and, therefore, this does not provide a specific method of predicting which infants will go on to die of the syndrome.

A major problem in comparing our results with those of other workers is that many have analysed the data in terms of the "sleep states." The differences seen in heart rate and its variability[4] and respiratory rate and its variability,[3] however, exist in all stages of sleep and therefore it might be expected that our approach would identify differences if these were present. It has been shown that the periodicity of sleep states is different in subsequent siblings of infants with sudden infant death syndrome[13] and it is possible that differences in rate and variability did exist in the cases studied here but were masked by differences in the organisation of the sleep states. It is not possible to "sleep stage" simple cardiorespiratory recordings directly. This has to be done indirectly using normative data collected in a similar manner but which include the electroencephalogram and electro-oculogram. Mason *et al* showed that the heart rate and heart rate variability probability density functions are different in different sleep states and that these could be used to classify sleep state.[14] The major problem with that approach, however, is that the variable being studied is also being used to classify the data, which in turn may mask differences.

Our findings suggest that the simplest of indices of respiratory rate, respiratory rate variability, heart rate, and heart rate variability measured over 24 hours are of little value in discriminating between infants who go on to be victims of the sudden infant death syndrome and control infants. There may, however, be a group difference, with the cases of sudden infant death syndrome showing a higher mean instantaneous heart rate than the controls.

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Brain shrinkage in chronic alcoholics: a pathological study

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Abstract

A quantitative neuropathological necropsy study of 22 control and 22 chronic alcoholic subjects showed a statistically significant loss of brain tissue in the chronic alcoholic group. The loss of tissue appeared to be from the white matter of the cerebral hemispheres rather than the cerebral cortex. This may reflect a primary alteration in the composition or structure of the white matter or it may be secondary to loss of nerve cells from the cortex with subsequent degeneration of the axons in the white matter. Further morphometric analyses including cortical neuronal counts will be necessary to clarify this issue.

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Introduction

A substantial proportion of chronic alcoholics and even heavy social drinkers have been shown to have brain shrinkage by neuroradiological techniques including pneumoencephalography[1] and computed tomography (CT).[2-4] Some of this shrinkage may be reversible after prolonged abstinence from alcohol.[5 6] There are associated cognitive defects,[7] and a more generalised global dementia may relate directly to chronic alcohol abuse.[8] Few objective neuropathological data are available to explain these changes, although studies of brain weight show that alcoholics have a lower mean brain weight than normal.[9 10] Brain weight is an unsatisfactory measurement, however, since it varies considerably from person to person.[11] As a result of the development of a relatively simple technique for measuring intracranial volume at necropsy using polyurethane foam casts[12] we have been able to derive accurate quantitative data on the volume of brain tissue lost in chronic alcoholic patients.

Brain volume (BV) bears a constant relation to intracranial volume (ICV) in normal adults.[13] The pericerebral space is an expression of this relation and is calculated (as a percentage) as: (ICV − BV)/ICV (× 100). Any decrease in brain volume is reflected by an increase in pericerebral space and vice versa, since the intracranial volume remains constant throughout life. The mean pericerebral space was 8·3% in 44 controls and 11·3% in 25 alcoholic patients.[14] The loss of brain tissue appeared to be

more severe (higher percentage of pericerebral space) in those alcoholic patients with the associated nutritional vitamin deficiency state Wernicke's encephalopathy or alcoholic liver disease.[14] In order to derive further data concerning which areas of the brain are abnormal in chronic alcoholic patients, 44 of the cases used in that study[14] were subjected to a quantitative morphometric analysis, and the data form the basis of this study.

Subjects and methods

One hundred and twenty cases were studied in conjunction with the forensic pathologists of the Perth City Coroner's Department. One of us (JK) attended the necropsies and carried out the procedures described below. The 44 cases for this study were selected from the 120 cases.

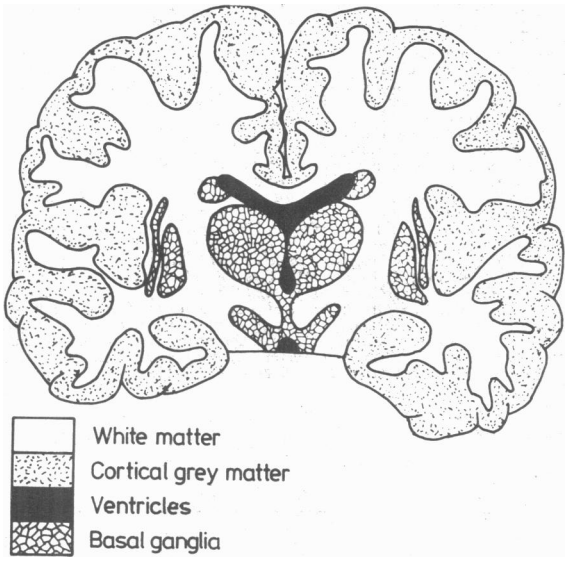

FIG 1—Diagrammatic representation of coronal slice of cerebral hemispheres showing four regions quantified.

