although the Memory Test data support this idea, it is the sleep data which provide the basis for this hypothesis. Consequently, the results of this study can be said to indicate the usefulness of electrophysiological sleep recording in toxicological studies to objectively characterize

symptomatic sleep complaints and to quantitate alterations in brain functions which might otherwise go undetected.

Subjects with higher levels of PBB are observed to have older sleep and to perform less well on the Mattis-Kovner Memory Recognition Test. If exposure to PBB has resulted in changes in central nervous system functioning, it is not known whether the possible causal connection consists of a primary or secondary involvement of PBB with the nervous system. The alteration in hepatic function noted by Anderson et al. (1979) do suggest the possibility that exposure to PBB may result in toxic metabolic changes which could then secondarily affect the central nervous system. The correlation of levels of PBB with sleep and neuropsychological dysfunction five years after the period of exposure to PBB seems to indicate that a relatively permanent change in the functioning of the central nervous system of the subjects may have occurred. However, data from the questionnaires and conversations with the subjects do suggest improvement in their sleep from 1974 to 1979. The present sleep disorder of the subjects is probably not as severe as when first experienced in 1974 or reported in 1976 but is certainly, still in 1979, a significant health concern for them.

Treatment which decreases the interruptions by wakefulness of SWS and increases stage 4 is recommended for the subjects. Any drug treatment used at night should attempt to increase stage 4 without interfering with the other sleep stages and without increasing wakefulness. Drugs may prove to be helpful in alleviating the sleep problem of the subjects. However, the long biological half-life of PBB suggests that drug treatment used to enhance the quality of sleep would probably be, of necessity, of a long duration, and few drugs used to improve sleep

continue to be efficacious with long term use (Kales et al., 1974). Furthermore, giving a stimulant such as dextroamphetamine to the subjects to combat their daytime tiredness and sleepiness is probably not appropriate, because such an attempt to increase daytime wakefulness might reinforce or worsen the nighttime interruptions of sleep by wakefulness.

SUMMARY

The sleep EEGs of twelve adult Michigan residents, who had been exposed to polybrominated biphenyls (PBBs) and who complained of hypersomnia, were recorded in order to determine objectively the character and extent of the reported sleep disturbance. In addition to this electrophysiological study, neuropsychological tests were administered to each of the subjects, and their serum PBB levels were measured.

Analysis of the sleep data revealed a greater number of awakenings, an increase in eye movement density of REM sleep, and a decrease in stage 4 sleep as compared to a normal population of the same age. The older subjects also showed a decrease in the amount of stage 3 sleep. The patterns of sleep were not consistent with the changes seen in pathological increases or decreases in the amount of sleep. To reconcile the observed sleep changes of the subjects with their subjective reports of hypersomnia, it is hypothesized that increased number of awakenings and decreased stage 4 may contribute to an inferior quality of sleep and to an increased time taken to complete a sleep cycle. This in turn might produce an increase in the time spent sleeping in order to achieve the presumed restorative effects of sleep.

The levels of PBB were found to correlate with the amount of stage 0, the average duration of an awakening, the duration of first REM period, and the eye movement density in that period. A significant negative correlation was found between PBB levels and total sleep time, sleep efficiency index, the number of slow wave sleep periods and the number of sleep cycles. A comparison of sleep profiles of this group with other classes of pathological sleep syndromes suggested closest

resemblance to the changes seen in aging.

The negative correlation of performance on the Mattis-Kovner Memory Recognition Test and the Associate Learning Test with measurements of wakefulness, and the results of the Benton Revised Visual Retention Test suggest that subjects may have some degree of impairment of cognitive functioning similar to that seen in aging.

Since this study was not designed to determine the status of PBB as a neurotoxin, no statement can be made about its causal relation to the sleep disturbances observed in this subject population. However, the investigation does establish the value of sleep analysis as an objective technique in environmental medicine for characterizing sleep complaints and for recognizing a low degree of diffuse organic brain dysfunction. Furthermore, the correlations found between serum levels of PBB and changes in sleep patterns suggest that if significant sleep complaints persist in the exposed population, a controlled study should be done designed to evaluate a causal connection between PBB and central nervous system changes.

APPENDIX A: SLEEP QUESTIONNAIRE

MOUNT SINAI SCHOOL OF MEDICINE
of The City University of New York
FIFTH AVENUE AND 100TH STREET • NEW YORK, N.Y. 10029

Department of Neurology

SLEEP QUESTIONNAIRE

NAME: _____ AGE: _____
LAST FIRST

ADDRESS: _____
NO. STREET CITY STATE ZIP

PHONE NO.: (____) _____ - _____ SEX: MALE ◯ FEMALE ◯

INSTRUCTIONS: Please check the circle ⊘ which is the most appropriate answer to the question or write the answer to the question in the space.

