AUTOMATIC ANALYSIS OF THE
ELECTROENCEPHALOGRAM IN
HEPATIC ENCEPHALOPATHY.

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SUMMARY.

1. A technique for recording the E.E.G. from the right temporo-occipital area under defined conditions was described. The activity from this area was first digitised and then processed on an Elliott 903B Computer which performed a Fourier Transform of the autocorrelogram based on a technique described by Milner (1954). The estimates of frequency obtained in this manner were accurate to 0.1 c/s within the alpha range.

2. The above technique was used in a study of a control group, consisting of 49 subjects and a hepatic group of 48 patients who nearly all suffered from cirrhosis of the liver.

3. A particular study was made of the mean dominant frequency (MDF). It was found that fluctuations of the order of ± 0.5 c/s occurred from day to day and over the course of 2 - 3 hours in both groups. Alterations of the test environment had no significant effect on this figure.

4. Oral lactose, neomycin and ammonium chloride had no significant effect on the E.E.G. of 12 members of the control group whereas injections of either heroin or morphine often induced marked shifts.

5. Injections of morphine or ammonium acetate in members of the hepatic group failed to give a clear indication of the existence of encephalopathy. The administration of neomycin or a high protein diet gave more promising results in a small series of patients.

6. The case histories and E.E.G. data were detailed in 9 patients who had experienced surgery for the relief of portal hypertension. Day to day monitoring of MDF appeared to be the most valuable measurement.
E.E.G. deterioration was characterised by a reduction of MDF and reactivity, with an increase of amplitude and delta activity. Monitoring was valuable in the detection of impending coma, regulation of dietary protein and assessment of therapeutic measures such as neomycin.

7. Biochemical measurements were performed on a limited scale and usually correlated poorly with the E.E.G. changes. In particular, no E.E.G. correlation could be demonstrated with venous ammonia levels. Measurements of venous ammonia after infusion of ammonium acetate correlated with a previous history of encephalopathy.

8. It was concluded that a suitable test of hepatic encephalopathy has yet to be described and that particular care should be taken in the selection of a group of patients suspected on historical grounds, to have present hepatic encephalopathy.
"I am a great eater of beef and I believe that does harm to my wit".

Sir Andrew Aguecheek (Twelfth Night).
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INTRODUCTION.

Initially it was only practicable to analyse the E.E.G by means of visual inspection of an ink writer trace. The development of a low frequency analog analyser by Baldock and Walter (1946) allowed objective measurements to be made in terms of frequency and amplitude. With the more recent emergence of high speed computers it has become possible to employ analytical procedures with a speed and accuracy hitherto unobtainable.

Using a modified BNI analyser Laidlaw and Read (1961b, 1963) had made some interesting observations on E.E.G. changes in hepatic encephalopathy. Various provocative tests had been described, which in conjunction with frequent E.E.G. monitoring, seemed to have value in controlling the patient's diet, assessing the response to neomycin and possibly deciding whether patients with portal hypertension were suitable for porto-systemic anastomoses.

Their work has gone largely unconfirmed. It was therefore thought worthwhile to determine the clinical usefulness of automatic frequency analysis in hepatic encephalopathy, using computer techniques.

The term hepatic encephalopathy is defined here as cerebral dysfunction consequent upon hepatic disease.
HISTORICAL REVIEW.
HISTORICAL REVIEW.

This section is divided into several parts, commencing initially with the earliest observations of E.E.G. changes in coma in general, followed by a review of the changes described in association with hepatic disease in particular. The problem of 'spontaneous' E.E.G. variation is discussed. Four tests of hepatic encephalopathy will be outlined, with a discussion of modern views on the cause of hepatic encephalopathy and finally a survey will be made of various methods of automatic E.E.G. analysis.

Early Studies.

The first observations of E.E.G. changes in coma were made by Berger (1932 a & b). In a case of gas poisoning he commented that the E.E.G. was of low voltage and showed extreme "lengthening of the alpha waves", to an average of 195 - 300 mSec. Subsequently, Berger (1937a) described a case of insulin induced coma which was typified by "lengthening of the alpha waves" up to 160 mSec. with a tendency to group formation. These groups had a length of 300 - 650 mSec. Clearly these descriptions were of what would now be termed intermittent delta activity. These observations were confirmed by Gibbs et al. (1937) who were probably first to observe that marked slowing of activity was characteristic of a variety of comatose states. Davis & Davis (1939) commented upon the similarity of the delta activity of coma to that of deep sleep.

Romano & Engel (1944) made the first detailed study of the development of coma in a description of 53 cases of delirium, of varying aetiology. By visual frequency analysis, they classified the E.E.G. changes into 5 grades of progressive severity.

1) Appearance of a small amount of regular and irregular slow frequencies (5 - 7 c/s).
2) Reduction of normal regular frequencies. Increase of low voltage fast activity and irregular slow waves (4-7 c/s).

3) Predominant low voltage, fast activity with some regular and irregular slow rhythms (3-6 c/s) and relatively little normal rhythms.

4) Dominant slow activity (2-7 c/s) with small amounts of low voltage fast rhythms and no alpha activity. High voltage slow waves (½-3 c/s) appearing in rhythmic fashion.

5) Fairly regular high voltage slow activity (3-7 c/s) with few or no normal frequencies.

Judging by their illustrations of each grade, the fourth phase would appear to be more abnormal than the fifth (by present-day criteria), unless there was a printer's error: i.e. Grade 4 shows continuous irregular delta activity whereas 5 shows some delta but considerable theta rhythms. Furthermore, stage 3, which is typified by a low voltage tracing, has not met with confirmation (see later in this section) but their observation that the changes in progressive delirium are very similar, irrespective of the aetiology of the disease, still holds good (Loeb 1964).

It has been claimed by Silverman (1963) that some indication of the depth of coma can be obtained by inspection of the ink writer trace and observations of the electrical responses to alerting stimuli. In a consideration of the "sleep like potentials" seen in a variety of comas, Silverman described four stages:

1) Coma reactivity and sleep approach normal i.e. blocking of slower components.

2) Reactivity and sleep become distorted. On arousal rhythmic delta and theta waves appear.
Reactivity and sleep like potentials disappear and the record becomes monorhythmic and finally isoelectric.

**Studies in Hepatic Disease.**

The first publication drawing attention to E.E.G. changes in hepatic encephalopathy was that of Foley Watson and Adams (1950) in a study of 26 patients with severe liver disease. They described abnormal activity of about 2 c/s which was uniform from patient to patient. They added that in the early stages the slow activity appeared in short bilaterally synchronous bursts, limited to the frontal areas (see fig. 1.2). As the patient became less responsive the bursts became longer in duration and more widespread in space, spreading laterally and posteriorly until the entire record consisted of 2 c/s activity (see fig. 1.4). It is stated that there was a preservation of the usual alpha activity in the intervals between the bursts of slow activity. They described two components to the slow wave when it first appeared in the frontal area i.e. a blunt spike and a slow wave - either fused or separate (see fig. 1.3). The similarity of the latter complex to Petit Mal was commented upon, and they considered these complexes to be evidence of damage to thalamic nuclei. They were unable to be definite about the specificity of the above changes but thought they might be phenomena peculiar to hepatic disease. It is of interest that they reported a striking similarity in two cases of hypokalaemia in which there were associated disturbances of consciousness. They remarked that there was a close correlation of the E.E.G. changes to the severity of the clinical condition. No mention was made of the possibility of anticipation of hepatic coma.

These observations were confirmed (in a study of 8 patients) by Bickford & Butt (1955), who donned the frontal complexes "Triphasic Waves"
Figure 1.1
An early phase in developing hepatic encephalopathy. There is slowing of dominant rhythm to 6 c/s with failure of eye opening (EO) to attenuate the background rhythm for more than a few seconds.
Figure 1.2

Moderate hepatic encephalopathy. This record shows brief runs of frontal symmetrical delta activity. The background activity appears irregular, containing a mixture of theta (5-6 c/s) and low voltage activity.
Figure 1.3

Triphasic waves. These are slightly asymmetrical and therefore atypical. The initial deflection is a pointed slow wave (positive) followed by a broad negative slow wave. The triphasic wave is maximal frontally. The background activity consists of a mixture of irregular low voltage theta and delta activity.
Figure 1.4

A fairly advanced stage of hepatic encephalopathy.

The record consists of long runs of irregular delta activity (1-2 c/s) which are fairly symmetrical.
(see fig. 1.3) and in so doing, initiated 15 years of controversy, hitherto unresolved. Such waves were shown to be of cerebral rather than artefactual origin by measurements of their fronto-occipital delay. Whilst Foley Watson and Adams (1950) reported preservation of the alpha rhythm to a late stage of hepatic coma, Bickford & Butt stated that at the time early mental changes became detectable there developed a "slowing and disorganisation of the alpha rhythm". Associated with this the latter authors found waves of 4-7 c/s ("theta phase") which correlated with "slight temporal and spatial disorientation". Only after this phase when further clinical deterioration occurred did the triphasic waves appear. They could not agree that the triphasic wave was a specific phenomenon and noted its occurrence in ether anaesthesia and convulsive disorders.

Should the clinical condition deteriorate, the next phase observed by Bickford & Butt was the appearance of "slower rhythmic delta waves", followed by "generalised suppression of activity".

No mention of anticipatory change was made, in fact they stated that "the existence of hepatic disease per se in the absence of mental change was not associated with any detectable E.E.G. abnormality".

The Triphasic Wave Controversy.

Two opposing viewpoints have emerged concerning the specificity of the triphasic wave. One school states that such complexes occur in metabolic disorders, other than hepatic disease (Bickford & Butt 1955; Fishgold & Mathis 1959; Bonnet et al 1963; Guggenheim et al 1964; Loeb 1964; Penin 1967; Macgillivray & Kennedy 1970). Disorders cited by the latter authors which may be associated with triphasic activity included cerebral tumour, head injury, cerebral vascular accidents, ether anaesthesia and convulsive disorders.
Macgillivray and Kennedy (1970) in a study of 615 patients with hepatic disease found the triphasic wave in approximately 25% of the subjects arbitrarily judged at risk on the basis of severity of the encephalopathy. It was noted that the wave never appeared in patients under 20 years.

The opposing school states that if the triphasic wave is carefully defined it will only be found in hepatic patients. Silverman (1962,1963) laid emphasis on the pseudo-paroxysmal nature of the complex and stated that "other less typical pseudo-paroxysmal activity may be seen in a variety of comas".

This line of thought was pursued further by Kobayashi (1963) and Reiher (1970). Both authors listed several conditions regarding the complex, which if obeyed, made the wave specific to hepatic disease. Kobayashi's criteria were:

1) A main deflection, surface positive or negative and two smaller deflections preceding or following it.
2) A frontal predominance and bilateral synchronisation.
3) Average duration of the complex 377 to 840 mSecs.
4) Of the three components the first deflection had the shortest deviation and the third the longest. The second deflection showed the largest amplitude.
5) Occipital delay.

This author stated that triphasic waves satisfying these criteria were never observed in non-hepatic diseases in over 1700 cases studied. Reiher's (1970) criteria are substantially similar.

A minority view was expressed by Parsons-Smith et al (1957), who in a study of 62 patients considered triphasic waves to be rarely a feature of hepatic encephalopathy.
Some authors have attempted to relate triphasic waves to a biochemical disturbance. It was suggested originally by Bickford & Butt (1955) that the triphasic complex might have a "chemical origin". Friedlander (1956) reported experiments concerning infusion of ammonium chloride in two patients with Porta-caval shunts. He showed that increased ammonia levels were accompanied by increased slowing in the E.E.G. without triphasic activity. Cloche (1957) observed such activity in hepatic coma patients but found no correlation with the blood ammonia levels.

Poser (1958) thought hyperammonaemia was the most important factor in the production of triphasic waves. However, he found some inconsistencies in his data and concluded that there was as yet unknown metabolic dysfunction which may affect the reticular activating systems and its diencephalo-cortical connections.

Silverman (1962) found no precise relationship between triphasic activity and blood constituents viz: standard liver function tests and arterial ammonia.

Macgillivray and Kennedy (1970) described a "general correlation with various biochemical disturbances particularly low serum sodium and bicarbonate levels, reflecting the severity of the liver disease". They concluded that this wave was multifactorially determined.

The obvious objection to all the above findings is that even if one accepts a triphasic wave as an entity specific for hepatic conditions, the lack of agreement regarding the characteristics of the wave, precludes any valid observation regarding its clinical correlations.

Correlation of E.E.G. with Clinical State.

Several authors have introduced clinical and E.E.G. grading in attempt to define a relationship between the E.E.G. and the clinical features.
Good correlations have been noted by: Foley, Watson & Adams (1950); Bickford & Butt (1955); Gordienko (1956); Parsons-Smith (1957); Golovchenko (1960) and Bonnet et al, (1963). Poor correlations were reported by Poser (1958); Velasco et al, (1961); Silverman (1962); and Guggenheim (1964).

Of those who have suggested a poor correlation, the usual discrepancy has been the presence of a relatively normal E.E.G. in the context of clinical features of encephalopathy, or the presence of an abnormal E.E.G. in the absence of clinical encephalopathy. Velasco et al, (1961) in a study of 46 cases of hepatic disease, observed 2 patients with slight confusion and 1 patient with marked confusion, all with normal records. Guggenheim (1964) noted a fairly marked clinical encephalopathy in some cases, which was associated with only moderate E.E.G. changes, whilst others with less encephalopathy showed considerable E.E.G. disturbances. Only in the most seriously affected cases could a correlation be found.

Silverman (1962) reported 28 patients classified as alert, who had a theta dominant and 2 who had a delta dominant record. He described one confused patient with an E.E.G classified as normal. However, he pointed out that of 13 patients who showed no abnormalities in their E.E.G's at any time, only one died, whilst of 13 showing unremitting or ultimately delta activity, 12 died; suggesting at least that the E.E.G. did have some prognostic value.

Parsons-Smith (1957) in a study of 62 patients who mostly had hepatic cirrhosis, stated that patients with no detectable neuropsychiatric abnormality usually showed normal E.E.G's. Seven patients, however, showed an E.E.G. abnormality - sometimes theta dominant - where there was a history of neurological disorder within six months, or where a high protein intake was being consumed. Patients with obvious neuropsychiatric abnormality always did have marked E.E.G. change. A theta dominant record was observed in two cases
where the neuropsychiatric state was only slightly involved and the E.E.G. features improved with neomycin. This crucial observation led to the suggestion that the apparent disagreement between clinical and E.E.G. rating may be of therapeutic significance. It was stated that "it is not surprising that in some patients the E.E.G. is a more sensitive index of cerebral disturbance than clinical assessment". In support of this they cited the work of Fazekas et al, (1956), where it was shown that the cerebral utilisation of oxygen in hepatic insufficiency may be decreased without obvious neurological disturbance.

A few years later it was pointed out that E.E.G. changes may precede the clinical development of hepatic pre-coma and that the E.E.G. changes lagged behind the clinical profile upon recovery from such an episode (Laidlaw & Read, 1961b, 1963). These observations probably explain the apparent E.E.G. clinical disparity.

Recent Advances.

The next advance has already been alluded to, and is the result of several years work performed by Laidlaw & Read (1959, 1961a & b, 1963). It was stated that E.E.G. changes occurred very early in the progression towards coma, often before there were "objective clinical, psychologic or biochemical disturbances". It was also noted that there was a delay in return of the E.E.G. to normal, following successful treatment of coma. These observations have subsequently been confirmed, (Bonnet et al, 1963; Lods 1964; Bogacz, 1965;) Anticipation, however, was not detected by Krump and Gerardy (1958).

The electrical changes suggesting deterioration have been delineated by Laidlaw and were as follows:-

1. Failure of alerting stimuli such as opening the eyes to reduce as
much or to maintain for so long a reduction of background rhythmic activity. (See fig. 1.2). This may be accompanied or preceded by:

2. A progressive reduction in the frequency of the rhythmic activity, with, when the dominant frequency has fallen to about 5 c/s,

3. The appearance of high amplitude waves at 2-3 c/s at first singly, then in shorter and longer runs and finally continuously dominating the record."

Point 1 was expanded later with the statement that a failure of blocking or failure to maintain blocking for as long as 30 seconds was an early E.E.G. sign of impending delirium, which "often occurred before clinical or psychological signs and which may be diagnostically more important than a reduction in dominant frequency". Laidlaw pointed out that in the past attention had largely been directed towards analysis of localised paroxysmal abnormalities and little regard paid to the study of the "background rhythmic activity"(1961b). The latter activity is difficult to assess by simple inspection although, Laidlaw did report the application of a visual method of frequency analysis (1959). Because of this problem and the importance of measurement of background rhythmic activity, automatic frequency analysis was used extensively by him.

Again a problem of specificity arises with regard to the earliest changes suggested above. Laidlaw commented (1961a) that it was "usually easy" to distinguish changes 1 and 2 from those of simple drowsiness - "only occasionally interpretation is difficult when drowsiness is a feature of the delirium and the E.E.G changes of the two conditions coexist".

This point will be discussed more fully below.

Laidlaw's Work

Because some of the author's work is closely related to that of Laidlaw's,
it is proposed to describe his method in some detail. There were some
differences in the exact methods used by him, but the following account which
is fairly typical is based on his 1961b and 1963 articles.

The E.E.G. was recorded from the postero-lateral aspect of the non-
dominant hemisphere and was fed into a modified BNI wave form analyser which
accepted epochs of 15 seconds duration. The activity at frequencies from
2-12 c/s was measured on a microammeter in arbitrary units. Each record consisted
of nine epochs taken 15 - 30 seconds after eye closure - "S1 - S5", two from 15 - 30
seconds after opening the eyes (01, 02) and two from 15 - 30 seconds after
opening the eyes when presented with a pattern of small lights illuminated on
a board (L1, L2). The epochs were presented in the order S1, 01, L1, S2, 02,
L2, S3, S4, S5. In the earlier paper (1961b) an additional epoch 'Lc' was
included, during which the subject counted a pattern of lights illuminated on
a board.

The choice and arrangement of the epochs was empirically determined.
It was stated that there must be enough epochs to allow assessment of inter-
epoch variability but that the recording must be short enough in order to
anticipate "possible deterioration in the patient's condition". He stated in
the absence of any experimental proof, that "it is very important that any two
records being compared should have the same number and arrangement of epochs".
It could easily be conjectured that the subject might find the procedure
excessively long, especially with repeated visits, and that there might be
justification for varying the order of tasks to avoid boredom. This point is
elaborated further under 'DISCUSSION'.

The first 15 seconds was ignored, by Laidlaw, to avoid errors that
might have resulted from transient fast activity just after eye closure. This
is a well documented phenomenon (Storm van Leeuwen & Bekkering, 1958).
The first 15 seconds was skipped in the eyes open epochs because any reappearance of rhythmic activity would be best detected after some delay. From the analysed signal a frequency spectrum was constructed for each epoch.

Certain indices were derived from the spectral estimates:

1. "Dominant frequency" (DF). That frequency at which there was most activity with the eyes shut.

2. "Rhythmic Activity". This was defined as the sum of activities from 2 c/s below to 2 c/s above the dominant frequency, less five times the lowest meter reading. This value was obtained when the eyes were open (RAO) and shut (RAS).

3. "Mean Dominant Frequency" (MDF). The formula for this was as follows:

\[
\text{Dominant frequency} + \frac{2(f + 2 - f - 2) + (f + 1 - f - 1)}{(f + 2) + (f + 1) + df + (f - 1) + (f - 2) - 5(f - 2 \text{ or } f + 2)}
\]

This formula was implemented by us and is described under RESULTS.

4. Reactivity when the eyes were passively open (LOG S/O) or when looking at a light pattern (LOG S/L).

Each index was obtained in a similar way from appropriately paired epochs by the following formula:

\[
\text{Log S/O; S/L} = \text{Log} \frac{\text{RAS}}{\text{RAO}}
\]

This index gave a measure of the degree of blocking, a higher index indicated more blocking and vice versa.

Certain observations were made, in particular regarding the behaviour of these indices.

(1) With the onset or resolution of hepatic coma "the E.E.G. changes are
generalised and although they show intra-record fluctuations they are not paroxysmal". It was stated that these changes were not specific for hepatic delirium and that similar changes are found in a variety of conditions associated with confusion.

(2) Clinical delirium was associated with delta dominant records. With recovery there was a progressive increase in mean dominant frequency (MDF). The MDF on full recovery from acute episodes varied from patient to patient but was often at the lower limit of or below the normal range of 8 - 13 c/s.

(3) RAS was highest when the record was delta dominant. Thereafter it was variable although it showed a slight tendency to decrease with recovery. Because of its variability it was not found to be a useful index. It was suggested that a reduction of MDF associated with a decrease of RAS implied drowsiness, whereas a reduction of MDF associated with increase of RAS implied delirium. RAL and RALc were less subject to spontaneous fluctuations than RAO and were, therefore, considered a better guide to deterioration.

(4) Delta dominant records and those soon after recovery were associated with little reactivity to eye opening. With recovery there was a consistent increase in reactivity. The reactivity changes associated with simply looking at the light pattern were more reliable and sensitive.

(5) The E.E.G. improvement continued for several days after recovery of delirium, as assessed by ordinary clinical observations. Conversely E.E.G. changes were noted before clinical evidence of delirium when patients were deteriorating.
(6) Inspection of a single E.E.G. taken from a patient under optimum clinical conditions could not allow one to measure with accuracy the degree of hepatic encephalopathy. With increasing clinical evidence of encephalopathy there was a reduction of MDF and reactivity but classification on these criteria was unreliable because of the amount of overlap of values in patients with encephalopathy of differing degrees of severity. Only those patients with certain encephalopathy and permanent mental changes had E.E.G's which were consistently of low MDF and poor reactivity.

(7) 9 out of 86 (about 10%) had low voltage records ("desynchronised") and could not be analysed.

(8) Records with a MDF of 7 - 8 c/s may be considered as showing a borderline abnormality whilst those less than 7 c/s may be classified as abnormal.

Delirium versus Drowsiness.

As stated above, differences between these two states have been described by Laidlaw. The essential difference was that in drowsiness RAS decreased, whereas in delirium RAS increased. Both conditions were associated with a slowing of MDF. The majority of researchers would support this view with regard to the onset of drowsiness (Berger 1930; Loomis et al, 1937; Gibbs & Gibbs, 1950; Simon & Emmons, 1956; Dement & Kleitman, 1957). However, it has been pointed out (Cobb, 1963; Davis et al, 1938) that with the onset of drowsiness the alpha rhythm may, in fact, increase in amplitude during the early stages. This phenomenon is probably related to a lessening of tension. Clearly, when one wishes to observe the effect of sedating drugs such as morphine, this phenomenon is likely to be a potent source of error and probably extremely difficult to assess.
Furthermore, the undoubted fact that delirium and drowsiness may co-exist makes one loath to accept the statement that distinction is "usually easy".

Romano & Engel (1945) described 5 stages in the onset of delirium but paid little attention to the early phase and its distinction from drowsiness.

The "Desynchronised" E.E.G.

The problem of the low voltage or "desynchronised" E.E.G. was well reviewed by Adams (1959). He defined a "flat" E.E.G. as a record showing spontaneous activity not greater than 20 µV. Using this criterion he made a study of 427 subjects without neurological or psychiatric disorders and 2000 subjects known to suffer from one of these conditions. He found that 10% of normal people had flat records and that the incidence increased with age. More of such records were found in cases with endocrine disease (18%) and with psychopathy and neurosis (19%).

The tendency for the incidence of flat E.E.G's to increase with age was noted by Gibbs & Gibbs (1950) who also pointed out that these records were also associated with fatigue, drowsiness and sleep.

Obviously the incidence of flat records will be closely related to the criteria used for definition. Some authors have defined this in terms of voltage, others in terms of percentage alpha activity.

It is not surprising, therefore, that estimates have differed widely. Cohn (1949) in a study of 251 normal adults put the estimate at 4.1%; Gibbs et al (1953) found an incidence of 11.6% in 1000 normal adult controls; Pine & Pine (1953) studied 2116 E.E.G's of 2000 patients and estimated at 7.25%. Other figures have been given by Jung (1953) of 10%; Meyer-Mickeleit (1953) of 15%, and Laidlaw (1961b) of 10%.

The possibility of an association of the flat E.E.G. with hepatic encephalopathy has been seldom discussed in the past. Parsons-Smith (1957)
concluded that there was no evidence that a flat E.E.G was the initial change in hepatic pre-coma, but commented that it was seen as a terminal phase. This latter phenomenon was also observed by Bickford & Butt (1955). It was presumably a transitional phase progressing to the isoelectric record preceding death.

Il'Ina (1964) classified the E.E.G in hepatic disease into 6 varieties where 1 was normal and 6 delta dominant. In phase 2 the alpha activity was normal but the Beta rhythms became prominent (16 - 20 c/s). In phase 3 the rhythm began to slow but retained an amplitude over 20 µV. In phase 4 there was "asynchronous activity of low voltage and predominance of fast rhythms (18 - 28 c/s). The amplitude of the potentials is below 20 µV". Clearly, this phase corresponded to an acceptable definition of a flat E.E.G. In a study of 123 patients with a variety of hepatic disease Il'Ina reported a grade 4 E.E.G most often in cirrhosis following infective hepatitis (11 out of 40); acute and sub-acute epidemic hepatitis (9 out of 20) and in chronic hepatitis (8 out of 15). No evidence, in the form of clinical correlation, was brought forward in support of these changes and it was not stated whether the patients were observed in a clinically stable condition or not. Furthermore, the lack of confirmation by other authors makes these observations uncertain evidence.

**Hepatic encephalopathy in Children.**

The author was unable to find any detailed study of E.E.G. changes in hepatic encephalopathy in children and no studies of E.E.G monitoring before and after porta-caval shunts. Certainly these operations are performed somewhat less frequently than in adults; nevertheless, large series of such cases have been published (e.g. Voorhees et al 1965 - 98 cases) but with no mention of E.E.G. changes.
Cadilhac et al, (1959) reviewed the visually-obvious E.E.G characteristics in metabolic disorders in adults, and children. They remarked upon the striking liability of records at all ages and divided the changes of hepatic encephalopathy into four grades without further comment. McDonald (1963) described the changes in one child, age 9 who became comatose during an attack of infectious hepatitis. The E.E.G showed much slow activity (2 – 3 c/s) and it was noted simply that as the child's condition improved, so did the E.E.G. By the time he had fully recovered consciousness, the tracing showed 7 – 8 c/s activity. Dumermuth (1965) commented upon the severe distortion of the E.E.G. in children with hepatic coma, and noted the presence of high amplitude delta activity and 'hypersynchronous elements', often in a tri-phasic form.

From the above it may be tentatively assumed that the basic changes of hepatic coma in children are similar to those of adults. It is usually stated (Pond 1963) that the child's E.E.G. is more unstable and more readily disorganised than that of the adult. According to him the changes usually took the form of higher voltage activity and more widespread distribution than those produced by corresponding lesions in adults. He stated that, the child's record was more easily affected by metabolic disturbances such as hypoglycaemia. According to Corbin & Bickford (1955) the E.E.G's of normal children were no more unstable than adults, provided attention was paid to the environmental conditions of recording. They stated, however, that there was a relatively greater effectiveness of "environmental and subjective variables" so that their original comment is only partially correct.

Pampiglione (1965) described the E.E.G. changes after cardiothoracic surgery in 24 children. The chief change was an increase of bilateral slow activity especially posteriorly on the 3rd post-operative day, and gradually
disappeared at the end of the first week. The slow activity was thought to be due to hyponatraemia; other variables such as blood potassium, pCO₂ and analgesics were thought to be non-contributory.

E.E.G Variation

A certain amount of fluctuation of E.E.G indices is inevitable. This may be considered as follows:

a) Variation occurring during the course of a single recording. "Intra-record variation".

b) Variation throughout the day "diurnal variation".

c) Variation from one day to the next "day to day" variation.

Because in disease studies, small shifts of indices may be significant, it is important to be able to compare these shifts with the effects of fluctuations of the types described above.

a) Intra-Record Variation

It has been known for many years that attention leads to a reduction of alpha amplitude (Berger 1930) but that too much alerting, such as severe tactile, visual, auditory or mental stimuli may abolish the alpha rhythm completely (Hill 1963). Obviously, this factor prevents analysis and was a finding related to one task in the work of Laidlaw & Catling (1964) described below.

If a record is obtained for more than, say, one minute without some form of alerting stimuli the changes of inattention and then drowsiness will appear (Gibbs & Gibbs 1950). These usually consist of reduced alpha blocking on eye opening, associated with a loss of alpha amplitude (Cobb 1963).

Clearly environmental control is important during an E.E.G recording, and the first to examine this problem in detail were Laidlaw & Read (1961b). The eyes were kept open or shut for periods no longer than 30 seconds and during
the eyes open periods the subjects were instructed a) to do nothing b) to look at a pattern of lights, c) to count a complex array of lights. Although no statistical analysis was performed, there was an impression of less variation in alpha frequency whilst the subject was looking at, rather than counting lights. They also observed a greater fluctuation in patients with hepatic encephalopathy than in normal people.

In a further study, Laidlaw & Catling (1964) compared the effects of 1) doing nothing, 2) counting from one to 100, 3) counting odd numbers backwards. The latter two tasks were done to the beat of a metronome. Less fluctuation in frequency was found with tasks 2) and 3), which was highly significant \((P < 0.001)\). Excessive blocking was obtained with the third task, so that the second was considered the most suitable.

A somewhat unusual approach was adopted by Cohn & Castell (1966) - "in all recordings great care was exercised to maintain the patients in an awake vigilant condition. This was accomplished by forced conversation on a topic of particular interest to the patient". They do not report whether this technique had the desired effect on the E.E.G. measurements.

Mental arithmetic and its E.E.G effects has been the subject of considerable interest. Most authors have described a decrease of alpha amplitude when mental arithmetic is performed, either with the eyes open or shut. (Berger 1931; Adrian 1947; Walter 1959; Glass & Kwiatowski 1970). A considerable body of work suggests that some people, possibly one-third of the normal population show an increase of alpha amplitude during mental tasks (Werre 1957; Toman 1943; Mundy Castle 1957; Kreitman & Shaw 1965).

No change in alpha frequency was found by Kreitman & Shaw (1965) but their technique was not sensitive to small changes of frequency. Legewie et al (1969)
found a slight increase of mean frequency during mental tasks, varying from 0.2 - 0.5 c/s. A similar increase was also noted by Jasper & Cruikshank (1937) and Gibbs & Maltby (1943).

b) **Diurnal Variation.**

There have been only a few studies related to variation of E.E.G. indices over the course of 24 hours. The first mention of such change was by Jasper & Cruikshank (1937) who reported that the frequency variability over the course of one hour on an individual may be 1.5 - 2.0 c/s. Rubin (1938) made a study of 16 normal subjects and found fluctuations "approximately half" those observed by Jasper & Cruikshank. Details regarding the normal subjects were not given nor was any mention made of the times of day the recordings were obtained. His conclusion was that there was a "little less" variation in mean alpha frequency for normal subjects on a given day, than from day to day.

Heninger (1969) made an analysis of variance of the E.E.G. power spectra in 6 healthy adult males, examined at 7 A.M. and 4 P.M. He found no significant differences between the energy estimates at these times. However, Scheich (1969) in a study of 20 healthy subjects, reported an increase of alpha frequency from morning until after mid-day. Unfortunately, the report was only in abstract form and no figures relating to these changes were supplied.

Naitoh et al (1969) made measurements of alpha percentage in 4 male students, following sleep deprivation up to one week. They found regular peaks and troughs in alpha percentage values in all subjects. The peaks were at 9 A.M. and 9 P.M. and the troughs at 3 P.M. and 3 A.M. and were probably related to fluctuations of adrenal steroid production. Similar observations were made by Frank et al (1966).

Thomson (1968 and personal communication) examined the diurnal changes
in 5 male subjects all aged 23 years, for 2½ to 10 days. Most subjects displayed slowing of alpha frequency, maximal at 3 A.M. with an acceleration, maximal in late afternoon. On occasion two peaks and troughs were detected, somewhat similar to the observations of Naitoh et al. (1969). There was a frequency difference of 0.2 - 0.5 c/s between each peak and trough observed. Adrenal steroid output correlated negatively with alpha frequency.

\textbf{c) Day to day variation.}

There have been several early studies of this aspect, usually by visual analysis. Estimates of day-to-day variation of alpha frequency in healthy subjects have ranged from less than 1% (Brazier & Finesinger 1944) to as much as 10% (Rubin 1938). Jasper & Andrews (1938) obtained 13 or 14 E.E.G's in healthy subjects over a period of 18 months. They stated that the "occipital alpha is remarkably constant for a given person over long periods, if precautions are taken to maintain the same psychologic and physical conditions of the experiment". In Brazier & Finesinger's study of 15 subjects, aged 17 - 38 years, it was found that there was more variation with increasing age. Loomis et al (1936) and Engel et al (1947) both gave a figure of approximately 1 c/s for range of alpha frequency when taken over periods of 8 months and 5 years respectively. Engel et al therefore considered only a change of more than 1 c/s to be significant. It is of interest that the alpha frequencies taken on separate occasions in all their three subjects studied was not normally distributed.

Laidlaw & Catling (1964) studied the variation of 25 healthy subjects of both sexes, aged 21 - 35 years. They all had four recordings each, one week apart, and estimates of E.E.G indices were obtained on a modified BN1 analyser. Although no precise figures were given, their illustrations
suggested a day-to-day variation of approximately ± 0.7 c/s for women and ± 0.5 c/s for men. The greater figure for women was attributed to the effects of menstruation.

Murawski (1966) performed an autocorrelation analysis on the E.E.G's of one healthy male student, taken over 22 days. There was a mean alpha frequency of 9.51 c/s with a standard deviation of ± 0.21 c/s. The undulations of alpha frequency correlated with steroid output.

Read et al (1968) briefly quoted the fluctuations of dominant frequency for 12 healthy subjects (ages unspecified), who were examined on 7 separate occasions. The mean MDF (mean dominant frequency) was 7.78 – 10.50 c/s with a standard deviation of ± 0.10 to ± 0.23. For 11 patients with liver disease with and without encephalopathy the mean MDF was 3.91 – 9.25 c/s with a standard deviation of ± 0.07 to ± 0.22. They decided that slowing of MDF between two random records for the same patient of more than -0.6 c/s represented a significant degree of change.

Many authors have found evidence of a change with the menstrual cycle. Dusser de Barenne and Gibbs (1942) described in 9 out of 11 females a decrease of alpha frequency by approximately 0.5 c/s for one or two days at the middle of the menstrual cycle, which they thought might be related to ovulation. At the start of menstrual loss a similar decrease of frequency was observed. Margerison et al (1964) in a study of the records of twelve healthy females throughout the menstrual cycle, noted a tendency for a reduction of amplitude pre-menstrually, associated with a fall of serum sodium levels. The majority of subjects showed no changes in frequency. However, their technique of analysis (modified BNI analyser) was sensitive only to changes of 1 c/s, and as the fluctuations may well be of this order or less, it is not surprising none were detected.
In the experiments already referred to, Laidlaw & Catling (1964) noted that after the beginning of menstruation, the average MDF was 0.23 c/s less than during the remainder of the cycle.

In summary of this section, it seems generally agreed that it is important to provide an alerting situation when recording the E.E.G, but that this must not be overdone. The alpha frequency appears to be slowest in the morning and accelerates towards evening, but further observations are needed in this sphere. With regard to day-to-day variation a figure of ± 0.5 c/s appears to be a reasonable overall figure, taking into account the effects of the menstrual cycle.

Tests related to hepatic encephalopathy.

The number of substances that have been claimed to have a beneficial or harmful effect on the course of hepatic encephalopathy must be legion. Each one of these compounds is a potential substance for the demonstration of encephalopathy using the E.E.G as a detector. The subsequent review will, however, be restricted to those tests that have been most commonly implemented, i.e. morphine injection; variations of dietary protein; oral neomycin; and ammonium salts. The role of ammonia in the production of E.E.G. changes and encephalopathy is discussed in the latter section.

(1) Morphine injection.

The earliest E.E.G. observations were made by Berger (1934) and (1937b) who noted that when morphine induced sedation and sleepiness, there was a slowing of alpha rhythm. Gibbs, Gibbs & Lennox (1937) gave 16 mg. morphine sulphate intravenously to three healthy subjects. They found a flattening of activity interspersed by bursts of high voltage 10 c/s activity. Subsequent Grass frequency analysis showed the appearance of a peak at 20 c/s which
gradually disappeared whilst the alpha peak slowed by about 1 c/s with a reduction in total voltage (Gibbs & Malthy 1943). These changes were thought similar to those of sleep, although the patient only seemed drowsy. Similar phenomena have been observed by Andrews (1941) and Cahen & Wikler (1944).