Selection of "alcoholic" and "control" cases was based on a compilation of clinical and pathological data. The data included clinical notes available from the teaching hospitals of Perth as a result of previous admissions, detailed questionnaires on alcohol intake and nutritional state provided by relatives of the subjects, reports concerning circumstances of death, and a complete necropsy with microscopical examination of tissues including the brain. In many cases liver function values were available, and in four cases CT scans had been done. Patients with a history or pathological evidence of neurological diseases other than those associated with alcoholism—for example, Wernicke's encephalopathy—were excluded. Any patient with macroscopic evidence of head injury was excluded from the study, as were control subjects in whom there was a history of moderate alcohol intake.

Twenty two alcoholic and 22 control cases were included in the study. Ten of the alcoholics had pathologically confirmed Wernicke's encephalopathy and 14 had liver disease (fatty liver or cirrhosis). The following measurements were made at necropsy in each case: fresh brain volume, fresh brain weight, intracranial volume, and the patient's height and weight. The brains were fixed in 10% formal saline for at least two weeks and the brain weights and volumes remeasured. The cerebellum and brain stem were removed by sectioning the midbrain and the volume of the cerebral hemispheres alone determined. The occipitofrontal length was measured with callipers. The brains were embedded in a 3% agarose block with the occipitofrontal axis at right angles to the face of the block. After the agarose solidified it was cooled in the refrigerator for several hours before the brain was cut into 3 mm coronal slices on an electric meat slicer. The thin brain slices were laid on numbered sheets of exposed radiographic film for ease of handling. Each slice was then photographed with a scale and glossy black and white prints prepared at a magnification of one. There were about 60 brain slices for each case and the mean slice thickness was determined by dividing the number of slices into the occipitofrontal length of the fixed cerebral hemispheres. Random measurements of the thickness of brain slices showed a variation of less than 0·25 mm.

The photographs were overlaid by a transparent square grid system, each square being 0·4 cm², and a standard point count technique carried out.[15] Four separate regions were counted: the cerebral cortical grey matter; white matter; ventricles, excluding the fourth ventricle; and diencephalic structures, including basal ganglia, thalamus, hypothalamus, and amygdala (fig 1). Henceforth we term the latter area the "basal ganglia."

Separate counts were made for the right and left hemispheres. Calculations were performed according to the Delessee principle[15] and areas and volumes were calculated for each of the four regions in the cerebral hemispheres. The data were analysed using the statistical package for the social sciences X system and the ANOVA program. Multivariate and discriminant analyses were performed.

Results

Table I summarises the clinical data and weights and volumes of the brains of the 22 control and 22 alcoholic subjects. Ages ranged from 17 to 78 years in the controls and from 24 to 73 years in the alcoholics. The mean brain weight of the alcoholics was 71 g less than that of the controls. The pericerebral space, which increases as the brain volume decreases,[14] was 4·9% higher in the alcoholic group than in the controls ($p = 0·005$).

Table II shows the relative proportions of the cerebral hemispheres occupied by cortical grey matter, white matter, basal ganglia, and ventricles (see fig 1) in the control and alcoholic groups. Since there was a significant reduction in brain volume in the alcoholic group, the mean volumes of the cerebral hemispheres were also calculated (table III). The most interesting and important findings were that there was no significant difference in the mean volumes of cortical grey matter of the alcoholic and control groups, whereas there was a significant reduction ($p < 0·001$) in the mean volume of white matter in the alcoholic group. The mean ventricular volume was significantly increased ($p < 0·001$) in the alcoholic group. There was no difference in the mean volumes of the basal ganglia.

