EFFECTS AND AFTER-EFFECTS OF ALCOHOL, TRANQUILLIZERS AND FATIGUE ON OCULAR PHENOMENA

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THE PRESENT communication is mainly concerned with quantitative studies on two ocular phenomena—positional alcohol nystagmus (PAN) and roving ocular movements (ROM)—elicited by the intake of various alcoholic beverages, and with their relation to certain central nervous system processes, as revealed by EEG, statometry and subjective mood estimates, and with their relation to the height of the blood alcohol curve.

Our interest in nystagmus was aroused in 1933 by experiments in animals and in man. The presence or absence of nystagmus and its direction and intensity served as part of a battery of tests on the functioning of the central nervous system. The clinical picture of alcohol nystagmus was elucidated by Frenzel (1939), Plenkers (1943) and Walter (1954). G. Aschan (1955 a), at the Department of Otology of the University of Uppsala, introduced direct-writing electronic equipment for recording of ocular movements as an essential part of nystagmus studies in otoneurology. The co-operation between Aschan's and my own group resulted in a series of studies on positional alcohol nystagmus, first published in 1955–56 (Aschan, Bergstedt, Goldberg and Laurell, 1955 b, 1956 a, b), showing that a positional alcohol nystagmus (PAN) could be elicited with a specific pattern and could be recorded for hours after alcohol had left the body (PAN II), hence demonstrating an objective after-effect of alcohol.

The studies in our laboratory in this field then concentrated on another ocular phenomenon, roving ocular movements (ROM), the interrelationship between PAN and ROM under varying conditions, and the possible interference with these phenomena by other agents, such as centrally-acting depressant drugs (especially tranquillizing agents), fatigue, food intake, high temperature and humidity (Goldberg, 1961). PAN and ROM have been studied in relation to other functions of the central nervous system, as revealed by electroencephalography, by recording of standing steadiness and by subjective estimates of psychological mood variables, the whole series of measurements being related to the corresponding blood alcohol levels found (Goldberg, 1961).

The studies on tranquillizing agents and EEG were started in 1958 in co-operation with W. Chan and the late H. W. Newman at the Division of Neurology, Stanford University School of Medicine, Calif., U.S.A. The studies on subjective mood estimates were carried out in co-operation with G. Ekman and M. Frankenheuser at the Department of Psychology of the University of Stockholm.

The aim of the present communication is to give a survey of a series of studies on the possible effects and after-effects of the intake of various alcoholic beverages, covering:

Ocular phenomena, mainly positional alcohol nystagmus (PAN) and roving ocular movements (ROM), recorded by electro-oculography (EOG).

Cortical activity, recorded by electroencephalography (EEG).

Standing steadiness, i.e. area of sway while standing, recorded quantitatively by a new device, Statometer II.

Subjective estimates of psychological mood variables including alertness, drowsiness and fatigue, in relation to Time course of blood alcohol, as influenced by Tranquillizing drugs, fatigue, food intake and high temperature and humidity.

METHODS

Material. A total of 250 subjects took part in the experiments, all of whom were moderate drinkers. No alcoholics were included.

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Electro-oculography (EOG). Ocular movements were recorded by using the standing cornea-retina potential. Electrodes were placed at the outer corners of the eyes for measuring horizontal movements and over or under the eye for vertical movements, the eyes acting as dipoles. The actual movements were recorded after amplification on a direct-writing ink-writer.* Determinations of spontaneous ocular movements were carried out in a supine position, and with the head in the right and left lateral positions, with open and closed eyes. Ocular movements induced by lateral fixation were recorded in a supine position. Evaluation was carried out as to direction, frequency, amplitude and velocity, in the case of nystagmus corresponding to the velocity (eye-speed) of the slow component. (For details see Aschan 1955 a, Aschan, Bergstedt, Goldberg and Laurell 1956 b, Aschan, Bergstedt and Stahle 1956 c, and Goldberg 1961.)

Electroencephalography (EEG). EEG recordings were made by a Grass EEG apparatus, and as a rule only frontal and parietal bipolar leads were used. The records were evaluated as to frequency of $\alpha$-waves, percentage of $\alpha$-activity and voltage.

Standing steadiness. Standing steadiness was recorded by bilaterally arranged transducers, placed on a stand and covered by a footplate, the arrangement of the transducers allowing the recording of sagittal and frontal movements. The activity of the transducers was recorded electronically on an ink-writer, and transformed and fed into a counter, which allowed quantitative evaluation of the area of sway while standing. The subject stood on the footplate in a Romberg position (feet together) for a total of 200 seconds. During this time 10 recordings of 10 seconds each with open eyes were made, and 10 with the eyes closed. The records were evaluated with regard to average scores and variability within the series of 10 consecutive recordings. Various modifications of this basic design are currently under testing, the main ones being the counter to an electric typewriter and the activity found on tape for later processing and analysis (Bjerver, Ferguson, Goldberg and Mackay).

Subjective estimates of mood variables. The subject was instructed to estimate the subjective intensities of various mood variables in relation to his conception of a "standard state", denoted by the number 10. Any change from the "standard" was assigned a different figure; if he felt an increase in the intensity, a higher figure; if a decrease, a lower figure. The mood variables ranged from elated, happy and hazy to restless, talkative, tense and tired. Subjective working capacity was compared to objective performance, and subjective estimation of "degree of intoxication" was referred to a hypothetical standard, denoted as 10. (For details see Ekman, Franken-haeuser, Goldberg, Bjerver, Hjärpe and Myrsten.)

