Department of Epidemiology and Biostatistics

Course 607A

Principles of Inferential Statistics

Final Examination
TAKE-HOME PORTION

Guidelines

1. The answers do not have to include any long arithmetic calculations, but they should include all the steps so that it is clear what is to be done (i.e. so that your research assistant, who knows no statistics, could complete the calculations).

2. The null hypothesis used in any test should be stated explicitly. Degrees of freedom (where applicable) should be indicated; also, it should be made clear whether you are using a one- or two-tailed test, and what Table in Colton (or elsewhere) would be used.

3. In answers that require discussion, be BRIEF; LIST only the points of major importance.

Answers Due

Room 34B , before 5 pm on Monday , December 17, 1984.

1. Ear-Canal Hair and the Ear-Lobe Crease as Predictors for Coronary-Artery Disease.

(i) Why did the authors consider it important to use an age-matched comparison when studying ear-canal hair but an unmatched comparison for ear-lobe crease?

(ii) Verify the X^2 of 11.1 in Table 1.

(iii) Reconstruct the X^2 of 4.0 in Table 2. What would the p-value be if the authors had used the binomial table rather than the X^2 table for Table 2? Can you reconcile the difference in the 2 p-values?

(iv) Do you agree with the authors' choice of analysis and interpretation of the data in Table 3?

(v) Comment on their statement regarding the sensitivity and false negative rate of the ear-lobe crease/ear-canal hair combination.

(If you wish, write your answers to (ii)-(v) in the form of the Letter to the Editor - we might consider submitting a letter from the best answers in the class.)

EAR-CANAL HAIR AND THE EAR-LOBE CREASE AS PREDICTORS FOR CORONARY-ARTERY DISEASE

To the Editor: The ear-lobe crease has been demonstrated to be significantly associated with coronary-artery disease in specific populations.[1] Patterns of hair growth have previously been suspected as possible risk factors for coronary-artery disease.[2,3] We investigated both the ear-lobe crease and ear-canal hair — the presence of one or more terminal hairs growing on the tragus or antitragus or from the external acoustic meatus (Fig. 1) — in 43 men and 20 women (36 to 76 years of age; mean, 56.3) who underwent coronary cineangiography. Coronary-artery disease was defined as a 50 per cent or greater luminal narrowing of one or more coronary arteries. Standard chi-square methods were used for the 63 subjects, and the McNemar test was used for 22 age-matched and sex-matched men (mean age, 51.2) on the variables of ear-lobe crease and ear-canal hair.

The ear-lobe crease was found to be significantly associated with coronary-artery disease ($n = 63$, $\chi^2 = 11.1$, $df = 1$, $P<0.001$, Table 1), and a significant difference was seen between men with and without coronary-artery disease in the presence of ear-canal hair ($n = 22$, $\chi^2 = 4.0$, $df = 1$, $P<0.05$, Table 2) when age was controlled for. The combined presence of ear-canal hair and the ear-lobe crease was found to be significantly associated with coronary-artery disease ($n = 43$, $\chi^2 = 4.77$, $df = 1$, $P<0.05$, Table 3). Moreover, combining the ear-lobe crease and ear-canal hair yielded the greatest sensitivity (90 per cent) and the lowest false negative rate (10 per cent).

The frequency of hairy pinnae in men varies according to genetically defined populations, and the penetrance of this trait is variable.[4] Various amounts of hair may grow anywhere on the external ear, and specific loci of hair growth are seen in specific populations.[4] Hairy pinnae are unusual in women,[5] and none were found in this study. Ear-canal hair was found to be present in 74.4 per cent of men in this study.

Figure 1. Presence of the Ear-Lobe Crease and Ear-Canal Hair in Addition to Hair on the Helix.

Table 1. Chi-Square Analysis of the Ear-Lobe Crease (ELC) in 63 Men and Women with and without Coronary-Artery Disease.

ELC	Coronary-Artery Disease: Present	Absent	
Present	28	4	32
Absent	15	16	31
	43	20	63

Table 2. McNemar's Test of Ear-Canal Hair (ECH) in 11 Pairs of Age-Matched Men with and without Coronary-Artery Disease (CAD).