Volumes of cortical grey matter and white matter can also be expressed as proportions of the intracranial volume (figs 2 and 3). There was a significant age related reduction in the volumes of white matter of both the control (slope $= -0·08$; $p = 0·005$) and alcoholic groups (slope $= -0·11$; $p = 0·04$). The proportional volume of white matter of the alcoholic group was significantly less ($p < 0·001$) than

TABLE I—*Quantitative comparison of brains of alcoholic and control patients*

Group	No of cases	Sex M	Sex F	Mean age (years) (SEM)	Mean brain weight (g) (SEM)	Mean pericerebral space (%) (SEM)
Control	22	18	4	54 (4)	1369 (29)	7·0 (0·8)
Alcoholic	22	17	5	52 (3)	1298 (34)	11·9 (1·4)*

*$p = 0·005$ (Student's t test).

TABLE II—*Relative proportions of cerebral hemispheres of alcoholic and control patients*

Group	No of cases	Cortex (%) (SEM)	White matter (%) (SEM)	Basal ganglia (%) (SEM)	Ventricles (%) (SEM)
Control	22	50·6 (0·4)	43·2 (0·4)	4·9 (0·1)	1·3 (0·1)
Alcoholic	22	54·5 (0·7)	38·6 (0·6)*	5·0 (0·1)	1·8 (0·2)*

*$p < 0·001$ (Student's t test).

TABLE III—*Mean cerebral hemisphere volumes in control and alcoholic patients*

Group	No of cases	Cerebral hemispheres (cm³) (SEM)	Cortex (cm³) (SEM)	White matter (cm³) (SEM)	Basal ganglia (cm³) (SEM)	Ventricles (cm³) (SEM)
Control	22	1085 (24)	549 (14)	469 (12)	53 (1·4)	14 (1·1)
Alcoholic	22	1048 (28)	572 (14)	405 (15)*	52 (1·9)	19 (1·8)†

*$p = 0·003$ (Student's t test).
†$p = 0·06$.

that of the control group (fig 2). There was a similar age related change in the volume of cortical grey matter (controls: slope = −0·11, p = 0·005; alcoholics: slope = −0·07, p = 0·3) but there was no significant difference between the control and alcoholic groups (fig 2).

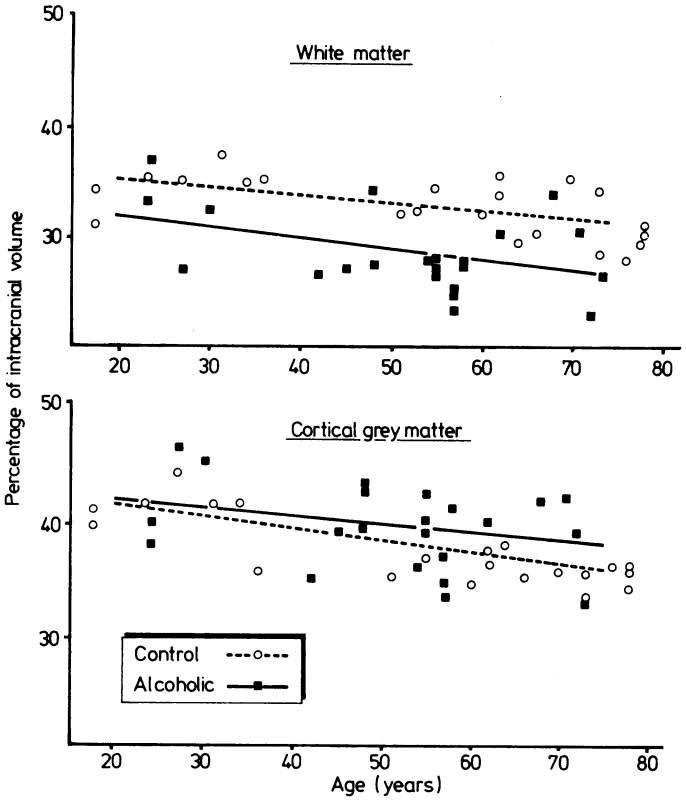

FIG 2—Volumes of white and cortical grey matter expressed as percentage of intracranial volume in alcoholic and control groups at all ages. Both groups showed significant decrease in volume of white matter with age (controls: slope = 0·08, p = 0·005; alcoholics: slope = 0·11, p = 0·04). Both groups showed trend towards decrease in volume of grey matter with age (controls: slope = 0·11, p = 0·005; alcoholics: slope = 0·07, p = 0·3).