Alcoholic beverages. The various alcoholic beverages used, ranging from distilled spirits (whisky, "brännvin"), to dessert wines (sherry), table wines (claret) and beer (light and export beer), were given in various amounts and administered in four different ways:

1. Single dose administration. The whole dose was given as one dose, taken within 20 minutes, independent of the amount given, resulting in a blood alcohol curve with a steep rise, and a subsequent rectilinear fall.

2. Two-dose administration. A large dose within 20 minutes as in single dose administration, and a second dose 5–10 hours after the initial one, resulting in a blood alcohol curve with two maxima, depending on the time interval.

3. Multiple dose administration. (a) Several doses at 20-minute intervals for 2–3 hours, in a quantity resulting in a rising blood alcohol curve, the administration being stopped at a chosen breaking point, e.g. inco-ordination while standing. (b) One large priming dose to obtain a certain blood alcohol level, and a number of doses at 30–60 minute intervals in a quantity to maintain a constant blood alcohol level, for a shorter or longer period of time, as a rule for 5–10 hours.

Alcohol analysis. Samples for blood alcohol analysis were obtained from the fingertip in Widmark capillaries in triplicate (0-1 ml. each) at regular intervals of 30–60 minutes for 7–12 hours, and for urine alcohol analysis in samples, taken at intervals of 1½–3 hours for up to 15 hours. Analyses of the alcohol content were carried out according to Widmark’s micro method, and occasionally checked by the ADH-method, the experimental error of a triplicate analysis being ± 2 mg./100 ml. The blood alcohol curve was evaluated with regard to maximal blood alcohol concentration reached, the time until all

alcohol had disappeared, the rate of disappearance of alcohol from the blood (factor B), the distribution ratio (factor r), and the total amount of alcohol metabolised per kg. per hour (factor B·r·60).

**Drugs.** The following drugs were tested:

- **Series I.** Buclozine 50 mg., chlorpromazine 10 mg., hydroxyzine 25 mg., meprobamate 400 mg. and phenoglycodole 300 mg. The drugs were given the night before the actual test, the same morning, and at noon immediately before the alcohol intake—the experiment starting at noon—and then at 4-hour intervals; the experiments usually lasted for 5–7 hours. In this series the alcohol was administered in several doses at 20-minute intervals.

- **Series II.** The following drugs were tested: Acetylsalicylic acid 0-5 g. + codeine 0-01 g., chlordiazepoxide 20 mg., and meprobamate 500 mg. All drugs in this series were administered orally in the doses stated, once before alcohol, and a second time 4 hours after alcohol. The alcohol was administered as a single dose, and the experiments lasted for 14–16 hours.

**General Procedure:** All drugs were given as coded tablets, including three placebo tablets, in a randomised scheme on a double-blind basis, neither experimenter nor subject knowing the nature or dosage of the actual drug used. The identity of the drugs used was not disclosed until after the analysis of the material collected. As a rule one or two “dry” runs with all tests were carried out before the alcohol intake—EOG, EEG, standing steadiness and mood estimates—in order to provide a baseline of initial values, the tests then being repeated at fixed intervals, usually 20–30 minutes, and followed for 5–15 hours. In the long-term multiple dose experiments EOG was run at 45–60 minute intervals for 15–24 hours.

## RESULTS

The results to be described will be divided into four main parts, covering effects of intake of alcohol, effects of various alcoholic beverages, effects of alcohol + tranquillizers, and effects of fatigue, food intake and increase in room temperature and humidity.

### INTAKE OF ALCOHOL

The effects and after-effects of alcohol intake will be described with regard to four areas of effects, Ocular phenomena, mena, Electroencephalography, Standing steadiness, Subjective mood estimates.

#### Ocular Phenomena

The ocular phenomena recorded comprise positional alcohol nystagmus (PAN), alcohol gaze nystagmus (AGN), and roving ocular movements (ROM).

- **Positional Alcohol Nystagmus (PAN)**
  
  Before alcohol intake no positional nystagmus was observed in healthy subjects partaking in the present study. Only individuals showing no oto-neurological disturbances took part in these series. Alcohol intake in man in doses inducing a higher blood alcohol level than 60–70 mg./100 ml. blood elicited a specific pattern of positional alcohol nystagmus (PAN), consisting of two phases of horizontal nystagmus (PAN I and PAN II) (mainly in lateral positions of the head behind closed eyelids) when the alcohol was taken as a single dose within a short period of time (Aschan, Bergstedt, Goldberg and Laurell, 1956 a, b). When the alcohol was taken in multiple doses within a longer period of time, the resulting positional alcohol nystagmus showed varying patterns of alternating PAN I and PAN II (Aschan, Bergstedt and Goldberg).

- **Single dose**
  
  **PAN I:** The first phase (PAN I) occurred on an average 30 minutes after the beginning of the intake of a single dose, and showed a characteristic pattern. When the subject was in a supine position and the head turned to the right in a lateral position, the rapid component of the nystagmus recorded jerked to the right, and it changed its direction to the left when the head was turned to a left lateral position. The amplitude varied around 5–10° on an average, the frequency around 1–2 per second and the velocity (eye-speed) of the slow component around 2–4° per second. Whereas the intensity of PAN I varied with the height of the blood alcohol reached, the duration of PAN I was constant, independent of the dose taken, and lasted usually around three to four hours. After PAN I there usually followed an intermediate period, with no nystagmic activity and lasting 1–2 hours. Examples of normal eye movements are given in Fig. I, and of
PAN I in Fig. 2. The time course is given in Fig. 5.