Distribution within Pair	No. of Pairs
CAD present and ECH present; CAD absent and ECH present	6
CAD present and ECH present; CAD absent and ECH absent	4
CAD present and ECH absent; CAD absent and ECH present	0
CAD present and ECH absent; CAD absent and ECH absent	1

Table 3. Chi-Square Analysis of the Ear-Lobe Crease (ELC) and Ear-Canal Hair (ECH) in 43 Men with and without Coronary-Artery Disease.

ELC & ECH	Coronary-Artery Disease: Present	Absent	
Present	18	2	20
Absent	14	9	23
	32	11	43

Androgens may facilitate the development of atherosclerosis and coronary-artery disease. The association between ear-canal hair and coronary-artery disease may be due to the long-term exposure to enough androgen to cause both ear-canal hair growth and coronary-artery disease. The degree of androgenicity in a patient over a period of years may explain the eventual virilization of the ear and the associated accelerated atherosclerosis in these patients. Another androgen-sensitive trait, male pattern baldness, has also been recognized as a predictor of coronary thrombosis in men, possibly on the same basis.

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1. Elliott WJ. Ear lobe crease and coronary artery disease: 1000 patients and review of the literature. Am J Med 1983; 75:1024-32.
2. DiGirolamo M, Schlant RC. Etiology of coronary atherosclerosis. In: Hurst JW, Logue RB, Schlant RG, Wenger NK. The heart, arteries, and veins. 4th ed. New York: McGraw-Hill 1978:1108.
3. Cotton SG, Nixon JM, Carpenter RG, Evans DW. Factors discriminating men with coronary heart disease from healthy controls. Br Heart J 1972; 34:458-64.
4. Stern C, Centerwall WR, Sarkar SS. New data on the problem of Y-linkage of hair pinnae. Am J Hum Genet 1964; 16:455-71.
5. Sarkar SS, Ghosh RR. Hairy pinnae in the Bengalee female. Lancet 1963; 1:1432.

 Blood Alcohol and Eye Movements

BLOOD ALCOHOL AND EYE MOVEMENTS

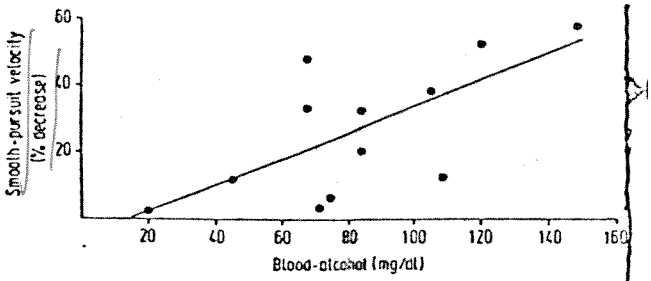
SIR,—Alcohol is known to affect eye movements.[1,2] Smooth pursuit and saccades are impaired when the blood ethanol concentration is in the region 60–100 mg/dl,[1] but the magnitude of the effect in relation to the blood concentration has not been examined.

The maximum velocity reached by the eyes during smooth pursuit is between 40 and 100°/s.[3] Above this threshold, eye tracking is accomplished largely by saccades. Since vision is not perfect during saccades[4] a decrease in the velocity capacity of the smooth-pursuit system will impair vision and even lead to nystagmus.[5] The smooth-pursuit system may be involved in producing the slow component of optokinetic nystagmus[6] and in suppression of vestibular induced nystagmus, both of which are important for maintaining foveal (optimum) vision.[3,4]

To study the relations between blood alcohol concentration and smooth-pursuit velocity, six male and six female healthy volunteers, aged 21–42 (mean 30) years, had baseline eye-movement tests done between 1530 and 1630 h. The volunteers then drank whisky and water or gin and tonic until they considered themselves unfit to drive. Eye-movement tests were then repeated and blood was taken for determination of ethanol concentration by gas-liquid chromatography.[7]

A standardised electro-oculographic procedure[3] was used to record smooth-pursuit eye movements on magnetic tape. The velocity of smooth-pursuit eye movements was measured by off-line computer analysis. This method measures the maximum velocity that the eyes can reach in smooth pursuit, before breaking down into saccades. The smooth-pursuit threshold velocity was 58·5±11 (SD) °/s before and 43±13·6 (SD) °/s after alcohol ingestion ($p<0·01$) when alcohol blood concentrations were 83±34 (SD) mg/dl.