It is thought that cerebral shrinkage is more severe in the frontal regions of the cerebral hemispheres in alcoholics.[2 16] Table IV summarises the mean volumes (in percentage form) of various regions of the cerebral hemispheres (basal ganglia and ventricular volumes not included). There was no difference between the right and left cerebral hemisphere volumes for the control or alcoholic groups. Similarly, there was no significant difference in the volumes of the two defined frontal regions (see table IV) in the control and alcoholic groups.

Consideration was given to other variables that might affect these results such as sex and the delay between death and necropsy. No significant correlative factors were identified. All the original results remained true when the female cases were deleted. Discriminant analysis using proportions of pericerebral space and volumes of white matter showed that 18 of the 22 alcoholics (82%) and 21 of the 22 controls (95%) were correctly classified.

Discussion

The results of this quantitative morphometric study confirm that there was a statistically significant reduction in the mean brain volume of a group of chronic alcoholics as reflected by an increase of 4·9% in pericerebral space. This is presumed to be the pathological counterpart of the cerebral shrinkage seen in the CT scans of alcoholics[2 3] and heavy social drinkers.[4] It should be noted that many of the alcoholic patients had either Wernicke's encephalopathy or chronic liver disease or both and the brain shrinkage may relate to these other potential pathogenetic factors rather than the toxin ethyl alcohol itself.

The major point of interest in this study is that the reduction in brain volume in the alcoholic cases related to a loss of white matter rather than cortical grey matter. The calculated percentage volumes of the hemispheres in the control group (table II) were similar to previous studies.[17–20] The interpretation and comparison of these volumes in this study, however, were complicated by the overall loss of brain tissue in the alcoholic group. To facilitate comparisons mean hemisphere volumes were calculated as shown in table III. The mean volumes of cortical grey matter and basal ganglia were similar in the control and alcoholic groups, whereas white matter was reduced by 14% and ventricular volume increased by 36% in the alcoholic group. There was no difference between the volumes of the left and right cerebral hemisphere in the control and alcoholic groups (table IV).

TABLE IV—*Mean volume proportions of cerebral hemispheres (not including basal ganglia and ventricles)*

	Left cerebral hemisphere (%)	Right cerebral hemisphere (%)	Frontal 1* (%)	Frontal 2† (%)
Controls (n = 22)	47	46	32	68
Alcoholics (n = 22)	46	46	31	69

*Frontal 1 = Frontal pole to genu of corpus callosum.
†Frontal 2 = Frontal pole to central sulcus.

Both neuroradiological[3] and neuropathological[16] studies of chronic alcoholics have emphasised that cortical shrinkage or atrophy is more severe in the frontal regions. This is not borne out by our study (table IV), which suggests that no particular lobe of the cerebral hemispheres is selectively damaged in chronic alcoholism. There was, however, more white matter compared with cortical grey in the frontal regions than in the occipital regions. (In controls the ratio of cortical grey to white matter was 1·22 in the frontal regions and 1·40 in the occipital.) Hence it is to be expected that a reduction in volume of white matter will be more evident on CT scan and macroscopically in the frontal region.

Selective reduction in the volume of white matter rather than the volume of cortical grey matter in the alcoholic group was a somewhat unexpected finding. Most clinicians and pathologists had thought that any loss of brain tissue in chronic alcoholism was most likely to be from the cerebral cortex. Many workers have commented on a patchy loss of neurones from the cerebral cortex in alcoholic patients.[16 21] We emphasise, however, that a normal volume of cortical grey matter is not synonymous with normal cortical neuronal counts. In a similar morphometric study of control brains and the effects of advanced old age, Anderson and his colleagues showed only a minor reduction in the volume of cortical grey matter despite a calculated loss of neurones of about 1% a year after 70 years of age.[22] Interestingly, they showed a reduction in the volume of white matter amounting to about 0·8% a year after 70 years of age. Conceivably either dendritic growth of surviving neurones or proliferations of astroglial cells as a response to the loss of neurones might account for a normal volume of cortical grey matter. Neuronal counts have yet to be evaluated in the brains of alcoholic patients.