**Fig. 2.** Positional alcohol nystagmus, phase I (PAN I), electro-oculographically recorded (exp. 5404). Recording made 61 min. after ingestion of 0-7 g. alcohol per kg. Blood alcohol concentration at time of recording 96 mg./100 ml. Horizontal nystagmus with rapid component beating to the right, subject in supine position, head turned to the right, eyes closed. Amplitude: 14-1° per beat. Frequency: 0-62 beats per sec. Velocity: 8-9° per sec.

PAN II: The second phase of positional alcohol nystagmus, separated from PAN I by the intermediate period, started 5-6 hours after the beginning of the intake of a single dose of alcohol, the latency time being usually independent of the dose of alcohol taken. The main characteristic of PAN II was the reversal of the direction as compared to PAN I. In a supine position with the head to the right in the lateral position, the PAN II had its beating direction (the fast component) to the left and was changed to the right in the left lateral direction.

The intensity and direction of PAN II were correlated with the height of the blood alcohol level, the intensity usually being somewhat lower than that of PAN I. PAN II could last for 5-15 hours, depending on the dose taken, but always lasted for many hours after alcohol had left the blood. Hence, PAN II is one objective after-effect of alcohol ingestion which can be recorded and evaluated quantitatively. An example is given in Fig. 3. The time course is given in Fig. 5.

**GENERAL CHARACTERISTICS:** Lower intensities of PAN I and PAN II are mainly recorded horizontally behind closed eyelids with the head in the right or left lateral positions. Opening of the eyes usually blocks the phenomenon, when the intensity is low. Higher intensities of PAN I and II will be recorded with open eyes also, and even in a supine position. Higher intensities of PAN I and PAN II are accompanied by diplopia and difficulty of fixation of gaze. Subjectively the higher intensities of both phases, PAN I and PAN II, are accompanied by dizziness, vertigo, nausea and sometimes vomiting.

Hence, phase II corresponds in character and in time after intake to the syndrome of post-alcoholic “hangover”, most probably being aetologically connected with those symptoms of hangover which range from vertigo and dizziness to nausea and vomiting. The relation between the intensity of the subjective symptoms and the intensity of the objective nystagmus recorded varies from individual to individual, females as a rule being somewhat more sensitive than males.

A characteristic observation is also that in some cases, when the initial recording before alcohol intake shows a rather irregular pattern with deviations from electroneutrality of 2-4° or more, the first few records after intake, but before the appearance of the alcohol nystagmus, showed a more regular pattern with very small deviations only, indicating a “relaxing” or “sedative” initial effect of alcohol.

With regard to the aetiology of the observed positional alcohol nystagmus, studies on humans with oto-neurological damage show that at least one functionally intact labyrinth is essential for the induce-ment of PAN I and of PAN II by alcohol (Aschan, Bergstedt and Goldberg). If one labyrinth or its central pathways is damaged, the positional alcohol nystagmus pattern will be changed in a characteristic
way. If both labyrinths are non-functioning, as tested by caloric and rotatory stimulation, no positional alcohol nystagmus is elicited (Aschan, Bergstedt and Goldberg). No PAN II has so far been induced in laboratory animals, ranging from rats and guinea-pigs to rabbits, cats and dogs (Goldberg and Stortebecker, 1941, 1943; Aschan (unpubl.), Goldberg (unpubl.).

Multiple dose administration

When alcohol was given in multiple doses, e.g. as a large priming dose and a series of small doses, an initial PAN I is observed during the time the blood alcohol is rising, and for several hours afterwards. In these experiments, started together with Aschan and Bergstedt, the administration of alcohol was continued for 8–10 hours, blood alcohol levels were followed for 10–15 hours, and a possible nystagmic activity followed by EOG for 24 hours. Depending on the actual course of the blood alcohol curve, whether rising or falling, different patterns of PAN I and PAN II were induced. In some cases, when blood alcohol is slowly rising for many hours and then slowly falling for several hours PAN I may also last for many hours, followed by a short intermediate period, during which no nystagmus is recorded, and then a long and very intense PAN II, also lasting for many hours. In other cases a series of rather short PAN I are seen, interspersed by shorter or longer intermediate periods, and then one or two PAN II also interspersed by shorter or longer intermediate periods. Finally a pattern has been observed, starting with a PAN I of usual latency time and a duration of 3–4 hours, a long intermediate period, lasting 6–8 hours, with no nystagmus, and a final PAN II, lasting 6–8 hours or more.

An analysis of the possible connection between the actual pattern observed and the course of blood alcohol shows that a rising blood alcohol curve after a short latency time of about 30 minutes brings about a PAN I, whereas a falling blood alcohol curve after a longer latency time, usually 3–4 hours, induces a PAN II.

If there already exists a positional nystagmus in a certain direction at the time a positional alcohol nystagmus is induced by alcohol intake, the alcohol-induced nystagmus is added to the existing nystagmus with its "sign". This means that the resulting nystagmus will be more intense than the alcohol-induced nystagmus, if the alcohol-induced nystagmus and the existing nystagmus are in the same direction. If the alcohol-induced and the existing nystagmus have different "signs", i.e. beat in different directions, the resulting nystagmus will be decreased, completely abolished or even reversed, depending on the intensity of the existing and the alcohol induced nystagmus. This means that not only is the dose of alcohol given of importance for the intensity of the resulting positional alcohol nystagmus, but also the pattern of administration. A certain amount of alcohol, if taken as a single dose within a short period of time, can bring about a high blood alcohol curve with a high maximum and elicit PAN I+PAN II of high intensities and long durations. The same quantity of alcohol, if divided into many small doses, spaced so as to be equal to the metabolic rate may, however, bring about such a low blood alcohol concentration, that a low intensity of PAN is elicited, or none at all.