There was a direct linear relation ($r=0·67$, $p<0·05$) between the decrease in smooth-pursuit velocity and the alcohol concentration (figure). This result provides reliable evidence that at a blood ethanol of 80 mg/dl (the legal limit in the U.K. for driving purposes) smooth-pursuit eye movements—i.e., the capacity of the eyes to track objects moving slowly across the visual fields—is impaired by about 25%.



Direct linear correlation between blood alcohol concentrations and % decrease in smooth-pursuit velocity.

$n=12$, $r=0·67$, $p<0·05$.

(1) What test do you think the authors used to show that the decrease of 58.5 - 43.0 = 15.5 degrees per second is statistically significant? Do you have enough data to verify their calculations?

(2) Verify that the p value is indeed less than 0.05 for the "direct linear relation".

(3) In fitting a regression line of the % decrease (y) on the blood alcohol (x), which would be a more suitable candidate (a) a straight line through the origin? (b) a straight line with nonzero intercept? Why?
[Answer as if you had been asked the question before seeing the data.]

(4) Do you agree that the regression result provides reliable evidence that at a blood ethanol of 80 mg/dl the capacity of the eyes to track objects moving slowly across the visual fields is imparied by about 25%? If a judge quoted you this statement, how would you defend yourself? [Your defense must be statistical but intelligible to the judge, who has never taken 607!] The data are given below (slightly rounded).

Subject	1	2	3	4	5	6	7	8	9	10	11	12
Sex	F	F	F	F	F	F	M	M*	M	M	M	M
Alcohol	84	67	71	105	109	74	148	45	67	20	84	120
Decrease	31	33	2	38	12	6	58	13	48	2	20	51

(5) List 3 suggestions for improving on this study.

3. . ACETAZOLAMIDE IN PREVENTION OF ACUTE MOUNTAIN SICKNESS: A DOUBLE-BLIND CROSS-OVER STUDY*

Abstract

Twenty-four amateur climbers took part in a double-blind controlled cross-over trial of acetazolamide versus placebo for the prevention of acute mountain sickness. They climbed Kilimanjaro (5895 m) and Mt Kenya (5186 m) in three weeks with five rest days between ascents. The severity of acute mountain sickness was gauged by a score derived from symptoms recorded daily by each subject. On Kilimanjaro those taking acetazolamide reached a higher altitude (11 v 4 reached the summit) and had a lower symptom score than those taking placebo (mean 4·8 v 14·3). Those who had taken acetazolamide on Kilimanjaro maintained their low symptom scores while taking placebo on Mt Kenya (mean score 1·9), whereas those who had taken placebo on Kilimanjaro experienced a pronounced improvement when they took acetazolamide on Mt Kenya (mean score 2·5). Acute mountain sickness prevented one subject from completing either ascent. Acetazolamide was acceptable to 23 of the 24 subjects.

Acetazolamide is recommended as an acceptable and effective prophylactic for acute mountain sickness.

Introduction

The present popularity of short trekking holidays with rapid ascents has concentrated attention on the problem of acute mountain sickness. This is a symptom complex in which weakness, breathlessness, dizziness, and nausea impair performance and enjoyment for those who are unacclimatised and who venture over 3000 metres. It is usually mild and transient and at its worst within three days; in a few people, however, it progresses rapidly to life-threatening pulmonary or cerebral oedema. Incidence is highest when ascent is rapid and exertion great. Susceptibility has been reported greatest in the young, decreasing up to the age of 40.[1] At high altitudes, the hyperventilation which would compensate for a falling arterial oxygen is inhibited by the respiratory alkalosis which it induces. This happens chiefly during sleep and it is at that time that acetazolamide may have a beneficial effect by producing a metabolic acidosis.[2,3] The place of acetazolamide in the prevention of altitude sickness has been explored through decompression experiments and in several clinical trials. No trekking expedition, however, has met all the requirements of a double-blind controlled trial, and a cross-over trial has not been attempted.[2,4-8] One study[5] compared the performances of five climbers on two expeditions a year apart.

We set out to meet the necessary conditions for a trial of acetazolamide during an attempt on Africa's two highest peaks by the Scout East Africa Expedition in the summer of 1980.