In addition to its usual depressant action morphine is known to have a stimulant effect on the central nervous system. Sub-convulsive doses of morphine in the cat (Wikler et al 1944) had no effect, but seizures produced by large doses were accompanied by rhythmical slow wave discharges in the electro-corticogram (Fisher & Lowenbach 1934).

The first mention of the toxic effect of morphine in hepatic disease appears to have been made by Mallory (1940). In the discussion of the case of an 11 year old schoolboy, who was suffering from severe hepatic failure and died shortly after 7.5 mg morphine (intramuscularly) he stated "I have been impressed that following a single dose of morphine it is not uncommon for a patient with cirrhosis to develop coma and never come out of it". Fagin & Thomson (1944) observed that in 6 of 15 patients dying in coma the development of stupor progressing to coma followed within a few hours of the administration of morphine in a dose of 10 - 15 mg. They did mention however that several other patients had been given morphine intermittently for the treatment of gastrointestinal haemorrhage without apparent injurious effects. Similar observations are made by Murphy et al (1948).

Andrews (1941) made a study of the effects of morphine in addicts, post-addicts and non-addicts. It was noted that the mean alpha frequency of the post addict group (whose addiction had ceased for at least one year) was significantly higher than that of the addicted group (10.2 c/s and 9.6 c/s) respectively. In the post-addicted group following a single sub-cutaneous
injection of 20 mg morphine there was a period of mild mental excitation which was accompanied on the E.E.G. by a tendency for the occipital alpha blocking time to increase. (No further details or definition of this term was given). When a dose of 12 - 15 mg was given to normal subjects marked nausea and lassitude was noted with no evidence of excitement. In some normal cases there was little change in the E.E.G apart from an increased blocking time of the alpha rhythm. However, in one case a typical sleep pattern developed 3 - 4 hours after the injection; paradoxically, the subject showed no clinical evidence of drowsiness. During addiction a high alpha percentage was found and in some cases this phenomenon continued through the period of acute withdrawal.

Wikler (1954) made a study of the effect of 30 mg morphine given intravenously to 11 healthy prisoners. All subjects were initially observed to be clinically more alert after morphine. This was followed usually by euphoria and occasionally by drowsiness. The E.E.G showed either no change or an increase of alpha percentage which was on occasion accompanied by slowing of the alpha frequency by as much as 1 c/s or more.

It was not until 1961 that morphine was given to patients with hepatic cirrhosis as a test of encephalopathy (Laidlaw et al 1961a). The object of the procedure was to determine whether or not morphine had a greater effect in patients with hepatic encephalopathy than in those without. It was stated that "small doses of morphine given to those without liver disease produce either no E.E.G changes or those of drowsiness or sleep". Whilst this is not entirely true as had been detailed above, the fact that changes of drowsiness may be induced is a priori evidence against the value of the test, as the changes of delirium and drowsiness may be difficult to distinguish especially where these two states co-exist.
Morphine was given in a dose of 8 mg or 16 mg intramuscularly in two groups of patient:

A) Those who were either healthy subjects or who had cirrhosis without encephalopathy. 15 cases.
B) Those who had cirrhosis and a past history of an episode of encephalopathy. 17 cases.

The E.E.G was taken before and 3 hours after injection. In group A, with the higher dose, 9 showed no change, 6 showed slight slowing of MDF but not exceeding 1 c/s, and one showed this type of change accompanied by an increase of RAO. With the lower dose (8 mg) no change was observed. In group B all patients receiving the lower dose showed some change, including 5 who exhibited a delta dominant record. The high dose of morphine was only given to 5 subjects in group B but the trend was similar.

It was stated that the E.E.G changes in patients who were passing spontaneously into hepatic coma "are identical with those which have been induced in certain patients with liver disease by therapeutic doses of morphine". Only a few pages earlier it is conceded that morphine may produce E.E.G. changes resembling sleep and in the following paragraph that delirium and drowsiness are easily distinguished on the E.E.G. These are clearly confusing statements.

No correlation of E.E.G. changes with arterial ammonia, serum potassium, pH, urinary volume and electrolytes could be found. It was concluded that 8 mg Morphine was the preferable dose and that the test might be useful in determining the liability to develop hepatic coma, especially in the context of candidates under consideration for porta-caval anastamosis.

The above work was expanded by Laidlaw & Read (1961b) using a larger series. There was a control group of 22, an encephalopathy group of 17 and
a further group consisting of cases of possible encephalopathy (20 subjects). The administration of 16 mg morphine to the control group produced in 3 tests a slowing of MDF of 0.3 to 1.0 c/s with an increase of RAO by more than 25%. This change, however, only occurred once with the 8 mg dose. Although 16 mg morphine induced a more severe change in the definite encephalopathy group, in 7 of the 34 tests where 8 mg was given to this group only minor changes were seen. These consisted of a reduction of MDF of -0.3 c/s or an increase in RAO of 25% or more. Thus, in approximately one fifth of tests morphine was failing to detect a suspected encephalopathy.

A further point raised by Laidlaw is that if one obtained a borderline change following a single injection of morphine one may then administer a high protein diet and repeat the test. A larger shift on a high protein intake added significance to the initial result and would perhaps clinch a clinical suspicion of hepatic encephalopathy. By this test it was "possible to attribute a non-specific sensitivity to morphine (or encephalopathy) to liver disease". However such a test cannot be entirely specific as protein loading causes deterioration in patients with renal impairment and would presumably result in an increase of renal encephalopathy and hence an exaggerated response to morphine. Provided one excludes renal dysfunction the differential test may be valid but no mention was made of this source of possible error.

Laidlaw's final observations regarding this test appeared in 1963, where he enumerated five salient points regarding the response to morphine in patients with certain evidence of encephalopathy.

" 1) In all cases morphine produces a reduction of mean frequency."
2) There is no important change in RAS. This makes it unlikely that the changes are merely those of drowsiness.

3) That in almost all cases there is a reduction in reactivity to opening the eyes. (Log S/O).

4) That in all cases there is usually greater reduction in reactivity to looking at the light pattern. (Log S/L).

5) That the E.E.G changes produced by morphine are similar to those produced by developing delirium, increased protein or the withdrawl of neomycin."

A further study of morphine in hepatic cirrhosis was made by Lods & Dupuy (1964). They examined the responses to this drug by visual inspection of the E.E.G in 46 cases before, one, and three hours after 10 mg morphine given subcutaneously. One of their subjects with a previous history of encephalopathy who at the time of testing had jaundice and ascites, lapsed into a coma 4 hours after the injection. Because of this, patients with previous encephalopathy were not tested with morphine. The drug was given to 9 hospital patients without liver disease and none of these were reported to show any E.E.G change. Alterations were induced in cirrhotic patients without previous encephalopathy, consisting of "instability or slight slowing down" (18 cases), "accentuation of slow waves" (3 cases) and in 11 cases no change was detected. Their conclusion regarding the value of the test was "...l'importance des altérations obtenues n'est pas parallèle au degré des perturbations biologiques ni même à l'état clinique". Whilst they were uncertain whether the test had any prognostic value they thought it might be useful in the assessment of patients for porta-caval shunts.

Guggenheim et al (1964) made a visual E.E.G study on 22 patients suffering from various types of hepatic dysfunction. Records were obtained before
and after 8 mg morphine, given subcutaneously. They detected no change in the E.E.G. of control subjects. In 13 of 17 hepatic patients who received morphine there was a clear worsening of the E.E.G, consisting of slowing of the dominant rhythm, frequently associated with frontally located delta activity. This change occurred even in those patients with no evidence of neuropsychiatric upset, contrary to the findings of Laidlaw. They were unable to say whether the morphine test was useful in selecting patients for porta-caval shunts but thought the results promising.

In summary, it would appear that after morphine E.E.G slowing may occur in healthy people especially if doses in excess of 10 mg are used. Similar or greater degrees of slowing have been observed in patients with hepatic dysfunction but there appears to be no agreement regarding the correlation of the degree of change with the presence or absence of previous encephalopathy.

(2) Protein Loading.

Shortly after the description of a means of creating a communication between the portal vein and inferior vena cava by Eck (1877) it was shown by Pavlov and his co-workers (Hahn et al 1893, Nencki et al 1896) that a neurological disorder consisting of stupor, ataxia, convulsions and finally coma occurred in Eck fistula dogs following the ingestion of meat - the so called "meat intoxication". These observations were confirmed some years later by Balo & Korpassy (1932). They observed that the 'intoxicated' dog did not eat, and after fasting the toxic symptoms disappeared only to reappear when the dog began to eat meat again.

The earliest observations of deleterious E.E.G changes following a high protein intake were made by Phillips et al. (1952), in a study of 9 cases of
hepatic cirrhosis. E.E.G changes were reported in two cases only, and these consisted of "rare slow activity" and "slight abnormality", each in association with a high protein intake.

McDermott & Adams (1954) made detailed observations of a patient on whom they performed a pancreatectomy and an anastomosis between the superior mesenteric vein and inferior vena cava, as treatment of a pancreatic carcinoma. There was no evidence of cirrhosis or hepatic metastases in this patient. Following protein loading with 125G daily for 3 days there was a marked deterioration in conscious level, accompanied by dominant theta activity on the E.E.G.

Parsons-Smith (1957) gave 120G Protein per day for one week to 7 patients with cirrhosis and stated that protein loading helped elucidation of borderline changes in the E.E.G. pattern.

Laidlaw & Read (1961 & 1963) used automatic E.E.G frequency analysis in a study of 7 patients known to have experienced previous encephalopathy. Protein loading (100 - 120G per day) for at least 7 days revealed a) a reduction of MDF and reactivity in nearly all cases, but that b) this deterioration was variable and sometimes small.

Vojtechovsky & Horky (1966) studied the E.E.G. effects of a 100G protein breakfast in 13 cases of "compensated hepatic cirrhosis". By visual inspection of the E.E.G. trace they reported that after 3 hours there were "very slight" changes in 9 cases, consisting of slowing of alpha rhythm by -0.5 to -1.0 c/s with sporadic diffuse slow waves. In 6 out of 7 healthy subjects similarly tested, E.E.G. changes of sleep were noted, but not until the 6th hour. They concluded that protein activation tests in cirrhotic patients with a normal E.E.G. and without clinical signs of decompensation were of little value.
In a more extensive study, the same group (Horky et al, 1967) reported the visually determined E.E.G changes in 22 patients with hepatic cirrhosis and 8 with other forms of hepatic dysfunction (unspecified), following unspecified periods of high protein loading. Some, but not all of the patients had clinical signs of encephalopathy. A deterioration of E.E.G. grade was frequently observed, in some cases only with 60G protein per day, but in others no change could be induced on a 250G protein per day. A reduction of protein intake reversed the changes. They commented that with different patients suffering from cirrhosis, there was a varying tolerance when tested on subsequent occasions. They did not attempt to correlate previous encephalopathy with changes following protein loading.

In summary it would appear to be generally agreed that protein loading causes abnormalities on the E.E.G. but that the response may be variable and most authors seem not to have found the test to be of great value.

(3) Neomycin.

The precise mode of action of neomycin is not known with certainty. It was initially thought (Dawson et al, 1957) that the drug acted simply by destroying proteolytic bacteria in the colon and hence reduced the quantity of nitrogenous material reaching the portal system, with a consequent improvement of encephalopathy. More recently Jacobsen et al (1960) and Dobbins et al (1968) have suggested that neomycin may be inducing a malabsorptive state by a direct action on the intestinal wall.

The literature has been found to be scanty regarding the use of Neomycin with E.E.G. observation as a test of encephalopathy. In most cases the E.E.G. has to be initially abnormal before administering Neomycin and perhaps the presence of an abnormal record has been enough to substantiate the existence
of an encephalopathy. In this sense Neomycin effects are merely confirmatory.

The earliest reports of the use of this drug in hepatic cirrhosis were by Fisher & Faloon (1956) who gave neomycin for 80 days to a patient with cirrhosis and chronic neuropsychiatric signs and were able to increase the protein tolerance. A fuller report was made by Dawson et al. (1957), who described the use of this drug in 20 cirrhotic patients, 8 of whom suffered from intermittent stupor. A detailed study of E.E.G changes was not made, but they stated that "the obvious clinical improvement was reflected in the E.E.G although in only one case did the tracings become completely normal".

Laidlaw & Read (1963) described the effect of neomycin in 7 patients with a previous history of encephalopathy. In all these cases neomycin produced an improvement as judged by an increase of MDF and reactivity. In 3 cases the improvement was only slight. The pre-neomycin MDF was always less than 8 c/s with one exception, so that the slight changes could not have been due to improvement within the normal alpha range. They considered the use of neomycin to be of value particularly in deciding whether a known encephalopathy was due to hepatic causes. Why some patients with abnormal records did not respond to Neomycin is an important point which was not discussed by them.

More recently Hawkes et al. (1970) described the effects of neomycin on the MDF of a patient with recurrent encephalopathy. A striking E.E.G improvement was noted on two occasions which promptly abated following withdrawal of the drug. It was thought that the speed of action of neomycin might be dose related. This patient is fully described in the case history section (Case I).

Despite the paucity of literature it seems generally agreed that
in hepatic disease neomycin will often improve an abnormal E.E.G and that this observation is perhaps of value in deciding whether an E.E.G. abnormality is due to an encephalopathy of hepatic origin.

(4) Ammonia Salts and The Role of Ammonia.

For over 40 years ammonia has been postulated by various workers as an important toxic agent in the genesis of hepatic coma. Burchi (1927) suggested that a disorder in ammonia metabolism might be the cause of the neurological symptoms in liver disease and subsequently Van Caulaert (1932) related the ingestion of ammonium salts by patients with cirrhosis to subsequent symptoms of drowsiness, confusion and coma. Kirk (1936) found elevated ammonia levels in blood taken from a collateral venous channel in the abdominal wall of a cirrhotic patient and emphasised the importance of spontaneous shunts in contributing to hyperammonaemia. These facts have subsequently been confirmed by Phillips et al (1952); McDermott (1954) and Stahl et al (1952) who stressed the effect of protein and other nitrogenous material in precipitating coma in cirrhotics.

These observations lead to the suggestion that there might be some correlation between the severity of encephalopathy and the level of ammonia in the blood. There has been no agreement however on this point. Those favouring such a correlation include Velasco (1961), Bessman & Bessman (1955), Eichler (1964), Phillips (1952), although none of these authors stated that the correlation was very close. Those against include Seegmuller et al (1954), Phear (1955), Summerskill (1957), Sullivan et al (1961), Stahl (1963), Egense (1963), Neilsen (1965) and Spellberg (1969). A better correlation of encephalopathy with CSF ammonia could not be found by Moore et al, (1963).

The explanation for this disagreement of opinion is at least threefold.
1. The majority have relied on either Conway's (1937) or Seligson's (1951) methods, or modifications thereof, in the estimation of blood ammonia levels. These methods are complex, prone to error (McDermott 1959) and whilst it is possible that with careful technique, repeatable results may be obtained, the method of Fenton (1962) and its modifications, e.g. Horn & Squire 1967) is now generally agreed to be more reliable. (Horn D.B. - personal communication).

2. There has probably been a failure to distinguish between the effects of porto-systemic shunting and deterioration in hepato-cellular function. Although these are frequently associated because the commonest cause of portal hypertension with a collateral circulation is intrahepatic disease, an attempt to separate these factors in each patient is important (McDermott, 1959). However, more recent work related to ammonia tolerance tests in the detection of collateral circulation suggests that hepato-cellular function is of relatively minor importance in determining the arterial ammonia levels, and that the degree of collateral circulation is far more significant. (Conn, 1967; Stahl, 1963).

3. Significant ammonia metabolism occurs in extra-hepatic sites, such as muscle and kidney, and erroneous estimates may be obtained if venous blood is used in the estimation of ammonia (Stahl (1963); Bessman & Bradley (1955)).

Considering the above, it is not surprising that there has also been disagreement regarding the correlation of blood ammonia with E.E.G changes. Kellaway & Wise (1954) described only a crude correlation, whilst Poser (1958) was impressed by a correlation with triphasic waves. Friedlander (1956) appeared
to favour a correlation, but his evidence was based on only two cases of cirrhosis. Silva et al. (1965) found some association but "not always present in a parallel way". Yoshida et al. (1968) described the effect of oral ammonium citrate on the E.E.G in two patients with hepatic disease and found that the slow waves increased parallel to the blood ammonia.

Abbott (1956), Parsons-Smith (1957) and Bogacz (1965) were all against a correlation of E.E.G changes with arterial blood ammonia levels. Using automatic frequency analysis, McFarland et al. (1964) commented that "in general high ammonia levels and markedly abnormal E.E.G's were attended by low levels of consciousness, but neither test measured accurately subtle alterations in the patient's condition nor was it reliable for inter-patient predictions". In another study, again using automatic frequency analysis, in 19 patients with liver disease, Cohn & Castell (1966) observed "in spite of the fact that arterial and venous ammonia levels were acutely elevated [by oral ammonium acetate] to very high concentrations, in the present study we were able to demonstrate a major change in E.E.G in only one patient out of the 19 studied". They concluded that chronic elevation of the blood ammonia "or associated abnormalities" were more important than the acute changes which they induced. Despite this, they offered no proof of their statement and the literature regarding this point discussed above appears to be largely against this hypothesis.

Studies of the effect of ammonium salts on the E.E.G. as a provocative test of hepatic encephalopathy have not been numerous. Following oral ammonium chloride (6g per day for 3 days) and a high protein diet in cirrhotic patients, Laidlaw & Read (1961b) described an increased E.E.G response, to morphine injection, when compared with the response to morphine in the context of a normal diet and no ammonium chloride. They did not detail the changes
associated with ammonium chloride itself. Tsukiyama et al (1961) described the E.E.G - provocative effect or oral ammonium chloride. E.E.G deterioration was obtained in 23 out of 28 patients with hepatic diseases of varying severity. Because of troublesome gastric side effects, they modified their technique (Tsukiyama et al 1963). A dose of 1 ml per Kg. of a 0.2M solution of ammonium chloride was given intravenously over 5 minutes. The E.E.G was recorded before, during and after the injection for 30 minutes and inspected visually. No changes were observed in all 7 patients with non-hepatic disease but in all of 10 patients with hepatic dysfunction, marked E.E.G changes were seen. In four there was an increase of theta activity; in another 4 there was a marked increase of delta activity and in two a slight decrease in dominant frequency. Triphasic waves occurred in two hepatic cases. No side effects were observed in any patient and it was concluded that the test was a rapid and specific test for hepatic encephalopathy.

Opposing the above findings are the findings of Cohn & Ulshafer (1958). They infused high doses of ammonium carbonate (27 - 220 mg/Kg) into the common carotid artery of rats. High voltage slow wave discharges were elicited if the cardiac output was allowed to fall, but if this was prevented, no E.E.G change occurred, implying that the changes were secondary to hypoxia, induced by a cardiotoxic action of the ammonium salt. It should be pointed out that Tsukiyama et al (1963) used a different substance i.e. the chloride and not the carbonate salt, and in considerably smaller dosage, and yet produced marked changes. It cannot necessarily be assumed that ammonium chloride produces the same changes as other ammonium salts. Warren et al (1960) have suggested that an acidosis would deter entry of ammonia into the brain and this would be an expected change with the chloride salt. Unfortunately, the E.E.G. changes associated with acidosis are ill-defined (Dawson & Greville, 1963) and the
majority of research is related to hypercapnoeic acidosis which causes overbreathing and consequent hypoxic effects on the E.E.G., in addition to any effects the acidosis may be producing.

What of the E.E.G. effect of ammonium salts in normal people? Marossero et al (1957) gave 26 Meq ammonia as a 10% solution of ammonium chloride by rapid intravenous injection. The ensuing E.E.G. changes consisted of bilaterally synchronous slow waves. Wilson & Tyor (1958) observed the E.E.G changes in 9 patients who had no evidence of hepatic, renal or central nervous system disease. An intravenous infusion of ammonium lactate or ammonium chloride in doses of 37 - 94 Meq was maintained for one hour during which the E.E.G. was continuously inspected. Despite very large rises of arterial ammonia, no E.E.G changes were detected, by visual methods.

The consensus of opinion is that both the E.E.G. and conscious level correlate poorly if at all with blood ammonia. There is disagreement regarding the effects of acutely induced hyperammonaemia in both normal and cirrhotic patients. There appears to be no literature regarding the E.E.G. in chronic hyperammonaemia in healthy persons, but regarding this problem in cirrhotic individuals there is again no agreement. Despite over 40 years research stemming from Burchi's (1927) original suggestion, we are very little further forward. All this suggests that ammonia is perhaps not a primary factor in hepatic coma, but merely one of the manifestations.

The cause of hepatic encephalopathy.

It is probable that no single agent is responsible for the production of every case of hepatic coma. In the majority of circumstances it is likely that several agents are involved (Sherlock, 1968). Although the precise mechanism of hepatic coma is as yet poorly understood there are some situations
that have been shown to have a causal relationship to the subsequent development of encephalopathy, and it is proposed to discuss in brief some of the possible factors.

Hippocrates & Galen were both acquainted with the disturbed mental function that often accompanies jaundice. It was, however, shown very early on that bilirubin itself was an unlikely cause of the mental changes by Frerichs (1861), who injected large amounts of ox bile into the blood of dogs and detected no effect on the nervous system. The lack of correlation between serum bilirubin levels and state of consciousness has been confirmed on many occasions since then (Murphy et al 1948; Parsons-Smith et al 1957; Zieve 1966). Despite this most studies have paid regard to the total serum bilirubin and it is possible that a better correlation may be found with the unconjugated fraction.

It seems generally agreed that nitrogenous material is intimately related to hepatic encephalopathy. The general theory relating to this is as follows:

Ingested protein reaches the colon where it is decomposed by bacterial action. The products of this process, which are potentially harmful, are carried via the portal vein to the liver where they are detoxicated. In cirrhosis of the liver these substances may accumulate and affect the brain adversely by two processes: 

a) by intra- or extra-hepatic shunts which allow some blood in the portal vein to bypass the liver.

b) Through failure of removal by the damaged liver.

The evidence for the above theory is as follows:

1. Procedures removing or altering the nitrogen producing bacteria in the
colon have a beneficial effect on hepatic encephalopathy. This effect has been observed following colectomy (McDermott et al. 1962); neomycin therapy (see previous section); purgation (Dawson et al. 1957); lactobacillus acidophilus (Read et al. 1966); and lactulose (Elkington et al. 1969).

Conversely, constipation aggravates encephalopathy (Sherlock, 1968).

2. Hepatic encephalopathy worsens if nitrogenous material is administered e.g. a high protein diet; urea; methionine and other amino acids; ammonium salts; and a haematemesis, which results in a 'protein meal' (Phillips et al. 1952; Sherlock et al. 1954). An encephalopathy often improves on a low protein intake (Parsons-Smith et al. 1957).

3. Porto-systemic anastomoses, especially followed by the administration of protein may result in coma - 'meat intoxication'. (Hahn et al. 1893; McDermott & Adams 1954). There is an increased incidence of encephalopathy in those patients with porto-caval anastomoses, compared with similar patients not so treated. (Read et al. 1961).

The above evidence has lead many people to postulate ammonia as the key toxic factor. Whilst the arterial ammonia is nearly always raised in severe cases of hepatic encephalopathy (Sherlock, 1958) there is no overall agreement on the correlation of ammonia levels in the blood or cerebrospinal fluid with the state of consciousness as measured by clinical or E.E.G methods (see previous section). Zieve (1966) summed up the ammonia problem by saying "one cannot escape the conclusion that disturbed cerebral ammonia metabolism is in some way basic to the syndrome of hepatic coma". He was however unable to explain the numerous anomalies of this problem.

Hepatic coma in cirrhotic individuals has been seen to develop on many occasions following severe diarrhoea, ACTH therapy, rapid abdominal paracentesis or a briskly induced diuresis, all of which are associated with
potassium depletion (Sherlock, 1968). A clear relationship between low serum potassium levels and the onset of encephalopathy in 20 cirrhotic patients was demonstrated by Read et al (1959). Hypokalaemia was induced by the administration of the diuretic chlorothiazide or by the use of a sodium-potassium exchanger resin. These measures were accompanied by slowing of the MDF as measured by a method of visual frequency analysis (Laidlaw, 1959). In 7 patients neuropsychiatric symptoms were induced including hepatic coma in 2 cases. The E.E.G. and clinical changes were reversed on addition of potassium supplements but not by the administration of Neomycin. Hypokalaemia was induced in two non-cirrhotic subjects who displayed a similar but less marked slowing of MDF.

Alkalosis is often found in hepatic coma possibly because of toxic stimulation of the respiratory centre by ammonia (Sherlock 1968). It is not known whether alkalosis per se is harmful or whether it is toxic through its effects on ammonia transfer. Warren (1960) demonstrated that alkalosis increased the diffusion of ammonia into the cerebro-spinal fluid and presumably this enhanced its toxicity. He was unable to demonstrate any clinical improvement following induction of an acidaemia. The validity of Warren's Hypothesis has recently been challenged by James et al (1969a) who demonstrated a striking clinical improvement following infusion of sodium bicarbonate in 5 patients with hepatic coma (James et al 1969b). Two patients showed a significant improvement on the E.E.G tracing but this was not as striking as their clinical response.

Cerebral hypoxia has been demonstrated in hepatic coma and may well be a causative agent. A reduction of cerebral oxygen consumption by approximately 50% and a reduction of cerebral blood flow by approximately 25% in hepatic coma, was demonstrated by Fazekas et al (1956). Hypoxia is
undoubtedly an important deleterious factor with regard to the E.E.G. (Gibbs et al 1935; Davis et al 1938; Gibbs et al 1940) and the changes induced are similar to those observed in hepatic coma. In this context it is important to reiterate that according to Cohn & Ulshafer (1958) the E.E.G changes observed after high dose ammonia infusion in rats were considered to be due to cerebral hypoxia secondary to the cardiotoxic action of the drug. However, apart from cases of hepatic coma secondary to haematemeses it is likely that hypoxia is not primarily involved in the production of coma and that it occurs only secondarily to other metabolic changes.

Other toxic agents that have been postulated include a variety of amino acids and fatty acids, especially short chain. Some years ago Bessman & Bessman (1955) suggested that the basic lesion in hepatic coma was the depletion of Krebs cycle intermediates by excessive conversion of alpha-keto glutarate to glutamic acid and glutamine. This theory has largely been discounted (Sherlock 1968) particularly as no such depletion has been demonstrated in humans, although Zieve (1966) still considers the theory worth further appraisal.

A concept which is clinically useful, was put forward by Sherlock (1961) namely that the brain is in some way "sensitised", presumably by nitrogenous material, such that it behaves abnormally to insults that would be without effect on the normal brain. In chronic encephalopathy structural changes such as astrocytic hyperplasia have been well described (Adams & Foley 1953). Whether structural change is necessary for brain sensitisation is uncertain. This concept is evoked to explain the increased response of some cirrhotic patients to certain drugs - especially morphine - and to potassium depletion. Unfortunately hypokalaemia has been shown to induce E.E.G
deterioration in the normal brain (Fourman 1954, Saunders 1954, Read et al, 1959). One might expect that in cirrhosis Neomycin would reverse EEG effects induced by hypokalaemia but this could not be shown by Read et al, 1959. A reversal was shown, however, by McKie et al (1958) in a similar experiment so that no firm conclusions can be drawn.

In summary, the best evidence is for nitrogenous material and hypokalaemia. How they induce coma is not known. Hypoxia is important, but in most cases is probably a secondary phenomenon. The role of other agents discussed here is uncertain.

**Automatic E.E.G. Analysis.**

The technique used in the current work consisted of performing a Fourier Transform of an auto correlogram derived from a 20 second epoch. To place this method in perspective it is proposed to review briefly the main types of automatic analysis. This section is partly based on a review of the topic by W.G. Walter (1963).

a) **Frequency Analysis.**

It was shown by Fourier that any waveform could be resolved into a number of sinusoidal components of specific amplitudes, frequencies and phase relations. Whilst this treatment is applicable to repetitive phenomena it cannot be applied to the E.E.G. which has no fundamental frequency. This difficulty was overcome by Grass & Gibbs (1938) by converting the E.E.G. into a repetitive phenomenon by recording the voltage changes on film and joining this end-to-end in the form of a continuous loop. The loop was then read by a photo-electric cell and the signal passed through an electric wave filter. The output of the latter at the desired bandwidths was measured on a galvanometer. The
system approximated to a Fourier Transform of the original record. It was prone to error however, chiefly from inaccuracies in the construction of the continuous loop and from variations in film speed. It was also a very time consuming method.

Another approach is to feed the E.E.G. signal to a number of electronically tuned filters designed to resonate at frequencies from, say, 1, 2, 3...... 30 c/s. This technique was developed by Baldock & Walter (1946) and is commercially available (BNI analyser). The device accepts an epoch of E.E.G signal usually 10 or 15 seconds, which is stored by the tuned filters, whose activities may be measured either by the height of a pen deflection, so arranged as to be alongside the appropriate section of the E.E.G tracing, or, in a subsequent modification, by measurements with a galvanometer. The pen deflections tend to be inaccurate because of non-linearity, but the galvanometer method is more precise and was used extensively by Laidlaw & Read (1961b, 1963) who considered the technique to be sufficiently accurate for clinical purposes. A fundamental disadvantage with the BNI analyser is that the bandwidths and frequency range are fixed as are the epoch lengths. Moreover, the apparatus requires frequent maintenance and calibration.

The above types of analysis relate only to the frequency content of a single channel, consequently they give no information regarding phase or spatial distribution. Phase information cannot be acquired but spatial relationships may be obtained by appropriate sharing of the filters between two E.E.G. channels (Walter, W.G. 1963).

b) **Period Analysis.**

This technique depends on a measurement of the time interval
between base-line crosses or wave peaks and troughs. The chief difficulty is in the choice of a fiducial event. It is important that "the indication is not amplitude sensitive, which means that either the input signal must be amplitude limited or squared, thus defining the fiducial points as cross-overs, or that the peaks and/or troughs of the waves should be clipped over an arbitrary range of amplitudes" (Walter, W.G. 1963).

Furst & Noell (1949) developed a base line cross analyser as an anoxia warning device, which produced an alarm signal on the occurrence of a train of 3 - 4 waves in the theta range.

The system developed by Burch (1959) attempted to abstract wave shape information from the E.E.G as an aperiodic function. The record was twice differentiated to obtain an indication of both "major periods" and "minor periods". The superimposed frequencies as well as the dominant rhythm may be characterised as count per second (reciprocal of frequency) and the sum of minor periods per second (wave shape coding). The data may be converted to digital form so that "numerical values can be obtained to emphasise such factors as wave symmetry, peakedness and phase". (Burch 1959). This method is unfortunately liable to serious error due to the presence of components slower than that of the major period. (Walter, W.G. 1963).

c) **Spatial Analysis.**

By this process one attempts to measure variations in electrical activity from one region of the brain to another with respect to amplitude and time. In one approach the E.E.G signals recorded simultaneously from different sites on the head are analysed using
frequency analysis (e.g., Kennard et al. 1955) or by cross-correlation analysis (Brazier & Barlow, 1956).

Another device for displaying spatial E.E.G features is the toposcope (Walter & Shipton, 1951), in which 22 cathode ray tubes each display the activity from a pair of E.E.G electrodes. The amplitude of the signals from each channel are displayed as variations in brilliance of the oscilloscope beam which is moved in a continuous spiral at a speed governed by the frequency and phase of the incoming signal in one channel. This system is of "particular value in studying any slight changes in frequency of intrinsic rhythms and for measuring their time relations in different regions" (Walter, W.G. 1963). The most serious disadvantages with this method are that it requires the formation of a special record by photography or on sensitive paper, and that after a long experiment the observer may be overwhelmed by the enormity of information thus obtained. (Walter, W.G. 1963).

Another technique was devised by Rémond (1960). The amplitude of activity from a line of equidistant electrodes was measured at a succession of equal time intervals. From these amplitude measurements a smooth curve was interpolated, which represented the potential distribution along the line of electrodes. The positions along the electrode line corresponding to given voltage increments are determined by repeating the process at each successive time instant, the positions along the electrode line corresponding to given voltage levels can be plotted against time and the results displayed as a contour map.

d) Autocorrelation and averaging techniques. The autocorrelogram is very closely related to the spectrum but has only recently been used for the study of electro-encephalogram activity. The operation of constructing
an autocorrelogram involves obtaining two copies of the sample of record which is to be studied and, for each element of the autocorrelogram, multiplying corresponding points on the two records and averaging the products. To obtain successive elements of the autocorrelogram one copy is delayed or moved backwards in the time dimension with respect to the other and again corresponding elements are taken, multiplied, and the products averaged. Thus the autocorrelogram is a function of delay, which may be signified by the letter \( n \):

\[
    r_n = \sum_{t=0}^{T} a_t a_{t-n} \quad n = 0, 1, 2, \ldots, N
\]

Where \( N \) is the maximum value of delay or lag.

The autocorrelogram thus described is a discreet approximation to the autocorrelation function which is a mathematical function derived from the convolution of two infinite signals.

A variety of analog methods have been used to construct autocorrelograms. The operation of multiplication can, for instance, be conveniently performed by recording one copy of the signal in the form of density modulation on photographic film and the other as an undulating line formed by the junction of a wholly dark and a wholly white area. If these two copies of the signal are now superimposed and the total light transmitted through them collected by a photovoltaic cell, then as one copy is moved with respect to the other the output of the photovoltaic cell describes the desired autocorrelogram.

An elegant variant of this technique was used by Tucker (1950).
Other more sophisticated devices have involved the use of a tape recorder to copy and delay the signal with analog multipliers and integrators to perform the multiplication and averaging (Brazier & Casby 1952).

More recently still, high speed digital computers have been used to calculate the autocorrelogram arithmetically from sequential samples of the original tracing, i.e. a time series. The small special digital computers like the CAT or Biomac have been provided with extension units which are capable of deriving correlograms on line. Most of these extension units utilise analog multipliers.

The autocorrelogram itself, although it contains all the information necessary to specify the amplitude and frequency of components in the E.E.G. has not been much favoured because it is difficult to extract useful information from the curve by simple inspection. The autocorrelogram, however, may be transformed into the spectrum by a process which involves another convolution operation. This is referred to as making a "Fourier Transform" and the details of the operation are as follows (Barber, 1961) -

The autocorrelogram is laid alongside a cosine function and corresponding elements of autocorrelogram and cosine function are multiplied, and the average of all the products so obtained gives the value of one element of the spectrum. Successive elements of the spectrum are obtained by altering the frequency of the cosine function appropriately. Thus to estimate the amount of activity present at 10 c/s a cosine function is used whose frequency is 10 c/s etc.
This method of investigation has been shown to provide unbiased but inconsistent estimates of the true spectral value and it is customary, therefore, to smooth the resulting spectrum. In the present study an alternative method suggested by A.J. Milner (1954) has been used. In this variant the autocorrelogram itself is first multiplied by a function which has the effect of acting as a smoothing function for the final spectrum. The advantages of Milner's method are partially that the amount of computation needed is reduced and partially that the smoothing function gives a good approximation to the desired square band pass shape, so that the estimate thus obtained of the spectrum at 10 c/s approximates closely to a consistent and unbiased estimate of the total amount of activity in a band of width $\delta$ centred at 10 c/s.

Recently an alternative method of deriving spectral estimates has been suggested which involves the use of the newly described fast Fourier Transform (Cooley & Tukey, 1965). This method requires large computer storage facilities and is not feasible on a small digital computer, such as that used in the present study.

There are certain inherent sources of error in both autocorrelation and averaging techniques, and in frequency analysis. The slower the frequency of a wave and the shorter the epoch length, the more inaccurate will be its estimation. Unless measures are instituted to control the E.E.G recording environment, intra-epoch fluctuation of frequency and/or amplitude may occur and adversely affect the accuracy of analysis (Walter, D.O. 1963). The latter author stressed that errors will also result from transient phenomena such as intermittent spikes or slow waves.
Conversely, the longer the record the more accurate will be the averaging process and the less will be the effects of disturbances due to random components (Cooper et al, 1969).

Hence the selection of epoch length is often arbitrary and represents a compromise between two extremes.
MATERIALS AND METHODS.
Subject Material.

HEPATIC GROUP.

A total of 48 patients with hepatic dysfunction were studied. Clinical details regarding these are presented in Table 2A. It will be observed that all but three subjects were thought to suffer from a variety of hepatic cirrhosis. The exceptions were one case each of portal vein thrombosis, possible fasciola hepatitis, and alcoholic hepatitis. The first two cases are dealt with separately but some of the data (the morphine test) in the case of alcoholic hepatitis have been included in the analysis of the hepatic group. It will be noted that there are 7 cases of lienorenal and 3 of porta-caval-anastamosis. A further patient (L32) had an initial porta-caval shunt which thrombosed and was followed later by a lienorenal anastamosis.