A reduction in white matter rather than cortical grey correlates better with the neuroradiological finding of some reversibility of brain shrinkage after prolonged abstinence from alcohol,[5 6] since the loss of neurones is an irreversible change. We can only speculate about the cause of the reduction in white matter. Until neuronal counts have been carried out we cannot discount the possibility that this is an epiphenomenon secondary to neuronal death and axonal degeneration. Studies in rats and mice have shown a loss of neurones in animals maintained on an alcohol containing diet followed by a period of abstinence.[23 24] Some evidence suggests, however, that primary changes do occur in the white matter of the brains of chronic alcoholic patients. These changes include alterations in tissue sodium and potassium concentrations[25] and in the lipid content of the white matter.[26] Increased protein synthesis has also been documented after alcohol withdrawal in experimental mouse models.[27 28] An obvious

simple explanation for a reversible change in the volume of the white matter in the cerebral hemispheres is an alteration in hydration. To date, there are no data to support this hypothesis.[25 29] There are many data on alterations in cerebral blood flow in alcoholic patients.[30-32] Most workers have shown that cerebral blood flow is reduced in both grey and white matter, but a more recent study by Johannesson and his coworkers showed a selective reduction in cerebral blood flow in the white matter of a group of 50 alcoholic patients. They suggested that this might reflect "a specific damage to the white matter caused by alcohol."[32] Certainly, the delay of several months in the reversal of cerebral shrinkage[5 6] and cognitive deficits[7 8] after abstinence from alcohol suggests a true structural abnormality rather than simply a change in the volume of the extracellular or intravascular compartments.

Further studies with larger numbers of cases may permit statistical evaluation and comparison of subgroups within the alcoholic population—for example, those with liver disease but no nutritional brain damage, or vice versa. This may help in identifying the most important pathogenetic factor or factors which cause the shrinkage of white matter. These factors include the toxin ethyl alcohol or its metabolites, associated vitamin nutritional states such as Wernicke's encephalopathy, and chronic liver disease.

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100 YEARS AGO

Our correspondent writes from Valencia, under date July 10th:—"My letter of this week is of necessity a melancholy and foreboding one in a two-fold sense; 1st, as regards the state of cholera in this country, and, 2nd, as regards the so-called "preventive cholera inoculation." I am pained to inform you that the fears expressed in my last communication are being fulfilled, as the cholera has daily increased in virulence, and in extension. To-day's papers give the number of 196 deaths yesterday, and large numbers of the attacked and deaths are concealed by all classes, assisted by their medical men, to avoid worrying the houses and families by the official interference of policemen, sanitary inspectors, the "forensic medical," and others who have to give the last certificate of death. Until this is given, they cannot be buried. Hence a large number of the bodies remain in their houses for two or more days, and others are taken to the cemetery and left exposed without burial, for want of death-certificates. So great an evil has come from concealment that the alcalde was compelled to issue a decree that any one concealing a case of attack or death from cholera, especially medical men, would be visited with extreme legal measures. On the 7th inst., in the town of Beneganim, lying between Jativa and Alcira, the alcalde, with help, was obliged to cremate fifty unburied corpses himself, as no grave-diggers could be hired for the work. He had lost his son by the disease, and his wife and four others in his house were ill with it. The two apothecaries in the place were laid up with the same, and the whole town was crying out for succour of every kind. This was written by a medical man who went from Jativa to render help to this devoted town. By decree, notice must be given at the "death-register office," of which there is one in each district (open day and night), by 8 a.m., of all deaths and attacks, and the cholera carts go their sickening rounds at 8 p.m. till 6 a.m., followed by a large wagon, to remove all the bedding and clothes of the infected houses, to be burnt outside the city. Independently of private and voluntary house-disinfections, the municipal authorities send out brigades of men to disinfect the houses attacked, and for the last two or three nights huge bonfires of green wood have been fired, and large quantities of sulphur thrown on them, in the streets most infected. The disease has been and is so terrible in the chief sea-bathing suburb of Cabañal, and the Grao of Valencia, that the owners and tenants of the houses have formed an amphibious encampment by vacating their houses, and living in the large and small fishing boats close in front of the town, with awnings over them. The cholera has followed them, and is now rife in the new camping ground. There is now building outside of this city a large encampment of canvas, where 300 to 400 families are to resort to live. Also there is being established an asylum for infants whose mothers have died, called "Asilo de Lactancia de Santa Eugenia"; but they cannot procure wet nurses in sufficient numbers, although high wages are offered. The panic here is great as ever, but the people are more subdued and quiet. Numbers of shops are closed. Whenever a death occurs, among rich or poor, all hands take to flight at once, leaving all behind; and many of the better classes, as well as poor, have fallen victims in the places to which they fled. The disease has left Jativa, but returned in force to Alcira, and as to Aranjuez, it is increasing fearfully in virulence. If the reports are true of the deaths, few will be left alive in another week. In Murcia and Alicante, Toledo and Madrid, it is also on the increase. (*British Medical Journal* 1885;ii:114.)