With regard to the intensity of the subjective symptoms, correlated with the appearance of PAN I and PAN II, i.e. dizziness, vertigo, nausea and vomiting, our studies indicate that the intensity of these symptoms within certain limits is proportional to the intensity of the existing or resulting nystagmus, and not only to the intensity of the alcohol-induced nystagmus.

Hangover

The hangover symptoms of dizziness, vertigo, nausea and vomiting coincide in time with the maximal intensity of PAN II, occurring 8–10 hours after a single dose administration of alcohol. Hence it was interesting to study the effect on PAN of a new dose of alcohol, given in the hangover phase, when the acute effects of the first alcohol dose had worn off and the blood alcohol level had reached zero, hence corresponding in time of administration to a "morning drink" ("the hair of the dog that bit you").

Experiments were carried out in conjunction with Aschan and Bergstedt, in which the second alcohol dose was given 8–10 hours after alcohol intake, at a time when the blood alcohol curve from the first dose had already reached zero, and PAN II was at its peak intensity. This new alcohol dose had very distinct effects.

Within ½–1 hour after its administration the existing PAN II was reduced or
completely abolished, and in some cases even reversed into a PAN I, the effect depending on the dose given and the intensity of the existing PAN II. Parallel to the diminution of PAN II, its abolition or reversal, a change in the intensity of the subjective symptoms such as dizziness, vertigo and nausea was noted. The phenomenon observed is due to the interference by PAN I induced by the new dose of alcohol, with the still existing PAN II, induced by the previous alcohol dose. The net result, whether reduction, disappearance or reversal, depends on the doses of alcohol given, and the time of the administration of the second dose. The effect described lasted for 3-4 hours, then the situation was changed again. PAN II reappeared of the same intensity as before, or was increased or reduced. This was due to the new dose of alcohol now inducing a PAN II, the intensity of which was added to the intensity of the PAN II induced by dose I.

The mechanism described can serve as a model for our understanding of the seemingly paradoxical phenomenon, how one and the same substance at one time can elicit one effect and on another occasion abolish the same effect. The background is that the initial dose induces two separate and opposite effects, separate in time (=PAN I and PAN II), and the new dose, by inducing first PAN I, abolishes an existing PAN II, if administered at the right moment because it beats in the opposite direction. Later an increased effect may be produced, because the resultant PAN II is now the sum of a previous only partially blocked PAN II and a PAN II induced by the second dose. This phenomenon gives us one reason for the taking of a new dose of alcohol to relieve hangover, and for withdrawal symptoms in the alcoholic.

Alcohol Gaze Nystagmus (AGN)

When looking in a lateral direction, e.g., when following a moving object such as the observer's finger, the lateral gaze may under normal circumstances be accompanied by a few nystagmus-like ocular movements. After large amounts of alcohol a distinct alcohol gaze nystagmus (AGN) may be elicited, showing a frequent nystagmus (several times per second), with the rapid component in the gazing direction, and often with a rather small amplitude of only a few degrees. Recordings of AGN have been made by Aschan (1958), showing AGN to be present in one phase only. AGN appears when the blood alcohol concentration is higher than a critical level, usually 60-70 mg./100 ml., and disappears when the blood alcohol falls below that level.

PAN versus AGN

In clinical practice it might be of value to be able to assert the presence or absence of a nystagmus, and to make a tentative diagnosis as to the nature of the nystagmus observed, if alcohol-induced or not. When observing nystagmus in clinical practice, the alcohol gaze nystagmus seems as a rule to be the one most easily observed, and is elicited by means of a moving object with the patient's eyes kept open.

In order to assess a possible positional alcohol nystagmus (PAN), existing mostly in lateral positions behind closed eyelids, the patient will have to be put on his back, his head turned laterally to one and the other side, and the eyes closely watched. An existing positional alcohol nystagmus, even if not recorded, may disclose itself by the observer seeing, and feeling, the cornea moving behind the closed eyelids. Opening of the eyes will block the positional alcohol nystagmus, if its intensity is low, but will disclose it if the intensity is high. The positional alcohol nystagmus (PAN) can be differentiated from a gaze nystagmus (AGN) by testing when the eyes look forward, and not only in lateral gaze direction, also by the direction of the fast component which changes with the position of the head and with the time after intake (PAN I or PAN II respectively).

Roving Ocular Movements (ROM)

Roving ocular movements (ROM) are one type of ocular phenomena, which can sometimes be recorded even before alcohol intake, either in states of drowsiness, sleepiness and fatigue, e.g. after lack of sleep (as when the subject has worked the night before) or after a heavy meal. ROM are also recorded during and after alcohol
intake and in connection with the administration of tranquilizing agents (Goldberg, 1961). A typical recording is shown in Fig. 4.

Roving ocular movements (ROM) are recorded mainly behind closed eyelids, in a supine position as well as in lateral positions, and show a regular pendular pattern of a sinusoidal character. They are horizontal and are seen only rarely in vertical recordings. The amplitude usually varies between 5—15°, the frequency around 1/4 period per second, and the velocity around 2—4° per second. Lower intensities are usually blocked by opening the eyes, higher intensities may also be recorded when the eyes are open. Higher intensities of the roving ocular movements are accompanied by subjective feelings of drowsiness, sleepiness and fatigue. The relation between the intensity of the recorded roving movements and the intensity of the subjective symptoms may vary considerably from individual to individual. If a subject displays a typical ROM pattern and is drowsy and sleepy, arousal—e.g. engaging him in conversation, having him count or solve a problem—causes the ROM pattern to disappear, ROM returning as soon as he becomes drowsy and sleepy again.