It is indicated in Table 2A whether varices were detected or not. They are only marked present where there was definite evidence from such procedures as barium swallow, oesophagoscopy, splenic venography or laparotomy. Where varices are marked absent this was usually on the basis of one or more barium meal examinations. It is accepted that this test does not always detect the presence of varices.

In 32 patients (67%) the diagnosis was firmly established by percutaneous or operative liver biopsy. Only when two or more of the four criteria detailed below were present was a presumptive diagnosis of cirrhosis accepted in the absence of liver biopsy.

(1) Oesophageal varices demonstrated as above.

(2) At least two abnormalities in the following four groups of liver function tests:
### TABLE 2A.

**LIST OF PATIENTS IN HEPATIC GROUP**

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>INITIAL</th>
<th>AGE</th>
<th>SEX</th>
<th>VARICES</th>
<th>BIOPSY</th>
<th>PSE</th>
<th>OPERATION</th>
<th>TYPE OF HEPATIC DISEASE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>EG</td>
<td>38</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>B</td>
<td>S; OT</td>
<td>Cryptogenic Cirrhosis.</td>
</tr>
<tr>
<td>6</td>
<td>TA</td>
<td>47</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>B</td>
<td></td>
<td>Alcoholic Cirrhosis.</td>
</tr>
<tr>
<td>9</td>
<td>DM</td>
<td>71</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td></td>
<td>Alcoholic Cirrhosis.</td>
</tr>
<tr>
<td>21</td>
<td>WR</td>
<td>65</td>
<td>M</td>
<td>0</td>
<td>+</td>
<td>A</td>
<td></td>
<td>Secondary biliary cirrhosis.</td>
</tr>
<tr>
<td>23</td>
<td>LH</td>
<td>10</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>B</td>
<td>S, LRA:</td>
<td>Cirrhosis following infectious hepatitis.</td>
</tr>
<tr>
<td>26</td>
<td>JC</td>
<td>24</td>
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KEY.  
PSE Indicates grade of porta-systemic encephalopathy.  
A = None.  B = Possible.  C = Definite.  See Text.  
PCA Porta–Caval Anastomosis.  
LRA Lienorenal Anastomosis.  
S. Splanectomy.  
OT. Oesophageal Transection.
TABLE 2A (contd).

**NOTES:**

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Age Range = 7 - 71 years.
Mean Age = 50 years.
Number of Males = 33
Number of Females = 15
(a) Raised serum alkaline phosphatase, serum alanine-aminotransferase, or serum bilirubin.

(b) Abnormal bromsulphalein retention at 45 minutes, i.e. greater than 5% following a dose of 5 mg/kg of a 5% solution.

(c) Low serum albumen.

(d) Raised serum gamma globulin fraction.

See appendix for range of normal values.

(3) History of infectious hepatitis or greatly excessive alcoholic intake, i.e. greater than 6 pints of beer or \(\frac{1}{2}\) bottle of whisky per day for a period of ten years or more.

(4) A hard irregular liver on palpation where by clinical screening and follow up, neoplasia was thought extremely unlikely.

It should be noted that where the term "cirrhotic group" appears this does not only imply those with biopsy proof of this condition.

The presence of encephalopathy is indicated by one of three letters.

(A) Where on clinical grounds there was never any evidence of an episode of encephalopathy.

(B) Where on clinical grounds there were some episodes that might have been due to hepatic encephalopathy. For example, one patient (L77) became irrational following a large haematemesis. Prior to this however, he had been consuming large quantities of alcohol and it was not certain whether this was hepatic pre-coma or delirium tremens or possibly both. Other patients had histories of confusional states but there were inadequate clinical details regarding these.

(C) Where on clinical grounds there was a definite episode of hepatic encephalopathy. This consisted of a confusional or comatose state associated with foetor hepaticus and usually a flapping tremor.
In most patients of this group there was confirmatory E.E.G. evidence in the form of intermittent or continuous delta activity.

CONTROL GROUP.

Forty-nine subjects comprised the control group and details regarding these appear in Table 2B.

All the control subjects had clinically and biochemically normal liver function. None had a history of any hepatic, metabolic or neurological disorder. The patient with a urinary tract infection had a normal blood urea, electrolytes and E.S.R. Several potential subjects had to be excluded on account of a previous history of infectious hepatitis.

In both the diseased and normal group standard E.E.Gs with hyperventilation were obtained in all cases. Subjects with abnormal records were, of course, excluded from the control group. In the diseased group the only abnormalities permitted were those considered compatible with the stage of encephalopathy thought to be present at that time.

The commonest reason for exclusion of potential volunteers from the control group was a low voltage record ("desynchronised"). Apart from the possibility that this is an abnormal feature, such records had to be excluded as they could not be analysed, that is, no peak or only a very ill defined one was obtained in the analysis of the alpha frequencies. One patient (L130), with a low voltage record was accepted for the study, as measurements of delta activity have been claimed to provide a measure of encephalopathy in the absence of a well defined peak in the theta or alpha range. (Laidlaw, 1966).

Of a total of 152 subjects studied (i.e. control and hepatic) who had a test E.E.G., 29 (19%) had to be excluded because of a desynchronised record.
**TABLE 2B.**

**LIST OF SUBJECTS IN CONTROL GROUP.**

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<td>SM</td>
<td>36</td>
<td>F</td>
<td>G.</td>
</tr>
<tr>
<td>140</td>
<td>GS</td>
<td>21</td>
<td>F</td>
<td>HS.</td>
</tr>
<tr>
<td>141</td>
<td>GC</td>
<td>38</td>
<td>M</td>
<td>HS.</td>
</tr>
<tr>
<td>142</td>
<td>JM</td>
<td>41</td>
<td>M</td>
<td>DU.</td>
</tr>
</tbody>
</table>
### TABLE 2B (contd)

<table>
<thead>
<tr>
<th>EEG No.</th>
<th>INITIAL</th>
<th>AGE</th>
<th>SEX</th>
<th>CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>148</td>
<td>WW</td>
<td>49</td>
<td>M</td>
<td>HS.</td>
</tr>
<tr>
<td>151</td>
<td>MB</td>
<td>45</td>
<td>F</td>
<td>HS.</td>
</tr>
<tr>
<td>165</td>
<td>CM</td>
<td>59</td>
<td>M</td>
<td>HS.</td>
</tr>
<tr>
<td>166</td>
<td>VR</td>
<td>49</td>
<td>F</td>
<td>HS.</td>
</tr>
</tbody>
</table>

**KEY.**

- **HS**: Members of Hospital Staff. (38)
- **DU**: Patients with Duodenal Ulceration. (8)
- **G**: Patients admitted for minor gynaecological operation. (2)
- **UTI**: Patient with mild urinary tract infection. (1)

**TOTAL** = 49

**Age range** = 18 - 61 years.

**Mean Age** = 34 years.

**Number of Males** = 31.

**Number of Females** = 18.
13 of these were patients with hepatic disease. Two more patients had to be excluded because one had a "double dominant" rhythm (i.e. well defined peaks of activity at closely adjacent frequencies) and the other had a highly unstable record.

12 subjects included in the analysis had records which most of the time could be analysed but occasionally their records flattened and presented difficulty. All but two of these were patients with hepatic dysfunction. The flattening would usually give rise to a falsely low or high estimate of one of the three measurements of mean dominant frequency. If this occurred, the average of the mean dominant frequency would be based on two values instead of the usual three. This was thought to contribute a very minor error.

Recording Technique.

The E.E.Gs. of the majority of ambulant hepatic patients and all control subjects were obtained in the E.E.G. laboratory. The subject, where this allowed, had the E.E.G. whilst seated. This was preferred to the usual method of recording on a trolley, as it was thought that the latter approach was conducive to drowsiness which might then confuse the interpretation of the E.E.G. Those patients confined to bed had their E.E.G. either on a trolley, or in bed using the portable apparatus to be described. No attempt was made during the recording to exclude everyday extraneous sounds. The noise of the high speed punch probably helped to maintain the patient alert, which was one of the main objectives of the recording technique.

Three chlorided silver "stick-on" electrodes were applied to the scalp using collodion. Their placement is shown in Fig. 2.1. Where serial recordings were performed the electrodes were frequently left in situ for periods of up to one week. Perfectly satisfactory records were obtained by this method. If the electrodes were removed from the scalp their position was
Figure 2.1

Distance 10% of line connecting Nasion and Inion

Distance 10% of line connecting External Auditory Meati

Earth

To EEG machine
indicated with gentian violet. Variations of interelectrode distance, of course, give rise to variations of amplitude and the latter was one of the more important indices.

The recordings were all performed in a standardised manner and were in most cases taken at the same time of day, by the same E.E.G. technician, (Mrs. H. Pryor), or by the author himself.

The procedure was as follows:-

1) Explain test to subject.
2) Apply electrodes and adjust their resistance to lie below 5 K ohms.
3) Set high frequency filter to 75 cycles per second, time constant 0.3 seconds, gain on paper record 10 μV/mm.
4) Check calibration of analog-digital convertor (ADC) and set to zero.
5) Feed 50 μV C/S sine wave calibration signal to ADC, and record a few seconds of this signal.
7) Eyes open and simultaneously start paper tape punch. Perform task 1 for 30 seconds.
8) Eyes shut 30 seconds.
9) Eyes open 30 seconds. Perform task 2.
10) Eyes shut 30 seconds.
11) Eyes open 30 seconds. Perform task 3.
12) Eyes shut 30 seconds.

The E.E.G. analysis time is thus three minutes of which 90 seconds is eyes open and 90 seconds eyes shut.

The visual tasks referred to above were designed to maintain the subject comfortably alert. They comprised:
1) To look at a regular pattern of black beads fastened on to a piece of white pegboard 2' x 2'.

2) To count an irregular pattern of black beads on the pegboard (see Fig.2.2). The number of beads was adjusted to be slightly greater than the subject's ability in the available time.

3) To maintain the eyes open and do nothing.

To test for effects related to the order in which the tasks were presented their sequence was systematically varied. This allowed six possible "pattern sequences" and these were referred to by a number (1 - 6).

Recording of Data.

The lead from the right temporo-occipital area was fed to a standard E.E.G. machine for visual inspection. One of two eight-channel E.E.G. machines were used:

1) Officine Galileo, Model E8A.
2) AEI Polygraph.

Only three of the available eight channels were used. One channel was used to display the unfiltered E.E.G. and via its amplifier, to drive the ADC. Another channel was used to copy and filter (15 c/s cut) the original signal and the third channel monitored the output of the ADC. (The latter had an output facility for digital to analog conversion).

The ADC was set to make a voltage measurement at 0.01 second intervals. The output consisted of 1" (8 level) paper tape. One channel was used as a marker to indicate to the computer a change from eyes open to eyes shut or vice versa. The remaining seven channels output a series of numbers to an accuracy of 7 binary digits (i.e. 1 - 127). The overall accuracy is thus of the order of 1%.

As mentioned above a standard calibration signal was fed to the ADC prior
Figure 2.2.

Photograph of apparatus used
during EEG Recordings
(The patient is seen counting an irregular pattern of beads mounted on the peg-board)

Key

TR   Tape reader
ADC  Analog - digital converter
LPF  Low Pass Filter
EEG  ARI Polygraph - preamplifier unit
HSP  High speed punch, producing paper tape
HB   EEG Head Box
to all recordings. The purpose of this was to allow direct comparisons of amplitude between records taken on separate occasions, where the gain setting of the ADC might have been altered.

The calibration sine wave was generated by a battery operated oscillator (Triumph Electronics VLF 1).

Where the patients condition necessitated portable recordings the following apparatus was used:

1) Pre-amplifier stage. Triumph Electronics battery operated pre-amplifier. Set at x10K, time constant 0.3 seconds, high frequency filter at 100 C/S.

2) Storage. Elliott Tandberg magnetic tape recorder series 64E2A. Quarter-inch tape was used at a speed of 7/8" per second. This speed gave a frequency response of DC - 600 C/S plus or minus 1dB. One channel of the recorder was used simultaneously as a speech channel so that when the tape was played back the patients name, time of eye opening, etc. were correctly known. The recorded E.E.G. signal was simultaneously monitored on an oscilloscope.

3) Playback. The tape recorder output was fed directly to the ADC and simultaneously the analog output of the latter was fed to one channel of a standard E.E.G. machine. All the data were processed by an Elliott 903 B digital computer.

Programming.

Basically three programs were used in the analysis and display of the E.E.G. data.

1) SPECTE PUT.
2) DAYRUN.
3) HEPLAN.
Modified versions of these were written but the above are representative of the ones most frequently utilised. The other programs consisted of modifications to calculate, for example, a slow wave index, to construct different graphs, or to calculate indices without plotting the graphs.

SPECTE PUT was entirely the work of Dr. H. R. A. Townsend. By his kind permission it is briefly described here as it is the most important step in the computer analysis. The other two programs were the work of the author and are described in full. Apart from being central to the theme of this work, they represented a major part of the research conducted over the past two years.

SPECTE PUT.

The ALGOL version is presented here but subsequently a version was written in the faster assembly language SIR. A flow diagram is displayed (Figs. 2.3 - 2.5) followed by a teleprinter print-up of the ALGOL version. There are fundamentally three steps in this program:

1) Calculation of the calibration correction factor.
2) Construction of the autocorrelogram.
3) The Fourier transform.

(1) CALIBRATION.

The estimates of amplitude obtained by the program are linearly related to the amplitude of activity in the original E.E.G. trace. To allow direct comparisons of amplitude between records taken on different occasions (where the gain setting of the ADC may be slightly different), the 10 C/S 50 µV sine wave is processed first. Twenty half-cycles of this signal are read and the peak-to-peak amplitude of each half-cycle is measured. A continuous measurement is performed until twenty consecutive half-cycles whose amplitudes lie within a specified range, have been obtained. This process has been implemented as a code procedure, "CALIBRATE". (See SPECTE PUT - 1).
Figures 2.3 - 2.5

Flow Diagram of SPECTE PUT
START

SET UP COSINE TABLE IN ARRAY COSWAVE[0:99]

READ SUBJECTS NAME AND NUMBER ETC.
READ PATTERN SEQUENCE NUMBER

WAIT

READ REPEAT, DELAY, T, B, NO

SET N TO 200/B

SET UP TABLE WHICH DEFINES BANDWIDTH IN ARRAY BAND[0:N]

READ DESIRED FREQUENCIES INTO ARRAY FREQUENCY[1:N]

READ SINE WAVES ON CALIBRATION TAPE

CALCULATE CALIBRATION CORRECTION FACTOR

Figure 2.3
Figure 2.4

See figure 2.5 for Flow diagram

of form correlogram
Figure 2.5
Flexowriter Printup of SPECTE PUT
sections 1-3
SPECTE PUT;

"BEGIN" "REAL" K,B,EST;
"INTEGER" I,J,T,N,NO,F,PATSEQ,REPEAT,DELAY,KK;
"ARRAY" COSWAVE[0:99];
"INTEGER" "ARRAY" NAME [1:100];

"CODE""PROCEDURE"CALIBRATE;"ALGOL";
"CODE""PROCEDURE"PUT(A);"INTEGER""ARRAY"A;"ALGOL";
"CODE""INTEGER""PROCEDURE"CALCULATION;"ALGOL";
"CODE""INTEGER""PROCEDURE"INEEG; "ALGOL";

"PROCEDURE" FORM CORRELLOGRAM(A,N,T);
"VALUE"N,T; "INTEGER"N,T;
"REAL""ARRAY"A;
"BEGIN""INTEGER"J,EEG;
"REAL"X;
"INTEGER""ARRAY"B[0:N];

"CODE""REAL""PROCEDURE"RAWCO (A,B,N,T);
"VALUE"N,T; "INTEGER"N,T;
"REAL""ARRAY"A; "INTEGER""ARRAY"B; "ALGOL";

T:=T*100;
"FOR" J:=N"STEP"-1"UNTIL"0"DO"
"BEGIN"
   EEG:=INEEG; "IF"EEG"GE"128"THEN"EEG:=EEG-128;
   B[J]:=EEG*512;
   A[J]:=0;
"END";

X:=RAWCO(A,B,N,T); X:=(X/T)**2;
"FOR"J:=0"STEP"1"UNTIL"N"DO"
"BEGIN"
   A[J]:=A[J]/T-X;
"END";
"END" FORMCO;

K:=2*3.14159/100; COSWAVE[0]:=1;
"FOR" J:= 1"STEP" 1 "UNTIL" 99 "DO"
   COSWAVE[J]:=COS(J*K);

"COMMENT" SETS UP TABLE OF COSINES;
I:=1; INSTRING(NAME,I); "READ" PATSEQ;
WAIT;

"READ" REPEAT,DELAY,T,B,N0;
"COMMENT" NO OF ANALYSES
DELAY FROM STATE CHANGE TO EPOCH START
NO OF SECONDS IN EPOCH
BANDWIDTH
NUMBER OF FREQUENCIES AT WHICH ESTIMATES
ARE REQUIRED;

N:=200/B;

"BEGIN"
"ARRAY" A,BAND[0:N];
"INTEGER" ARRAY FREQUENCY[1:N0],
RESULTS[1:N0,1:REPEAT];
K:=0; BAND[0]:=3.14159;
"FOR" J:=1 "STEP" 1 "UNTIL" N "DO"
"BEGIN"
K:=K+B/100;
BAND[J]:=SIN(3.14159*K)/K
"END";
"COMMENT" SETS UP TABLE WHICH DEFINES BANDWIDTH;

"FOR" J:=1 "STEP" 1 "UNTIL" NO "DO" "READ" FREQUENCY [J];

CALIBRATE;
"COMMENT" READS CALIBRATION SEQUENCE & OBTAINS A
CALIBRATION CORRECTION FACTOR;

"FOR" KK:=1 "STEP" 1 "UNTIL" REPEAT "DO"
"BEGIN"
"SWITCH" C1:=CONT,Skip1,Skip2;
"IF" INEEG GE 128 "THEN" "GOTO" Skip1 "ELSE" "GOTO" Skip2;
Skip1: "IF" INEEG GE 128 "THEN" "GOTO" Skip1
"ELSE" "GOTO" Cont;
Skip2: "IF" INEEG < 128 "THEN" "GOTO" Skip2
"ELSE" "GOTO" Cont;
Cont: "FOR" J:=1 "STEP" 1 "UNTIL" DELAY*100 "DO" I:=INEEG;

"COMMENT" FINDS CHANGE OF MARKER CHANNEL INDICATING
EYES OPEN OR EYES SHUT;
SPECTE PUT - 3

FURMCO (A,N,T);

"FOR" J:=0 "STEP" 1 "UNTIL" N "DO" A[J]:=A[J]*BAND[J];

"FOR" I:=1 "STEP" 1 "UNTIL" N "DO"

"BEGIN"

EST:=A[0]/2; F:=0;

"FOR" J:=1 "STEP" 1 "UNTIL" N "DO"

"BEGIN" F:=F+ FREQUENCY[I];

"IF" F > 99 "THEN" F:=F-100;

EST:=EST+A[J]*COSWAVE[F]

"END";

EST:=EST/(N+1);

"IF" EST>0

"THEN" EST:=SQR(EST)* (1000/CALCOCORRECTION)

"ELSE" EST:=0;

RESULTS[I,JK]:=ENTER(EST*20+0.5);

"COMMENT" COPIES ESTIMATES INTO RESULTS MATRIX;

"END" FOURIER TRANSFORM;

"END" REPEAT;

I:=1; "PRINT" "R5OL2E39"; OUTSTRING(NAME,I);

"PRINT" SAMELINE,DIGITS(3),"R192L2"

PATTERN SEQUENCE', PATSEQ,

"L" REPEAT', REPEAT

"L" DELAY', DELAY, "L" T,

"L" BANDWIDTH', B,

"L" NO', NO, "L" T;

"FOR" J:=1 "STEP" 1 "UNTIL" NO "DO"

"PRINT" SAMELINE,

DIGITS(2), FREQUENCY[J];

"PRINT" "LR50"; PUT(RESULTS);

"END";

"END";

"END";
(2) AUTOCORRELGRAM. (A typical autocorrelogram is shown in fig. 2.6).

The E.E.G. is considered as a discrete series of amplitude measurements \( a_0, a_1, a_2 \ldots \). The formula for the approximation to the autocorrelogram used in this program is as follows:

\[
r_n = \sum_{t=0}^{T} a_t a_{t-n}
\]

\( n = 0, 1, 2, \ldots, N \)

\( N = \) number of lags

\( T = \) total number of samples.

The autocorrelation function is strictly the convolution of two infinite functions, but in practice an approximation is used, the autocorrelogram, which is obtained by summing products over a finite time (T). In this study six such periods, referred to as epochs, each of 20 seconds duration, have been used. Autocorrelograms are constructed with a maximum delay of 2 seconds (i.e. number of lags equals 200), so that the epoch is ten times the maximum delay.

The part of the program which performs the autocorrelogram is written as a code procedure RAWCO ("raw correlogram"). This is embedded in an algol procedure FORM CORRELOGRAM which takes as parameters the array in which the completed correlogram will be held (A) the number of lags (N) and the epoch (T). (See SPECTE PUT-1).

(3) FOURIER TRANSFORM.

The formula used was that given by Milner (1954).

\[
2 \int_0^\infty r(\gamma) \cos (\omega \pi \gamma / m) \left\{ \left[ \sin (\pi \gamma / m) \right] / \gamma \right\} d\gamma \quad (25)
\]
Figure 2.6

An Autocorrelogram Calculated From a 20 second sample of an EEG Record.

Horizontal Axis - Time in seconds
Vertical Axis - Arbitrary Units
Where the band limits are \((h - 1) \pi/m\) to \((h + 1) \pi/m\)
m is the length of the sample correlogram \(r(\tau)\).
From this an estimate is derived for the power in the band \(\omega \pm \delta\)
\[
2 \int_0^T r(\tau) \cos \omega \tau \left\{ \frac{\sin \delta \tau}{\tau} \right\} d\tau
\]
where \(T\) is the length of the sample correlogram \(r(\tau)\)

Our approximate correlogram is \(r_n\) and \(N\) is the corresponding length.

We first compute:
\[
B_n = \frac{\sin (\delta \lambda_n)}{\lambda_n}
\]
\(n = 0, 1, 2, \ldots, N\)
\(\delta\) is half the bandwidth desired expressed as an angular frequency. \(\lambda\) is
the sampling interval in seconds.
A modified correlogram is then derived:
\[
r_n' = r_n B_n
\]
and then estimates of the amplitude of activity in a band \(\omega \pm \delta\) are derived
as
\[
Q_f = 2 \sum_{1}^{N} r_n' \cos 2\pi f \lambda + r_0'
\]
f = frequency (in C/S) at which estimate is desired. See Milner (30).

Figure 2.7 shows the real shape of the pass band which is plotted for
the estimate \(\sqrt{Q_{10}}\) and the bandwidth \((2 \delta)\) is equivalent to 1C/S.

When the pass band is estimated with a cosine wave, the estimates show
oscillation which is greatest in the vicinity of 9 C/S and 11 C/S and even
negative estimates of amount of activity can be obtained. In practice,
however, the E.E.G. is not a regular sine wave and its autocorrelogram
**Figure 2.7**

**TOP RIGHT HAND FIGURE**
Graph of damped cosine wave according to formula given beneath figure.

**MAIN FIGURE**
Pass band of an equivalent filter whose centre frequency is 10 c/s & nominal bandwidth 1 c/s.
\( \cos(\frac{2\pi \sqrt{f}}{1}) \exp(-\pi t \times 0.3) \)
approximates to that shown in the upper right hand corner of figure 2.7 (cf fig.2.6), rather than to an undamped cosine wave.

When the pass band is estimated with an exponentially damped cosine wave of this form then the oscillations almost completely disappear but a small positive value is added to the estimate by frequencies quite far removed from the nominal pass band, while the estimate for frequencies within the band is slightly decreased.

The approximation to the ideal square pass band remains reasonably good.

A table of cosines is set up and stored in array COSWAVE. This enables the corresponding values COSwn to be derived from a simple indexing procedure instead of having to be calculated each time.

The resulting sum of products is proportional to the square of the amplitude of the corresponding components in the original record, and its square root is taken so that the output estimates will be linear with respect to the original trace.

The estimates, rounded to integer values, are output as a sum-checked binary paper tape. This instruction is found in the program as PUT (RESULTS) where PUT is a code procedure to print out a sum-checked binary algol array (Elliott NCR APPS group programming abstracts GETPUT 1, No.303).

DAYRUN. This and the following program HEPLAN were both the work of the author. A simplified flow diagram of DAYRUN is shown (figs. 2.8 - 2.11), followed by a formal print up of the algol program.

The program starts by reading three parameters:

REC - the number of records to be analysed.

LP - the lower point of the dominant frequency scan.

UP - the upper point of the dominant frequency scan.
Figures 2.8 - 2.11

Flow diagram of DAYRUN
Figure 2.8
Figure 2.9
Figure 2.10

- Find and print lowest value (min) in array C, ignoring rows 1 to 6.
- Print dominant frequencies (array Maxf).
- Calculate, store and print total activity, rhythmic activity and log reactivity.
- Store and print average of log reactivities.
- Is any dominant frequency below 4 c/s?
  - Yes: Do not interpolate & assume a value of 36 c/s.
  - No: Are secondary peaks present 2c/s either side of main peak?
    - Yes: Skip; interpolate using amplitude estimates 1c/s either side of main peak.
    - No: Interpolate using amplitude estimates 2c/s either side of main peak and obtain mean dominant frequencies.
Figure 2.11

PRINT AND STORE MEAN DOMINANT FREQUENCIES AND THEIR AVERAGE

PRINT GRAPH OF MEAN SPECTRUM

DOES J EQUAL N

READ NEXT RECORD

YES

PRINT STORED VALUES OF RHYTHMIC ACTIVITY, LOG REACTIVITY AND MEAN DOMINANT FREQUENCY

FINISH
Flexowriter Printup of DAYRUN

Sections 1-8
DAYRUN

"BEGIN"
"CODE" "PROCEDURE" GET(A); "VALUE" A; "INTEGER" "ARRAY" A; "ALGOL";
"INTEGER" REC, LP, UP;
"READ" REC, LP, UP;
"COMMENT" RECORD NUMBER, LOWER & UPPER BOUNDS OF DOMINANT FREQUENCY SCAN;

"BEGIN"
"REAL" L, M, MREACT, REACT, MF;
"INTEGER" 11, I, J, JJ, PATSEQ, REPEAT, DELAY, T, N, NO, SCALE, P,
K, Z, Q, MAX, DOMFRE, MIN, TOTAC, R, X, Y, FLAG, E, G, H, F,
HD, TROF1, TROF2, ZZ;
"INTEGER" "ARRAY" NAME[1:200], RHYAC[1:6], SEQ[1:6, 1:6],
PLOT[1:20, 1:2], MAXF[1:3], TOPS[1:13],
PARAMS[1:7], A[1:6, 1:REC];
"REAL" "ARRAY" MREQ[1:6], PEAK[1:13], B[1:8, 1:REC];
"BOOLEAN" JUMP, ZIGZAG;
"SWITCH" SS:= OUT, HOP, SKIP, EXIT, S1, S2, S3, S4, S5;
"SWITCH" FFS:= F1, F2, F3, F4;

"PRINT" "L" NUMBER OF RECORDS, SAMELINE, DIGITS(2), REC, "L"
LOWER BOUND OF SCAN*, SAMELINE, DIGITS(1), LP,
"LR100B12*";
I:=1; INSTRING (NAME, I); II:=1;
"FOR" JJ:=1 "STEP" 1 "UNTIL" REC "DO"
"BEGIN"
I:=II; INSTRING (NAME, I);
"PRINT" "LR100B12*";
GET(PARAMS);
PATSEQ:= PARAMS[1];
REPEAT:= PARAMS[2];
DELAY:= PARAMS[3];
T:= PARAMS[4];
N:= PARAMS[5];
NO:= PARAMS[6];
SCALE:= PARAMS[7];
"BEGIN" "INTEGER" "ARRAY" F[1:NO],C[1:REPEAT,1:NO],
RESULTS[1:NO,1:REPEAT];

GET(F); GET(RESULTS);

J:=X:=1;
"FOR" Y:=
1,2,3,4,5,6,
1,2,5,6,3,4,
5,6,1,2,3,4,
3,4,1,2,5,6,
5,6,3,4,1,2,
3,4,5,6,1,2 "DO"

"BEGIN"
SEQ[X,j]:=Y;
X:=X+1; "IF" X > 6 "THEN"
"BEGIN"
X:=1; J:=J+1
"END"
"END";

"FOR" P:=1 "STEP" 1 "UNTIL" 20 "DO"
"BEGIN"
"FOR" Q:= 1 "STEP" 1 "UNTIL" 6 "DO"
C[Q,P]:= RESULTS[P,SEQ(Q,PATSEQ)];
"END" OF EPOCH SORTING;

I:=II; OUTSTRING(NAME,I);
"PRINT" "L" PATTERN SEQUENCE",SAMELINE,DIGITS(8),
PATSEQ,
"L" DELAY",ALIGNED(1,0),DELAY/100,
"L" EPOCH",ALIGNED(2,0),T/100,
"L";
"PRINT" "L" MATRIX OF AMPLITUDE ESTIMATES";

"FOR" P:=1 "STEP" 1 "UNTIL" 20 "DO"

"BEGIN" "PRINT" "L";
"FOR" Q:=1 "STEP" 1 "UNTIL" 6 "DO"
"PRINT" SAMELINE,DIGITS(8), C[Q,P];
"END";
"FOR" Q:= 3,4,6 "DO"
"BEGIN"
"FOR" J:= 1 "STEP" 1 "UNTIL" 13 "DO"
"BEGIN"
    PEAK[J]:=0;
    TOPS[J]:=0;
"END";
P:= UP;
S1: P:= P-1;
    "IF" C[Q,P] > C[Q,P-1]
    "THEN" "GOTO" S1
    "ELSE" TROF1:=C[Q,P];
S2: P:= P-1;
    "IF" P < LP "THEN" "GOTO" S5;
    "IF" C[Q,P] < C[Q,P-1]
    "THEN" "GOTO" S2
    "ELSE" "BEGIN"
        X:=P;
        TOPS[X]:=C[Q,P];
    "END";
S3: P:= P-1;
    "IF" P < LP "THEN" "BEGIN"
        TROF2:=C[Q,P];
        "GOTO" S4;
    "END";
    "IF" C[Q,P] > C[Q,P-1]
    "THEN" "GOTO" S3
    "ELSE" TROF2:=C[Q,P];
S4: PEAK[X]:=TOPS[X]-(TROF1 + TROF2)/2;
    TROF1:=TROF2;
    "IF" P < LP "THEN" "GOTO" S5
    "ELSE" "GOTO" S2;
S5: MAX:=0;
    "FOR" J:= 13 "STEP" -1 "UNTIL" 1 "DO"
    "IF" PEAK[J] > MAX
    "THEN" "BEGIN" MAX:=PEAK[J];
        MAXF[Q/2]:=J;
    "END";
    "IF" MAX<4 "THEN" "PRINT"
POOR PEAK COLUMN,SAMELINE,DIGITS(1),Q;
    "IF" MAX=0 "THEN" MAXF[Q/2]:=3;
"END" OF SCAN FOR BEST PEAK;
HD:=0;
"FOR" I:= 1,2,3 "DO"
  "BEGIN" "IF" MAXF[I] > HD
     "THEN" HD:= MAXF[I]
  "END";
"FOR" I:= 1,2,3 "DO"
  "BEGIN" "IF" HD-MAXF[I] > 1
     "THEN" PRINT
"WARNING: FLUCTUATING DOMINANT FREQUENCIES"
"END";
MIN:=200;
"FOR" P:= 6 "STEP" 1 "UNTIL" 20 "DO"
"FOR" Q:= 1 "STEP" 1 "UNTIL" 6 "DO"
  "IF" C[Q,P]<MIN "THEN" MIN:=C[Q,P];
"PRINT" "L2 DOMINANT FREQUENCIES = ",SAMELINE,
  MAXF[1],SAMELINE,MAXF[2],SAMELINE,MAXF[3];
"PRINT" "L2 RHYTHMIC ACTIVITY";
"FOR" Q:=1"STEP" 1 "UNTIL" 6 "DO"
  "BEGIN"
    DOMFRE:=MAXF((Q+1) "DIV" 2); TOTAC:=0;
    "FOR" P:=DOMFRE-2 "STEP" 1 "UNTIL" DOMFRE+2 "DO"
      TOTAC:=TOTAC+C[Q,P];
      RHYAC[Q]:=TOTAC-S*MN;
    "PRINT" SAMELINE,DIGITS(4),RHYAC[Q];
    A[Q,JJ]:=RHYAC[Q];
   "END" CALCULATES TOTAL & RHYTHMIC ACTIVITIES &
   STORES RESULTS IN ARRAY A;
"PRINT" "L2"
   LOG OF REACTIVITY EYES SHUT:EYES OPEN FOR EACH EPOCH PAIR;`
MREACT:=0;
"FOR" R:=2"STEP" 2 "UNTIL" 6 "DO"
  "BEGIN"
    REACT:=LN(RHYAC[R]/RHYAC[R-1])/2.302585;
    MREACT:=MREACT+REACT;
    B[R/2,JJ]:=REACT;
  "PRINT"ALIGNED(2,3), REACT;
"END";
"PRINT" "L2 LOG MEAN REACTIVITY = ",SAMELINE,ALIGNED(2,3),
  MREACT/3;
  B[4,JJ]:=MREACT/3;
"COMMENT" CALCULATES LOG REACTIVITIES AND THEIR MEAN
  AND STORES THESE VALUES IN ARRAY B;
"FOR" Q = 2 "STEP" 2 "UNTIL" 6 "DO"
"BEGIN"
"IF" MAXF[Q/2] < 4
"THEN"
"BEGIN"
  Mfreq(q) = MAXF[Q/2];
  GOTO" HOP;
  "END";
  DOMFRE = MAXF[Q/2];
"COMMENT" LOOKS FOR ANY DOMINANT FREQUENCY UNDER 4C/5
  AND IF PRESENT SKIPS INTERPOLATION;
  ZIGZAG = "FALSE";
  "IF" C[Q,DOMFRE-2] > C[Q,DOMFRE-1]
  "OR" C[Q,DOMFRE+2] > C[Q,DOMFRE+1]
  "THEN" "BEGIN"
    ZIGZAG = "TRUE";
    "GOTO" SKIP;
  "END";
"COMMENT" LOOKS FOR SECONDARY PEAKS AND IF PRESENT GOES
  TO SKIP, AND PERFORMS A MODIFIED INTERPOLATION;

  "IF" C[Q,DOMFRE-2] > C[Q,DOMFRE+2]
  "THEN" Z = C[Q,DOMFRE+2]
  "ELSE" Z = C[Q,DOMFRE-2];
  L = 2 * (C[Q,DOMFRE+2] - C[Q,DOMFRE-2])
    + C[Q,DOMFRE+1] - C[Q,DOMFRE-1];
  M = C[Q,DOMFRE+2] + C[Q,DOMFRE+1]
"COMMENT" STANDARD INTERPOLATION;

SKIP: "IF" ZIGZAG "THEN"
"BEGIN"
  "IF" C[Q,DOMFRE-1] > C[Q,DOMFRE+1]
  "THEN" ZZ = C[Q,DOMFRE+1]
  "ELSE" ZZ = C[Q,DOMFRE-1];
  L = C[Q,DOMFRE+1] - C[Q,DOMFRE-1];
  M = C[Q,DOMFRE+1] + C[Q,DOMFRE] + C[Q,DOMFRE-1] - 3 * ZZ;
"END";
"COMMENT" MODIFIED INTERPOLATION, FOR PRESENCE OF
  SECONDARY PEAKS;

  Mfreq(q) = DOMFRE + L/M;

HOP: "END" INTERPOLATION;
"PRINT" " L2 MEAN FREQUENCY EYES SHUT";
"FOR" Q:= 2,4,6 "DO"
"PRINT" SAMELINE, ALIGNED(2,3), M_FREQ[Q];

B[5, JJ]:=M_FREQ[2];
B[6, JJ]:=M_FREQ[4];
B[7, JJ]:=M_FREQ[6];

"COMMENT" STORES MEAN FREQUENCY ESTIMATES
AND THEIR AVERAGE IN ARRAY B;

"PRINT"
" L2 AVERAGE OF MEAN FREQUENCIES EYES SHUT = SAMELINE,
ALIGNED(2,3), M;
"PRINT" "L2080B12"
MEAN AMPS. FOR EYES OPEN & EYES SHUT DIVIDED BY FOUR";
"PRINT" " L2 ";

"FOR" P:= 1 "STEP" 1 "UNTIL" 18 "DO"
"BEGIN"
PLOT[P,1]:=(C[1,P]+C[3,P]+C[5,P])/12;
"END";

"COMMENT" SCALES AND AVERAGES AMPLITUDE ESTIMATES FOR
EASE OF GRAPH PLOTTING;

"FOR" H:=1,2 "DO"
"BEGIN" "PRINT" " LSS ";
"FOR" G:= 1 "STEP" 1 "UNTIL" 18 "DO"
"PRINT" SAMELINE,DIGITS(2),PLOT[G,H];
"END";
"PRINT" " L2 "
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
... ... ... ... ... ...