1. Do you continue to have the problem of sleeping longer than usual? NO ◯ YES ◯
2. If you no longer have this problem, when did the problem disappear? _____(DATE).
3. Do you now have any other sleeping problems? NO ◯ YES ◯
   If "YES", please briefly describe the new sleep problem: _____
   _____
   _____
4. What is your normal bedtime? _____(PM/AM).
5. When do you usually awaken from your night's sleep? _____(AM/PM).
6. On the average, for how long do you sleep at night? _____(HOURS).
   1: TST < 8 hrs
   2: 8 ≤ TST < 10
   3: TST > 10 hr.
7. Approximately how quickly do you fall asleep at night?
   WITHIN 15 MINUTES (3) 15--45 MINUTES (2) LONGER THAN 45 MINUTES (1)
8. During the night, how often do you awaken from sleep?
   RARELY (3) OCCASIONALLY (2) FREQUENTLY (1)
9. When you awaken from sleep during the night, for how long do you remain awake?
   SHORT TIME (3) MEDIUM TIME (2) LONG TIME (1)
10. Do you ever snore heavily during sleep? NO ◯ YES ◯
11. Do you have frequent nightmares? NO ◯ YES ◯

SLEEP QUESTIONNAIRE

12. After awakening from a night's sleep, for how long do you remain in bed?

    LESS THAN 2 MINUTES (3) 2--5 MINUTES (2) LONGER THAN 5 MINUTES (1)

13. When you awaken from a night's sleep, how do you feel in terms of your mind?

    BRIGHT (1) REASONABLY ALERT (2) DULL (3)

14. When you awaken from a night's sleep, how do you feel in terms of your body?

    WELL RESTED (1) REASONABLE RESTED (2) TIRED (3)

15. How often do you fall asleep during the day?

    RARELY (1) OCCASIONALLY (2) FREQUENTLY (3)

16. When you fall asleep during the day, for how long do you sleep?

    LESS THAN 15 MINUTES (1) 15--45 MINUTES (2) LONGER THAN 45 MINUTES (3)

17. Do you take any medication? NO ◯ YES ◯

    If "YES", please write the name of the drug and the reason for taking it:

    DRUG #1:_____ REASON:_____

    _____

    DRUG #2:_____ REASON:_____

    _____

APPENDIX B: PRE-SLEEP QUESTIONNAIRE

PRE-SLEEP QUESTIONNAIRE

NAME: _____ NIGHT: (1) (2) (3) DATE: _____
LAST FIRST

INSTRUCTIONS:
1. Please check the circle (✓) which is the most appropriate answer to the question and, where applicable, write the answer to the question in the space.
2. Check only one circle for each question.
3. Answer all questions.

1. How much physical exertion did you do today?

none	small amount	medium amount	large amount	enormous amount
(1)	(2)	(3)	(4)	(5)

2. How much mental exertion did you do today?

none	small amount	medium amount	large amount	enormous amount
(5)	(4)	(3)	(2)	(1)

3. How do you feel this evening in terms of your body?

very rested	rested	average	tired	very tired
(1)	(2)	(3)	(4)	(5)

4. How do you feel tonight in terms of your mind?

very alert	alert	medium	dull	very dull
(1)	(2)	(3)	(4)	(5)

5. How do you feel now physically?

very relaxed	relaxed	average	tense	very tense
(5)	(4)	(3)	(2)	(1)

6. How do you feel mentally tonight?

very peaceful	peaceful	normal	anxious	very anxious
(5)	(4)	(3)	(2)	(1)

7. Are you experiencing any physical or mental discomfort this evening? NO ◯ YES ◯
If "YES", please briefly describe your discomfort: _____

_____

_____

8. Did you fall asleep or take any naps today? NO ◯ YES ◯ If "YES", how many times:_____, for how long each time:_____(minutes), and at what times during the day:_____.

9. Today did you drink any coffee, tea, soft drinks or alcohol? NO ◯ YES ◯ If "YES", how many times:_____, how much each time:_____(approximate number of ounces), and at what times during the day:_____.

10. Did you take any medicines or drugs today? NO ◯ YES ◯ If "YES", which drugs or medicines:_____, how many times:_____, how much each time:_____, and at what times during the day:_____.

APPENDIX C: POST-SLEEP QUESTIONNAIRE

POST-SLEEP QUESTIONNAIRE

NAME: _____ MORNING: (1) (2) (3) DATE: _____
LAST FIRST

INSTRUCTIONS:
1. Please check the circle (✓) which is the most appropriate answer to the question.
2. Check only one circle for each question.
3. Answer all questions.

FALLING ASLEEP

1. How long did it take you to fall asleep initially?

never fell asleep	long time	medium time	short time	immediately fell asleep
(1)	(2)	(3)	(4)	(5)

2. When you were falling asleep, how many thoughts did you have?

none	few	moderate	many	was constantly thinking
(5)	(4)	(3)	(2)	(1)

3. When you were falling asleep, how many body movements did you have?

none	few	moderate	many	constantly tossed and turned
(5)	(4)	(3)	(2)	(1)

SLEEP DURING THE NIGHT

4. How many times did you awaken during the night?

never	once	twice	three times	four times or more
(5)	(4)	(3)	(2)	(1)

5. If you awoke during the night, on the average how long did it take you to fall asleep again?

never fell asleep again	long time	medium time	short time	immediately fell asleep
(1)	(2)	(3)	(4)	(5)

6. How would you describe your sleep last night in terms of "lightness" or "deepness"?

very light	light	medium	deep	very deep
(1)	(2)	(3)	(4)	(5)

7. During the night, how many body movements did you have?

none	few	moderate	many	constantly tossed and turned
(5)	(4)	(3)	(2)	(1)

ON AWAKENING

8. On your final awakening how long did it take you to become awake once you started to wake up?

was awake immediately	short time	medium time	long time	never fully woke up
(5)	(4)	(3)	(2)	(1)

9. After your final awakening how did you feel in terms of your mind?

very dull	dull	medium	alert	very alert
(1)	(2)	(3)	(4)	(5)

10. After your final awakening how did you feel in terms of your body?

very tired	tired	average	rested	very rested
(1)	(2)	(3)	(4)	(5)

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