Methods

The party comprised 24 British residents, including two women. None were professional sportsmen; five were medically trained. They were paired for age, sex, and likely activities, and each member of each pair was allocated at random to one of two treatment groups. Treatment group 1 received acetazolamide (sustained release 500 mg nightly) on five nights before and during the first ascent and identically presented placebo before and during the second ascent. The treatment order was reversed for group 2 (see fig 1, which also gives expedition objectives).

An error in allocation of capsules led to the re-arrangement of two pairs; the pairs of subject 22 and subject 20 and of subject 19 and subject 21 being changed to 19/20 and 21/22: the table shows the pairs actually used. The conclusions from statistical analysis are unaffected if these pairs are excluded, and they are therefore included.

The entire party travelled by air from London to Nairobi, by road to Kilimanjaro, and then on foot from 2000 m. Kit weighing about 10 kg was carried. Nights were spent at the hut camps provided.

On Mt Kenya the expedition divided into four activity groups, the participants being decided during the trek. The table gives identification numbers of subjects. Subjects 2, 3, 7, and 21 left in advance and climbed the central rock pinnacles Nelian (5174 m) and Batian (5186 m); subjects 4, 8, 12, and 19, acting as support party, climbed on rock and glacier around 5000 m; and subjects 6, 16, 17, and 23 circumnavigated the central pinnacles and climbed point Lenana (4972 m). The remainder climbed point Lenana only. The party slept in tents and carried an average of 10 kg each.

Before departure the medical project was explained and full co-operation obtained. Every subject recorded each day's symptoms nightly on a card. A list of common symptoms of acute mountain sickness was printed down one side of the squared card and expedition days across the top. One tick was to be entered if a symptom was experienced on a given day. Spaces were provided for: distance walked, load carried, night altitude, metres climbed, symptoms not related to acute mountain sickness, and medication. Comments were invited. Permitted drugs for treatment were: aspirin for headache; diphenoxylate and atropine (Lomotil) for diarrhoea; temazepam and nitrazepam for sleeplessness; and chloroquine, pyrimethamine, and dapsone for malarial prophylaxis.

Scores for acute mountain sickness were calculated from symptom cards by giving one point for mild headache, loss of appetite, feeling sick, severe inappropriate weakness, dizziness, depression, irritability, drowsiness, cough, and shortness of breath walking on the flat, and three points each for severe headache, vomiting, staggering, shortness of breath at rest, and frothy spit. If severe headache or shortness of breath at rest was scored then its milder form was not. Each subject's score was calculated for days spent off the mountains and was averaged to give a baseline score. This was subtracted from each ascent day's score, giving rise to some negative scores. The analysis uses three-day (ascent period) scores for each person, as both acute mountain sickness and acetazolamide were expected to have most effect during these periods. Each analysis started on the first night over 3000 m and so included the summit for everyone on Kilimanjaro and comparable altitudes for everyone on Mt Kenya (see fig 1).

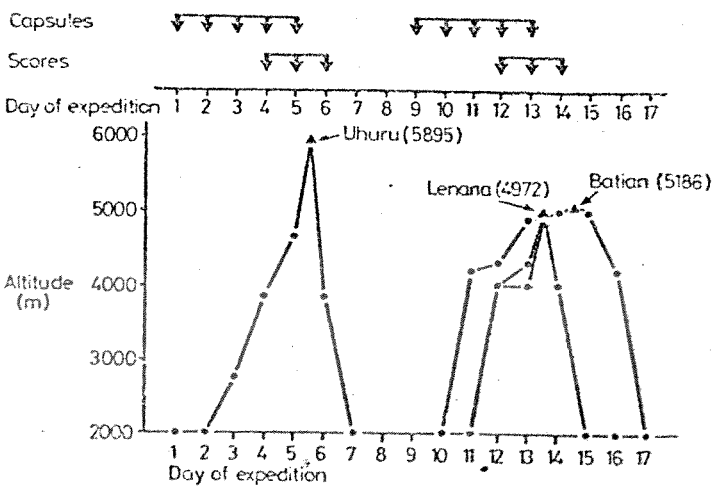


FIG 1—Expedition programme.

The data do not conform to normal distributions, therefore non-parametric tests of significance (Wilcoxon and Spearman rank correlation tests) were used. The test used to examine interaction between the first and second treatment periods and ascents is based on that described by Hills and Armitage[9] with an adaptation to allow for the pairing in our design.