"FOR" H:=1,2 "DO"
"FOR" G:=1 "STEP" 1 "UNTIL" 18 "DO"
"FOR" P:=45"STEP"-1"UNTIL"0"DO"
"BEGIN"
"PRINT" "L",SAMELINE,DIGITS(3),P,";
JUMP:="TRUE"
"FOR" G:=1"STEP" 1 "UNTIL" 18 "DO"
"BEGIN"
"FOR" H:=1,2"DO"
"IF" PLOT[G,H]=P"THEN" JUMP:="FALSE"
"END"
"IF" JUMP"THEN" "GOTO" OUT
"FOR" G:=1"STEP" 1"UNTIL" 18 "DO"
"BEGIN"
   FLAG:=1;
   "FOR" E:=2,3"DO"
   "BEGIN"
   "IF" PLOT[G,E-1]=E"THEN"
   "BEGIN"
   "IF" FLAG=1"THEN"FLAG:=E
   "ELSE"FLAG:=4
   "END"
   "END"
   "PRINT" "s"; "GOTO" FPS[FLAG];

F1:"PRINT" ";" "GOTO" EXIT;
F2:"PRINT" "O"; "GOTO" EXIT;
F3:"PRINT" "X"; "GOTO" EXIT;
F4:"PRINT" ";" "GOTO" EXIT;

EXIT:"END" OF GRAPH PLOTTING;
OUT:"END";

"PRINT"
  1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
  CYCLES PER SECOND >>>
"END";
"END";
"PRINT" "B12R300L2";

"PRINT" "L'NUMBER OF RECORDS',SAMELINE,DIGITS(2),REC,"L'
LOWER BOUND OF SCAN',SAMELINE,DIGITS(2),LP,"L2'';

"PRINT" "LB39'';
I:=1;OUTSTRING(NAME,1);"PRINT" "B192'';

"PRINT" "L2''
SERIAL AMPLITUDE ESTIMATES EYES OPEN & SHUT'L2'';

"FOR" J:= 1 "STEP" 1 "UNTIL" REC "DO"
"BEGIN" "PRINT" "L'';
"FOR" K:= 1 "STEP" 1 "UNTIL" 6 "DO"
"PRINT" SAMELINE,DIGITS(3),A[K,J];
"END'';

"PRINT" "L2''
SERIAL FREQUENCY ESTIMATES EYES SHUT'L2'';
"FOR" J:= 1 "STEP" 1 "UNTIL" REC "DO"
"BEGIN" "PRINT" "L'';
"FOR" K:= 1 "STEP" 1 "UNTIL" 8 "DO"
"PRINT" SAMELINE,ALIGNED(2,3),B[K,J];
"END'';

"END" OUTPUT OF SUMMARY OF INDICES IN ALL RECORDS;
"END" OF PROGRAM;
The meaning of these latter two terms is explained below. It prints out the first two parameters and then reads a string, subsequently output, which contains details of the patient in terms of neomycin therapy, protein loading etc. (See fig. 2.12).

Next the output of SPECTE PUT is read in. This tape contains other parameters, in particular, the pattern sequence number. The instruction GET (RESULTS) is the opposite of code procedure PUT, i.e. the computer is instructed to read in a sum-checked binary tape. A sorting procedure follows which restores all the epochs to the same order, so as to facilitate subsequent comparisons regarding epoch variability. (See DAYRUN-2).

The sorted data are then printed out, as six columns corresponding to the six epochs and 20 rows corresponding to frequencies 1, 2, 3........ 20 C/S. (see Fig. 2.12).

The program then scans the three eyes shut epochs (columns 2, 4 and 6), one by one. It looks for the peaks in each column, scanning between the rows indicated by the upper and lower bound parameters mentioned above. This is achieved by finding a row number with a trough (TROF 1), finding an adjacent row with a peak (TOPS [X]), and then the next adjacent trough (TROF 2). Thus:

\[
\text{PEAK } [X] = \text{TOPS } [X] - \frac{\text{((TROF 1 + TROF 2)/2)}}
\]

(See DAYRUN - 3).

Several values for \text{PEAK } [X] may be obtained and the tallest of these is selected, for each of the three epochs in turn.

As the rows correspond to cycles per second the three values obtained represent a dominant frequency. These are printed out (See Fig. 2.12). Several methods of finding the best peak were tried but this approach appeared to be the most satisfactory. Usually LP and UP were set to 3 and 14 respectively but on occasion LP had to be set to 6 where sporadic theta or delta
JOHN NIMMO
EEG No L129/1
DATE 26/10/69
PRE NM3

PATTERN SEQUENCE 1
DELAY 5
EPOCH 20

MATRIX OF AMPLITUDE ESTIMATES

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>65</td>
<td>8</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>44</td>
<td>42</td>
<td>37</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>23</td>
<td>32</td>
<td>21</td>
<td>26</td>
<td>35</td>
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<tr>
<td>23</td>
<td>22</td>
<td>20</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>11</td>
<td>19</td>
<td>13</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>17</td>
<td>26</td>
<td>16</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>0</td>
<td>23</td>
<td>13</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>12</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>20</td>
<td>79</td>
<td>14</td>
<td>62</td>
<td>11</td>
</tr>
<tr>
<td>19</td>
<td>88</td>
<td>19</td>
<td>122</td>
<td>10</td>
</tr>
<tr>
<td>19</td>
<td>34</td>
<td>19</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
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<td>8</td>
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<td>9</td>
<td>10</td>
<td>14</td>
<td>9</td>
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<td>8</td>
<td>13</td>
<td>9</td>
<td>11</td>
<td>9</td>
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<tr>
<td>5</td>
<td>15</td>
<td>10</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>9</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>

DOMINANT FREQUENCIES = 10 10 10

RHYTHMIC ACTIVITY 84 247 76 291 73 320

LOG OF REACTIVITY EYES SHUT:EYES OPEN FOR EACH EPOCH PAIR
0.468
0.583
0.564

LOG MEAN REACTIVITY = 0.564

MEAN FREQUENCY EYES SHUT 9.612 9.612 9.613

AVERAGE OF MEAN FREQUENCIES EYES SHUT = 9.635

Figure 2.12

The initial output of Dayrun
peaks occurred.

Warning messages are printed out 1) if the tallest peak obtained has a low value, implying a low voltage record, 2) if the peaks differ from each other by more than 1 c/s suggesting inter-epoch lability.

"Total activity", "rhythmic activity", "log reactivity" and "mean dominant frequency" are all terms used by Laidlaw et al (1961 and 1963) and are calculated in this program, using his formulae as follows:

Consider a series of 5 amplitude estimates forming a well defined peak, e.g.

<table>
<thead>
<tr>
<th>Cycles per second</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude estimates</td>
<td>18</td>
<td>28</td>
<td>40</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Symbols</td>
<td>DF-2</td>
<td>DF-1</td>
<td>DF</td>
<td>DF+1</td>
<td>DF+2</td>
</tr>
</tbody>
</table>

Thus:

\[
\text{Total activity} = (\text{DF} - 2) + (\text{DF} - 1) + \text{DF} + (\text{DF} + 1) + (\text{DF} + 2)
\]

(Array TOTAC).

Note: The dominant frequency for the eyes open epochs is assumed to have the same value as that for the adjacent eyes shut epoch. This was not always found to be the case.

Rhythmic activity = Total activity - 5 (MIN).

(Array RHYAC).

Where MIN = lowest amplitude in the matrix

MIN may be considered as a correction factor implementing a deduction for "background noise". Estimates of total and rhythmic activity are obtained for each of the six columns. Rhythmic activity is printed out (See Fig. 2.12). Total activity is not printed out as it was considered less important than rhythmic activity.

\[
\text{LOG REACTIVITY} = \text{Common Log} \frac{\text{Rhythmic activity eyes open}}{\text{Rhythmic activity eyes shut}}
\]
The rhythmic activity values are obtained for adjacent eyes open/eyes shut epochs. This index is basically a logarithmic expression of the amount of "blocking" in the E.E.G. The three estimates of log reactivity and their mean (MREACT) are printed.

Mean Dominant Frequency * (Array MFRSEQ) =

\[
DF + \frac{2 \cdot (DF+1) - (DF-2) - (DF+1) - (DF-1)}{(DF+2) + (DF+1) + DF + (DF-1) + (DF-2) - 2Z}
\]

\[Z = \text{the lower of } DF+2 \text{ and } DF-2.\]

This is a standard interpolation, based on the estimates at and \(\pm 2\) C/S the dominant frequency. It allows a more precise estimation of the true peak, to an accuracy of one decimal place. This statement was verified and is expounded more fully in the results section.

Two possible difficulties not discussed by Laidlaw, may arise in the course of interpolation.

1) The presence of adjacent secondary peaks may cause: \(DF+2 > DF+1\) or \(DF-2 > DF-1\)

Interpolation here produces inaccurate results and because of this a BOOLEAN procedure ZIGZAG was used, which spotted secondary peaks and performed a simpler interpolation using \(DF \pm 1\) cycle. (See DAYRUN - 5). This was found to produce more meaningful results.

Footnote. * The term "dominant frequency" in the script implies frequencies measured initially in the analysis and on the figures they appear as whole numbers. The term "mean dominant frequency" (MDF) refers to the interpolated estimates and on the figures they appear as decimal numbers. Unfortunately, as many of the figures had been prepared at an early stage, some inconsistencies will be found and MDF may be referred to as "mean frequency" or "dominant frequency".
2) Where the dominant frequency was found to be less than 4 C/S, interpolation was omitted as in this range, artefact often produced falsely low values and the accuracy of the amplitude estimates is less at these frequencies. Furthermore, differences of 1 cycle in this territory are probably of little clinical value as the patient will have obvious signs of encephalopathy. Therefore, an arbitrary value of 3 C/S was usually substituted wherever the dominant frequency was less than 4 C/S. (An earlier program did not have this facility, consequently some figures show values less than 3.0 C/S). Furthermore, if no peak could be found during the scanning process a value of 3 C/S was also assumed. The latter situation occurred where the record was desynchronised or where the patient displayed a severe encephalopathy. (See Fig. 2.13). Either case resulted in a warning message.

Three estimates of mean dominant frequency are obtained which thus represent the eyes shut values after the patient has performed a particular task. Laidlaw & Read (1961b) claimed that less day-to-day variation occurred in the mean dominant frequency estimates taken after looking at a pattern (of lights in his case). This point is discussed more fully later, but initial observations suggested that no particular mean dominant frequency estimate was more stable, and therefore most of the time the average of the three was taken. Where the term "mean dominant frequency" is used, it will therefore imply that this figure is the average of three estimates unless otherwise stated.

The rest of the program plots a graph of amplitude estimates (0 - 45 units) against frequency (1 - 18 or 20 C/S). The average of the three eyes shut and average of the three eyes open estimates are taken at each frequency from 1 - 18 or 20 C/S and plotted as a 2-line graph. (See Fig. 2.14 and DAYRUN - 7).

After all the records have been read in, the values for rhythmic activity, log reactivity and mean dominant frequency (which have been stored in
### Figure 2.13

EEG Spectrum from a case with a severe Encephalopathy
Figure 2.14
EEG Spectrum from a normal subject

X = Eyes closed estimates
O = Eyes open estimates
the main body of the program) are printed out. The rhythmic activity values are derived both for eyes open or shut. For the sake of clarity these will subsequently be referred to by the following symbols:-

\[
\begin{align*}
\text{AMPO} &= \text{rhythmic activity eyes open.} \\
\text{AMPS} &= \text{rhythmic activity eyes shut.}
\end{align*}
\]

**HEPLAN.**

A simplified flow diagram is shown in figures 2.15 and 2.16 followed by a print up of the program. HEPLAN operates on the information dumped at the end of DAYHUN. The data is contained within two arrays:

1. AMP (comprising AMPO and AMPS).
2. GC (comprising log reactivities and mean dominant frequencies).

These arrays are arranged in three columns which correspond to

a) the indices obtained at rest.

b) the indices obtained whilst looking at a pattern.

c) the indices obtained whilst counting beads.

The procedure CODEIT allows the user to call any matching set of columns i.e. the values of AMPO, AMPS, log reactivity and MDF whilst looking at a pattern, or counting beads etc. (See HEPLAN-2). The values in the selected columns are then used to construct a day-to-day plot. (See figs. 2.17 and 2.18 and HEPLAN -3-5). It should be pointed out that the day-to-day plot is non-linear with respect to time. As the recordings were performed mostly on consecutive days, this does not affect the display significantly. In subsequent figures column 'RECORD' is replaced by a column 'DAY NO' in order to indicate temporal relationships. This alteration was done 'by hand' on a teleprinter or visual display unit. Whilst a linear day-to-day plot is desirable
Figures 2.15 and 2.16
Flow diagram of HEPLAN
READ CODE, MARK, NUMBER OF RECORDS (N) & LOWER BOUND OF SCAN (LP).

READ SUBJECTS NAME AND DETAILS

READ DATA: AMPLITUDE ESTIMATES LOG REACTIVITY & MEAN DOMINANT FREQUENCY, AND STORE IN ARRAYS AMP AND CC

DOES MARK EQUAL 100?

YES

HOP: SELECTING VALUES IN ARRAYS CC AND AMP ACCORDING TO PROCEDURE CODEIT, PLOT OUT SERIAL VALUES FOR 1) AMPLITUDE, EYES OPEN & SHUT 2) LOG REACTIVITY 3) MEAN DOMINANT FREQUENCY

CONSTRUCT SCATTERGRAM OF MEAN DOMINANT FREQUENCY AGAINST LOG REACTIVITY USING VALUES IN ARRAY 'C' AS SPECIFIED BY PROCEDURE CODEIT

Figure 2.15
Figure 2.16
Flexowriter Printup of HEPLAN

Sections 1-9
HEPLAN;

"BEGIN"
"INTEGER" CODE, EO, ES, MARK, LP, N, V, X, Y;
"INTEGER" "ARRAY" NAME[1:200];

"PROCEDURE" STADEV(A, PP, QQ, J); "VALUE" PP, QQ, J;
"INTEGER" PP, QQ, J; "ARRAY" A;
"BEGIN"
"INTEGER" K, R;
"REAL" SUMSQ, SUM, SD;
SUMSQ := SUM := 0;
R := (QQ-PP)+1;

"FOR" K:= PP "STEP" 1 "UNTIL" QQ "DO"
"BEGIN"
SUMSQ := SUMSQ + (A[J,K]*2);
SUM := SUM + A[J,K];
"END";
SD := SQRT((SUMSQ - (SUM*2/R))/(R-1));

"PRINT" SAMELINE, ALIGNED(2,3), SUM/R, "S16";
ALIGNED(2,3), SD, "S20"; ALIGNED(2,3),
(SUM/R)+2*SD, "TO", ALIGNED(2,3),
(SUM/R)-2*SD, "L";
"END" OF STANDARD DEVIATION PROCEDURE FOR REAL NUMBERS;

"PROCEDURE" I5TADEV(A, PP, QQ, J); "VALUE" PP, QQ, J;
"INTEGER" PP, QQ, J;
"INTEGER" "ARRAY" A;
"BEGIN" "ARRAY" AA[1:8, 1:N];
"INTEGER" L, M;
"FOR" L:= 1 "STEP" 1 "UNTIL" N "DO"
"FOR" M:= 1 "STEP" 1 "UNTIL" 8 "DO"
STADEV (AA, PP, QQ, J);
"END" OF STANDARD DEVIATION PROCEDURE FOR INTEGERS;
"PROCEDURE" CODEIT(CODE);"VALUE" CODE;"INTEGER" CODE;
"BEGIN"
"SWITCH"SS:=F1,F2,F3,F4,F5;
"GOTO" SS(CODE);
F1: X:=EO:=1;Y:=5;ES:=2;
"PRINT""L"GRAPH BASED ON VALUES AT REST";
"GOTO"F5;
F2: X:=2;Y:=3;ED:=3;ES:=4;
"PRINT""L"GRAPH BASED ON VALUES LOOKING AT PATTERN";
"GOTO"F5;
F3: X:=3;Y:=7;ED:=5;ES:=6;
"PRINT""L"GRAPH BASED ON VALUES COUNTING BEADS";
"GOTO"F5;
F4: X:=4;Y:=ES:=8;ED:=7;
"PRINT""L"GRAPH BASED ON MEAN VALUES";
"GOTO"F5;
F5:
"END";

"COMMENT"
THE IDENTIFIER,CODE, ALLOWS ANY TWO ROWS OF ARRAY CC AND AMP TO BE CALLED. FOR VALUES AT REST, TYPE 1, FOR VALUES LOOKING AT A PATTERN TYPE 2, FOR VALUES COUNTING BEADS TYPE 3, FOR THE MEAN VALUES TYPE 4. SETTING MARK TO 100 CAUSES THE STANDARD DEVIATION OF THE SELECTED VALUES TO BE OUTPUT. SETTING MARK TO 101 CAUSES THE GRAPH PLOTTING TO BE SKIPPED AND JUST THE REQUIRED SD. CALCULATED. IDENTIFIERS PP AND QQ SPECIFY THOSE RECORDS ON WHICH THE STANDARD DEVIATION IS TO BE CALCULATED. TO REPEAT THE PROGRAM TYPE 110 AT THE END, FOLLOWED BY THE RELEVANT CODE NUMBER. TO FINISH TYPE 102;
"READ" CODE, MARK, N, LP;

"COMMENT" CODE, MARK, NUMBER OF RECORDS, AND LOWER
BOUND OF DOMINANT FREQUENCY SCAN;

V:=1; INSTRING(NAME, V);
V:=1; OUTSTRING(NAME, V);
CODEIT(CODE);

"BEGIN"
"INTEGER" J, K, POINT, E, S, L, M, PP, QQ, ONE, TWO;
"REAL" S1, S2, P, Q, YMAX, YMIX;
"INTEGER" "ARRAY" AMP[1:8, 1:N];
"REAL" "ARRAY" CC[1:8, 1:N], C[1:2, 1:N];
"SWITCH" SS:= HEP, FIN, SKIP, LOOP1, JUMP, BANG, OUT, EXIT, POW;
"BOOLEAN" CLASH;

"FOR" J:= 1 "STEP" 1 "UNTIL" N "DO"

"BEGIN"
"FOR" K:= 1 "STEP" 1 "UNTIL" 6 "DO"
"BEGIN"
"READ" E;
AMP[K, J]:= E/12;
"END";
"END";

"COMMENT" THE AMPLITUDE VALUES ARE SCALED DOWN BY A FACTOR
OF TWELVE, AND THE MEANS OF THE THREE EYES OPEN
AND THE THREE EYES SHUT VALUES ARE OBTAINED
AND STORED IN COLUMNS 7 & 8 OF ARRAY AMP;

"FOR" J:= 1 "STEP" 1 "UNTIL" N "DO"
"FOR" K:= 1 "STEP" 1 "UNTIL" 8 "DO"
"READ" CC[K, J]:= Q;

"IF" MARK=101 "THEN" "GOTO" EXIT;
HOP:

"PRINT" "L2"

"FOR" J:= 1 "STEP" 1 "UNTIL" N "DO"

"BEGIN" "PRINT" "L2",SAMELINE,DIGITS(2),J,"S2",DIGITS(2),AMP[EO,J],"S",DIGITS(2),AMP[ES,J],"S"

ONE:=AMP[EO,J]; TWO:=AMP[ES,J];
"IF" AMP[EO,J] > AMP[ES,J] "THEN"

"BEGIN"
 ONE:= AMP[ES,J];
 TWO:= AMP[EO,J];
"END";

"IF" ONE > 58 "THEN" "BEGIN"
 "PRINT" "S88->";
 "GOTO" POW;
 "END";

"FOR" K:= 2 "STEP"1 "UNTIL" ONE "DO"

"PRINT" "S8";

"IF" ONE=TW0 "THEN"

"BEGIN" "PRINT" "O"; "GOTO" POW;
"END"

"ELSE" "IF" ONE=AMP[EO,J] "THEN" "PRINT" "O"

"ELSE" "PRINT" "X";
"IF" TWO > 58 "THEN"

"BEGIN"
 "FOR" K:= 2 "STEP" 1 "UNTIL" 58-ONE "DO"
 "PRINT" "S"; "PRINT" ";";
 "GOTO" POW;
 "END";

"FOR" K:= 2 "STEP" 1 "UNTIL" TWO-ONE "DO"

"PRINT" "S8";

"IF" TWO = AMP[ES,J] "THEN" "PRINT" "X"

"ELSE" "PRINT" "O";

POW:"END" OF PLOT FOR AMPO AND AMPS;
HEPLAN - 5

"PRINT"
'S17`...
'S22`10 8 20 30 40 50 60
'S30`AMPLITUDE ESTIMATES`<<<`;

"PRINT"`"L4`GRAPH OF LOG REACTIVITIES`'L2``;

J:=30; K:=0;

"FOR" E:=X,Y "DO"
"BEGIN"
"PRINT""RECORD VALUE`'S30` PLOT`'L``;
"FOR" S:=1 "STEP" 1 "UNTIL" N "DO"
"BEGIN"
"PRINT"DIGITS(3),S,SAMELINE,""S2"
ALIGNED(2,3),CC[E,S],i``;
 M:=ENTER((CC[E,S]*J-K)+0.5);
"FOR" L:=1 "STEP" 1 "UNTIL" M "DO"
"PRINT"`"S`;
"IF" M < 1
"THEN" "PRINT"`"S`;
"ELSE" "PRINT"`"S`;
"END``;

"IF" E=X
"THEN"
"PRINT"``S16``
'S18`9.1 0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9 2.1
'S28`LOG REACTIVITY`<<<``;

"ELSE``
"BEGIN"
"PRINT"`"S13``
'S12`3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0
DOMINANT FREQUENCIES`<<<``;
"GOTO" OUT;
"END``;

"PRINT"`"L4`GRAPH OF DOMINANT FREQUENCIES`'L2``;

J:=5; K:=15;

OUT:""END" OF PLOTS FOR LOG REACTIVITY AND MEAN
DOMINANT FREQUENCY;
"FOR" K:= 1 "STEP" 1 "UNTIL" N "DO"
"BEGIN" C[1,K]:=ENTER(CC[X,K]*10+0.5)/10;
                      C[2,K]:=ENTER(CC[Y,K]*10+0.5)/10;
"END" THIS TRANSFERS THE TWO REQUIRED ROWS OF ARRAY
              CC INTO ARRAY C AND ROUNDS OFF THEIR VALUES
                   TO ONE DECIMAL PLACE;

"FOR" J:= 1 "STEP" 1 "UNTIL" N-1 "DO"
"FOR" K:= 1 "STEP" 1 "UNTIL" N-J "DO"
"IF" C[1,K]<C[1,K+1]
"THEN" "BEGIN"
                      S1:=C[1,K]; S2:=C[2,K];
                      C[1,K]:=C[1,K+1];
                      C[2,K]:=C[2,K+1];
                      C[1,K+1]:=S1;
                      C[2,K+1]:=S2;
"END" THIS SORTS THE FIRST ROW INTO DESCENDING
         ORDER CARRYING WITH IT THE CORRESPONDING
              MEMBER IN THE BOTTOM ROW;

"FOR" J:= 1 "STEP" 1 "UNTIL" N-1 "DO"
"FOR" K:= 1 "STEP" 1 "UNTIL" N-J "DO"
"THEN"
"BEGIN"
                      S1:=C[2,K]; C[2,K]:=C[2,K+1];
                      C[2,K+1]:=S1;
"END" THIS SORTS THE BOTTOM ROW INTO ASCENDING
         ORDER WHERE THE VALUES OF THE FIRST ROW
              ARE THE SAME;

"PRINT" "La SCATTERGRAM:
LOG REACTIVITIES DOWN, MEAN FREQUENCIES ACROSS.
* CLASH SYMBOL.
<- LOWER BOUND OVERFLOW.
-> UPPER BOUND OVERFLOW. "L2";
HEPLAN - 7

POINT:= 1; YMAX:=1.5; YMIN:=0;

"FOR" P:= 1 "STEP" 1 "UNTIL" N "DO"
BEGIN "IF" C[1,P] > YMAX "THEN" YMAX:= C[1,P];
"IF" C[1,P] < 0 "THEN" YMIN:= C[1,P];
END" THIS ALLOWS FOR OVERFLOW ON THE Y AXIS;
"FOR" P:= YMAX "STEP" -0.1 "UNTIL" YMIN-0.0001 "DO"
BEGIN
"PRINT" ALIGNED(1,1),P, ':';
"IF" POINT>N "THEN" "GOTO" FIN;
"IF" C[2,POINT] > P-.0001 "THEN"
BEGIN
"IF" C[3,POINT]+0.0001 > 6.0 "THEN" "PRINT" '"S2"'
ELSE
BEGIN
"PRINT" '=<';
BANG:
POINT:=POINT+1;
"IF" POINT>N "THEN" "GOTO" FIN;
"IF" C[1,POINT] < P-.0001 "THEN" "GOTO" SKIP;
"IF" C[3,POINT]+0.0001 < 6.0 "THEN" "GOTO" BANG;
END" THIS PUTS A LOWER BOUND OVERFLOW MARK IN AND ADVANCES POINT UNTIL THE WORKING SCALE IS REACHED;
"FOR" Q:= 6.0 "STEP" 0.1 "UNTIL" 12.15 "DO"
BEGIN
"IF" C[3,POINT] > 12.0 "THEN"
BEGIN" K:=122-Q*10;
"FOR" J:= 1 "STEP" 1 "UNTIL" K "DO"
"PRINT" '"S"';
"PRINT" '>'
JUMP:POINT:=POINT+1;
"IF" POINT>N "THEN" "GOTO" FIN;
"IF" C[1,POINT] > P-.0001 "THEN" "GOTO" JUMP
ELSE" "GOTO" SKIP;
END" THIS PUTS THE UPPER BOUND MARKER IN THE CORRECT PLACE AND ADVANCES UNTIL A NEW VALUE OF P IS REACHED;
"IF" C[2,POINT]-0.0001 > Q "THEN"
"PRINT" 'S'
"ELSE"
"BEGIN" CLASH:="FALSE"
LOOP1: "IF" POINT<N "THEN"
"BEGIN"
"IF" "NOT"(C[2,POINT+1]-0.0001 > Q)
"AND"(C[1,POINT+1] > P-.0001)
"THEN"
"BEGIN"
CLASH:="TRUE"
POINT:= POINT+1;
"GOTO" LOOP1;
"END";
"END"
"IF" CLASH "THEN" "PRINT" 'S'
"ELSE" "PRINT" 'X';
POINT:=POINT+1;
"IF" POINT>N "THEN" "GOTO" FIN;
"IF" "NOT" (C[1,POINT] >( P-.0001))
"THEN" "GOTO" SKIP;
"END";
"END" TAKE THE NEXT VALUE OF Q;
SKIP:"END" TAKE THE NEXT VALUE OF P;
FIN:"END";

"PRINT" "LS7". . . . . . . . . . . .
'.'
6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5 11.0 11.5
'.' 12.0
'S25 MEAN FREQUENCIES >>>"L4";
EXIT:
"IF" MARK=100 "OR" MARK=101
"THEN"
"BEGIN"
WAIT; "READ"PP;
"IF" PP=110
"THEN"
"BEGIN"
"READ" CODE;
CODEIT(CODE);
"GOTO" HOP;
"END"
"ELSE"
"IF" PP= 102 "THEN" STOP
"ELSE"
"BEGIN"
"READ"QQ, CODE;
CODEIT(CODE);
"PRINT"
STANDARD DEVIATION CALCULATED FROM RECORDS', SAMELINE,
DIGITS(2), PP, TO', DIGITS(2), QQ;
"PRINT"
MEAN'S13' STANDARD DEVIATION'S12' BOUNDS: + OR - TWO SD.'L'';
STADEV(CC, PP, QQ, X);
STADEV(CC, PP, QQ, Y);
I STADEV(AM, PP, QQ, EO);
ISTADEV(AM, PP, QQ, ES);
"GOTO"EXIT;
"END";
"END";
"END";
"END";
"END";
Figure 2.17
First output of Heplan
**Figure 2.18**

Second output of Heplan
this is not a practicable facility in ALOOL.

Later in the program a scattergram is constructed (See HEPLAN 6-8) and (figure 2.18). This consists of log reactivity (horizontal axis) against mean dominant frequency (vertical axis). The values here are again specified by CODEIT.

An additional facility allows the calculation of a mean and standard deviation of the above indices over a specified number of records (See HEPLAN - 9). The operator types a number (100) which tells the computer to wait after finishing the scattergram, and to expect further parameters. These are the row numbers between which a mean and standard deviation is required. (See Flow diagram). Another facility allows the program to be restarted and to plot out a different set of indices obtained whilst performing a different visual task. (See Flow diagram). The program will repetitively perform standard deviations or graph plotting until either no more parameters are read in or until number 102 is typed which then causes the computer to stop (See Flow diagram).

Towards the end of the period of investigation, DAYRUN was modified to include a slow wave index (SWI) in place of log reactivity, which clinically did not appear to be very sensitive.

According to Laidlaw and Aitken (1966) -

\[
\text{SWI} = A \left( \frac{rAb_2 + rAb_2}{100} \right)^2
\]

\[
A = \frac{TAb}{100}
\]

\[
TAb = \text{Sum of abundances from 2-13 c/s inclusive.}
\]

\[
rAb_f = \frac{Ab_f \times 100}{TAb}
\]

\[
Ab_f = \text{Abundance at specified frequency (f).}
\]

HEPLAN was subsequently modified to plot out the serial values for SWI.
APPLICATION OF ANALYSIS.

This section is divided into four parts:

1. Assessment of spontaneous variation.
2. A drug trial.
3. Tests related to hepatic encephalopathy.
4. Miscellaneous observations.

A test of the accuracy of the E.E.G. analysis was made and is described in detail in the RESULTS section.

(1) **Assessment of Spontaneous Variation.**

For purposes of discussion this factor will be defined as the degree of variation observed in the E.E.G. indices which is thought to be due to random variation of brain activity, in the absence of any known provocative agent or procedure other than that involved in recording the E.E.G. in a manner already described.

Spontaneous variation may be assessed on a day-to-day basis (inter-record variation) or over the course of a recording (inter-epoch variation).

These factors required measurement in both control and hepatic groups.

Several questions needed resolving:

a) Was there any difference between the two groups and did age or sex play a part?

b) Was there any relationship between inter-record and inter-epoch variation?

c) Did the nature of the visual tasks - "visual task variation" - or their order - "visual task order variation", have any bearing on the E.E.G. changes?

In an attempt to answer these questions a group of 27 control and 7 hepatic subjects was studied. Details regarding these people are shown in
Table (2c). Each subject had between seven and twelve recordings performed usually on consecutive days. The controls did not receive any special diet, but were requested to refrain from dietary excess during the period of study. The seven hepatic subjects received a 70 G protein diet and were considered on clinical and biochemical grounds to be in a stable metabolic condition.

Five indices were examined, i.e.

Mean dominant frequency - MDF
Log reactivity - LR
'Amplitude' eyes open - AMPO
'Amplitude' eyes shut - AMPS
Slow wave index - SWI

The SWI could not be studied in great detail as this index was only implemented towards the latter end of the project.

(2) A DRUG TRIAL.

The trial was devised in an attempt to assess the effects, in normal people, of drugs relevant to hepatic encephalopathy. The drugs were Ammonium Chloride, Neomycin Sulphate and Lactose given orally; injections of water (intravenous and intramuscular), heroin (intravenous) and morphine (intramuscular). We hoped to run the trial on a double blind basis but this did not materialise. In the time available identical preparations of the three oral drugs could not be obtained. Hence the volunteers could have guessed what they were taking; however this probably occurred (by retrospective enquiry) in one case only (L24). The side effects of Neomycin were such that all volunteers were aware an active preparation was being ingested. With regard to the intramuscular and intravenous injections (given by the author) the nature of the side effects again enabled the volunteers to determine an
TABLE 2G.

SUBJECTS USED FOR ASSESSMENT OF "SPONTANEOUS VARIATION".

CONTROL GROUP.

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>29</td>
<td>M</td>
<td>53</td>
<td>47</td>
<td>M</td>
</tr>
<tr>
<td>14</td>
<td>19</td>
<td>F</td>
<td>54</td>
<td>23</td>
<td>F</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>M</td>
<td>55</td>
<td>26</td>
<td>M</td>
</tr>
<tr>
<td>17</td>
<td>38</td>
<td>F</td>
<td>56</td>
<td>27</td>
<td>M</td>
</tr>
<tr>
<td>34</td>
<td>23</td>
<td>F</td>
<td>61</td>
<td>25</td>
<td>M</td>
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<tr>
<td>37</td>
<td>23</td>
<td>F</td>
<td>62</td>
<td>25</td>
<td>M</td>
</tr>
<tr>
<td>38</td>
<td>18</td>
<td>F</td>
<td>67</td>
<td>25</td>
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<tr>
<td>39</td>
<td>27</td>
<td>M</td>
<td>70</td>
<td>30</td>
<td>M</td>
</tr>
<tr>
<td>40</td>
<td>22</td>
<td>F</td>
<td>87</td>
<td>19</td>
<td>M</td>
</tr>
<tr>
<td>41</td>
<td>53</td>
<td>F</td>
<td>109</td>
<td>58</td>
<td>M</td>
</tr>
<tr>
<td>44</td>
<td>22</td>
<td>F</td>
<td>110</td>
<td>36</td>
<td>M</td>
</tr>
<tr>
<td>50</td>
<td>59</td>
<td>M</td>
<td>116</td>
<td>23</td>
<td>M</td>
</tr>
<tr>
<td>51</td>
<td>36</td>
<td>F</td>
<td>117</td>
<td>24</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>124</td>
<td>22</td>
<td>F</td>
</tr>
</tbody>
</table>

Mean Age = 30 years
Age Range = 19 - 59 years.
Number of Males = 16
Number of Females = 11
TOTAL = 27

Range of Average MDF 8.08 - 11.78 C/S.
TABLE 26 (contd).

HEPATIC GROUP.

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>38</td>
<td>F</td>
</tr>
<tr>
<td>28</td>
<td>25</td>
<td>F</td>
</tr>
<tr>
<td>58</td>
<td>60</td>
<td>F</td>
</tr>
<tr>
<td>79</td>
<td>57</td>
<td>M</td>
</tr>
<tr>
<td>86</td>
<td>55</td>
<td>M</td>
</tr>
<tr>
<td>92</td>
<td>34</td>
<td>M</td>
</tr>
<tr>
<td>96</td>
<td>56</td>
<td>M</td>
</tr>
</tbody>
</table>

Mean Age = 46 years.
Age Range = 25 - 57 years.
Number of Males = 4
Number of Females = 3
TOTAL = 7.

Range of Average MDF = 4.59 - 9.98 c/s.
active preparation was given, although none knew that inert material would also be injected.

The oral drugs were issued by Dr. P. W. Brunt, who was aware of the particular drug given but did not communicate this information to the volunteers or to the author until the trial was complete. The order of receiving tablets was varied.

Of 14 people who were admitted to the trial 2 had to be withdrawn because analysis of their E.E.G. showed, in one case, a low voltage record and marked instability in the other. The details of the subjects are shown in Table 2D.

The oral drugs used were -

1. Tab. Ammonium Chloride 2G twice daily for four days.
2. Tab. Neomycin Sulphate 1G " " " "
3. Tab. Lactose 0.5G " " " "

Eleven tests were completed with respect to each drug.

The subjects received a different drug each week. Each drug started on a Sunday and continued to the Wednesday of that week, making four whole days. The E.E.Gs were recorded each day from Monday to Friday inclusive. They were obtained after the drug had been discontinued in order to see if there were any lag effects. One person (L55) had to discontinue neomycin because of unpleasant gastro-intestinal side effects.

After this the subjects were given various injections (there are two exceptions mentioned below).

1. 2cc sterile water (intramuscular). The E.E.G. was recorded immediately before and three hours after the injection (12 tests).
2. Morphine sulphate (intramuscular). 0.14 mg/kg. The E.E.G. was recorded as in (1) (11 tests).
### TABLE 2D.

**SUBJECTS OF CONTROL GROUP USED IN DRUG TRIAL.**

<table>
<thead>
<tr>
<th>EEG No.</th>
<th>AGE</th>
<th>SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>27</td>
<td>M</td>
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<td>25</td>
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<tr>
<td>34</td>
<td>23</td>
<td>F</td>
</tr>
<tr>
<td>39</td>
<td>27</td>
<td>M</td>
</tr>
<tr>
<td>40</td>
<td>22</td>
<td>F</td>
</tr>
<tr>
<td>41</td>
<td>53</td>
<td>F</td>
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<tr>
<td>44</td>
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<td>F</td>
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<tr>
<td>50</td>
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<tr>
<td>54</td>
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<td>F</td>
</tr>
<tr>
<td>55</td>
<td>26</td>
<td>M</td>
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<tr>
<td>56</td>
<td>27</td>
<td>M</td>
</tr>
<tr>
<td>70</td>
<td>30</td>
<td>M</td>
</tr>
</tbody>
</table>

Mean Age = 30 years.