After alcohol intake the appearance of a positional alcohol nystagmus is the rule. If ROM appears it is usually observed some hours after intake and lasts for 1—2 hours—the movements are usually rather small and insignificant. In other cases ROM may be observed for several hours, in many cases even after alcohol has left the blood, i.e. as an objective after-effect.

Under certain circumstances, especially if the subject already feels tired before the intake of alcohol, roving ocular movements dominate the picture. During the time ROM is present, it blocks completely a positional alcohol nystagmus. In some recordings periods of ROM and PAN patterns may alternate within seconds to minutes. The ROM pattern is in these cases accompanied by a subjective feeling

Fig. 4. Roving ocular movements (ROM). Horizontal electro-oculographical recording, made 4 hours after ingestion of 0.7 g. alcohol per kg. +0.4 g. meprobamate, blood alcohol 40 mg./100 ml. Subject in supine position, head in right lateral position, eyes closed (exp. 5426). Amplitude: 4.5° per beat. Frequency: 0.28 beats per sec. Velocity: 2.5° per sec.

of drowsiness, sleepiness or overt sleep. When analysing the intensity of PAN and ROM in a large number of experiments carried out under varying conditions it was found that the mean intensity of PAN during a fixed period of time was inversely proportional to the mean intensity of ROM during the same period of time (Goldberg, to be publ.).

With regard to the aetiology an analysis of the evidence makes it probable that roving ocular movements (ROM) may be elicited in the reticular system. The presence of a ROM pattern is often accompanied by a “sleep pattern” in the EEG (see below), and the absence of a ROM pattern is often accompanied by an arousal pattern in the EEG (Goldberg, to be publ.).

The antagonism between PAN and ROM may thus be due to the interrelationship between the reticular and the labyrinthine systems (Goldberg, 1961). The very rapid alteration which is often seen within

Fig. 5. Relation between PAN, ROM and blood alcohol (from Goldberg 1961). Horizontal electro-oculographic recordings made after 0.7 g. alcohol per kg., subject in supine position; head in right and left lateral positions, eyes closed. Average intensities: PAN I. Ampl.: 5.0° per beat. Freq.: 1.1 beats per sec. Veloc.: 5.6° per sec. Dur.: 150 min. PAN II. Ampl.: 2.0° per beat. Freq.: 1.2 beats per sec. Veloc.: 2.4° per sec. Dur.: 600 min. ROM. Ampl.: 1.6° per beat. Freq.: 0.3 beats per sec. Veloc.: 0.4° per sec. Dur.: 225 min.
minutes between PAN and ROM is an objective indication of the rapidly varying state of affairs in the central nervous system, illustrating how various parts of the CNS dominate the picture at various times.

**Electroencephalography**

Alcohol intake induces three changes in the EEG, when recorded with bipolar leads frontally or parietally.

There was a slowing of the α-frequency, usually falling from an average of 10–11 per second to 8–9 per second, i.e. by 20–30%, when blood alcohol reached about 100 mg./100 ml. The fall in α-frequency was in the whole proportional to the increase in blood alcohol in one and the same individual. The relation may vary, however, very considerably from individual to individual. There was also an increase to be noted in the θ-percentage, i.e. in the fraction of time occupied by periods of α-frequency patterns as compared to the time of the whole record. The α-frequency usually rose up to 60–70% after alcohol intake. Finally there was an increase in the voltage, predominantly within the spindles; the increase from normal amounted to about 100% when blood alcohol rose to about 100 mg./100 ml. The increase in voltage was roughly proportional to the blood alcohol in one and the same individual, but may vary considerably from subject to subject.

These studies are still of a preliminary nature, awaiting the completion of a technique under development, allowing of automatic quantitative evaluation in the EEG of changes in several frequency ranges and their relation to blood alcohol.

**Standing Steadiness**

The main results to be reported are still of a preliminary nature, because the technique employed is still under development. The present apparatus, comprising one set of transducers, enables the measurement of changes in standing steadiness by recording the variations in the area of sway while standing. After proper transformation the information obtained from the transducers was fed into a counter, which was read off ten times in two 100-second periods, during the first period the subject stood with open eyes and during the second with closed eyes. The average sway and the variability of sway, i.e. the coefficient of variation (standard deviation in per cent of mean) were evaluated. Before alcohol intake there were already variations in standing steadiness within one and the same individual from time to time as well as between individuals. When repeating the measurements at short intervals, e.g. 10–30 minutes, a distinct learning curve was observed, a constant level usually being obtained after 3–4 measurements. The present technique allows the recording of the difference in area of sway while standing with open eyes and with closed eyes, the difference being in the order of several hundred per cent.

After alcohol intake a rise in the area of sway was noted, parallel to an increase in the blood alcohol level, the maximal deviation from pre-alcohol values as a rule being noted simultaneously with the blood alcohol maximum. The area of sway then fell, parallel to a fall in blood alcohol, and in our subjects approached the pre-alcohol levels at blood alcohol concentrations of 30–40 mg./100 ml. if the experiments did not last longer than about five hours. The same principal changes were observed both with open and closed eyes, when the time course only is taken into account, as both curves seemed to reach pre-alcohol levels at about the same time. There was, however, as was to be expected, considerably more swaying with closed eyes.
eyes than with open eyes. A typical result is shown in Fig. 6.