* MK Greene, AM Kerr, IB McIntosh, RJ Prescott. British Medical Journal, 26 Sept. 1981.

Results (continued)

No one left the expedition. Illness other than acute mountain sickness was trivial. Diarrhoea was reported on 11 days (five on acetazolamide and six others). Acute mountain sickness manifest as severe headache and vomiting prevented subject 24 from making the final six-hour ascent (on placebo) of the summit of Kilimanjaro. On Mt Kenya breathlessness at rest and severe inappropriate weakness prevented her from climbing (on acetazolamide) above 3500 m. On this occasion her two tent mates (subjects 20 and 22) remained with her voluntarily; both were taking acetazolamide. As exclusion of these two subjects from statistical analysis does not alter the conclusions, they have been included. Compliance was in general excellent. On Mt Kenya subject 18 stopped his acetazolamide after taking one, saying that he felt ill, and subject 10 mislaid his acetazolamide after taking two. Subject 7 failed to complete his card on Mt Kenya. The double blind was entirely successful.

Of side effects, tingling in the extremities was reported by 7 out of 24 subjects (29%) on acetazolamide and three out of 24 (12%) on placebo. Diuresis was not remarked on, perhaps because of concurrent changes in living conditions. Nausea was reported on the first day of taking acetazolamide by two of 24 (8%) (none on placebo).

With the exceptions mentioned above, planned objectives were reached by all subjects on Mt Kenya.

Fig 2 compares the altitudes reached on Kilimanjaro by subjects on acetazolamide and placebo. Those taking acetazolamide showed a striking advantage (Wilcoxon signed rank sum test $p < 0.01$). The symptom scores of each treatment group on each mountain also show an impressive advantage for those taking acetazolamide on Kilimanjaro

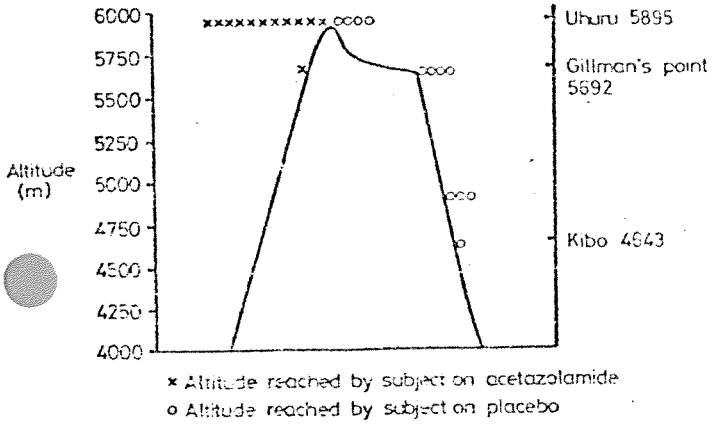


FIG 2—Altitudes reached on Kilimanjaro.

(see table). In every pair the partner on acetazolamide had the lower symptom score (Wilcoxon signed rank sum test $p < 0.001$). On Mt Kenya the two groups performed equally well. Those previously on placebo improved greatly on acetazolamide, while those previously on acetazolamide maintained their low scores although taking placebo. It is clear that the first treatment and ascent period had an effect on the second. The presence of this interaction was confirmed statistically using a test based on that described by Armitage and Hills ($p < 0.01$).[9]

Fig 3 shows the total cross-over experience graphically. Pairs 9/10 and 17/18 failed to take the full course of acetazolamide. No statistically significant association was found between the ages of subjects and their scores. On Kilimanjaro there was a suggestion of a negative association among subjects on acetazolamide (Spearman rank correlation coefficient $= -0.55$ $(0.05 < p < 0.1)$). The corresponding subjects on placebo, however, showed no correlation ($r = -0.04$), and the scores on Mt Kenya showed no correlation with age.