Age Range = 19 - 59 years.

Number of Males = 6

Number of Females = 6

TOTAL = 12
3. 2cc sterile water by rapid intravenous injection. The E.E.G. was recorded immediately before and then after the injection at 15 minute intervals for 2 hours (12 tests).

4. Heroin by rapid intravenous injection. 0.04 mg/kg. The E.E.G. was recorded as in 3. (9 tests).

An average dose for morphine was 10 mg. and for heroin 2.5 mg. These values are slightly below their usual therapeutic doses. Subjects were deliberately not fasted for any of these tests as this could possibly affect the E.E.G. One subject (L41) was not given either opiate because she occasionally suffered from mild bronchitis. (During the trial she was symptom free).

In two subjects (L24 and L25) the heroin data were discounted as they had both received a nominal dose of 5 mg. This occurred in the early part of the trial. A body weight related dose was subsequently used in all other cases.

In one case (L25) the ammonium chloride and lactose data had to be excluded because of a persistently lowered MDF due to prior administration of opiate. Because the lag effect of opiates (which was not appreciated at the start of the trial) these drugs were not given until the testing of the three tablets had been concluded.

3. **TESTS RELATED TO HEPATIC ENCEPHALOPATHY.**

a) The morphine provocation test.

This has already been described above under (2). The morphine was given in this manner to other volunteers in the control group. The drug was administered in exactly the same manner to patients with hepatic dysfunction. Also injections of sterile water (2 cc intramuscular) were given to patients in the hepatic group as in (1) above. This was to act as a control to the active drug given to patients with hepatic disease.
The total number of tests was as follows:

- Morphine given to healthy subjects: 22 tests
- Morphine given to hepatic patients: 33 tests
- Sterile water given to hepatic patients: 7 tests (6 patients)

Further details regarding these subjects appear in the RESULTS section.

b) PROTEIN LOADING.

Protein diets varying from 30 - 130G were administered to 12 of the hepatic group for at least five days. The diet was supervised by a hospital dietician who frequently supplemented the diet with "COMPLAN" to achieve the necessary intake. No suitable data were obtained regarding protein loading in normal subjects.

c) NEOMYCIN SULPHATE.

The effect of this drug on the E.E.G. was observed in 8 patients with liver disease. The dose varied from 3 - 8G according to clinical circumstances. Information regarding neomycin effects in healthy subjects was obtained in the drug trial mentioned already.

d) AMMONIUM ACETATE INFUSION.

This substance was prepared as an aqueous 2 molar solution. The doses actually used varied slightly at the beginning of the trial as a safe level had to be found empirically. The amount used latterly was 10 mg/kg for both control and hepatic subjects - See Table 3H and 3i.

The test was performed on 17 subjects from the control group and 16 from the hepatic.

The technique of the test was as follows: The aqueous ammonium acetate solution (usually 10 mg/kg body weight) was diluted in 45 ml 5% dextrose and was delivered as an intravenous injection over exactly 10 minutes by means of a
constant infusion pump. Venous blood for plasma ammonia estimations and
E.E.Gs were sampled as follows:–

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>E.E.G.</th>
<th>Venous Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Infusion</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>30</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>40</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Post Infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

In 5 controls and 9 cirrhotic E.E.Gs were obtained additionally at 150 and
180 minutes.

In a few normal subjects the arterial ammonia and blood pH were determined.
The subjects were not requested to fast for the test as this might affect
the E.E.G. A few subjects had consumed a fairly large meal prior to the
procedure and this produced an elevation of the basal ammonia level.

**PLASMA AMMONIA ASSAY.**

The technique used was that described by Horn & Squire (1966), a
modification of Fenton's technique (1962). It is now known to be preferable
to Conway's method (1935) and variants thereof as it is more specific and gives
accurate results i.e. ± 2 pg per 100 ml. (Horn & Squire 1966).
The method involves basically the separation of ammonia from the plasma by an ion exchange technique. The estimation of the separated ammonia is determined by its conversion to indophenol blue using hypochlorite and sodium phenate (Horn and Squire 1966).

By this process the accepted normal range for fasting subjects is 20 - 60 μg/100ml. As mentioned above a few normal subjects had high basal values where a large meal had been consumed prior to the test.

e) **INTRAVENOUS DEXTROSE OR SALINE.**

20 ml of 5% Dextrose or 0.9% sodium chloride was delivered as a slow infusion in a similar manner to the ammonium acetate test. E.E.G's, but not blood samples were also obtained in a similar fashion. The test was performed on four patients with hepatic dysfunction and was intended as a control test to the injection of ammonium acetate.

(4) **MISCELLANEOUS OBSERVATIONS.**

An analysis of the inter-relationship of AMPO, AMPS and MDF was made in few subjects and will be described in more detail in the RESULTS section.

Numerous biochemical tests were performed on one subject (L68) who also had several E.E.G's. The correlation of biochemistry and E.E.G. indices was studied and is described in the next section.

Detailed observations were made on nine patients who had at some time surgery for portal hypertension. Five had lienorenal anastomosis (2 were children). One had a porta-caval shunt and three an oesophageal transection. One other case of interest is also described.
RESULTS.
RESULTS.

This section is divided into four parts:

(A) Tests of the accuracy of analysis.
(B) Spontaneous variation.
(C) A drug trial.
(D) Tests related to hepatic encephalopathy.

Some of the material was suitable for statistical analysis, and this was kindly undertaken by Dr. R. J. Prescott. Frequently however, the nature of the data rendered conventional statistical techniques inappropriate and in some instances the data could only be interpreted subjectively or by non-standard methods.

(A) TESTS OF THE ACCURACY OF ANALYSIS.

With the present method there are four sources of possible error:

(1) In analog to digital conversion.
(2) From the Fourier Transform.
(3) From the use of a short E.E.G. sample.
(4) From interpolation in calculating the MDF.

These factors have been assessed by Dr. H. R. A. Townsend, and by his kind permission the data are presented here in brief.

(1) Analog to digital conversion.

The sampling rate of the ADC was one conversion every 0.01 second. This limits the high frequencies in the converted signal. It was suggested by Shannon (1949) that frequencies above half the sampling rate should be excluded and therefore a filter was incorporated which was designed to be -24dB at 50 c/s.
To test for errors from this filter, a random noise signal was fed to the ADC, using as source, a HEWLETT-PACKARD NOISE GENERATOR (Model 3722A). The signal was of equal amplitude at all frequencies from 0-50 c/s. The resulting estimates for a four minute epoch are plotted (fig. 3.1a). Ideally all values should have the same amplitude. However, there is a slight under-estimation of amplitude up to 10 c/s, which becomes more marked at frequencies above this.

The error could be occurring either in the ADC or in the Fourier Transform. To elucidate this further, a random binary signal was analysed. Such a signal avoids the ADC filtering mechanism and gives a known correlogram (wedge shaped), and a known spectrum (SIN x/x). The signal was analysed over a 60 second epoch and the result plotted together with a model curve for SIN x/x (fig. 3.1b). This shows a tendency for over-estimation at low frequencies and under-estimation at high, but these errors are small and suggest that the predominant error is arising from the ADC filter.

(2) Fourier Transform.

An artificial correlogram was constructed for the SIN x/x spectrum. A Fourier Transform was performed on this and then compared with its known theoretical values (fig. 3.1d). Here the errors are very small but in the same direction as previously noted, suggesting that the systematic errors shown in fig. (3.1b) are due to the Fourier Transform.

(3) Use of a short sample.

To elucidate the effects of a short sample, the random binary signal was analysed again, this time using ten separate 20 second epochs. This epoch length was selected as it is of the same duration as that used for the E.E.G. analysis in the rest of this work. The means and standard deviations (± 2 SD)
Figure 3.1

a) Top left. Analysis of a four minute random noise signal of equal amplitude from 0-50 c/s.

b) Top right. Comparison of model curve for sin x/x with values obtained from analysis of the random binary signal.
   - model curve for sin x/x
   - analysis of random binary signal over a 60 second epoch.
   - clash symbol.

c) Bottom left. Analysis of random binary signal over ten separate 20 second epochs, compared with model curve for sin x/x
   - model curve for sin x/x
   - mean for estimates of binary signal
   - upper & lower limits (two standard deviations)

d) Bottom right. Comparison of Fourier Transform of artificial correlogram for sin x/x spectrum with its theoretical values.
   - theoretical values
   - obtained values
   - clash symbol

NOTE.
As the graphs were constructed on a teleprinter the model curves cannot be made completely smooth.
**RANDOM NOISE 50Hz BANDWIDTH**

**PATTERN SEQUENCE 1**
**REPEAT** 1
**DELAY** 0
**ESTIMATES** - BANDWIDTH 1.00C/S
**EPOCH** 240SECS

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</thead>
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**PLOT**

**PATTERN SEQUENCE 1**
**REPEAT** 1
**DELAY** 5

**ESTIMATES** - BANDWIDTH 1.00 C/S
**EPOCH** 60 SECS

**ESTIMATES** - BANDWIDTH 1.00 C/S
**EPOCH** 60 SECS

**RANDOM BINARY SIGNAL**
33.3mS CLOCK RATE

**PATTERN SEQUENCE 1**
**REPEAT** 13
**DELAY** 0

**ESTIMATES** - BANDWIDTH 1.00 C/S
**EPOCH** 23 SECS

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</table>

**PLOT**

**SIN X/X SPECTRUM FROM THEORETICAL CORRELOGRAM**

**PATTERN SEQUENCE 0**
**REPEAT** 1
**DELAY** 0

**ESTIMATES** - BANDWIDTH 1.00 C/S
**EPOCH** 0 SECS

**ESTIMATES** - BANDWIDTH 1.00 C/S
**EPOCH** 0 SECS

**PLOT**
were obtained at each frequency and compared with a theoretical curve for \( \text{SIN} x/x \) (fig. 3.1c).

This shows on the whole a good correlation of mean values with the theoretical curve, but considerable variation, especially at lower frequencies. It would appear that the slower the frequency of a wave, the more serious is the effect of a short sample.

4) **Interpolation in calculating the MDF.**

To assess for errors in the estimation by interpolation, of mean dominant frequency (see MATERIALS AND METHODS), the random noise signal was again used. It was of equal amplitude from 0 - 50 c/s. A simulated filter was devised which could be centred at various frequencies of constant "Q". The latter was altered empirically to produce a similar spectrum to that of an E.E.G. signal, for both eyes open and eyes shut. Seven eyes open/shut models were thus constructed, with filters centred at 8.0 c/s, 8.3 c/s..... 9.8 c/s. The spectrum of the 9.8 c/s signal is shown (fig. 3.2b), and the plotted values of log reactivity and mean dominant frequency (fig. 3.2a).

Whilst the estimates of log reactivity appear somewhat variable, the estimates of MDF are quite satisfactory:

Mean of the MDF errors = 0.05 ± .04 c/s

(B) **SPONTANEOUS VARIATION.**

Unless specified to the contrary, the average of the three estimates of each index was obtained.

As it was found that the readings did not follow a normal distribution, wherever possible a non-parametric test was used rather than one based on an assumption of normality.

a) **Sex Age and Group Variation.**

To determine whether there was any difference in the degree of variation
Figure 3.2

a) Left. Result of analysis of artificial EEG signals - 8.0 c/s to 9.8 c/s. Log reactivities upper figure; mean dominant frequencies, lower figure.

b) Right. Spectrum of the 9.8 c/s signal.
SIMULATED RECORDS

GRAPH OF LOG REACTIVITIES

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<td>0.635</td>
<td>X</td>
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<tr>
<td>7</td>
<td>0.790</td>
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</tr>
</tbody>
</table>

0.1 0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9 2.1
LOG REACTIVITY >>>

GRAPH OF DOMINANT FREQUENCIES

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<th>RECORd</th>
<th>VALUE</th>
<th>PLOT</th>
</tr>
</thead>
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</tr>
<tr>
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<td>X</td>
</tr>
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<td>9.253</td>
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<td>8.356</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>8.060</td>
<td>X</td>
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</table>

6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5 11.0 11.5
DOMINANT FREQUENCIES >>>>

Cycles per second >>>
according to sex age or group (i.e. hepatic or control), all indices except the SW1 were tested statistically. For each index the variance was used as a measure of the degree of spontaneous variation and by means of the median test and the WALKER-WOLFOMITZ runs test, comparisons were made. In each case no significant difference was found ($P > 0.05$) thereby implying that spontaneous variation is a factor independent of the above variables.

b) Inter-record Variation.

For the reason stated above it was found difficult to assess this factor by standard statistical methods. An ad hoc technique was implemented and is described below:

Let us assume that ten E.E.G.s were obtained from one subject. Ten sets of five indices will be obtained. The mean of each index over the ten-day period was obtained, then the difference of each index from its mean was derived. This process was repeated for each person in the control group and each person in the hepatic group; no sub-division was made on the basis of age or sex. The differences from the means were accumulated and assembled to form a histogram. As this process was extremely tedious an ALGOL program was written by the author, which enabled the task to be completed in a few minutes. Altogether 262 'mean differences' were obtained in the control group and 50 in the hepatic.

The results of the above procedure are displayed in figs. 3.3 to 3.5. The degree of variation may be expressed simply by subtracting 3.5% of the data from the upper and lower extremes of the histograms. This obtains the 95% limits:(See Table 3A).

These values are remarkably similar between the groups. There is probably a slightly higher degree of variability of MDF in the control group. Some idea of individual variation is shown in figs. 3.6 and 3.7. Both sets of data were taken from healthy members of hospital staff. In the first case (L.38)
Comparisons of index variability in control & hepatic group.
Figure 3.3.
Figure 3.5
**TABLE 3A.**

<table>
<thead>
<tr>
<th>INDEX</th>
<th>CONTROL GROUP</th>
<th>HEPATIC GROUP</th>
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<tbody>
<tr>
<td>MDF</td>
<td>± .49</td>
<td>+.36 to -.38</td>
</tr>
<tr>
<td>LR</td>
<td>± .19</td>
<td>+.20 to -.24</td>
</tr>
<tr>
<td>SWI</td>
<td>+ 15 to -9</td>
<td>+ 12 to -9</td>
</tr>
<tr>
<td>AMPO</td>
<td>± 3</td>
<td>+ 5 to -3</td>
</tr>
<tr>
<td>AMPS</td>
<td>± 6</td>
<td>+ 6 to -5</td>
</tr>
</tbody>
</table>

**ESTIMATED VARIATION OF EEG INDICES IN CONTROL & HEPATIC GROUPS**
Association of menstruation with fluctuation in MDF in a healthy female (18 yrs)
MR.TM.(36)
EEG NO L15 1 TO 12
DATE SEPTEMBER 1968

<table>
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<td>14</td>
<td>10.26</td>
</tr>
<tr>
<td>15</td>
<td>10.45</td>
</tr>
</tbody>
</table>

Unexplained fluctuation of MDF in a healthy male (36 yrs)
it appears there is a menstrual acceleration of MDF. In the second case no explanation could be found for the observed changes.

c) Visual Task Variation

It would be valuable to know if any particular visual task was consistently associated with less index fluctuation. This problem was examined for all indices except SWI.

AMPO AND AMPS.

For each subject the variances of the AMPO and AMPS values related to each of the three visual tasks were found and tested for homogeneity by BARTLETT'S TEST. Unfortunately this test assumes a normal distribution and therefore the probability levels cannot be regarded as exact, although a high degree of significance would be expected to indicate some degree of difference. The hepatic group generally showed no marked difference (only one out of seven was significant), although the control group did (only four out of 27 showed no difference). For the control group AMPO and AMPS were tested separately and BARTLETT'S TEST applied to these groups. For AMPO, five out of 27 showed some degree of significance (P<0.05) and for AMPS 3 were significant (P<0.05). Although AMPO had a smaller variance than AMPS the different visual tasks therefore had little effect.

LR and MDF

Bartlett's test was again used for these indices. Very little significant difference was found. For LR, five of the control group and one of the hepatic group were significant (P<0.05) whilst for MDF, two controls and two of the hepatic group showed significantly different variances.

Further testing of those subjects showing a significantly different variance revealed no particular visual task that had a smaller variance.
The proportion of significant results for all four indices was not significantly different for the males or females or for the hepatic group (chi-squared test $P > 0.05$).

d) Visual Task Order Variation.

There were only seven of the control group who had twelve recordings and who therefore had been exposed to each of the six pattern sequences on two occasions. On these seven, a KRUSKAL-WALLIS one way analysis of variance was performed. For each subject the difference in mean values for pattern sequences of the same number was found. No significant difference in the differences of paired pattern sequences was found ($P > 0.05$).

Thus, no particular order of presenting the visual tasks was better than another with regard to lability.

e) Interepoch and Inter-record variation.

It could be postulated that a subject showing marked fluctuation over the course of one recording would be likely to show marked fluctuation the next day.

For this problem, only the MDF was examined. The average of the three MDF values was obtained for each day. The variance of these values was obtained as a measure of inter-record variation. A measure of interepoch variation was derived by subtracting the inter-record variation from the overall variation. This gave two values (inter-record and interepoch variation), for each individual and by taking these values over all individuals a correlation test was performed between them.

It was found that for the control group there was quite a high degree of correlation but not for the hepatic group. Thus for the hepatic group no prediction of inter-record variation could be made.
In summary of the above data, with respect to spontaneous variation:

a) Differences of age, sex or group had no significant effect.

b) Comparing the control and hepatic groups as a whole there was little difference in the fluctuation of all five indices, with the exception of MDF which appeared slightly more variable in the control group.

c) None of the three visual tasks had much effect on any index. This held for both groups.

d) The order of presentation of the visual tasks had little effect. This was only tested in the control group.

e) Marked interepoch variability suggested there will be marked inter-record fluctuation but this held only for the control and not the hepatic group.

(C) 

DRUG TRIAL.

a) 2 ml. sterile water (intramuscular). The raw data are summarised in Table (3B). No side effects were observed apart from L39 who vomited about one hour after the injection.

The interrelations of MDF with the other four indices in both groups are shown in fig. (3.8). This figure clearly indicates no consistent difference of response between the two groups.

As the results were not of a normal distribution, statistical assessment of expected variability (e.g. standard deviation) was not possible. Interpretation of the diagrams suggests the following after injection of water in the control group:
### TABLE 3B.

**SHIFTS 3 HOURS AFTER INJECTION OF 2cc STERILE WATER (1M).**

**CONTROL GROUP.**

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>MDF</th>
<th>LR</th>
<th>AMPO</th>
<th>AMPs</th>
<th>S.W.i</th>
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<tr>
<td>24</td>
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<td>.11</td>
<td>.14</td>
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<td>-1</td>
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<td>44</td>
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<td>-1</td>
<td>2</td>
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<td>2</td>
<td>1</td>
<td>-1</td>
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</table>

*Age Range = 19 - 59.*  
*Mean Age = 30 years.*  
*Number of Males = 6*  
*Number of Females = 6*  
*TOTAL = 12*
Figure 3.8
Effect of 2 ml intramuscular water on MDF related to shifts of LR, SWI, AMPO & AMPS in control & hepatic groups.
The intramuscular water changes are compared statistically with the morphine results in a later section.

b) Morphine Sulphate (0.14 mg/kg, intramuscularly). The results of this test are summarised in Table (3c). The table includes the results of eleven tests performed on other subjects from the control group.

The test frequently induced nausea, drowsiness or dizziness and on occasion vomiting. These symptoms were most prominent at about one hour after the injection but often persisted until the time of the post injection recording.

The interrelationships of MDF and the other indices are shown in fig. (3.9) and a histogram with age division and comparison with the cirrhotic group appears in figs. (3.10 and 3.11). Whilst there was an impression that those controls of 30 years or under showed more slowing of MDF after morphine, this was not statistically valid and will be discussed later.

The same restrictions to statistical analysis mentioned above, apply here. The data suggest the following with regard to the control group:

<table>
<thead>
<tr>
<th>Index</th>
<th>Expected Change</th>
<th>Mean Change</th>
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<td>MDF</td>
<td>± 0.3 c/s</td>
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<td>LR</td>
<td>± 0.15</td>
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<tr>
<td>AMPO</td>
<td>± 2</td>
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<tr>
<td>AMPS</td>
<td>± 3</td>
<td>0.42</td>
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<tr>
<td>SWI</td>
<td>± 12</td>
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</table>
### Table 3C.

**Shifts 3 Hours After Morphine Injection (0.14 mg/kg intramuscular).**

**Control Group.**

<table>
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<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
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<th>LR</th>
<th>AMFO</th>
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<td>F</td>
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</table>
Figure 3.9
Effect of intramuscular morphine on MDF related to shifts of LR, SWI, AMPO & AMPS in the control group.
Figure 3.10
Histogram of effect of intramuscular morphine on MDF in control & hepatic groups with age division.
Figure 3.11
Effect of intramuscular morphine on MDF related to age in control & hepatic groups.
## Table

<table>
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<th>Index</th>
<th>Expected Change</th>
<th>Mean Change</th>
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<td>-0.26 c/s</td>
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<tr>
<td>AMPO</td>
<td>+5 to -3</td>
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<td>AMPS</td>
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<tr>
<td>SWI</td>
<td>+16 to -24</td>
<td>-3.3</td>
</tr>
</tbody>
</table>

Further information regarding statistical analysis of the morphine test appears later.

c) Heroin (0.04 mg/kg, intravenously). The changes are shown in fig.3.12a and Table 3D. With reference to the pre-injection values, the shifts of each index were obtained at every sampling interval. The overall change is displayed as the mean shift and range at each interval. This rudimentary approach was necessary here and in the subsequent data because a normal distribution was not obtained.

The heroin injection in most subjects induced transient feelings of nausea and dizziness but no vomiting. These effects lasted approximately 10 - 20 minutes.

The diagram shows well marked slowing of MDF which appears immediately and is sustained for the period of the test. A similar fall occurs with SWI, whereas little mean change occurs with AMPO.

Some increase of LR is observed whilst there is a sharp increase of AMPS. In both instances the same increment is maintained for the period of the test.

d) Sterile water (2 cc. intravenously). The changes are shown in fig.3.126 and Table 3D, again as mean and range.
Figure 3.12

a) Left, shifts of EEG indices following intravenous heroin.

b) Right, shifts of EEG indices following intravenous water.

The bold line represents the mean shift & the thin lines the upper & lower ranges.

All data relate to the control group.
<table>
<thead>
<tr>
<th>AGE</th>
<th>SEX</th>
<th>NO.</th>
<th>EEG BASAL</th>
<th>MDF</th>
<th>SHIFTS OF MDF FOLLOWING WATER OR HEROIN GIVEN INTRAVENTRICULARLY (CONTROL GROUP).</th>
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</table>

*SHIFTS OF MDF FOLLOWING WATER OR HEROIN GIVEN INTRAVENTRICULARLY (CONTROL GROUP).*

*AGE SEX NO. EEG BASAL MDF*
The diagram suggests a very slight depression of MDF, AMPO and SWI over the two hour period. AMPS and LR tend to increase very slightly. However, the range of variation at each fifteen minute interval seems considerable, making it likely that the above observations are of no significance.

e) Neomycin, Ammonium Chloride and Lactose. The results of all these are shown in figs. 3.13 and 3.14 and Table 3E. The shifts again represent the mean changes and range, with respect to the pre-drug recording.

**Neomycin Sulphate (fig. 3.13a).**

There is a minor slowing of MDF in the presence of a wide range of values. AMPS and LR increase slightly. AMPO and SWI appear to fluctuate in a random manner.

**Ammonium Chloride (fig. 3.13b).**

The only index showing any definite change is SWI which displays an increase, whilst the drug was taken. The MDF shows a small increase in mean values but the upper and lower ranges are considerable.

**Lactose (fig. 3.14).**

MDF increases gradually whilst LR is virtually unchanged. AMPO and AMPS decrease a little whilst a considerable, fairly well sustained fall in SWI is seen.

The only preparation to produce side effects was Neomycin, which frequently induced mild diarrhoea or nausea. One person had to withdraw because these effects were severe.

(D) **TESTS RELATED TO HEPATIC ENCEPHALOPATHY.**

a) **Morphine Provocation Test.**

The data for the control group have already been presented and are summarised in Table 3E. Thirty three tests were performed in the hepatic group, the results
Figure 3.13

a) Left. Shifts of EEG indices following oral neomycin.

b) Right. Shifts of EEG indices following oral ammonium chloride.

All data relate to the control group.
Figure 3.14.
Shifts of EEG indices following oral lactose (Control group)
### TABLE 3E.

**SHIFTS OF MDF FOLLOWING LACTOSE, NEOMYCIN & AMMONIUM CHLORIDE.**

*(CONTROL GROUP)*

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<th>AGE</th>
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<th>NEOMYCIN</th>
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AMMONIUM CHLORIDE
of which appear in Table 3F. The side effects associated with this test were similar to and just as frequent as those observed in the control group. The shifts in the various indices in the hepatic group are shown in fig. 3.15. The changes in MDF are shown in histogram form in fig. 3.10 and with age division in fig. 3.11. Fig. 3.16 relates oesophageal varices and encephalopathy type to MDF shift.

Typical changes in the E.E.G. spectra after morphine injection in two hepatic patients (both received 8 mg.) are shown in fig. 3.17 (L3) and fig.3.18 (L9).

Clearly the MDF tends to slow in the majority of cases, sometimes by almost -1.2 c/s. The mean change for the group as a whole is -0.55 c/s. LR appears to increase in about half the patients but this is not a large change (mean shift 0.06). Around half the subjects show some reduction of SWI which appears to be positively correlated with a reduction of MDF. The mean SWI change is -0.51. AMPO appears virtually unchanged (mean shift 0.33), whilst AMPS shows an increase in about two thirds of the group (mean shift 2.4).

The histograms in fig. 3.16 show a fair correlation of encephalopathy group C with MDF shift, although the numbers are small (5 cases). The mean MDF shift in group A is -0.50 c/s whereas that of group C is -0.72 c/s. This probably indicates some difference, especially as some members of group A must be potential group C candidates. Of the four patients in group B, 2 fall within group C territory whilst the other two show no slowing at all. The correlation of varices (15 cases) with MDF shift is clearly poor; one case shows no slowing at all. The mean MDF shift of those known to have varices is -0.61 c/s.

An interesting association was found when the degree of MDF shift was correlated with the variety of cirrhosis. For each of the three main types of cirrhosis the mean MDF shift was found. As only one person with post-hepatitis
### TABLE 3F.

**SHIFTS 3 HOURS AFTER MORPHINE INJECTION (0.14 mg/kg INTRAMUSCULAR).**

**HEPATIC GROUP.**

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<th>EEG No.</th>
<th>Age</th>
<th>Sex</th>
<th>Type</th>
<th>Varices</th>
<th>MDF</th>
<th>LR</th>
<th>AMPO</th>
<th>AMPS</th>
<th>SWi</th>
<th>Pre-Injection MDF.</th>
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<td>86</td>
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<td>+</td>
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<td>.03</td>
<td>-1</td>
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<td>-10</td>
<td>9.93</td>
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<td>94</td>
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<td>M</td>
<td>A</td>
<td>0</td>
<td>.21</td>
<td>.15</td>
<td>-3</td>
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<td>-1</td>
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<td>0</td>
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<td>-.04</td>
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<td>5</td>
<td>-3</td>
<td>9.13</td>
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<tr>
<td>99</td>
<td>39</td>
<td>F</td>
<td>A</td>
<td>0</td>
<td>-1.11</td>
<td>.17</td>
<td>-1</td>
<td>2</td>
<td>2</td>
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<td>100</td>
<td>59</td>
<td>M</td>
<td>A</td>
<td>0</td>
<td>-.55</td>
<td>-.17</td>
<td>-2</td>
<td>-1</td>
<td>2</td>
<td>9.18</td>
</tr>
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</table>
### TABLE 3F (contd)

<table>
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<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>TYPE</th>
<th>VARICES</th>
<th>MDF</th>
<th>LR</th>
<th>AMPF</th>
<th>AMPS</th>
<th>SWI</th>
<th>PRE-INJECTION MDF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>47</td>
<td>M</td>
<td>A</td>
<td>+</td>
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</tr>
<tr>
<td>112</td>
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<td>M</td>
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<td>0</td>
<td>-.66</td>
<td>.11</td>
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<td>1</td>
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<td>.01</td>
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<td>-.05</td>
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<td>3</td>
<td>1</td>
<td>9.77</td>
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<td>49</td>
<td>F</td>
<td>C</td>
<td>+</td>
<td>-.59</td>
<td>-.35</td>
<td>1</td>
<td>-7</td>
<td>0</td>
<td>9.72</td>
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<td>139</td>
<td>63</td>
<td>M</td>
<td>A</td>
<td>0</td>
<td>-.78</td>
<td>-.12</td>
<td>-2</td>
<td>-1</td>
<td>2</td>
<td>9.12</td>
</tr>
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<td>143</td>
<td>54</td>
<td>F</td>
<td>C</td>
<td>0</td>
<td>-.73</td>
<td>-.02</td>
<td>7</td>
<td>8</td>
<td>-3</td>
<td>7.55</td>
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<tr>
<td>163</td>
<td>70</td>
<td>F</td>
<td>A</td>
<td>+</td>
<td>-1.05</td>
<td>.79</td>
<td>-6</td>
<td>8</td>
<td>-1</td>
<td>9.53</td>
</tr>
<tr>
<td>164</td>
<td>64</td>
<td>M</td>
<td>C</td>
<td>+</td>
<td>-.78</td>
<td>-.03</td>
<td>1</td>
<td>0</td>
<td>-7</td>
<td>7.89</td>
</tr>
</tbody>
</table>

**Age Range** = 24 - 71 years  
**Mean Age** = 53 years  
**Number of Males** = 23  
**Number of Females** = 10  
**TOTAL.** = 33
Figure 3.15
Effect of intramuscular morphine on MDF related to LR, SWI, AMPO & AMPS shifts in the hepatic group.
Figure 3.16

Effect of intramuscular morphine on MDF in the hepatic group, related to encephalopathy type (upper figure) & the presence or absence of varices (lower figure)
Number of Tests

- Encephalopathy Group C
- Encephalopathy Group B
- Cirrhotic Patients with Varices

Shift in MoF c/s
Figure 3.17.

Change in EEG spectrum following 8mg morphine, intramuscularly in patient L3
BEFORE MORPHINE (8 mg INTRAMUSCULAR)

3 HOURS AFTER MORPHINE INJECTION
Figure 3.18

Change in EEG spectrum following 8 mg morphine intramuscularly in patient L 9
cirrhosis had morphine this group could not be tested. The results given below suggest a significant overall difference of behaviour to morphine between the three groups.

Mean MDF shift in:

(a) Chronic active hepatitis. (4 tests) -0.82 c/s
(b) Cryptogenic cirrhosis. (8 tests) -0.64 c/s
(c) Alcoholic cirrhosis. (19 tests) -0.37 c/s

Further information regarding the morphine test appears later in this section.

b) Water Injection (intramuscular).

The results of this test, performed on 6 patients appear in Table 3G. The changes of the E.E.G. indices appeared in fig. 3.8. The procedure is sometimes associated with surprisingly large changes. The spectral changes in one patient (L28 second test) showing a large change, is shown in fig. 3.19. This patient had chronic active hepatitis.

The mean changes of the indices are:

<table>
<thead>
<tr>
<th>Index</th>
<th>Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDF</td>
<td>0</td>
</tr>
<tr>
<td>AMPO</td>
<td>0.6</td>
</tr>
<tr>
<td>LR</td>
<td>0.02</td>
</tr>
<tr>
<td>AMPS</td>
<td>2.3</td>
</tr>
<tr>
<td>SWI</td>
<td>1</td>
</tr>
</tbody>
</table>

These changes are all very small except for the slight increase of AMPS; however the range of shifts found is quite considerable, e.g. MDF varies from 0.90 to -0.33 c/s.

Some of the above data was suitable for statistical analysis. This was confined to examination of the results of the morphine test performed on the hepatic and control groups. These results were compared to the responses of the control group to intramuscular water. As so few of the hepatic patients
TABLE 3G.

SHIFTS 3 HOURS AFTER WATER INJECTION (2cc INTRAMUSCULAR).

HEPATIC GROUP.

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>MDF</th>
<th>LR</th>
<th>AMPO</th>
<th>AMPS</th>
<th>Swi</th>
<th>PRE-INJECTION MDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>38</td>
<td>F</td>
<td>-.33</td>
<td>.26</td>
<td>4</td>
<td>1</td>
<td>8</td>
<td>8.17</td>
</tr>
<tr>
<td>21</td>
<td>65</td>
<td>M</td>
<td>0</td>
<td>.06</td>
<td>0</td>
<td>-3</td>
<td>2</td>
<td>8.98</td>
</tr>
<tr>
<td>27</td>
<td>25</td>
<td>F</td>
<td>.05</td>
<td>-.02</td>
<td>1</td>
<td>2</td>
<td>-3</td>
<td>9.03</td>
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<tr>
<td>28</td>
<td>25</td>
<td>F</td>
<td>-.26</td>
<td>.16</td>
<td>2</td>
<td>24</td>
<td>16</td>
<td>10.34</td>
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<tr>
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<td>25</td>
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<td>.09</td>
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<td>-14</td>
<td>9.63</td>
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<tr>
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<td>F</td>
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<td>.10</td>
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<td>6</td>
<td>-5</td>
<td>9.06</td>
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<tr>
<td>168</td>
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<td>0</td>
<td>-1</td>
<td>-3</td>
<td>3</td>
<td>8.93</td>
</tr>
</tbody>
</table>

NOTE: Two tests performed on L28.

Age Range = 25 - 70.
Mean Age = 46 years
Number of Males = 2
Number of Females = 4
TOTAL = 6
Figure 3.19
Change in EEG Spectrum after
2 ML water given intramuscularly
(L 28)
BEFORE INJECTION OF 2cc WATER (INTRAMUSCULAR)

3 HOURS AFTER WATER INJECTION

HOURS AFTER WATER INJECTION

CYCLES PER SECOND
received intramuscular water the analysis was not extended to include them.

All indices were examined excepting SWI. We were especially interested to see if there was any difference shown by the hepatic patients on the morphine test when compared with the control group and to see if age and sex had any bearing on the degree of E.E.G. change.

AGE. The controls showed no significant correlation between age and shift of either MDF or LR. (Spearmann's rank correlation test $P>0.05$). Although there was an impression that controls of 30 years or under, had greater slowing of MDF after morphine, this was, therefore, not verifiable statistically. The same test showed no correlation for the hepatic group between age and MDF ($P>0.05$), but their age was significantly (negatively) correlated with LR i.e. the older the patient the less LR increased after morphine, see Fig. 3.20a. Because of the many tied values Spearmann's test was inappropriate for AMPO and AMPS but a median test showed that neither group displayed any significant correlation of AMPO and AMPS shift with age.

SEX. The control group showed no sex difference for any index ($P>0.05$) on the median test). The hepatic group showed differences for sex and MDF and AMPS ($P<0.05$ median test). The women showed greater slowing of MDF than men (see fig. 3.20b). They also showed a higher AMPS shift than men.

GROUP There were no significant differences in LR, AMPO or AMPS between normals and cirrhotics for the sexes individually or combined (median test $P>0.05$). Control and hepatic group males did not exhibit significantly different MDF shifts ($P>0.05$ median test), but female cirrhotic subjects displayed greater slowing than control females and when the sexes were combined, the hepatic group had a significantly greater MDF slowing than controls ($P<0.05$ median test).
Figure 3.20

a) LEFT. Correlation of age with shift in LR following intramuscular morphine (Hepatic group)

b) RIGHT. Correlation of age with shift in MDF with sex, following intramuscular morphine (Hepatic group)
Testing those of the control group who had morphine against those in that group treated with water, it was found that water gave a numerically higher MDF shift than morphine ($P<0.05$ median test), but there was no significant difference with the other indices.

In summary, following morphine:

1) Age is negatively correlated with LR in the hepatic group.
2) Women in the hepatic group have greater MDF slowing and a higher AMPS shift than men of this group.
3) Females in the hepatic group have greater MDF slowing than females in the control group.
4) The hepatic group as a whole shows a greater slowing of MDF than the control group.
5) In the control group injections of water or morphine produce similar effects, except for MDF which slows less with water than with morphine.

c) Protein Loading.

The results of thirteen tests (twelve patients) who took varying protein diets are summarised in Table 3H. Only the MDF shifts are displayed as this index was thought to be the most sensitive. The MDF was obtained one or two days before commencing the diet. Using this value as a baseline, the shifts of MDF were calculated for each subsequent day.