When evaluating the variability between a series of consecutive readings, it was noted that during establishment of the learning curve, i.e. before alcohol intake, the variability was constant, i.e. the standard deviation changed in proportion to the change in the mean area of sway while standing. When after alcohol intake the mean values rose in proportion to the rise in blood alcohol, and later fell again in proportion to the fall in blood alcohol, the variability changed parallel to the change in the mean values, i.e. rose with rising values and fell with falling values. If, however, the mean values rose due to other reasons, e.g. fatigue, the variability seemed to be constant or even to fall, thus changing in the opposite direction during alcohol intoxication.

Hence alcohol intake seemed to have a two-fold effect on the standing steadiness. Alcohol caused an increase in the area of sway and an increase in the variability (i.e. a larger variation from time to time during one series of readings) both changes being an indication of an impaired coordinating mechanism. The site of action will be studied in detail by recording action potentials from agonists and antagonists; preliminary studies showed that the amplitude of the action potentials rose simultaneously in agonists and antagonists of the lower limb (Bjerver, to be publ.).

Subjective Estimates of Mood Variables

The primary experiments in this series on subjective mood estimates in relation to blood alcohol levels were carried out in co-operation with G. Ekman and M. Frankenhaeuser of the Department of Psychology at the University of Stockholm (Ekman, Frankenhaeuser, Goldberg, Bjerver, Hjärpe and Myrsten 1963).

The experiments have since been extended to include mood estimates after alcohol + drugs (Goldberg, to be publ.).

Self-estimation of Degree of Intoxication

The subject was asked to estimate his "degree of intoxication" by comparing his actual state with a "standard", called "a little high" and denoted by the figure 10. If he did not feel intoxicated the degree was denoted as 0. The subjective estimates followed very closely the course of the blood alcohol curve, the maximal subjective intensity coinciding in time with the objective maximal blood alcohol intoxication. A relation was also found with the amount of alcohol taken. In one and the same subject a higher blood alcohol level corresponded to a higher subjective degree of intoxication.

Other Mood Variables

With regard to other mood variables it was noted that moods denoted as "talkative", "elated", "tense", etc., showed an increase in intensity, parallel to the maximum of blood alcohol and corresponding in course to the subjective estimation of "degree of intoxication", but of shorter duration. It was interesting to note that subjective "working capacity" showed a short improvement at the maximal blood alcohol, at the same time that objective work performance showed an impairment.

With regard to "fatigue" and "drowsiness", the time course of the intensity of subjective estimates of these mood variables differed considerably from the time course of the blood alcohol. The subjects as a rule felt less fatigued with rising blood alcohol, parallel to the improvement in subjective "working capacity" and corresponding in time to an impairment in objective work performance.

At the end of an experimental period, 5 hours after alcohol intake, when blood alcohol had fallen and was almost zero, the subjects felt very fatigued and sleepy, considerably more than during blood alcohol maximum, in some cases even as late as 10–12 hours after intake, and many hours after alcohol had left the blood. This late increase in the intensity of the subjective estimates of fatigue and drowsiness corresponds in time both to positional alcohol nystagmus PAN II, and to the late appearance of roving ocular movements (ROM) after the alcohol has disappeared from the blood, as well as to the late increase in area of sway, seen in standing steadiness tests.

The adopted methods of subjective estimates of mood variables thus seem to give a picture of the variations and time course of the subjective experience of alcohol, and how the mood varies with changes in blood alcohol and hence with the amount of alcohol taken and with the time after intake.

EFFECT OF DIFFERENT ALCOHOLIC BEVERAGES

When studying the effect of different alcoholic beverages on the ocular phenomena described, quantitative as well as
PHARMACOLOGICAL AND PHYSIOLOGICAL ASPECTS

Qualitative differences between different beverages were noted.

When a fixed dose of alcohol is given in various types of beverages—e.g. 50 g. alcohol corresponding to 140 ml. whisky, 280 ml. dessert wine as sherry or port, 560 ml. red or white wine, or about 1½ litres of beer of 3-2% alcohol by weight—it is found that these different beverages do not bring about the same blood alcohol curves. The curves after distilled spirits show the highest peak, then dessert wine and table wines, beer as a rule bringing about the lowest blood alcohol curves. The differences are mainly due to differences in the absorption rate, depending partly on the difference in concentration and partly on the presence of various compounds in the beverages which modify the absorption, e.g. carbohydrates. The buffer capacity of the beverage influences the absorption and emptying time of the stomach (Bjerver, Goldberg and Movin). Whether metabolic differences exist is not yet established.

Parallel to the observed changes in the blood alcohol level changes in the intensity of the induced alcohol nystagmus (PAN) are observed. Hence, as a rule beverages other than distilled spirits induce PAN of a lower intensity, seemingly in proportion to the blood alcohol curve. It was also observed in preliminary experiments that various beverages induced more or less roving ocular movements (ROM). When trying to keep all conditions constant: including temperature humidity, and state of alertness and fatigue, it seems as if wines might bring about a somewhat higher intensity of ROM than other alcoholic beverages; whether this is accompanied by a lower intensity of PAN is not yet established.

The method of electro-oculography, including quantitative evaluation of PAN and ROM, when combined with EEG and standing steadiness studies, will serve to help pin-point the site and the mode of action of various alcoholic beverages and thus help to explain existing differences in acute and long-term effects of various beverages.