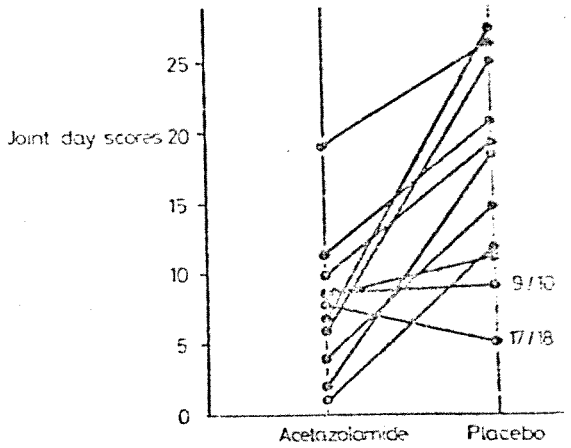


FIG 3—Joint symptom scores for each pair on each ascent. Numbers indicate pairs who failed to take full course of acetazolamide.

Discussion

The weaknesses of symptom reporting as a means of assessing acute mountain sickness are obvious but must be accepted, since there are no reliable signs of the mild form of acute mountain sickness. Advantages of our method were its simplicity and the promptness of reporting. Baseline scores helped to reduce the effect of personal differences in symptom recognition. Co-operation was excellent. The allocation of points for symptoms, while arbitrary, distinguishes clearly between the mild ones and those which indicate cerebral or pulmonary oedema.

Acetazolamide was found to be a useful prophylactic for acute mountain sickness on this expedition during rapid ascent on foot from 2500 m to 5000 m. The advantage to those on acetazolamide was most evident on the ascent of the first mountain, Kilimanjaro, when conditions were ideally standardised, the whole party was walking at the same pace and with the same objective. On Mt Kenya, activity subgroups made comparisons more difficult, but assessment over three days during which altitudes and activities were similar allowed valid comparisons to be made. On this ascent, as the table shows, low scores were achieved by both treatment groups.

The slightly lower altitude of Mt Kenya and some carry-over both of physical fitness and of acclimatisation from the ascent of Kilimanjaro may have contributed to this general improvement. It may be that taking acetazolamide on the first ascent permitted trouble-free acclimatisation and training which remained of benefit on the second ascent and that the improvement in performance experienced by those who changed to acetazolamide for the second ascent was partly due to the drug. We can only speculate on this point, however, as we did not have enough subjects to allocate a group to placebo throughout.

Subject 24 is an important exception to the general experience of benefit from acetazolamide. Clearly no general conclusion can be drawn from her case, but it would seem to indicate that not all those liable to develop severe acute mountain sickness will be helped by acetazolamide.

It seems clear that acetazolamide is a useful prophylactic for acute mountain sickness in most cases.

Symptom scores for each subject on each mountain in order of ascent (after deduction for non-ascent days symptoms)

Treatment group 1				Treatment group 2			
Subject No	Age	Acetazolamide Kilimanjaro	Placebo Mt Kenya	Subject No	Age	Placebo Kilimanjaro	Acetazolamide Mt Kenya
1	20	7	0	2	20	25	−1
3	20	13	7	4	21	19	5
5	49	3	3	6	43	17	9
7	36	4	missing	8	23	7	1
9	17	5	−1	10	18	9	3
11	45	6	−1	12	45	12	2
13	45	0	0	14	50	18	2
15	36	1	0	16	36	12	0
17	45	3	0	18	41	5	4
19	41	5	2	20	19	12	−1
21	27	9	9	22	19	18	−2
23	42 (F)	2	2	24	24 (F)	17	8
Total score		58	21			171	30
Mean		4·8	1·9			14·3	2·5

3. (continued)

Parts 1-3 refer only to the Kilimanjaro portion of the expedition.

1. "Those taking acetazolamide reached a higher altitude (11 versus 4 reached the summit)" (abstract).
   What is the appropriate test of the 11 versus 4 to see if it is statistically significant?
2. "Fig. 2 compares the altitudes reached by subjects taking the drug and those taking placebo ... the drug group showed a striking advantage $p < 0.01$" (4th paragraph, 1st column 2nd page)
   Can you verify this p-value from the diagram? What other statistical test might you have used?
3. "In every pair the partner on acetazolamide had the lower symptom score." (immediately below Fig. 2.)
   To what value of the Wilcoxon signed rank statistic does this statement correspond? What other test is suggested by this statement?
4. What if this study had not paired the subjects by age, sex and likely activities? How might the analysis have been carried out (a) if the expedition involved just Kilimanjaro (b) using the fact that the expedition actually involved Mt. Kenya as well?