The serial changes in a representative sample of five patients are displayed in fig. 3.21.

No side effects were observed during the course of these tests and in particular there was no clinical suggestion of encephalopathy.

Three tests show a large shift (L3 and L68), two a moderate change (L26 and L28), and the remainder show little change. Of those showing moderate or large shifts the lowest point appears to be reached after 7 days whereupon
<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Diet (g)</th>
<th>Gain in hf after protein loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>f</td>
<td>120</td>
<td>9.07</td>
</tr>
<tr>
<td>38</td>
<td>f</td>
<td>130</td>
<td>8.48</td>
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<td>71</td>
<td>m</td>
<td>120</td>
<td>7.88</td>
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<tr>
<td>24</td>
<td>m</td>
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<td>8.20</td>
</tr>
<tr>
<td>23</td>
<td>f</td>
<td>120</td>
<td>10.22</td>
</tr>
<tr>
<td>68</td>
<td>k</td>
<td>30</td>
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</tr>
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<td>120</td>
<td>-0.68</td>
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<tr>
<td>58</td>
<td>f</td>
<td>120</td>
<td>-0.21</td>
</tr>
<tr>
<td>51</td>
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<td>120</td>
<td>-0.68</td>
</tr>
<tr>
<td>56</td>
<td>m</td>
<td>120</td>
<td>-0.97</td>
</tr>
<tr>
<td>39</td>
<td>f</td>
<td>120</td>
<td>-0.59</td>
</tr>
<tr>
<td>47</td>
<td>m</td>
<td>120</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

**Table 3H:**

Shifts in hf after protein loading.
<table>
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<tr>
<th>12</th>
<th>3</th>
<th>7</th>
<th>Year Range = 24-71 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5</td>
<td>7</td>
<td>Number of Females</td>
<td>Number of Males</td>
</tr>
<tr>
<td>38</td>
<td>38</td>
<td>71</td>
<td>Mean Age = 48 years</td>
<td>Median Age = 24-71 years</td>
</tr>
</tbody>
</table>

**NOTE:** (a) Two Tests performed on L7.
(b) Day 0 represents the value of MDF prior to protein loading.

Values:
- -1.12
- -1.78
- -1.15
- -1.12
- -1.15
- -1.12

**DIET (G)**
- 120
- 120
- 120
- 120
- 120
- 120

**SEX**
- M
- F
- M
- F
- M
- F

**AGE**
- 28
- 38
- 38
- 38
- 38
- 38

**NOTE:**
- Eyg No.
Figure 3.21

Shifts in MDF following protein loading in five Patients from the Hepatic Group. All had varices. The numbers at the end of each line indicate the daily protein intake in grams.
the change levels off. However L68 did not level off in this manner and probably would have lapsed into coma had E.G. monitoring not given an early warning of this.

On both occasions L3 shows a levelling off followed by a secondary depression starting at day 12 in each instance.

L68 shows a gradual increase of SWI, AMPO and AMPS and a decrease of LR whilst the MDF slows. There is a suggestion of this type of change in the other cases showing MDF slowing, but the values are frequently inconsistent.

The degree of change at the 5th, 6th or 7th day (whichever was the later) on a high protein diet was taken as a measure of maximum response to the dietary stress. The second set of values was taken in the case of L3. Unfortunately there were insufficient members of each of the three main cirrhosis groups to allow a satisfactory comparison of possible differences of behaviour to be made. The mean shift of MDF in each group was as follows:

| Chronic active hepatitis (2 cases) | -0.15 c/s |
| Cryptogenic cirrhosis (4 cases) | -1.03 c/s |
| Alcoholic cirrhosis (5 cases) | -0.04 c/s |

The extremely low value in the cryptogenic group is mostly due to the value of -2.74 c/s in L68 on the 5th day.

Of the 12 patients studied 9 were encephalopathy group A, 2 group B and 1 group C and because of this imbalance further analysis would be superfluous.

A slight association was found between the degree of MDF shift and the presence of varices. Using the above approach, the mean changes were as follows:

| Varices present (7 cases) | -0.56 c/s |
| Varices absent (5 cases) | +0.12 c/s |
d) **Neomycin.**

The MDF changes in 8 patients are presented in Table (3.1). The manner of calculating the shifts was similar to that relating to the protein data. No side effects, other than mild diarrhoea were experienced, except No. L146 who experienced considerable nausea as well as some diarrhoea. There was never any electrolyte imbalance attributable to the diarrhoea. No clinical alteration of conscious level was detected.

Four representative cases are selected and displayed in fig. 3.22. Three of these cases show well defined increases (Nos. L68, L71 and L146) and this response is well marked after seven days. The MDF of all these three subjects commenced within the theta range. L72 shows a rapid increase of MDF followed by a fall and then a further increase. The explanation of this is not at all clear. L76 shows a borderline response.

On the remaining indices, the administration of neomycin (when the basal record is slowed) is associated with a fall of AMPO, AMPS and SWI, whereas LR tends to show no consistent change.

e) **Ammonium Acetate (Intravenous).**

For each group, hepatic and control, the mean and range of each index was calculated at every sampling interval. These values, as before, represent shifts with respect to the pre-injection value. The data are displayed in figs. 3.23 and 3.24. Typical shifts in three control subjects and four cirrhotics are shown in figs. 3.25 and 3.26 respectively. Details regarding each subject are tabulated. (Tables 3J and 3K).

Two of the control group had unsuitable E.E.Gs because their records became desynchronised at some stage during the experiment. The serial changes in MDF with respect to the pre-injection value are shown in Table 3L.
TABLE 3i.

SHIFTS IN MDF AFTER ADMINISTRATION OF NEOMYCIN.

HEPATIC GROUP.

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>6</th>
<th>68</th>
<th>69</th>
<th>72</th>
<th>76</th>
<th>84</th>
<th>90</th>
<th>146</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>47</td>
<td>68</td>
<td>68</td>
<td>58</td>
<td>63</td>
<td>65</td>
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<td>SEX</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>DOSE (g)</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>4</td>
</tr>
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<th>9.03</th>
<th>7.98</th>
<th>6.82</th>
<th>6.47</th>
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<td>-</td>
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<td>.11</td>
<td>.19</td>
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<tr>
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<td>.82</td>
<td>-</td>
<td>.11</td>
<td>.59</td>
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<td>.80</td>
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<td>.43</td>
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<td>.63</td>
<td>.43</td>
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<td>.12</td>
<td>.20</td>
<td>-</td>
<td>1.93</td>
<td></td>
</tr>
</tbody>
</table>

NOTE:  

a) Day 'O' represents the value of MDF prior to Protein Loading.  
b) o/p = unregulated diet as out patient.  
c) Dose of Neomycin and protein content are total daily values in grams.
TABLE 34 (contd)

<table>
<thead>
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<th>Description</th>
<th>Value</th>
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<td>Age Range</td>
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<tr>
<td>Mean Age</td>
<td>64 years</td>
</tr>
<tr>
<td>Number of Males</td>
<td>5</td>
</tr>
<tr>
<td>Number of Females</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 3.22

Shifts in MDF following Neomycin in the Hepatic Group.

N = Neomycin, followed by total daily dosage in grams

P = Protein, followed by total daily intake in grams
Figure 3.23

Effect of intravenous ammonium acetate on MDF & SWI in cirrhotic & control groups. The centre marking (0 or X) indicates the mean value and the straight or dotted vertical lines, the range.
Figure 3.24

Effect of intravenous ammonium acetate on LR, AMPO, & AMPS in cirrhotic & control groups. The centre marking (O or X) indicates the mean value & the straight or dotted vertical lines, the range.
Effect of intravenous ammonium acetate on MDF in three members of the control group, followed for up to 180 minutes.
Figure 3.26

Effect of intravenous Ammonium Acetate on MDF in four members of the Hepatic Group, followed for 120 minutes.
## TABLE 3J.

**AMMONIUM ACETATE INFUSION**

**EXPERIMENTAL DETAILS.**

**CONTROL GROUP.**

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>DOSE (mg/kg)</th>
<th>ACTUAL DOSE (mg)</th>
<th>PLASMA AMMONIA (µmol/100ml) AT EACH INTERVAL (MINS).</th>
<th>SIDE EFFECTS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>29</td>
<td>M</td>
<td>7</td>
<td>460</td>
<td>46  49  40  43  46  49</td>
<td>A</td>
</tr>
<tr>
<td>41</td>
<td>53</td>
<td>F</td>
<td>10</td>
<td>525</td>
<td>53  132 93  96  94  53</td>
<td>V</td>
</tr>
<tr>
<td>56</td>
<td>27</td>
<td>M</td>
<td>16</td>
<td>924</td>
<td>43  344 125 86 81 53</td>
<td>A</td>
</tr>
<tr>
<td>70</td>
<td>30</td>
<td>M</td>
<td>16</td>
<td>1540</td>
<td>24  693 100 78 86 82</td>
<td>A</td>
</tr>
<tr>
<td>87</td>
<td>19</td>
<td>M</td>
<td>16</td>
<td>1078</td>
<td>37  167 82  60  63 56</td>
<td>V</td>
</tr>
<tr>
<td>104</td>
<td>33</td>
<td>M</td>
<td>12</td>
<td>924</td>
<td>87  301 130 201 107 100</td>
<td>A</td>
</tr>
<tr>
<td>116</td>
<td>23</td>
<td>M</td>
<td>12</td>
<td>876</td>
<td>56  205 88  73  64  62</td>
<td>V</td>
</tr>
<tr>
<td>117</td>
<td>24</td>
<td>M</td>
<td>14</td>
<td>1100</td>
<td>77  218 122 100 98 78</td>
<td>V</td>
</tr>
<tr>
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<td>22</td>
<td>F</td>
<td>12</td>
<td>828</td>
<td>42  108 67  38  38  35</td>
<td>V</td>
</tr>
<tr>
<td>129</td>
<td>29</td>
<td>M</td>
<td>12</td>
<td>900</td>
<td>57  110 104 107 89</td>
<td>V</td>
</tr>
<tr>
<td>134</td>
<td>21</td>
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</tr>
<tr>
<td>140</td>
<td>21</td>
<td>F</td>
<td>10</td>
<td>600</td>
<td>62  98  68  78  68  83</td>
<td>V</td>
</tr>
<tr>
<td>141</td>
<td>38</td>
<td>M</td>
<td>10</td>
<td>720</td>
<td>94  248 142 109 97 105</td>
<td>V</td>
</tr>
<tr>
<td>148</td>
<td>49</td>
<td>M</td>
<td>10</td>
<td>730</td>
<td>49  114 59  54  51 45</td>
<td>V</td>
</tr>
<tr>
<td>151</td>
<td>45</td>
<td>F</td>
<td>10</td>
<td>650</td>
<td>46  174 80  66  52 50</td>
<td>V</td>
</tr>
<tr>
<td>165</td>
<td>59</td>
<td>M</td>
<td>10</td>
<td>760</td>
<td>-    -    -    -    -    -</td>
<td>V</td>
</tr>
<tr>
<td>166</td>
<td>49</td>
<td>F</td>
<td>10</td>
<td>480</td>
<td>-    -    -    -    -    -</td>
<td>V</td>
</tr>
</tbody>
</table>

A = Arterial Assay.

V = Venous Assay.

Age Range = 19 - 59 years

Mean Age = 34 years.

Number of Males = 11

Number of Females = 6

TOTAL = 17.
**TABLE 3K.**

AMMONIUM ACETATE INFUSION - EXPERIMENTAL DETAILS.

**HEPATIC GROUP.**

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>DOSE ACTUAL (mg/Kg)</th>
<th>EEG DOSE</th>
<th>ACTUAL NO.</th>
<th>AGE RANGE</th>
<th>SEX</th>
<th>PLASMA AMMONIA (µg/ml) AT EACH INTERVAL (mins)</th>
<th>SIDE EFFECTS</th>
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<td>3</td>
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<td>10</td>
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<td>241</td>
<td>441</td>
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<td>720</td>
<td>210</td>
<td>307</td>
<td>272</td>
<td>238</td>
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<tr>
<td>68</td>
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<td>F</td>
<td>10</td>
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<td>419</td>
<td>498</td>
<td>469</td>
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<td>544</td>
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<td>8</td>
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<td>628</td>
<td>550</td>
<td>561</td>
<td>592</td>
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<td>560</td>
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<td>518</td>
<td>V + C</td>
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</tbody>
</table>

**V = Venous Assay**

**Age Range = 19 - 69**

**Mean Age = 50 years.**

**Number of Males = 9**

**" " Females = 7**

**TOTAL = 16**
<table>
<thead>
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<th>150</th>
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<td>0.01</td>
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<td>-0.25</td>
<td>-0.34</td>
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<td>-0.32</td>
<td>0.03</td>
<td>-0.20</td>
<td>-0.25</td>
<td>-0.37</td>
<td>-0.22</td>
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<td>-0.04</td>
<td>-0.1</td>
<td>-0.1</td>
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<td>-0.37</td>
<td>-0.52</td>
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<td>-0.29</td>
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<td>-0.36</td>
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<td>0.05</td>
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<td>8.95</td>
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<td>-</td>
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<td>-0.32</td>
<td>0.03</td>
<td>-0.20</td>
<td>-0.25</td>
<td>-0.37</td>
<td>-0.22</td>
<td>-0.18</td>
<td>-0.04</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

| TABLE 21 |

CONTROL GROUP

TIME IN MINUTES AFTER INFUSION
Of the hepatic group, one was excluded because of a desynchronised record. The serial changes of MDF with respect to the pre-injection value are shown in Table 3M.

Consideration of figs. (3.23) and (3.24) shows that in control subjects, with reference to mean values:

1) There is a gradual slowing of MDF of approximately -0.2 c/s until 75 minutes, whereafter there are small fluctuations until 180 minutes where the MDF is still low. The range of variation is clearly considerable at all sampling intervals.

2) SWI shows no change although the range is considerable.

3) LR remains unchanged up to 120 minutes, when there is a considerable increase by approximately 0.2. Again the range is considerable, particularly at 75 minutes.

4) AMPO gradually increases by a small amount to a value of 1 unit at 105 minutes and thereafter returns to pre-injection levels.

5) AMPS shows equivocal changes up to 120 minutes and thereafter increases by approximately 2 units. The range of these values is considerable, especially at 30 minutes.

In the hepatic group with reference to the mean values:

1) MDF immediately falls and then fluctuates, reaching a trough at 75 minutes where the change is -0.2 c/s. Thereafter the MDF remains depressed at about the same level. The range of MDF is considerable, falling to 1.1 c/s at 75 minutes. At nearly every sampling interval the mean and lower range values are depressed more than in the control group.

2) SWI shows a small downward shift maximal at 40', but apart from this the changes are minor. The range is large and at all times the lower
| TIME IN MINUTES AFTER INFUSION | PSE | VARICES | NO. | PSE | BASEL | MD | Type | PSE | BASEL | MD | Type | PSE | BASEL | MD | Type | PSE | BASEL | MD | Type |
|-------------------------------|-----|---------|-----|-----|-------|----|------|-----|-------|----|------|-----|-------|----|------|-----|-------|----|------|-----|------|
| 10                            | 0.9 | 0.9     | 0.9 | 0.9 | 0.9   | 0.9| 0.9  | 0.9 | 0.9   | 0.9| 0.9 | 0.9 | 0.9   | 0.9| 0.9 | 0.9 | 0.9   | 0.9| 0.9 | 0.9 | 0.9 |
| 15                            | 1.5 | 1.5     | 1.5 | 1.5 | 1.5   | 1.5| 1.5  | 1.5 | 1.5   | 1.5| 1.5 | 1.5 | 1.5   | 1.5| 1.5 | 1.5 | 1.5   | 1.5| 1.5 | 1.5 | 1.5 |
| 20                            | 2.0 | 2.0     | 2.0 | 2.0 | 2.0   | 2.0| 2.0  | 2.0 | 2.0   | 2.0| 2.0 | 2.0 | 2.0   | 2.0| 2.0 | 2.0 | 2.0   | 2.0| 2.0 | 2.0 | 2.0 |
| 30                            | 3.0 | 3.0     | 3.0 | 3.0 | 3.0   | 3.0| 3.0  | 3.0 | 3.0   | 3.0| 3.0 | 3.0 | 3.0   | 3.0| 3.0 | 3.0 | 3.0   | 3.0| 3.0 | 3.0 | 3.0 |
| 40                            | 4.0 | 4.0     | 4.0 | 4.0 | 4.0   | 4.0| 4.0  | 4.0 | 4.0   | 4.0| 4.0 | 4.0 | 4.0   | 4.0| 4.0 | 4.0 | 4.0   | 4.0| 4.0 | 4.0 | 4.0 |
| 50                            | 5.0 | 5.0     | 5.0 | 5.0 | 5.0   | 5.0| 5.0  | 5.0 | 5.0   | 5.0| 5.0 | 5.0 | 5.0   | 5.0| 5.0 | 5.0 | 5.0   | 5.0| 5.0 | 5.0 | 5.0 |
| 60                            | 6.0 | 6.0     | 6.0 | 6.0 | 6.0   | 6.0| 6.0  | 6.0 | 6.0   | 6.0| 6.0 | 6.0 | 6.0   | 6.0| 6.0 | 6.0 | 6.0   | 6.0| 6.0 | 6.0 | 6.0 |
| 75                            | 7.5 | 7.5     | 7.5 | 7.5 | 7.5   | 7.5| 7.5  | 7.5 | 7.5   | 7.5| 7.5 | 7.5 | 7.5   | 7.5| 7.5 | 7.5 | 7.5   | 7.5| 7.5 | 7.5 | 7.5 |
| 90                            | 9.0 | 9.0     | 9.0 | 9.0 | 9.0   | 9.0| 9.0  | 9.0 | 9.0   | 9.0| 9.0 | 9.0 | 9.0   | 9.0| 9.0 | 9.0 | 9.0   | 9.0| 9.0 | 9.0 | 9.0 |
| 105                           | 10.5| 10.5    | 10.5| 10.5| 10.5   | 10.5|10.5 | 10.5 | 10.5   | 10.5| 10.5 | 10.5 | 10.5   | 10.5| 10.5 | 10.5 | 10.5   | 10.5| 10.5 | 10.5 | 10.5 |
| 120                           | 12.0| 12.0    | 12.0| 12.0| 12.0   | 12.0|12.0 | 12.0 | 12.0   | 12.0| 12.0 | 12.0 | 12.0   | 12.0| 12.0 | 12.0 | 12.0   | 12.0| 12.0 | 12.0 | 12.0 |
| 150                           | 15.0| 15.0    | 15.0| 15.0| 15.0   | 15.0|15.0 | 15.0 | 15.0   | 15.0| 15.0 | 15.0 | 15.0   | 15.0| 15.0 | 15.0 | 15.0   | 15.0| 15.0 | 15.0 | 15.0 |
| 180                           | 18.0| 18.0    | 18.0| 18.0| 18.0   | 18.0|18.0 | 18.0 | 18.0   | 18.0| 18.0 | 18.0 | 18.0   | 18.0| 18.0 | 18.0 | 18.0   | 18.0| 18.0 | 18.0 | 18.0 |

**PSE = Portal-Systolic Encephalopathy.**

**PSE** = Porto-Systolic Encephalopathy.

**HEPATIC GROUP.**

**SHIFTS IN MDP FOLLOWING INTRAVENOUS AMMONIUM ACETATE.**

**Table 4.**
range figure in the cirrhotics is considerably below the controls.

3. LR shows a minor increase at 60 and 150 minutes but no appreciable change at other intervals.

4. AMPO shows a slight tendency to increase throughout the experiment.

5. AMPS shows a similar tendency to increase, especially at 105 and 120 minutes where the upper range values reach 7 - 8 units.

In summary, the chief effect of ammonium acetate is to slow MDF. This is more marked in the cirrhotic group. SWI and LR show little consistent trend although there may be more reduction of SWI in the cirrhotics. AMPO and AMPS tend to increase slightly in both groups.

Some idea of individual variation is illustrated in figs. (3.25) and (3.26).

Whilst a general trend may be discerned for each subject, the fluctuation of adjacent samples is considerable, particularly in the hepatic group.

Measurements of arterial pH were made on 5 subjects from the control group (Nos. L13, 56, 70, 87 and 104). No change was observed in this index in any of these subjects, who were monitored before and up to 60 minutes after injection of ammonium acetate, except for L56, who received a high dose (16 mg/kg). At 10 minutes his arterial pH rose to 7.55 but had returned to normal levels at 20 minutes (7.42). It is significant that this subject's E.E.G. was virtually unchanged at 10 minutes (+0.10 c/s), in the presence of such a marked alkalosis.

In view of the smaller doses used in the cirrhotic patients, it was thought unlikely that any significant alteration in blood pH would occur, and even if it did, the change would be unlikely to affect the E.E.G. response.

E.E.G.-Ammonia Correlations.

In order to determine whether there was a correlation between the E.E.G.
changes and plasma ammonia, the shifts of MDF were compared to the ammonia shifts with respect to their basal values. As a different dose was used in some cases, only those of the control group who received 10 or 12 mg/kg were used and were compared with those of the hepatic group who received 10 mg/kg. The shifts were then plotted in fig. 3.27.

It is immediately obvious that no correlation exists between shift of plasma ammonia and shift of MDF in either group. There does appear to be a difference between the two groups and with the eye of faith a general trend downwards to the right can be discerned in the hepatic group. However, there is too wide a scatter of points and far too much overlap with the control group for these changes to be of any clinical value.

Was there any correlation between EEG change and encephalopathy type? Inspection of Table 3K readily shows the lack of correlation between these two parameters. Whereas large shifts are shown by L68, 143 and 164, the other three in group C show only slight slowing or even an increase of frequency (see fig. 3.26, L120). Furthermore, a large shift is shown by one member of group A i.e. L156. Possibly the latter patient is a future group C candidate but the exceptions already given tend initially to suggest that the test is poorly selective with regard to encephalopathy type.

However, four of the six group C patients had episodes of encephalopathy 2 years or more before the ammonium acetate test was performed. The other two in this group had episodes more recently than this - L68 six months previously and L143 three weeks previously. The latter two patients do show large changes following the infusion, especially at the 75 minute sample. The duration between the last episode of encephalopathy and the time of the ammonia test for the other patients is as follows:
Figure 3.27
Plot of shift in MDF against shift of venous Plasma Ammonia in control and Hepatic Groups, following intravenous infusion of Ammonium Acetate
Of these few only L164 shows an E.E.G. slowing, whereas the other three are virtually unaffected.

Although the numbers are small this time factor is possibly significant and had not been appreciated in the selection of group C patients for this test. However, when the group C Morphine results were re-examined all 5 members receiving the drug reacted quite vigorously yet the duration of time between the episode of encephalopathy and the morphine tests was just as large as with the ammonia test. Four of the above five patients receiving morphine subsequently had an ammonia test (Nos. L68, 120, 143 and 164) so that this difference is not likely to be due to a difference of population.

To see if there was any difference in behaviour of MDF to ammonia infusion, shown by the different types of cirrhosis, the response of the four patients with alcoholic cirrhosis was compared with that of the 10 with the cryptogenic variety. Of the alcoholic group two showed no change, one (L103) a delayed slowing and the other (L161) a mild early sustained fall. In view of the lack of homogeneity of response in the alcoholic group and the smallness of numbers, it was thought that further comparisons would be meaningless.

It was not possible to make any worthwhile observations regarding a possible MDF/varices correlation. There were only three patients with no varices in whom data were available. Of these three, two showed no change of MDF (Nos. L79 & 152), whereas one showed marked slowing (No.L143). Inspection of Table 3K reveals a wide variation of response in those who were known to have varices, suggesting that the correlation of MDF with the presence or absence
Ammonia - Clinical Correlations.

There appeared to be a more promising correlation between blood ammonia levels, encephalopathy type and the presence or absence of varices. These data were statistically analysed. The ammonia values prior to infusion ('0' minutes), and at 20, 30 and 50 minutes were examined. The 10 minute ammonia values were ignored as this sample was obtained only 5 minutes after the end of infusion, where errors due to recirculation and of sampling timing would be most prominent. The 75 minute sample was also ignored as some subjects for no apparent reason showed a late rise at this time. The hepatic patients used for this analysis had all received a dose of 8 or 10 mg/kg, and the control subjects a uniform dose of 10 mg/kg.

The tests were performed on the original ammonia values, on the absolute shifts with respect to the pre-infusion values and on the percentage shifts with respect to the pre-infusion values. In view of the smallness of the population and its variability, Wilcoxon's test was applied throughout, rather than other tests assuming normal distribution.

The numbers of patients in the various groups were as follows:

a) For a test of possible correlation of ammonia levels and encephalopathy type:-

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>5</td>
</tr>
<tr>
<td>Group C</td>
<td>5</td>
</tr>
<tr>
<td>Controls</td>
<td>6</td>
</tr>
</tbody>
</table>

b) For a test of possible correlation of ammonia levels and the presence or absence of varices:-
With varices 7 subjects
Without varices 4 "
Controls 6 "

The results of the analysis were as follows:

1. With respect to the original values, both group A and C patients were significantly different from the controls \((P < 0.01)\), at all intervals i.e. 0, 20, 30 and 50 minutes.

2. With regard to the absolute shifts between readings there was a significant difference between group A and group C at all intervals, but particularly at 30 minutes \((P = 0.01)\). This statement also held true at a similar level of significance for the measurements of percentage increase at each interval, again particularly at 30 minutes. The original values were not significantly different between groups A and C.

3. With respect to the original values there was a significant difference \((P < 0.01)\) between the control group and the patient group, consisting of those with and without varices. There was, however, no significant difference between those patients with varices compared to those without, at any interval, whether original, absolute or percentage values were used.

The most useful piece of information provided by this analysis was the difference of behaviour of encephalopathy groups A and C which was most evident at the 30 minute interval. In an attempt to put this information into practical terms, the mean and range of the ammonia determinations were found at each interval and are shown in Table 3N. All these values (apart from the basal figures) refer to the absolute shifts with respect to the basal value. This somewhat crude approach was necessary as the smallness and variability of the values precluded further statistical analysis.
TABLE 3N.

CORRELATION OF MEAN VENOUS AMMONIA SHIFTS (µg/100 ml) WITH ENCEPHALOPATHY TYPE.

<table>
<thead>
<tr>
<th></th>
<th>Mean Basal Value and Range</th>
<th>Mean Shifts &amp; Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20’</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>(46 - 94)</td>
<td>(6 - 48)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A.</td>
<td>332</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>(203 - 550)</td>
<td>(11 - 74)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type C</td>
<td>248</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>(124 - 410)</td>
<td>(47 - 124)</td>
</tr>
</tbody>
</table>

NOTE: All Values except mean basal are absolute shifts with respect to Basal Values.
Table 3.0 shows the relationship between mean venous ammonia shifts, determined as above, and the existence of varices. There is an impression of good separation between the three groups in the Table, but the wide range of values prevents the emergence of any statistically significant information.

It would have been desirable to determine if the type of cirrhosis correlated with the degree of change observed in ammonia levels. However, only seven patients of the cryptogenic group and three from the alcoholic group had data suitable for study. Furthermore, all three alcoholic patients were encephalopathy group A, and nearly all the cryptogenic patients were group C, and had varices, so that any differences between the two types of cirrhosis could not be assessed.

In summary of this section, no correlation could be demonstrated between MDF shift and a) plasma ammonia shift, b) the presence of varices, and c) encephalopathy type. No observations could be made regarding a possible correlation of type of cirrhosis with MDF change. The plasma ammonia shifts correlated well with encephalopathy type, showing a particularly good differentiation at the 30 minute sample. No correlation emerged between the existence of varices and plasma ammonia although there was a subjective impression of some association. No observations could be made regarding a possible correlation of type of cirrhosis with ammonia shifts.

f) **Intravenous Saline or Dextrose.**

This test was performed on few subjects only, all belonging to the hepatic group. The changes in MDF with respect to the pre-injection values are shown in fig. 3.28. The raw data appear in Table 3.9.

There were no side effects. Only one person has a stable response but even this varies at 105 minutes. The other three remain stable for 30 minutes and thereafter
TABLE 3.0.

CORRELATION OF MEAN VENOUS AMMONIA SHIFTS (µg/ml/100ml) WITH THE PRESENCE OF OESOPHAGEAL VARICES.

<table>
<thead>
<tr>
<th></th>
<th>Mean Basal Value and Range</th>
<th>Mean Shifts and Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20'</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(46 - 94)</td>
</tr>
<tr>
<td>Varices not detected</td>
<td></td>
<td>324</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(124 - 550)</td>
</tr>
<tr>
<td>Varices detected</td>
<td></td>
<td>263</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(163 - 410)</td>
</tr>
</tbody>
</table>

**NOTE:** All values except mean basal are absolute shifts with respect to basal values.
Figure 3.28
Shifts in MDF following intravenous saline or Dextrose, given to four members of the Hepatic Group.
<table>
<thead>
<tr>
<th>TIME</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

**Time 0 = Pre Infection Values**

**Intravenous Injection with Dextrose**

**Hepatic Group**

**TABLE 3**
fluctuate considerably but not in any particular direction.

With regard to the other indices, LR and AMPO show little change. L152 and L163 both show increases of AMPS especially around 60 minutes. SWI tends to decrease except in L168 who shows a marked increase over the first 30 minutes.

'Inter-Test' Correlations.

In order to determine whether there was any correlation between the responses of a particular patient to various provocative tests, the shift of MDF was graded arbitrarily into 4 groups - see Table 3.Q. The responses to the morphine, protein loading and ammonium acetate tests were examined for those patients who had been exposed to two or more of these tests. For the protein test, the value of MDF at the 5th, 6th and 7th day was taken, whichever was the later. For ammonium acetate it was difficult to decide which time to select, but as an approximation the lowest shift of MDF decided the grade as long as there were two or more values within this grade. A subjective assessment of correlation was obtained and was judged meaningful if any two or more tests were graded either the same or not more than one grade different.

By this approximate method, agreement was obtained in 12 of the 17 patients examined.

MISCELLANEOUS RESULTS.

a) Correlation of MDF with AMPO/S.

There was an impression that in most cases both AMPO and AMPS tended to increase as MDF decreased. Simultaneously LR tended to diminish whilst SWI increased, but the association was most marked with AMPO and AMPS. It was therefore of interest to determine -

i) if this association could be statistically substantiated.
**TABLE 3.0**

**AGREEMENT BETWEEN TESTS OF ENCEPHALOPATHY**

<table>
<thead>
<tr>
<th>EEG NO.</th>
<th>MORPHINE TEST</th>
<th>PROTEIN TEST</th>
<th>AMMONIA TEST</th>
<th>AGREEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>!</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>!</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>!</td>
</tr>
<tr>
<td>28</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>!</td>
</tr>
<tr>
<td>68</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>69</td>
<td>++</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>++</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>+</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>+++</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>+</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>143</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>163</td>
<td>++</td>
<td>0</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>164</td>
<td>+</td>
<td>+</td>
<td>!</td>
<td></td>
</tr>
</tbody>
</table>

**KEY**

0  MDF shift ± 0.50 c/s  
+  " " -0.51 to -0.80 c/s  
++ " " -0.81 to -1.10 c/s  
+++ " " -1.10 or more.  
!  Agreement between tests.  
?  No agreement between tests.
ii) which of the two amplitude measurements correlated better with MDF.

iii) whether the correlation was linear.

Four subjects from the hepatic group were selected for testing. They were chosen because all had numerous recordings (between 30 and 70) which displayed considerable fluctuation as a result of surgery, varying protein intake etc.

The relation of AMPO and MDF, based on 70 recordings on L68, is shown in fig. 3.29. Regression lines were found for the four subjects and they were all found to be "not significantly non-linear" and to have not significantly different slopes. However, because of the wide variation of the observed points from the fitted line, any confidence intervals would have been too wide to be of much practical use. Which of AMPO and AMPS were more linear could not be determined.

b) Biochemical Correlations.

Non-statistical comparisons of standard biochemistry and E.E.G. indices were made in most patients - see case history section. In one patient, L68, a statistical study of the above factors was made. All the E.E.G indices except SWI were matched against:

i) Serum Urea, Potassium, Sodium and Bicarbonate.

ii) Serum Bilirubin, Alkaline Phosphatase, Thymol Turbidity and Alanine-Aminotransferase.

The data available allowed a comparison of 33 sets of matched E.E.G and biochemical measurements - each component was obtained on the same day.

The urea and bilirubin were both positively correlated with both AMPO and AMPS. ($p < 0.05$).
Figure 3.29

To show the correlation between MDF and AMPO in Patient L68. The regression line shown is based on the analysis of 70 separate daily recordings on this Patient.
SCATTERGRAM:
MEAN FREQUENCIES ACROSS, MEAN AMPLITUDES DOWN (EYES OPEN)
♦ CLASH SYMBOL.
<- LOWER BOUND OVERFLOW.
-> UPPER BOUND OVERFLOW.

71: X
70: X
69: X
68: X
67: X
66: X
65: X
64: X
63: X
62: X
61: X
60: X
59: X
58: X
57: X
56: X
55: X
54: X
53: X
52: X
51: X
50: X
49: X
48: X
47: X
46: X
45: X
44: X
43: X
42: X
41: X
40: X
39: X
38: X
37: X
36: X
35: X
34: X
33: X
32: X
31: X
30: X
29: X
28: X
27: X
26: X
25: X
24: X
23: X
22: X
21: X
20: X
19: X
18: X
17: X
16: X
15: X
14: X
13: X
12: X
11: X
10: X
9: X
8: X
7: X
6: X
5: X
4: X
3: X
2: X
1: X
0: X

3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0
MEAN FREQUENCIES
The alkaline phosphatase was almost significantly correlated at 5% (0.1 > P > 0.05) with AMPS (negatively correlated). The urea was negatively correlated with MDF (P < 0.05); bilirubin was negatively correlated with LR and MDF (P < 0.01) and alanine-aminotransferase was negatively correlated with LR.

The best correlation was, therefore, of bilirubin with LR and MDF, whilst thymol turbidity correlated with none of the E.E.G. indices.

The serial changes of MDF, bilirubin and urea in this patient are plotted (fig. 3.30). Inspection of this drawing clearly reveals that bilirubin correlates with MDF better than urea. The initial urea values correlate well with MDF but after day 17 only minor undulations of urea occur whereas the other two parameters show considerable fluctuation.

The coefficient of variation for these bilirubin estimations is 8%, so that a value of 1.0 mg/100 ml is accurate to ± 0.08 mg/100 ml. Fluctuations even within the normal range may, therefore, have significance.
Figure 3.30
Serial changes in MDF, Serum bilirubin and Urea followed for 60 days in patient L68.
In this section there is a description of ten cases of hepatic disease. Emphasis is laid on the clinical and biochemical correlations of the E.E.G changes. Some comment is deliberately included here, to avoid excess cross-referral in the main DISCUSSION.

The age of each patient refers to the age at the time of the E.E.G. study.

Where the term "70G protein diet" appears, this always indicates total daily protein intake. All ammonia levels refer to the venous plasma values of this substance.

The author himself did not always examine patients for encephalopathy and in some instances statements regarding the degree of encephalopathy were based on the observations of the clinician in charge, or his medical staff.

Only the biochemical measurements that in general showed some abnormality are detailed. When the serum urea and potassium were determined, so were the serum sodium and bicarbonate values, but as the latter two never showed any change, these figures have not been included. Abnormalities in serum albumen and gamma globulin levels were frequently observed, but only in Case 1 are these data included. Whilst protein measurements give some index of hepatic failure, they are probably not directly related to hepatic encephalopathy and change very slowly, and for these reasons were not performed frequently.
MRS. C. H. - EEG No. L68.

This 68 year old housewife was admitted in February 1968 with a history of 3 recent haematemeses. She was found to have gross oesophageal varices, marked ascites and moderate enlargement of the liver and spleen. Hepatic function was considerably depressed (see Table 4A) and estimated hepatic blood flow considerably reduced (0.94 L/min). A diagnosis of cryptogenic cirrhosis with portal hypertension was made. She was treated with a low sodium diet, potassium supplements and a diuretic for one month, when she had a further haematemesis. In spite of her age and poor hepatic function it was decided that surgical intervention was necessary and an oesophageal transection was performed on 8.3.68. Convalescence was smooth and she was discharged home two weeks later. For ten months she remained symptom free but had to be re-admitted in February and again in May 1969, following further haematemeses. On the second occasion she was drowsy and confused. This state of hepatic pre-coma slowly improved, but a few days later there was another haematemesis which settled with balloon tamponade, but recurred on withdrawal of the balloon tube. The overall picture of the hepatic function tests was unchanged (see Table 4A).