ALCOHOL+TRANQUILLIZERS

The first set of experiments designed to study the combined effect of alcohol and tranquillizers was carried out at the Division of Neurology, Stanford University, California, U.S.A., together with W. Chan and the late H. W. Newman. The various tranquillizers used—buclozine, chlorpromazine, hydroxyzine, meprobamate and phenoglycodol—were given in therapeutic doses the night before, the same morning, at noon, and at 4-hour intervals during the actual experiment, on a double-blind basis as coded tablets; three placebo tablets being included in the series, together with alcohol. A number of tests with various drugs, including several placebos, were run on each subject, a total of 10 subjects partaking in this study.

Alcohol was given in a dose of 2 c.c. whisky per 10 lbs. body weight every 20 minutes, electro-oculography, electroencephalography and standing steadiness (standing on one foot per 30 second), being tested immediately after each dose. Blood alcohol was followed, and the administration of alcohol stopped when the subject failed to stand on one foot, which occurred after 2–4 hours.

The second set of experiments comprised chlordiazepoxide, meprobamate and a number of other CNS—depressant drugs, including codeine and hydrocodone, given once before, and once 4 hours after, alcohol intake. Alcohol was given as a single dose, and all tests, including blood alcohol, were followed for 14–16 hours.

The results of the alcohol+drug experiments, as compared to alcohol+placebo, are still being analysed; some preliminary results will be given here.

Blood Alcohol Thresholds

The blood alcohol curves (followed during the rising part only for 3–4 hours due to the design of the first set of experiments) showed the same course after alcohol+placebo as after alcohol+drug. The blood alcohol level, when incoordination while standing occurred, was, however, considerably lower after alcohol+tranquillizer than after alcohol+placebo. The average after alcohol+placebo was 130 mg./100 ml., against 100 mg./100 ml. after alcohol+tranquillizers. The results indicate that at a certain blood alcohol level the subject was considerably more intoxicated and showed a higher degree of intoxication when having taken alcohol+tranquillizer, than after taking alcohol+placebo.

As the degree of intoxication increased logarithmically with the increase in blood alcohol at higher blood alcohol levels (Goldberg, 1943), and as the degree of intoxication is approximately proportional to the area of the blood alcohol curve over
a certain limit value, rather than to the concentration of alcohol at the peak value (Goldberg and Isaksson, 1957), the difference in degree of intoxication between alcohol + tranquilizer and alcohol + placebo is larger than the ratio between the two blood alcohol levels quoted.

Hence, while the intake of a moderate dose of alcohol by an individual when he is being treated with tranquilizing drugs may induce a marked intoxication, the same alcohol dose under normal circumstances, when the individual has not taken tranquilizing agents, might bring about no apparent intoxication.

**Ocular Phenomena**

**Positional Alcohol Nystagmus (PAN)**

None of the tranquilizers in the therapeutic doses used in these tests induced a positional nystagmus, when given alone. When given prior to alcohol intake, they all reduced the intensity of the positional alcohol nystagmus induced by the alcohol intake, varying in degree from drug to drug. The reduction was seen both with PAN I and PAN II. A quantitative analysis is under way to determine whether it is possible to find quantitative differences between the various drugs.

**Roving Ocular Movements (ROM)**

The tranquilizing agents used in this study when given in therapeutic doses produced in our healthy subjects few subjective effects of drowsiness, relaxation and tiredness. Parallel to this lack of subjective reaction no, or only small, roving ocular movements (ROM) were recorded before alcohol intake. It seems reasonable to assume, however, that higher doses of tranquilizing agents, parallel to subjective effects of higher intensity, will bring about roving ocular movements even without alcohol; experiments in this direction are in progress. After alcohol + tranquilizers there was a very sharp increase observed in the intensity of ROM, corresponding to an increase in the subjective feeling of fatigue, drowsiness and sleepiness, some subjects sleeping for shorter or longer periods between recordings (and even during actual recording of EOG and EEG).

As already mentioned, there was an alternation between PAN and ROM. When ROM appeared simultaneously with a feeling of drowsiness or sleepiness, PAN disappeared, and when the subject was aroused by being spoken to, or having to count or talk, ROM disappeared and PAN reappeared. These changes in ocular pattern sometimes occurred several times per minute. When plotting the average mean intensity of PAN during an experiment against the mean intensity of ROM during the same time, an inverse relationship was found. When ROM increased in intensity, PAN decreased, and with a high ROM activity PAN could be completely abolished. This implies that the reduction or abolition of PAN and its accompanying symptoms of dizziness, vertigo and nausea by tranquilizing agents is followed by a corresponding increase in ROM, and hence in drowsiness, sleepiness, fatigue, and in inco-ordination, as revealed by standing steadiness tests.

**Electroencephalography**

When given alone the tranquilizers, even in healthy individuals, if taken in therapeutic doses, might in some cases bring about a slowing of the $\alpha$-frequency by $10-20\%$, an increase in $\alpha$-percentage, and an increase in voltage, especially of the spindles. The changes were qualitatively not unlike the changes brought about by alcohol intake, but the "sleep pattern" dominated. Alcohol + tranquilizers usually accentuated the changes brought about by the alcohol alone, and in the same direction as described, i.e. a further slowing of the $\alpha$-frequency, a higher $\alpha$-percentage and an increase in voltage, especially of the spindles. Hence a correlation between ROM and specific changes in the EEG may be postulated, parallel to a change in the subjective mood variables. A more detailed analysis of these phenomena is in progress. The analysis so far carried out indicates that the presence of ROM in the EOG record and subjective feelings of drowsiness, sleepiness and fatigue, are accompanied by a "sleep pattern" in the EEG, with a clear reduction of the arousal pattern.