Despite her poor clinical condition, operation was considered to offer her the best chance and splenectomy with end to side lienorenal venous anastomosis was performed on 5.6.69. At operation the liver was found to be diffusely fibrosed, and biopsy showed well established portal cirrhosis with evidence of regenerating nodules and no bile stasis. For the first 48 hours after operation she was drowsy but rational and thereafter made a rapid clinical recovery.
The E.E.G. studies were begun on 28.5.69 - three days after admission. See fig. 4.1. The initial measurements were all in the theta range (days 1 - 7), and show a slow improvement more or less synchronous with the improvement in clinical state. The changes in AMPO and AMPS are also shown up to day 33 - see fig. 4.2. It will be seen that these changes are closely negatively correlated with MDF i.e. a rise of MDF is associated with a fall of both AMPO and AMPS. The association of LR with MDF may be judged from fig. 4.3.

At day 8, Morphine 8 mg.lm was given and caused a MDF shift of -0.50 c/s. AMPO changed +9, AMPS +1 and LR -.29. The E.E.G was still depressed the following day and this is likely to be a lag effect of the drug.

Following the lieno-renal anastomosis there was a fall in MDF to 3.03 c/s, then a slow rise. At day 22 (twelve days after operation) because the patient was physically and mentally well, the protein intake was increased to 50 G/day. This induced a rapid deterioration in the E.E.G which fell to the delta range in 3 days, ante-dating the onset of clinical pre-coma by twenty-four hours. In this instance no action was taken partly due to delay in E.E.G analysis, and over the following two days she lapsed into pre-coma. Treatment with Neomycin Sulphate (6G per day), bowel washouts and protein withdrawal produced a rapid clinical response, which was again paralleled by the E.E.G changes. Protein was then cautiously re-introduced to a 30G level. As both the patient and E.E.G were satisfactory, Neomycin was stopped but the low protein diet continued. The patient remained clinically alert but there was a fairly steep deterioration of the E.E.G. (fig. 4.4) suggesting that coma was again imminent. Neomycin was started again and was followed by an improvement in the E.E.G which was more gradual than with the higher dose. There was a slight E.E.G. deterioration at days 50 & 51, for which no explanation could be found.
**Figure 4.1**

Serial changes in MDF - L68 (Case 1)

Days 1 - 33
Figure 4.2

Serial changes in AMPO (O) & AMPS (X) L68 (Case 1)

Days 1 - 33
**Figure 4.3**

Serial changes in LR - L68 (Case 1)

Days 1 - 33
MRS: C. H.

**GRAPH OF DOMINANT FREQUENCIES**

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**Figure 4.4**

Serial changes in MDF - L68 (Case 1)

Days 35 - 61
Figure 4.5

Serial changes in MDF - L68 (Case 1)

Days 73 - 105
On day 53, when the clinical state and the E.E.G. appeared to be steady, Neomycin was stopped and the disaccharide Lactulose ("Duphalac") substituted in doses of 30 ml. twice daily. Treatment was not altered in any other respect. Over the succeeding eight days there was a gradual improvement in the E.E.G. and she was discharged home on day 61 on Lactulose and a 3OG protein diet.

Eleven days later re-admission was necessary because of recurrence of encephalopathy. The reason for this appeared to be the addition, by the patient, of meat extracts to the 30G protein allowance. The MDF had fallen to 2.31 c/s (See fig. 4.5). Neomycin 6G/day was given, with rapid improvement. Once the E.E.G. had reached the normal range the protein intake was slowly stepped up to 40G. Neomycin was gradually withdrawn and the Lactulose continued. Observation for a further nine days showed no deterioration and the patient was allowed home on Lactulose 30 ml. twice daily and a 40G protein diet. Two further recordings as an out-patient, at day 98 and day 105 showed sustained E.E.G. improvement, commensurate with her clinical well being. The hepatic function tests showed no significant change - see Table 4A.

**BIOCHEMISTRY.**

The biochemical correlations in this case are described in the RESULTS Section (p 212 ) and will be reviewed further under "DISCUSSION".

**DISCUSSION.**

This case illustrates several important factors:–

1) It confirms that an episode of hepatic encephalopathy is associated with a low MDF.

2) Significant slowing of the MDF may precede the symptoms of encephalopathy by two days or more. (Had a record been taken on day 24, there would almost certainly have been a significant deterioration, thus allowing a two-day warning).
With immediate E.E.G analysis, action may be taken in time to prevent the development of overt encephalopathy.

3). Changes in AMPO and AMPS were reciprocally related to MDF. This association has been examined further, and is discussed fully in the next section. A graph showing the correlation of AMPO and MDF is shown in fig. 3.29.

4). On the whole there was a positive correlation of LR and MDF (fig. 4.3). However, this was not seen between days 15-25 where MDF was changing considerably, reflecting the clinical fluctuations, whereas LR was varying in an apparently random manner, at a continually abnormal level (for this patient). At day 33 MDF returned to the normal alpha range, whereas LR was still depressed, but improving. The MDF on day 35 showed an immediate fall consequent upon withdrawal of neomycin whereas LR continued to improve (0.18 day 33, 0.62 day 36).

These observations suggest a) LR tends to lag behind improvement and deterioration of MDF. b) LR is consequently not such a helpful index in the early detection of encephalopathy. c) Perhaps an E.E.G should not be considered completely normal on the basis of MDF, but only when LR has returned to the patient's optimum level.

5). Neomycin was used on three occasions in this patient and it is interesting to observe that the effect on the E.E.G is dose related i.e. the improvement on 6g is about twice as fast as on 3g. This suggests that the action of Neomycin may not only be on the intestinal flora and that it may be acting in a malabsorptive capacity (Jacobsen et al, 1960, Dobbins et al 1968).

6). The efficiency of Lactulose in preventing encephalopathy is shown. Lactulose is a synthetic disaccharide (beta-galactosido-fructose), which reaches the ileo caecal region unchanged because the specific enzyme necessary for its hydrolysis is not present in the human small intestine (Dahlquist & Gryboski, 1965).
The presence of Lactulose in the lower ileum and right colon favours the growth of saccharolytic organisms at the expense of proteolytic (Rottiers et al 1968). There is also the possibility that it may reduce the ionisation and absorption of ammonia in the colon (Summerskill et al, 1966; Elkington et al 1969).

Whilst on Lactulose the patient has taken a diet containing 10G more protein than when she was on Neomycin (3G/day). However, this increased protein tolerance was not unlimited, as evidenced by the relapse when she went home and added an unspecified amount of meat extracts to her diet. As a substitute for Neomycin, Lactulose has an advantage in being almost completely free of serious, undesirable side effects, and our experience, and that of Bircher et al (1966), suggests that it may be the preferable prophylactic against the occurrence of hepatic encephalopathy in the chronically susceptible case:

| TABLE 4A. |
|-----------------|-----------------|-----------------|
| Serum Bilirubin mg/100 ml | 22.2.68 | 25.5.69 | 31.10.69 |
| Serum alanine-aminotransferase Units/ml | 35. | 50. | 32. |
| Serum Alkaline Phosphatase (KA units/100 ml) | 28 | 30 | 60 |
| Serum Proteins: | | | |
| Total G/100 ml | 5.6 | 5.9 | 6.2 |
| Albumin G/100 ml | 2.3 | 3.1 | 3.0 |

For normal range of values - see Appendix 1a.

This 24 year old University student enjoyed good health until October 1968 when he required admission because of a massive haematemesis. The liver and spleen at that time were both found to be enlarged on palpation. No varices were demonstrated on barium swallow or on oesophagoscopy but a splenic venogram suggested the presence of a vascular malformation within the liver and spleen and laparoscopy revealed a large nodular liver. The exact diagnosis was, therefore, in some doubt at this time, but seemed to be either an arterio-venous malformation or hepato-lienal fibrosis associated with portal hypertension. It was, however, decided that some form of porto-systemic anastomosis should be performed at a later date to prevent further bleeding.

In the late convalescent phase of this admission, four EEGs were performed which gave values for MDF of around 8-50 c/s (not illustrated). The patient was re-admitted for further investigation with a view to surgery in July 1969. A coeliac angiogram was performed, which revealed gross dilatation of the splenic artery, but no evidence of a vascular malformation.

Presumably the gross dilatation of the splenic artery had suggested the vascular anomaly.

The first EEG at this time was within normal limits (Fig. 4.6 - day 1). Administration of morphine had virtually no effect on the MDF. ( -0.05 c/s)

At operation (day 7) the liver was found to be the site of marked post necrotic scarring and this was confirmed microscopically. A splenectomy and lienorenal anastomosis was performed, in preference to a porto-caval shunt for two reasons a) the spleen was large and the patient was conscious of it, b) the surgeon did not wish to risk any cerebral deterioration in a student of this age.
### Figure 4.6

Serial changes in MDF - L26 (Case 2)

Days 1 - 216
The EEG studies were resumed on the third post operative day (Day 10). There was a clear downward trend of the MDF falling to 7.49 c/s on Day 17. This represented a change of -1.40 c/s from the immediate pre-operative level but at no time in the post operative period was there any clinical evidence of encephalopathy. There were no biochemical changes to account for this (see Table 4.3) but the patient was receiving Chloral and Nepenthe for pain at night and Pentazocine ("Fortral" a non-opiate analgesic) during the day. It is, therefore, possible that the EEG changes were entirely due to the effect of these drugs. As mentioned above, morphine given once only prior to the operation had no effect. However, the Chloral and Nepenthe was administered every night until Day 18 and it could be argued that the drug was producing a cumulative effect. It is interesting that after the drug was withdrawn the MDF gradually began to rise, reaching a peak of 8.34 c/s on Day 24.

In order to evaluate the need for protein restriction, the patient was stressed for 5 days with a 100 gm protein diet. This was shortly followed by a gradual downward shift reaching 7.67 c/s on Day 27.

The patient resumed his university studies a few months later and since has kept very well. The final EEG (Day 216) taken seven months after the operation was very close to his optimum level.

During the seventh post operative month he attended for an ammonium acetate infusion test. The changes in MDF are shown in Table 3K. The shifts are all fairly small and are probably just outwith the control group range for this test.

DISCUSSION.

This case again shows a tendency for the MDF to fall after a shunt procedure. However, in this instance it seems fairly certain that the fall
was at least partly if not wholly due to opiates given for the relief of pain. Unfortunately, some of the value of the protein loading test was lost as only 100 gm instead of the usual 120 gm diet was administered. Despite this, it is probable that there was a mild latent encephalopathy which had been exposed by protein loading. The latter procedure would, therefore, appear to be at variance with the result of the morphine test. An objection to this statement is that one is comparing tests under a different milieu, i.e. pre- and post-operative. To test this hypothesis it would have been necessary to give morphine again during the post operative period. Unfortunately, this was not done.

The interpretation of all this is difficult but it is likely that if any encephalopathy was present it must indeed be mild.

**TABLE 4 B**

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For range of normal values see Appendix 1a
MR. D. R. - EEG NO.1103.

This 47 year old brewery worker first presented in 1949 because of recurrent haematemesis. At that time he was noted to have ascites, splenomegaly and oesophageal varices. He had been drinking up to 20 pints of beer per day for ten years at least. This history lead to a diagnosis of alcoholic cirrhosis. A splenectomy was performed and it was observed that the liver was coarsely cirrhotic. This was verified by hepatic biopsy. Following the operation the patient kept well until 1963, whereafter he required admission on several occasions either because of ascites or bleeding from oesophageal varices which had become very large.

He was re-admitted in August 1969 because of ascites and melaena. A few EEGs were obtained at that time, (not illustrated), which were all within the normal range. A morphine provocation test produced a shift of -0.26 c/s, and a protein loading test of 120 G/day for one week produced no change. There was a good clinical response to medical measures alone and the patient was allowed home. A recording subsequently taken as an out-patient showed a normal MDF (Fig. 4.7, day "0"). In November 1969 he was re-admitted because of a massive haematemesis. At this time there was a depression of the MDF to 7.48 c/s, some 2 c/s below his optimum level suggesting a mild encephalopathy. Although he was weak and quite anaemic (Haemoglobin 64%) there was, however, no clinical evidence of alteration of consciousness at this or at any other time.

There was a good clinical response to a bland low protein diet which was paralleled by the EEG changes. An ammonium acetate provocation test by the method already described was performed on Day 9, in which a dose of 544 mg was given (8mg/kg). Little change occurred for the first hour but after
Serial changes in MDF in L103 (Case 3) Days 0-58. The numbers in the right hand column refer to time in minutes following infusion of ammonium acetate.

\[ \text{O/P = Out Patient.} \]
MR DR.
EEG NO L103

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0/P WELL

HAEMATEMESIS
30 G-PROTEIN

PRE AMMUNIA
POST AMMUNIA
10' 20'
30' 40'
50' 60'
75' 90'
105' 120'

END AMMUNIA TEST

3/7 POST-OP
NO PROTEIN

30 G. PROTEIN

O/P WELL

MEAN DOMINANT FREQUENCIES >>>>
this there was a slight depression of MDF to 8.39 c/s representing a shift of -0.51 c/s.

Because of the history of repeated blood loss from oesophageal varices, further surgery was considered mandatory and a porta-caval shunt would have been the ideal procedure. However, at operation the portal vein was found unsuitable and the previous splenectomy precluded a lienorenal shunt. An oesophageal transection was therefore performed which was the only practical alternative.

Following surgery there was again no alteration of consciousness but a slight depression of MDF. The introduction of a 30G protein diet which was gradually increased to a normal ward diet (approximately 60G) was associated with a gradual improvement in the MDF. Shortly before discharge (Day 27) the MDF was within normal limits but approximately 1 c/s below the patient's optimum level. A further recording about four weeks after discharge showed a return to the patient's normal level.

BIOCHEMISTRY. For details see Table 4C

On admission the urea was elevated (98 mgms/100ml two days prior to the EEG study on Day 1). This had fallen to normal levels on Day 2. The serum potassium was slightly depressed on Days 1 - 8. It is therefore possible that the depression of the EEG on Days 1 - 3 was, in part, due to electrolyte and urea disturbance. However, this must be only a minor factor as the potassium was still abnormal on Day 8 when the EEG had returned almost to the patient's normal level. Following the operation on Day 13 the serum potassium fell slightly and the blood urea rose. (See Table 4C - Days 16 and 19). The urea fairly rapidly returned to normal limits possibly because of protein restriction but the serum potassium was still seen to be depressed throughout the post-operative period. These changes in general paralleled the EEG measurements.
DISCUSSION.

This patient is of interest because he has been exposed to several types of stress. 1) Morphine, protein loading and ammonium acetate. All these tests, with a possible exception of ammonium acetate were associated with very little EEG deterioration.

2) A large haematemesis and a fairly major operation (The operation does not, of course, increase the amount of nitrogenous material reaching the brain). Both these events were associated with a depression of MDF by as much as 2.0 c/s.

Are these two situations compatible? Undoubtedly the stresses in 2) above were considerably greater and were also accompanied by minor derangements of urea and electrolytes. If a normal person were exposed to stress in the second group would the MDF change and, if so, by how much? According to (Lehmann and Schmitz 1966) changes of -1.5 c/s may be seen in patients up to two weeks after major operations. There is no information in the literature on EEG analysis following a haematemesis in non-cirrhotic individuals. A study of EEG changes in patients with a haematemesis from, for example, a duodenal ulcer would be of considerable interest. One might postulate however, that the presence of anaemia and resultant cerebral hypoxia would cause a proportionate slowing of MDF, and that at least part of the slowing in this patient was due to hypoxia.

At all events, the patient was known to be well both from the clinical and EEG standpoint at three months after the operation.
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For range of normal values see Appendix 1a.
CASE 4.

MRS. C. C. — EEG NO. L27.

This 25 year old schoolteacher first presented at the age of 17 years, with an episode of jaundice which was subsequently shown on histological grounds to be chronic active hepatitis ("Lupoid Hepatitis"). Despite corticosteroid therapy she insidiously developed hepatic cirrhosis and oesophageal varices, from which she experienced a massive haematemesis in October 1968. This responded well to medical measures but the degree of haemorrhage suggested that surgery would eventually be necessary.

In December 1968 she was admitted for pre-operative assessment. Three EEG's performed shortly after admission, whilst receiving a 70G protein diet, showed a normal record, with a MDF ranging from 8.97 to 9.43 — see fig. 4.8. A downward shift (-0.75 c/s) was observed on Day 4 following a splenic venogram which had been carried out 20 hours previously. This change was considered to be the result of a pethidine injection which was used as premedication for venography. On Day 7 an injection of water (2 ml intramuscular) was given which was without effect on the EEG. However, the morphine test (Day 9) produced a shift of -0.70 c/s i.e. very similar to that following venography.

Following this she was placed on a 120G protein diet, which unfortunately could not be sustained for more than three days. (The date of operation had been brought forward to allow the patient home for Christmas). The MDF remained slow, probably because of the lag effect of morphine. (A similar lag effect was seen after the splenic venogram.) Whilst on the high protein intake, morphine was given again and produced a shift of -0.16 c/s.

An end-to-side porta-caval shunt was performed on Day 14.
Figure 4.8

Serial changes in MDF in L 27 (Case 4)
Days 1-461
MRS. CC
EEG NO L27

GRAPH OF DOMINANT FREQUENCIES

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70 G. PROTEIN
POST SPLENIC VENOGRAM
PRE WATER(IM)
POST WATER
PRE MORPHINE
POST MORPHINE
120 G. PROTEIN
PRE MORPHINE
POST MORPHINE
1/52 POST SHUNT
4/12 POST SHUNT
9/12 POST SHUNT
14/12 POST SHUNT

MEAN DOMINANT FREQUENCIES >>>
At operation the liver was found to be grossly irregular with visible fibrotic areas between nodules several centimetres across. The EEG's were resumed one week later. The MDF was transiently slowed to 6.13 c/s then gradually improved to approximately 7.8 c/s, but never reached the pre-operative optimum level. The diet initially consisted of 30G protein per day but was slowly increased to 70G/day, by Day 23. At no time did she show any clinical signs of encephalopathy.

Further records taken at 4, 9 and 14 months after the operation were all abnormal - see figure 4.8. During this time the patient was reviewed at approximately 3 monthly intervals and was found on all occasions to be in excellent health. It was also noted that her periods had returned, having been absent for several years previously. She was taking no drugs and had an unrestricted diet.

**Biochemistry.**

Prior to the porta-caval shunt no abnormality was detected in the standard liver function tests, urea or electrolytes - see Table 4D - Day 2. The plasma ammonia was normal on this day, but varied in the pre-operative period from 28 - 100 µgm/100 ml. It did not show any association with the EEG changes but the high value on Day 10 may have been related to the start of a high protein diet.

The plasma ammonia was determined at the same time as the EEG's for the morphine test. Before and after this the values for venous blood were 55 and 30 µgm/100 ml respectively - both within the normal range and not displaying any EEG correlation.

Following the operation, the chief alteration was a transient rise in alanine-aminotransferase and bilirubin - Day 17. These returned to normal
on Day 24. Although only a few biochemical data were available for the post-operative period they, in general, paralleled the EEG changes. There was a marked rise in plasma ammonia following the operation (Day 24) and this change is to be expected (Sherlock 1968).

**DRUGS.**

During the pre-operative period, the patient received Triclofos ('Tricloryl') - 1G nocte. After the operation "OMNOPON" was given for relief of pain on several occasions, but was discontinued three days prior to resumption of the EEG study.

**DISCUSSION.**

Do the pre-operative values suggest a latent encephalopathy? Although there was never any clinical suggestion of this, the post-operative EEG's, especially as an out-patient, were clearly indicative of a latent form, and one might have expected a prediction of this by one of the pre-operative tests. The response to the first morphine test (on 70G protein/day) was marked and might suggest a latent encephalopathy. What is disturbing is that the second morphine test produced only a trivial change and this occurred whilst on a high protein intake, when a heightened response might be expected (Laidlaw and Read 1961a). The variability of response to morphine tends to cast doubt upon the reliability of this test, as a measure of latent encephalopathy.

Ritchie & Shead (1962) demonstrated in dogs a diminished removal of ammonia by the liver following injection of morphine. However, Lods and Dupuy (1964) and Laidlaw et al (1961a) found no elevation of arterial ammonia levels three hours after injection of morphine (8 - 10 mg intramuscular).

The result on this patient is thus in agreement with those of Lods & Dupuy (1964) and Laidlaw et al (1961a) regarding ammonia changes after morphine.
Why there should be an apparent fall in venous plasma ammonia in this case is not clear, but it has been pointed out (Stahl 1963) that fluctuations in ammonia levels may be found if venous blood is used.

After the operation it is clear that the MDF never returns to its pre-operative level and, in fact, remains at about 3.0 c/s below the patient's optimum value. What is remarkable is the fact that for over a year the MDF remains virtually unchanged. According to Read, McCarthy et al (1968) the presence of an abnormal MDF after a porta-caval shunt may constitute an indication for neomycin therapy in order to prevent the development of neuro-psychiatric symptoms which are considered irreversible. It would be thought likely that after 1-4 months there might be some hint of mental impairment, although Read claims that 5 years may elapse before such symptoms become manifest. Perhaps those people whose employment is intellectually not demanding may show mental symptoms only until later on. However, this patient, a school-teacher, would surely be acutely sensitive to any hint of intellectual impairment. It might be postulated that this subject has achieved a delicate balance between the rates of accumulation and breakdown of nitrogenous material, but it does seem probable that this balance could easily be offset by some relatively minor influence.
**TABLE 4D.**

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For normal values see appendix 1b.
MRS. C. C. - EEG NO. L130.

This 60 year old housewife first presented in 1967 on account of haematemeses and ascites, which were found to be due to hepatic cirrhosis associated with portal hypertension and oesophageal varices. A splenectomy was performed at that time, following which she remained fairly well for a period of eight months, but then experienced further haematemeses. Investigations revealed that the bleeding was coming from oesophageal varices which were extremely large. Further surgery was again indicated but for technical reasons only an oesophageal transaction could be performed. Following this she experienced recurrent trouble from ascites but no further bleeding.

She was next admitted in November 1969 because of endogenous hepatic pre-coma and at this stage the EEG study began. The amplitude of her alpha and theta components was not found to be sufficiently large to enable any measurements to be obtained. However, an interesting clinical correlation was obtained using the slow wave index (SWI). In health this index should be less than 10. (Read 1967). At Day 1 (Fig. 4.9) the SWI was 26 units, which was mildly abnormal. 24 hours after this she was unrousable and admitted to hospital in pre-coma. The EEG taken on Day 3, i.e. 24 hours after admission, was highly abnormal. Following protein withdrawal and Neomycin administration (4G per day) the SWI returned sharply to near normal levels. The dose of Neomycin was then reduced and a 30 gm protein diet introduced at Day 6. The drug Lactulose was started at this time with a view to withdrawing the Neomycin completely. At Day 10 there was a transient deterioration, possibly resulting from the introduction of protein into the diet, but it could also have been due
Mrs CC. EEG No L130

Graph of Slow Wave Indices

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Figure 4.9

Serial changes in SWI - L130 (Case 5)

Days 1 - 29

O/p = Out patient
to a reduction of Neomycin to 2G/day. At Day 13 the Neomycin was stopped and following this there was an immediate, steadily progressive increase in the SWI to the very high level of 135 on Day 20. She was not noticed to be drowsy clinically until Day 20 but it is clear that this transition had been anticipated by the EEG some 3 days previously.

With the onset of clinical encephalopathy, protein was withdrawn and the patient improved. However, three days after the re-introduction of the 30G protein intake (whilst still receiving Lactulose) there was a further EEG deterioration, not accompanied by drowsiness or confusion. She was allowed home a few days after the final EEG on Day 29. Unfortunately the results of the SWI analysis were not available at that time and preventive measures were not undertaken. She continued to experience trouble with fluid retention despite intensive diuretic therapy and ultimately died three months after discharge.

**Biochemistry**

The details appear in Table 4E. On day 1 when she showed no clinical signs of encephalopathy all three liver function tests were abnormal - especially bilirubin - and so was the serum urea. However, on Day 3 when she was in pre-coma there was no additional biochemical deterioration - if anything a slight improvement. Between Days 3 and 8 the urea levels fell whilst the SWI improved from 100 to 16 units, thus displaying some correlation.

The EEG deterioration on Days 20 and 29 was associated with high urea values (118 and 114 mg/100 ml respectively) and on Day 29 the bilirubin was considerably elevated (9.5 mg/100 ml). Unfortunately, the liver function tests were not performed between Days 5 and 20. The potassium was low on day 8 (3.1 Meq/Litre), but there was no deterioration of SWI at this stage.

**Discussion**

It should be emphasised that measurements in the delta range can
only be regarded as approximate:— a) because of the presence of artefacts of similar frequency to cerebral activity, b) because of the relative inaccuracy of the EEG analysis in this range — (see RESULTS p 135).

Despite this the majority of the SWI estimates, in this case at least, appeared to be consistent with the clinical situation. The most obvious disparity was the presence at Day 1 of a modest elevation of SWI, only 24 hours prior to the onset of hepatic pre-coma. It might be argued that the SWI is insufficiently sensitive for reliable predictions to be made, but this is not born out by the subsequent changes in this case, e.g. DAYS 17 – 20). It is perhaps more likely that the encephalopathy prior to admission developed extremely rapidly and in turn emphasises the need for daily or even twice daily EEG monitoring of patients judged at risk with respect to encephalopathy.

It has been mentioned previously that in this Project approximately 19% of both normal and cirrhotic people have a desynchronised record i.e. no recognisable alpha or theta components on analysis. This case, therefore, suggests that some of these people may be suitable for analysis by measurement of the slow wave index. Although this index was measured for a period of approximately eight months, no striking correlations were obtained in other cases apart from this. However, these other patients were not fluctuating greatly and it is not possible to say that the slow wave index would not have been of value had there been more variation in their clinical state. This case is also encouraging because it suggests that the technique of obtaining the EEG was associated with few artefacts and that the computer analysis was sufficiently accurate for clinical correlations to be obtained.
TABLE 4E.

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<td>66</td>
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For range of normal values see Appendix 1a.
MISS H. R. - EEG NO. L163.

This patient, aged 69, who was known to have pernicious anaemia, presented in December 1969 with a 3 month history of malaise, anaemia and weight loss. At the age of 18 she had been jaundiced probably due to a mild attack of infectious hepatitis. On examination there was marked enlargement of both liver and spleen, and varices were readily demonstrated on a barium swallow. The liver function tests at that time were all abnormal (Table 4F) but there had never been any suggestion of encephalopathy. A provisional diagnosis of hepatic cirrhosis with portal hypertension, was made.

Figure 4.10 shows a MDF within normal limits (Day 1). The injection of 2 ml. water intra-muscularly had little effect at 3 hours (shift of -0.29 c/s). Ammonium acetate, in a dose of 500 mg. was administered on Day 8 by the technique described under "Materials and Methods." The effect on the EEG was followed for 3 hours. There were small downward shifts at 40 and 75 minutes of -0.42 c/s and -0.40 c/s respectively, but at 90 minutes the MDF suddenly changed in the opposite direction by +1.18 c/s (representing a shift of +0.78 c/s with respect to the pre-injection value). There were no side effects throughout the test, the cause of this jump was not apparent. On a separate occasion, the effect of 20 ml. 0.9% saline (intravenously) was observed for 2 hours. The technique was that described under "Materials and Methods." The largest downward shift was at 60 minutes (-0.34 c/s). The magnitude of this is similar to the downward shifts associated with ammonium acetate. There is a distinct impression of considerably less lability with the saline test compared with the ammonium acetate test.
Figure 4.10
Serial changes in MDF in L163 (Case 6).
The numbers in the right hand column
represent time in minutes, following the
infusion of either ammonium acetate or
0.9% sodium chloride.
MRS. HR
EEG NO L163

GRAPH OF DOMINANT FREQUENCIES

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PLOT: 70 G PROTEIN
PRE WATER (IM)
POST WATER
PRE AMMONIA
10
20
30
40
50
60
70
90
100
120
150
PRE SALINE
10
20
30
40
50
60
70
90
100
120
PRE MORMHINE
POST MORMHINE
1/52 POST SHUNT
30 G PROTEIN
50 G PROTEIN

MEAN DOMINANT FREQUENCIES >>>
Intramuscular morphine (6.5 mg on Day 13) resulted in a large shift (-1.05 c/s) which is the third largest shift observed in the current series.

Subsequently, it became clear especially from splenic venography, that extensive varices were present and that surgical intervention would be necessary to prevent haemorrhage. At operation the liver was found to be enlarged, firm and diffusely nodular, but there was no microscopic evidence of any malignancy. A hepatic biopsy confirmed the presence of cirrhosis which appeared to be in a late inactive phase. A splenectomy with lienorenal anastomosis was the preferred operation. It is stated (MacPherson 1965) that this procedure carries a smaller risk of subsequent encephalopathy than a porta-caval anastomosis, probably because the amount of blood shunted from the liver is less. The result of the morphine test was not available at the time of operation, but her age alone (Read et al 1961) indicated that the safer procedure (from the encephalopathy standpoint) should be undertaken.

After operation there was never any alteration of consciousness. The EEGs were resumed on the seventh post operative day and revealed a slight depression of MDF. The urea and potassium one day prior to this were normal as were the other electrolytes – see Table 4F – Day 25. A 30 gm protein diet was prescribed and was accompanied by a rise in the MDF to the patient's optimum level (Day 29). Over the course of the following week a slight deterioration in MDF was observed. However, only two recordings were performed at this time. The urea and potassium on Day 32 were normal and the liver function tests virtually unchanged from pre-operative levels (See Table 4F). On Day 36 the patient was in good health and, therefore, the dietary protein was increased to 50 G/day. The following day she was allowed home on the same protein intake.
DISCUSSION.

There is a striking difference in inter-record fluctuation if one compares the saline and ammonium acetate tests. As these tests are similar apart from the nature of the infused substance, it would appear that the greater fluctuation with ammonia is due to the drug and not the experiment. Unfortunately it is difficult to make any sense of the shifts following ammonia which appear to deteriorate by a small amount at 40 and 75 minutes, then rapidly improve at 90 minutes. The degree of MDF slowing is similar with both tests so that overall it is unlikely that the altered response to ammonia is of clinical significance, although the explanation of the difference is not at all forthcoming.

There is a striking difference between the results of intramuscular water and morphine. This should allow one to place more confidence in the validity of the morphine shift. As this is a large change it might be interpreted as presaging encephalopathy, and perhaps contra-indicating a portacaval shunt. Despite this there was never any clinical evidence of encephalopathy, either in the immediate post-operative period nor when reviewed as an out-patient some four months later, when she was reported in excellent health.

Prior to the patient's discharge there was a slight slowing of MDF (7.53 c/s) some 2 c/s below her optimum level. The cause of this was not clear. Throughout most of the EEG study, Nitrazepam, 10 mg nocte (Mogadon) was given. This is a mild hyprotic and was not thought to contribute to any of the EEG changes. Her diet had just been increased to 50 G/day and this may have been partly contributary, and presumably some of the slowing is due to the cerebral effects of the anastomosis. All this came to nothing, however, as she maintained good health as an out-patient on a 50G protein diet. Unfortunately, no further EEG's could be done following her discharge and it remains possible that the EEG persisted in the theta range, in a manner comparable to Case 4.
### TABLE 4F.

<table>
<thead>
<tr>
<th></th>
<th>Dec. 1969</th>
<th>DAY 6</th>
<th>DAY 25</th>
<th>DAY 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea mg/100 ml</td>
<td>—</td>
<td>26</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>Serum Potassium Meq/Litre</td>
<td>—</td>
<td>3.9</td>
<td>3.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Serum Bilirubin mg/100 ml</td>
<td>1.5</td>
<td>1.9</td>
<td>—</td>
<td>1.8</td>
</tr>
<tr>
<td>Serum alanine-aminotransferase Units/ml</td>
<td>46</td>
<td>60</td>
<td>—</td>
<td>38</td>
</tr>
<tr>
<td>Serum Alkaline Phosphatase</td>
<td>105</td>
<td>120</td>
<td>—</td>
<td>100</td>
</tr>
</tbody>
</table>

*For normal range of values see appendix la.*
CASE 7.

MRS. E. G. - EEG NO. L3.

This 39 year old housewife presented in 1950 with a haematemesis which was found to stem from oesophageal varices. A splenectomy was performed and operative biopsy of the liver was reported to show "early cirrhosis".

She kept well thereafter until 1968 when further haematemeses occurred. The bleeding was again found to stem from oesophageal varices and because medical measures failed to halt the blood loss, a gastric transection was performed. The liver was then noted to be finely nodular and a hepatic biopsy suggested micronodular cirrhosis. During the first post operative week she was noted to be slightly irrational and confused and it was thought she might have had a mild hepatic encephalopathy. Because the clinical changes were no worse than this and an EEG was not obtained at the time, she was placed in encephalopathy group B.

Three weeks after the gastric transection, the EEG study began (fig. 4.11). By clinical assessment she appeared well, and as a test of encephalopathy was given a 120 G protein diet over a period of 19 days. A fairly consistent fall of MDF was observed which gave an overall shift of ~1.6 c/s. Careful clinical observations were made daily, but no evidence of encephalopathy could be detected.

Five months later she was readmitted for assessment of abdominal pain which had developed recently. Subsequent investigation made it likely that the discomfort was related to post-operative adhesions. The initial values of MDF (Days 1 - 8, second admission) were all taken whilst receiving a 70G protein diet. They show a fairly steady value of approximately 8.4 c/s.
Figure 4.11
Serial changes in MDF in L3 (Case 7).
### Graph of Dominant Frequencies

<table>
<thead>
<tr>
<th>DAY</th>
<th>VALUE</th>
<th>PLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>8.481</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.991</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8.291</td>
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<td>5</td>
<td>7.911</td>
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<td>6</td>
<td>7.821</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>8.071</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8.111</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>8.231</td>
<td></td>
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<td>10</td>
<td>7.951</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>7.291</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7.471</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>8.431</td>
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<td>14</td>
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<tr>
<td>15</td>
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<td></td>
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<tr>
<td>16</td>
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<tr>
<td>17</td>
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</tr>
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<td>18</td>
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<td></td>
</tr>
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<td>19</td>
<td>8.841</td>
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<td>20</td>
<td>8.481</td>
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<td>21</td>
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<td>22</td>
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<td>23</td>
<td>7.931</td>
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</tr>
<tr>
<td>24</td>
<td>8.351</td>
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<tr>
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<td>8.281</td>
<td></td>
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<td>26</td>
<td>8.411</td>
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<td>27</td>
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<td>29</td>
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<td>30</td>
<td>7.631</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>7.581</td>
<td></td>
</tr>
</tbody>
</table>

- **6.0** 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5
- **Mean Dominant Frequencies »»»»**

- **5/12 Late** 7.0 & Protein
- **120 g. Protein**
- **PRE WATER (IM)**
- **POST WATER**
- **PRE MORPHINE**
- **POST MORPHINE**
- **130 g. Protein**

**ARCH AORTAGRAM**
The injection of water (intramuscularly) on Day 8 was associated with a change, three hours later, of -0.33 c/s. The morphine test resulted in a change of -0.83 c/s and a lag effect was in evidence for the ensuing two days.

On Day 10 (second admission) a 130G protein intake was commenced. Following this, there was a gradual fall to 7.50 c/s on the 15th day of the diet - an overall change of approximately -0.9 c/s. Careful clinical assessment again revealed no evidence of encephalopathy. A transient depression was noted on Day 17, which was almost certainly due to pethidine, premedication for an arch aortogram. (The latter procedure was performed to display the gastric blood supply as part of the investigation of her abdominal pain).

Unfortunately no record of menstruation was kept in this case.

**BIOCHEMISTRY.**

The data are shown in Table 4G. Normal levels of urea, potassium and alanine-aminotransferase were consistently obtained, whilst the bilirubin was mildly elevated on all but one occasion (Day 14). None of these results had any clinical or EEG correlation. The plasma ammonia was consistently elevated particularly after Day 10 (second admission), when the high protein intake commenced. This is an expected change.

**DRUGS.**

The only drugs administered during these studies were Nitrazepam ("Mogadon"), 10 mg nocte and Paracetamol, for the relief of pain.

**DISCUSSION.**

The salient features of this case are the large shifts after protein loading and the shift following morphine. The most reasonable interpretation of this is that latent encephalopathy is present and that the early suspicions
of this by clinical criteria were well founded. Considering the length of this patient's history (18 years) it is perhaps surprising that she does not show more clinical and/or EEG abnormality. The protein loading data imply that a 120G intake is not tolerable, but that a 70G diet is probably safe (see fig. 4.11, Days 1 - 8, second admission). This sort of information is clearly of great value to the clinician who usually has to find an optimum protein intake by empirical means.

A large shift occurred after morphine, but the validity of this finding is offset by the surprisingly large downward shift following water. It has been mentioned by Laidlaw & Read (1961) that less EEG stability is shown by patients with hepatic encephalopathy. In the absence of any provocative agent, it is probable that the change following water is due to a 'spontaneous' fluctuation. One cannot however attach significance to the morphine result, in view of this diurnal lability.