**Standing Steadiness**

Standing steadiness in these experiments was estimated by having the subject stand on one foot, noting the time when he fell, stopping the test at 30 seconds and later at 60 seconds. Tranquilizers alone brought about a certain impairment in standing steadiness in some cases. The combination of alcohol + tranquilizers brought about two main changes: (1) The amount of alcohol necessary to produce a defined state of inco-ordination was reduced, and inco-ordination occurred at lower blood
alcohol levels than after alcohol alone, (2) at a given blood alcohol level the degree of incoordination was higher after alcohol+tranquillizer than after alcohol+placebo.

Experiments are in progress to adopt a quantitative measurement of standing steadiness, as already described, for the analysis of the combined effect of alcohol+tranquillizers.

Subjective Mood Variables

Only a few individuals noted obvious changes from normal after the intake of therapeutic doses of the tranquilizers tested, which is to be expected in healthy individuals. The majority noted an increase in the degree of intoxication after alcohol+tranquillizer, as compared to alcohol+placebo, an increase in fatigue, drowsiness and sleepiness being the regular symptoms mentioned, and these were also noted by the observer. Relaxation, feeling calm, less talkative or restless, less tense, were mentioned only occasionally, which is to be expected in healthy individuals. No patients with anxiety, tension or other nervous symptoms were included in the present series.

The studies are being extended to include systematic quantitative subjective estimates of a number of mood variables with a series of tranquilizers, alone and together with alcohol, and related to ocular phenomena, EEG, standing steadiness and blood alcohol levels; some ten drugs are in the process of being tested on healthy subjects.

FATIGUE, FOOD INTAKE, INCREASE IN TEMPERATURE AND HUMIDITY

From the vast number of experiments carried out, the effects of a number of other interfering agents could be evaluated.

Fatigue. When the subjects were very fatigued, e.g. when they came to the experiment in the morning, having worked late the night before, the EOG recording prior to the alcohol intake showed a ROM pattern, which interfered with the PAN induced by the alcohol intake. The resulting PAN was reduced, or even completely abolished, for some hours. Some hours later PAN II usually showed normal intensity, as seen in earlier experiments in the same subject with alcohol intake after a normal night's sleep.

Standing steadiness showed an increased area of sway under the same conditions, and subjective estimates of fatigue and drowsiness completed the picture. Intake of food under certain conditions brings about an increased feeling of fatigue and drowsiness—special experiments were conducted to elucidate this phenomenon.

Food intake. The intake of food some hours after the intake of alcohol, especially a substantial meal including carbohydrates, fats and proteins totalling 1,500 calories had considerable effects on the tests performed. The EOG recordings showed a ROM pattern reducing or blocking an existing PAN pattern. The standing steadiness test showed a large increase in the area of sway, marking itself as a new maximum if the intensity curve of area of sway was falling. Subjective mood estimates showed an increase in the intensity of fatigue, drowsiness and sleepiness, and a corresponding decrease in alertness and working capacity.

These changes occurred not only within the first 3–4 hours after alcohol intake—they were also observed 8–10 hours or later after alcohol intake, i.e. long after alcohol had left the blood. The changes were substantially larger than in "dry" runs at the same time of day without alcohol intake, the previous alcohol intake hence accentuating or potentiating the impairment in mental alertness and coordination.

A typical experiment is illustrated in Fig. 6.

Increase in temperature and humidity. From experiments run on a double blind basis with coded placebo tablets at different temperatures and degrees of humidity, it was established that an increase in room temperature from 65–68°F. (18–20°C.) to 79–86°F. (26–30°C.) and a corresponding increase in humidity had the same effect as a therapeutic dose of a tranquilizer+alcohol. The increase in temperature and humidity induced a decrease in PAN, a corresponding increase in the ROM pattern, as well as a change in the EEG towards a "sleep" pattern, an increase in incoordination at a fixed blood alcohol level and a lowered critical blood alcohol level, an increase in the intensity of subjective estimates of fatigue, drowsiness and sleepiness, the subjects being overtly sleepy and tired (Goldberg, 1961).

Especially with regard to fatigue, induced by different factors, from drugs to other agents, the methods employed seem promising in picking up variations in the subjective feeling of being tired and its objective correlates, as seen in electrooculographic recordings, in quantitative
EEG recordings, and in measurements of standing steadiness. The set of objective and subjective tools used seems also to make it possible to obtain a closer view of the possible site of action and mode of action of a number of factors, influencing the normal functioning of the central nervous system.

Summary
The methods used in the present study include electro-oculography (EOG) to record alcohol nystagmus (PAN) and roving ocular movements (ROM), EEG, statometry to record standing steadiness, subjective estimates of alertness, fatigue and drowsiness and determinations of the concentration of alcohol in blood, breath and urine. The battery of tests was run at regular intervals for 10–15 hours in experimental subjects before and after intake of distilled spirits, wine or beer + placebo or drugs on a double-blind basis.

The main results reached were:

1. Objective and subjective effects and after-effects were recorded for many hours after alcohol had left the blood. These effects were especially noticeable on PAN, ROM, standing steadiness and fatigue, i.e. in the period of hangover.

2. The addition of various drugs, e.g. tranquilizers, modified the objective and subjective effects and after-effects in various quantitatively different ways for the various drugs.

3. The intake of food, even hours after alcohol ingestion, increased the intensity of ROM, impaired standing steadiness and increased drowsiness and fatigue, even after the alcohol had left the blood.

4. The procedure used allows the action of tranquilizers, stimulants or other agents on the effects and after-effects of alcohol, to be tested objectively, e.g. the potentiating effect of food intake, fatigue, increased temperature and humidity or lack of sleep.

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