The clinical features suggested that further surgery would probably be needed. It is considered that gastric or oesophageal transection is only a "stop-gap" measure which affords only temporary protection from recurrent bleeding (Sherlock 1968). Do the EEG results suggest that a porta-caval shunt could be performed without producing frank encephalopathy? The disparity between the morphine and protein loading tests make it difficult to answer this question. Parsons-Smith et al (1957), considered that the development of a theta dominant EEG following protein loading (120G for one week) usually contra-indicated a porta-caval shunt. The MDF in this patient did, in fact, reach the theta range, but only after intervals of 16 and 13 Days, so that it would be wise to conclude that there is no definite contra-indication for such surgery in this case.
First admission.

<table>
<thead>
<tr>
<th>DAY NUMBER</th>
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<tbody>
<tr>
<td>Serum Urea mg/100 ml.</td>
<td>24</td>
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</tr>
<tr>
<td>&quot; Potassium Meq/litre</td>
<td>3.6</td>
<td>4.4</td>
</tr>
<tr>
<td>&quot; Bilirubin mg/100 ml</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>&quot; Alanine-aminotransferase units/ml</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>&quot; Alkaline Phosphatase KA units</td>
<td>65</td>
<td>72</td>
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</table>

Second admission.

<table>
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<tr>
<th>DAY NUMBER</th>
<th>2</th>
<th>6</th>
<th>10</th>
<th>14</th>
<th>16</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea mg/100 ml.</td>
<td>23</td>
<td>4.5</td>
<td>1.6</td>
<td>1.4</td>
<td>10</td>
<td>1.24</td>
</tr>
<tr>
<td>&quot; Potassium Meq/Litre</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot; Bilirubin mg/100 ml.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot; Alanine-aminotransferase Units/ml</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot; Alkaline Phosphatase KA units</td>
<td>-</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>Venous plasma ammonia µgm/100-1.</td>
<td>74</td>
<td>95</td>
<td>124</td>
<td>133</td>
<td>145</td>
<td>111</td>
</tr>
</tbody>
</table>

For normal range of values see Appendix 1b.
MR. G. H. - EEG NO. L48.

This 38 year old patient who worked as a mechanic in the Royal Navy and consequently travelled extensively, was well until 4 years ago. Over this period he suffered from intermittent bouts of right hypochondrial pain associated with fever, malaise and weight loss. Following extensive investigations there was no evidence at any time of oesophageal varices or of an encephalopathy. A wedge biopsy of the liver taken 2 years previously had revealed heavy portal tract inflammation and areas of focal necrosis. No convincing explanation could be offered for these changes. He had been suspected on various occasions of amoebic hepatitis, chronic active hepatitis, Hodgkin's disease and tuberculosis, but all appropriate tests were non-confirmatory. A dramatic response was obtained with steroid therapy and as soon as the dose was reduced he relapsed. At the time of writing a diagnosis of fasciola hepatitis was being considered but this awaited proof.

He was of interest from the EEG point of view because the venous plasma ammonia levels were persistently high. The levels ranged from 224 - 462 µg/ml. The other liver function tests appear in Table 4H.

The EEG changes over a period of ten days are shown in fig. 4.12. Throughout the EEG study he was receiving Prednisone 10 mg per day. The plasma ammonia obtained on Day 7 was grossly elevated (370 µg/ml), yet this was accompanied by no EEG or clinical abnormality.

Cohn & Castell (1966) emphasise the importance of chronic hyperammonaemia in the production of EEG changes in cirrhosis and yet this case, with a persistently severe hyperammonaemia is displaying no adverse EEG phenomena. Admittedly this patient does not have cirrhosis, but the data
MR GH
EEG NO L48

GRAPH OF DOMINANT FREQUENCIES

<table>
<thead>
<tr>
<th>DAY</th>
<th>VALUE</th>
<th>PLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.96</td>
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</tr>
<tr>
<td>3</td>
<td>9.40</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>9.41</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>9.03</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>9.60</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>9.51</td>
<td>X</td>
</tr>
<tr>
<td>9</td>
<td>9.20</td>
<td>X</td>
</tr>
<tr>
<td>10</td>
<td>9.46</td>
<td>X</td>
</tr>
</tbody>
</table>

Figure 4.12

Serial changes in MDF - L48 (Case 8)

Days 1 - 10
lend some support to the hypothesis that elevated ammonia levels are not responsible per se in the production of hepatic encephalopathy.

**TABLE 4H.**

<table>
<thead>
<tr>
<th></th>
<th>DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Serum Urea mg/100 ml</td>
<td>16</td>
</tr>
<tr>
<td>Serum Potassium Meq/Litre</td>
<td>3.8</td>
</tr>
<tr>
<td>Serum Bilirubin mg/100 ml</td>
<td>0.7</td>
</tr>
<tr>
<td>Serum alanine-aminotransferase Units/ml</td>
<td>25</td>
</tr>
<tr>
<td>Serum Alkaline phosphatase KA Units.</td>
<td>520</td>
</tr>
<tr>
<td>Venous plasma ammonia µgm/100 ml.</td>
<td>-</td>
</tr>
</tbody>
</table>

For normal range of values see appendix 1b.
These last two cases are both instances of shunt procedures carried out on children. No previous description of EEG frequency analysis in this situation has hitherto been described.

CASE 9.

MISS L. H. L.23.

This 11 year old school girl was in good health until the age of 6, when she experienced a severe attack of infectious hepatitis. From this she apparently made a satisfactory recovery until the age of 8, when she suffered repeated severe haematemeses. At that time she was found to have marked enlargement of both liver and spleen with considerable diminution of liver function, and further investigation demonstrated large oesophageal varices. Surgical treatment was clearly needed and to this end a splenectomy and lienorenal anastomosis was performed. Operative biopsy revealed micronodular cirrhosis.

The EEG study was begun two weeks after operation. At this time she was withdrawn and tearful and took several days to accept even the application of the EEG electrodes without a great deal of protest. The first reading was quite abnormal - fig. 4.13, Day 1. At this time she was receiving a 60G protein, high calorie intake, together with a diuretic and potassium supplements. Ampicillin (1G daily) was given until Day 14, to sterilise the bowel. She was not confused or drowsy at this stage, but as mentioned above, her behaviour was unusual and this could have been due to hepatic encephalopathy. The MDF improved up to Day 3 but then deteriorated, reaching 3.0 c/s on Day 9. This change was not accompanied by any
Serial changes in MDF in L23 (Case 9) Days 1-119. The numbers in the right hand column represent venous plasma ammonia values in µgm/100ml.
Graph of Dominant Frequencies

Day | Value | Plot
--- | --- | ---
1   | 3.00:| 2752 Post Shunt 60 G. Protein 160
2   | 3.99:| 167
3   | 6.63:| 235
4   | 4.99:| 70 G. Protein 332
5   | 4.50:| 337
6   | 3.94:| HOME FREE PROTEIN 220
7   | 3.57:| 153
8   | 3.00:| 112
9   | 4.57:| 130
10  | 4.34:| 196
11  | 5.45:| 318
12  | 7.00:| 256
13  | 7.13:| 191
14  | 6.65:| PRE MORPHINE
15  | 6.50:| POST MORPHINE
16  | 7.88:| 243
17  | 8.54:| 110
18  | 7.73:| 112
19  | 9.19:| 337
20  | 8.47:| 337
21  | 6.33:| 337
22  | 5.80:| 337
23  | 8.53:| 337
24  | 7.44:| 337
25  | 7.97:| 337
26  | 6.71:| 337
worsening of her mental state and, in fact, the surgeon in charge (who was not aware of the EEG changes) increased the protein intake by 10g/day. Following this, the record improved to 7.0 c/s (Day 14) when she was allowed home. Her treatment then consisted of a diuretic and potassium supplements, with an unrestricted diet. At approximately monthly intervals she was seen as an out-patient. The readings showed a gradual improvement to 9.19 c/s (Day 63), followed by a fluctuant downward trend, but no signs of encephalopathy were detected by clinical assessment. A morphine test (5.4 mg intramuscularly) was performed on Day 119. The injection made her vomit and she became pale and drowsy. There was a fall in MDF of -1.26 c/s, the largest change seen in this project.

She had not reached the menarche during the EEG study.

After this the EEG studies were discontinued, but 10 months later she experienced a further haematemesis, resulting in a hepatic coma which proved fatal.

**BIOCHEMISTRY.**

The biochemical changes are shown in Table 4 i up to Day 105. Additional plasma ammonia values appear in the right-hand column of figure 4.13.

Where the EEG is severely abnormal at Day 1 only a mild elevation of alkaline phosphatase and plasma ammonia is noted. The latter is always raised after porto-systemic anastomoses. (Sherlock 1968). The records are improved on Day 3 but no significant biochemical change is seen on the following day (see Table 4 i). Days 4 - 9 are associated with a gradual EEG deterioration which is accompanied by worsening of plasma ammonia, potassium, alkaline phosphatase and alanine-aminotransferase. The ensuing EEG
improvement (Days 10 - 14) appears to correlate with a falling ammonia, but
the other values seem to fluctuate in a manner unrelated to the EEG changes.
The ammonia values as an out-patient (Days 21 - 119) do not match the EEG
changes very closely, - see graph.

Overall there appears to be a crude correlation of EEG with plasma
ammonia but not with the remaining biochemistry.

DISCUSSION.

This case is of particular interest. Because of the marked slowing
one would have expected clinical evidence of encephalopathy at Days 1 and 9;
whilst there was a fairly strong suspicion of this in the first instance,
there was none in the second. A possible explanation is that the EEG
rapidly improved after transiently reaching a low value on Day 9, and there
was not enough time for overt encephalopathy to develop. Nevertheless, this
disparity seems to be at variance with comparable adult data illustrated here.

The values obtained as an out-patient showed considerable variation
especially Days 83 - 105. There was no good clinical or biochemical
explanation for this and one must assume it was due to 'spontaneous' fluctuation
a phenomenon stated to be more common in children (Pond 1963) as well as those
with hepatic encephalopathy (Laidlaw and Read 1961 b).

The data obtained on Days 83, 98, and 112 would all be considered
abnormal for a child of this age, if one accepts the criteria of Lindsley (1939).
The majority of children aged 10 or more had dominant rhythms greater than
8 c/s according to him. There was no explanation for the EEG abnormalities
at this stage but they appeared to indicate a latent encephalopathy and
perhaps suggested that the patient was at risk.

The morphine test revealed a large shift. (This result was not
included in the analysed morphine data). Were this patient an adult it should imply latent encephalopathy; however, there is no literature on this subject, nor could any data be found regarding diurnal variation of MDF in children of this age.

Hence the interpretation of this result must be cautious. Nevertheless, the fact that the EEG was severely abnormal on two occasions makes it very likely that encephalopathy was present and that the morphine result is valid. This contention is further reinforced by the fact that 10 months afterwards she lapsed into terminal hepatic coma.
### TABLE 41.

<table>
<thead>
<tr>
<th>DAY NUMBER</th>
<th>1</th>
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<th>7</th>
<th>11</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Urea mg/100 ml.</td>
<td>24</td>
<td>14</td>
<td>26</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>&quot; Potassium Meq/Litre</td>
<td>4.4</td>
<td>4.2</td>
<td>2.8</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>&quot; Bilirubin mg/100 ml</td>
<td>0.9</td>
<td>-</td>
<td>0.9</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>&quot; Alanine-aminotransferase units/ml</td>
<td>13</td>
<td>-</td>
<td>24</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>&quot; Alkaline Phosphatase</td>
<td>92</td>
<td>-</td>
<td>114</td>
<td>121</td>
<td>117</td>
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<tr>
<td>&quot; KA units.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous plasma ammonia µgm/100 ml</td>
<td>160</td>
<td>167</td>
<td>235</td>
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<td>-</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY NUMBER</th>
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<th>28</th>
<th>56</th>
<th>83</th>
<th>98</th>
<th>105</th>
</tr>
</thead>
<tbody>
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<td>18</td>
<td>18</td>
<td>27</td>
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<td>22</td>
<td>16</td>
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<td>&quot; Potassium Meq/Litre</td>
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<td>4.5</td>
<td>4.3</td>
</tr>
<tr>
<td>&quot; Bilirubin mg/100 ml</td>
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<td>1.2</td>
<td>1.3</td>
<td>1.4</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>&quot; Alanine-aminotransferase units/ml</td>
<td>29</td>
<td>44</td>
<td>-</td>
<td>35</td>
<td>51</td>
<td>17</td>
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<td>&quot; Alkaline Phosphatase</td>
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<td>167</td>
<td>-</td>
<td>203</td>
<td>164</td>
<td>223</td>
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</tr>
<tr>
<td>Venous plasma ammonia µgm/100 ml</td>
<td>220</td>
<td>153</td>
<td>318</td>
<td>191</td>
<td>-</td>
<td>243</td>
</tr>
</tbody>
</table>

For range of normal values see Appendix 1b
This 7 year old schoolboy developed a staphylococcal peritonitis secondary to ruptured multiple staphylococcal abscesses of his liver, a few weeks after birth. The infection probably originated from umbilical sepsis. As a result of his liver infection he developed portal vein thrombosis which at the age of 4 lead to repeated gross haemorrhage from oesophageal and gastric varices. A porta-caval shunt was performed at this time and biopsy of the liver at operation revealed no evidence of cirrhosis.

At the age of 6, further haematemeses developed. It was subsequently shown that varices had reformed because the anastomosis thrombosed, leading to a further rise of portal venous pressure. An attempt at re-establishing the shunt was made which was unsuccessful. Nevertheless, he remained untroubled by blood loss until one year afterwards. Further haematemeses were then experienced, which clearly required surgical intervention. The only procedure possible was a lienorenal anastomosis.

The EEG study commenced 3 days after his latest admission, mentioned above. He was pale, drowsy and irritable at this time and was receiving a 10G protein intake, with Neomycin 2G daily. The EEG was markedly abnormal—see fig. 4.14. The haemoglobin was 6.16/100 ml and clearly he was suffering from overt hepatic encephalopathy. His clinical condition did not allow frequent removal from the ward and no portable apparatus was then available, hence the 12 day gap in the recordings. Upon resumption of the study he was very alert and had lost all clinical signs of encephalopathy. The neomycin had been discontinued and the protein intake increased to 20G/day. His MDF was
### Graph of Dominant Frequencies

<table>
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<td>3.001*</td>
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</tr>
<tr>
<td>16</td>
<td>7.781</td>
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</tr>
<tr>
<td>17</td>
<td>7.821</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>7.781</td>
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<td>7.781</td>
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<td>7.821</td>
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<td>20</td>
<td>7.941</td>
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<tr>
<td>21</td>
<td>7.791</td>
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<tr>
<td>23</td>
<td>7.941</td>
<td></td>
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<tr>
<td>24</td>
<td>8.021</td>
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<td>27</td>
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<td>28</td>
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<td>32</td>
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</tr>
<tr>
<td>33</td>
<td>7.031</td>
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<td>34</td>
<td>7.881</td>
<td></td>
</tr>
<tr>
<td>145</td>
<td>7.541</td>
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</tr>
</tbody>
</table>

Figure 4.14

Serial changes in MDF - L32 (Case 10)

Days 1 - 145
within normal limits for a person of this age (Lindsley 1939), thus confirming the clinical impression. A morphine provocation test was intended on Day 17; however, due to an oversight, Heroin (3.2 mg) was given. He therefore received about twice as much as desired had he received a body weight dose. Despite this, the EEG was virtually unaffected (MDF = 0.04 c/s) and remained thus for the ensuing 6 days. As the result was surprising the test was repeated and, although he became sick and felt unwell, there was no slowing of MDF (+0.33 c/s).

The recordings were resumed two days after the shunt operation. This early start was made possible by the availability of portable apparatus. During this period he frequently received injections of Heroin for the relief of pain, but these were discontinued on Day 29. Despite a slight slowing in the early post-operative period (Day 27) the MDF returned fairly rapidly to near pre-operative levels. Simultaneously, the dietary protein allowance was increased without any clinical evidence of encephalopathy. A further analysis four months later confirmed his clinical well being.

BIOCHEMISTRY

The biochemistry is shown in Table 4J.

At the commencement of the EEG study (Day 1) where he was showing definite signs of encephalopathy the biochemistry was disturbed little, apart from the mildly elevated ammonia and urea levels. Thereafter, with clinical improvement, no consistent biochemical change was observed, although more data would have been desirable. After the operation the only definite alteration was a slight fall in serum potassium (Day 30) which was not accompanied by a slowing of MDF.

The blood ammonia was not obtained again until Day 240 when it was 208 µgm/100 ml, well over twice the pre-operative levels.
DISCUSSION.

A good EEG-clinical correlation was obtained in this case and considerably less 'spontaneous' EEG fluctuation was observed in comparison with the previous child - Case 9.

It should be stressed that there was no pathological evidence of hepatic cirrhosis in this case. However, we are not concerned with the diagnosis of cirrhosis per se, but with the detection of encephalopathy consequent upon hepatic dysfunction from virtually any cause.

The interpretation of the heroin results presents difficulty. Clearly the EEG was unaffected on both occasions, yet the child had only recently recovered from an episode of encephalopathy. It is unlikely that the behaviour of a child to an opiate should be very different from that of an adult. In the below 30 years control group of the present work there was an impression (not statistically substantiated) of greater change in MDF following morphine. One might therefore expect an even greater change in children. It could be argued, as Zieve (1966) mentions, that all patients with hepatic dysfunction can lapse into coma if sufficiently provoked, and certainly this patient was exposed to extremely severe blood loss prior to the lienorenal shunt. Thus a previous episode of encephalopathy may not necessarily mean that there will subsequently be marked slowing of MDF after morphine. This leads to a possibility that morphine detects present chronic encephalopathy and not past acute forms. This point will be expanded in the 'DISCUSSION' section.

It is pertinent that in this case the patient was known to be in good health, nine months after the operation and in the prognostic sense the result of the heroin test was correct.
After the operation an MDF slowing (as in the adult group) was observed which gradually improved. Although this patient showed no change to a single dose of heroin, it is probable that the repeated administration of this drug in part accounted for the MDF slowing.

As there were no clinical or EEG signs of encephalopathy after Day 31 it might have been possible to allow an increased protein intake. As an outpatient he received an unrestricted diet and this was being tolerated well (Day 145).

There are three points of interest regarding the biochemistry:

a) during the period of encephalopathy the liver function tests were all normal apart from the plasma ammonia. This form of EEG-clinical disparity is a well recognised phenomenon (Zieve 1966, Sherlock 1968).

b) The low potassium on Day 30 was not associated with a slowing of MDF as described by Read, Laidlaw et al (1959). Perhaps the potassium level here was insufficiently low to affect the EEG.

c) The high plasma ammonia post operatively (Day 240) seems at variance with the patient's clinical well being. It is probable, however, that this change in ammonia levels is a manifestation of increased shunting of nitrogenous material, rather than an indication of hepatic dysfunction.
### TABLE 4J.

<table>
<thead>
<tr>
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<th>DAY NUMBER.</th>
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<td>1</td>
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<td>26</td>
<td>27</td>
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<tr>
<td>Serum Urea mg/100 ml.</td>
<td>54</td>
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<td>-</td>
<td>11</td>
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<tr>
<td>&quot; Potassium Meq/Litre.</td>
<td>4.1</td>
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<td>-</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>&quot; Bilirubin mg/100 ml.</td>
<td>0.3</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot; Alanine-aminotransferase Units/ml.</td>
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<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot; Alkaline Phosphatase</td>
<td>33</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KA Units.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Venous plasma ammonia</td>
<td>93</td>
<td>52</td>
<td>82</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(µg/m/100 ml)

For normal range of values see Appendix 1b.
DISCUSSION.
DISCUSSION.

Before embarking upon a discussion of the results of this work, it would be pertinent to comment upon the use of the term 'encephalopathy'. By this the author means simply 'disturbed brain function'. Where disturbed brain function is found by various means to be due to liver dysfunction this is a hepatic encephalopathy. Where encephalopathy is detectable by clinical examination, it is usual to call this 'overt encephalopathy' and where encephalopathy is thought to be present on the basis of E.E.G. examinations this may be called a 'latent encephalopathy'. Often it is unnecessary to specify 'overt' or 'latent' as the context of the sentence usually makes it apparent which type is meant.

Laidlaw & Read (1961b) defined encephalopathy with a particular emphasis i.e. "not the acute episode of delirium but the underlying state which makes certain patients liable to develop such episodes". This is a somewhat unsatisfactory definition because a) most clinicians would refer to an episode of hepatic coma (or pre-coma) as an encephalopathy b) what is the 'underlying state' - a 'sensitised' brain or the presence of a collateral circulation? Because of these difficulties the very wide definition mentioned above is preferred.

It was the basic aim of the current work to define the value of automatic frequency analysis in hepatic encephalopathy. The technique was hitherto untried and it first became necessary to measure its accuracy. As the assessment of encephalopathy depends on measurement of small fluctuations in the E.E.G. rhythms over the course of hours or days it was also important to assess the degree of change that may be found with the technique in normal
people, hence the measurements of day-to-day variation and drug effects. Once
the behaviour of normal people in circumstances similar to cirrhotic patients
is known, it is then possible to assess what is abnormal in those patients.
Such lines of thought dictated the structure of this section:

A. Subject material, recording and analytical techniques.
B. E.E.G. variance.
C. 'Drug trial' (in normal subjects).
D. Tests of hepatic encephalopathy.
E. Case histories.
F. Concluding remarks.

A. SUBJECT MATERIAL.

Control Group. This group as a whole was somewhat unbalanced with regard
to age and sex. Although there was a satisfactory age range (18 - 61 years)
the mean was weighted towards the younger ages (34 years). Males
outnumbered females in the Morphine test (15:7), spontaneous variation
test (15 : 11) and Ammonium Acetate test (11 : 6) but were equally matched
for the 'drug trial' (6 : 6).

None of the 8 patients with duodenal ulceration had evidence of
a hepatic lesion as judged by clinical and biochemical methods. They all
had normal routine E.E.G's as judged by careful visual inspection by the
author and Dr. H. R. A. Townsend. At an advanced stage in the project it
was discovered that E.E.G changes had been described in cases of duodenal
ulceration (Rubin 1942, Moses 1946; and Yagamata et al, 1969). These
authors all commented upon a high incidence of alpha activity and increased
alpha amplitude in patients with duodenal ulceration. No abnormality in
terms of frequency or abnormal waves was detected. These changes were
thought to be an expression of the 'driving' personality associated with this disease. The possible errors introduced by inclusion of the duodenal ulcer subjects in the control group is discussed in conjunction with the morphine results (p.292). These subjects did not partake in any examination other than the morphine test.

The control group as a whole cannot be assumed to be representative of a normal population. They were 'selected' by the act of volunteering, sometimes for financial reward, and it may be argued that the personality of a volunteer may be associated with a particular type of E.E.G. Also 19% of records (whether control or cirrhotic) had to be rejected because of a low voltage trace. Hence those with higher alpha amplitudes would automatically be included in the study, and it is possible that a particular class of person was being selected whose reaction to drugs etc. may not be representative of a larger unselected population. However, this was unavoidable and applied equally to hepatic and control groups.

**Hepatic Group.** The age range for the hepatic group as a whole was considerable (7 - 71 years) with a mean age of 50 years. Again males outnumbered females (33 : 15) but this discrepancy was only significant in the morphine test (23 : 10). In most of the other tests involving the hepatic group the sexes were fairly well balanced, although the mean age was always higher than in the control group.

The most common variety of cirrhosis was the alcoholic (24 cases) followed by cryptogenic type (12 cases), with only a few examples of post-hepatitis cirrhosis and chronic active hepatitis.

The excess of alcoholic cirrhosis may be accounted for by the high incidence of male subjects, in whom this variety of cirrhosis is more common. (Summerskill et al, 1960).
It is accepted that unless biopsy evidence is obtained, one cannot be certain that cirrhosis is present - as this is a pathological diagnosis. Such a criticism is, therefore, applicable to 33% of the hepatic group. However stringent criteria were adopted before the diagnosis of cirrhosis was accepted in the absence of biopsy proof and in no case was it ever doubted that cirrhosis was present. In some cases, biopsy was avoided because a confident clinical diagnosis had already been made, or because the procedure might have been risky due to impaired clotting mechanisms or ascites. Furthermore, we were more concerned with the application of E.E.G. techniques in the diagnosis of hepatic encephalopathy and not with the diagnosis of cirrhosis per se.

Apart from problems in diagnosis of cirrhosis it may also be difficult to decide whether a patient has suffered a period of encephalopathy. There was no doubt with the Group C patients who had all been overtly comatose or in precoma. A complex situation especially occurred with alcoholic cirrhotics in whom the distinction of withdrawal symptoms from the early phases of hepatic coma may be impossible. This situation arose particularly with L77 who had a severe haematemesis necessitating hospital admission, which resulted in an abrupt termination of his high alcohol intake. Thereafter he became delirious and needed high doses of chlorpromazine, whereupon he became drowsy and confused. This sort of difficulty was noted by Summerskill et al. (1960) who commented that "the personality changes of a Korsakoff syndrome and other disorders incident to alcoholism" may be difficult to distinguish from hepatic pre-coma.

If a patient had experienced an episode of coma, it is likely that at the time of E.E.G. testing he or she still had encephalopathy (by the author's definition) but this may not always be true. The liver has powers of regeneration and might recover sufficiently to reverse an encephalopathy.
For example, patient L120 had an episode of hepatic coma 8 years previously and was accordingly classed in Group C. Her routine E.E.G record and reaction to ammonium acetate appeared to be normal, but whether encephalopathy was present, at the time of the E.E.G tests is a matter for conjecture. Conversely some patients with no history of encephalopathy may lapse into coma the next day if sufficiently provoked (Zieve 1966). Does this mean that encephalopathy was already present in such patients and does it mean that the encephalopathy will persist following recovery from coma?

In order to make a valid assessment of a test designed to detect latent encephalopathy, it is clearly desirable to examine homogeneous groups who at the time of testing are known to have either no trace of, or definite evidence of encephalopathy. As this is difficult, it is necessary to rely on a classification on the basis of the history, which is at best an approximate guide. It seems certain that both groups A and C were non-homogeneous. It would therefore be reasonable to expect considerable overlap in the responses of these groups to provocative tests.

It was equally difficult to be certain about the absence of varices. It was only possible to say 'none were detected' - usually on the basis of a barium swallow and/or oesophagoscopy, but a collateral circulation may exist either via intra-hepatic shunts or via mesenteric anastomoses.

Of patients shown to have varices by autopsy or splenoportography, investigation by barium meal or oesophagoscopy may reveal their presence in approximately three quarters of cases (Atkinson et al, 1955); an even lower estimate (40%) was given by Conn (1967). If varices are used as a criterion for grouping of patients, there is bound to be some overlap of results due to misclassification of individuals with undiagnosed varices.
Recording Technique.

The choice of recording position was determined arbitrarily. The differences in electrical phenomena obtained by our temporo-occipital lead and those obtained by Laidlaw & Read's (1961b) more posterior montage must indeed be minor. B. Magillivray (personal communication) used a parieto-occipital montage and considered that this detected less muscle activity and that it was more sensitive to the frontal slow waves of early encephalopathy. Muscle artefact was rarely a problem with our montage, and these nuances of positioning probably were not important.

Stick-on electrodes were definitely superior to the conventional cap and pad system. The electrodes were frequently left in situ for several days without any adverse effect on recording quality, and they gave a more artefact and trouble-free tracing than pads. Furthermore, a rubber cap becomes painful when worn for over one hour, and as many of our experiments involved intermittent recordings for well over this period, the stick-on electrodes were clearly superior.

The choice of visual task and epoch length was again arbitrary. The main object during the recording was to keep the subject comfortably, but not excessively alert, whilst maintaining the duration of each epoch as short as possible without affecting the resolution of the analysis. The six 20 second epochs used appeared to give satisfactory readings - see Results section.

It was considered that the procedure did in fact achieve a constant state of alertness and this contention was supported by the lack of any difference of variance with each visual task. The only exceptions were related to those experiments involving recording at 10 minute intervals (ammonium acetate in controls and cirrhotics and saline or dextrose in cirrhotics). Because of the
repetitive nature of the tasks, an element of inattention probably occurred in some cases after 30 - 60 minutes recording.

Laidlaw & Read (1961b) used as an alerting device, an array of illuminated lights, whereas we used beads mounted on pegboard. The virtue of our technique rested in the simplicity and cheapness of construction, and in the ease of transport. Recordings could be performed at the patients' bedside with the minimum of trouble and in conditions similar to those obtained in the E.E.G. laboratory.

Computer Programs.

The data presented in RESULTS regarding the accuracy of analysis suggest that the major errors occur from the use of a short sample and that the errors are greater in the estimation of slower frequencies. The selection of epoch length is most difficult. The longer the epoch the more accurate is the averaging process, assuming that the tracing is constant with respect to frequency and amplitude. The latter case unfortunately rarely holds true. There is often a transient acceleration of alpha frequency just after eye closure (Storm Van Leuwen et al, 1958) about 30 seconds after this there may well be some fluctuations in frequency especially if, as in our work, no mental task is given when the eyes are shut. Accordingly, the first 5 seconds after eye closure were skipped and only the following 20 seconds analysed. Clearly a short epoch length will result in a poor estimate of slow waves, i.e. in a 20 second epoch consisting of 2 c/s activity the program can only make an average of 40 waves, whereas a similar epoch consisting of 10 c/s activity will involve 200 such waves. The analysis was, however, accurate in the range where it was most needed; visual inspection will often suffice in the analysis of delta dominant tracings.
A further effect which must be allowed for was the increasing attenuation of frequencies over 10 c/s due to the ADC filter, whereas only minor errors may be attributed to the Fourier Transform.

It should be stressed that in assessing the accuracy of E.E.G analysis an artificial signal was (of necessity) used. This was a filtered random noise signal and was arranged to be similar to a true E.E.G. signal.

Despite these restrictions the final estimate of MDF appeared reasonably accurate within the tested range (8.0 - 9.8 c/s). Probably greater errors are to be expected at frequencies slower than this. Less confidence may be placed in the log reactivity index - see fig. 3.2a.

SPECTE PUT had a running time of 18 minutes and the times for HEPLAN and DAYRUN were about 5 minutes, so that an estimate of MDF could be obtained in about half an hour - allowing for loading and printing up. Despite this, it was found that the computer was occupied for several hours per day, doing nothing but E.E.G. analysis and clearly a faster machine would be necessary in order to carry out this sort of work as a routine clinical service.

No completely foolproof method of rejecting low voltage records was found. Initially a program was used which scanned for the highest mean amplitude between specified band-widths - say 3 to 12 c/s. Sometimes a 3 c/s peak was mistakenly selected where there was an obvious alpha peak, although of lower mean amplitude. This difficulty could be avoided by scanning from 4 - 12 c/s, but even so this was time consuming, and difficulties were obtained with 'double dominant' records. The method of searching for peaks and troughs as described in MATERIALS AND METHODS was found to be the most satisfactory, and only seldom was it necessary to adjust the scanning limits. One problem that was not overcome related to the appearance of intermittent theta peaks.
in addition to an alpha peak. Thus the program would occasionally select a theta peak where all previous analyses on the subject in question had shown an alpha peak. This situation occurred in the 20-30 year age group and was thought to be due to excessive blocking of the alpha rhythm either by anxiety or because of sustained mental activity following the counting task.

All graphs had to be plotted on a teleprinter so that construction of smooth curves was difficult. Information regarding diet etc. on the day-to-day plots could have been incorporated into HEPLAN but this would have made loading of the program complex. It was found to be more convenient to add this information later, using a visual display unit.

The most valuable index was MDF and from this all other indices except SWI are derived. Because of this, most emphasis has been laid on the changes in MDF, although measurements of AMPO or AMPS would probably be just as valid, as these were inversely related to MDF (see below).

Other observations.

All the E.E.G. tracings were examined by visual inspection. Whilst a change of less than 1 c/s was difficult to detect by this means, changes greater than this were usually obvious. In this we were in agreement with the observations of Gibbs & Gibbs (1947).

The object of employing 5 indices was partly to obviate the need of visual examination. Apart from changes of frequency, other variations such as the degree of blocking, or alterations of amplitude are all detected by LR, AMPO and AMPS. The SWI gave a measure of slow activity although it is accepted that it usually erred on the high side because of eye movement and other artefacts. Transient phenomena, of course, cannot be assessed accurately
by our method of automatic analysis. However, triphasic waves and intermittent delta activity were not seen often. As these phenomena usually appear intermittently and frontally, then continuously and posteriorly, errors from these transients were probably few with the posteriorly situated montage used by us.

A significant correlation of MDF with both AMPO and AMPS was found and the association of MDF with AMPO in L68 is illustrated in fig. 3.29. This correlation was found in 3 other hepatic subjects whose indices were examined statistically and it is probable that this association is generally correct. There is quite a large scatter of values in L68, especially at frequencies slower than 6.0 c/s. In this range, however, the accuracy of analysis diminishes (q.v.). It was not possible to determine on the basis of the current work whether AMPO or AMPS can ever change without an associated change of MDF. As MDF was based on the amplitude measurements, it was thought unlikely that one index could change independently. If this were so, an apparent reduction of frequency unaccompanied by an increase of AMPO or AMPS may be considered to be due to an error of analysis, but where an amplitude increase is observed in this circumstance, the reduction of frequency is likely to represent a true alteration of cerebral activity.

The observations regarding an inverse relationship of frequency and amplitude were thus in agreement with many authors (Berger, 1932b; Brazier and Finesinger 1944; and Reihl, 1966). Our data were based chiefly on the observations of patients with hepatic disease. It has been pointed out, however, that in the progression from wakefulness to drowsiness, it is common for MDF and AMPS to fall together (Laidlaw & Read 1961b). These authors
in fact suggested that this difference might help differentiation of drowsiness from developing coma. We made no observations on developing drowsiness so that further comment cannot be made.

The incidence of desynchronised records obtained (19%) was somewhat higher than that obtained by most other authors - see historical review. The highest incidence to be reported for normal people was by Meyer Mickeleit (1953) who gave a figure of 15%. As already mentioned the fundamental difficulty rested in definition of the criteria for low voltage. In the present work analysis of a desynchronised record produced either a spectrum without an evident peak or gave estimates of MDF on different occasions, often one or more cycles apart. Thus our criteria were simply the absence of any peak of activity on analysis or the lack of consistent day-to-day values. A more precise approach was implemented by Read (1967), who defined a low voltage record as one in which "the peak abundance is less than twice the least abundance". Such a definition has undoubted merits but it was felt that fewer records would be rejected if measurements were concentrated on the peak amplitude more with respect to its immediately adjacent values rather than to an undefined least abundance measurement.

Our data did not suggest that a low voltage record was more common in the hepatic group. Adams (1959) found a higher incidence of such records in subjects with endocrine disease and one might expect a higher incidence in other metabolic disorders such as hepatic disease, but so far this possibility has not been investigated.

B. EEG VARIANCE.

It has already been stressed that the results of the serial tests for each individual were not normally distributed and thus conventional
statistics were inappropriate. A similar distribution of data was noted by Engel et al (1947). Although our series was small this observation regarding data distribution may be valid, however Read et al (1968) expressed his results in terms of standard deviation (a test which assumes a normal distribution). Presumably such a distribution was tested for, but this was not specified.

As mentioned earlier in this section the control and hepatic subjects for the variability study were poorly matched. As only a few positive results were obtained from an initial statistical examination, the author, on the advice of Dr. R. J. Prescott, did not attempt to obtain more data, to make a more balanced series. Statements regarding comparisons of the hepatic and control group cannot be regarded as exact, but those regarding each group separately may be more meaningful.

No significant difference in variance was found according to age and sex or group (i.e. hepatic and control) for all indices except SWI. All but one of the 11 females in the control group were pre-menopausal so that it was likely that the menstrual cycle had no significant effect upon the degree of variance between the sexes. Previous authors have concentrated on the fluctuations in alpha amplitude and frequency shown by females, and have rarely made comparisons with day-to-day variation in males of similar age. In a small study, Laidlaw & Catling (1965) did find a slightly greater fluctuation in females, and attributed this to the effects of menstruation. Whilst it would not be disputed that cyclical fluctuations in alpha frequency do occur in menstruating females, these changes are probably small (Dusser de Barenne, 1942) (see Historical Review), and changes of this order are not different from the day-to-day changes found by us in male subjects (compare figs. 3.6 and 3.7).
No significant difference of E.E.G. index variance was found to be related to age. Whilst the age range of both control and hepatic groups was considerable (19 - 59 years) the mean age of the control group was low (30 years) and the size of the hepatic group small, so that not too much significance should be attached to this observation. There have been few studies of alpha frequency variance and age, but according to Brazier & Finesinger (1944) there was increasing variability of alpha frequency over the age range 17 - 38 years. Our results extended to 59 years and are, therefore, not comparable.

No overall difference was found between the hepatic and control groups for any index. Due to the imbalance of the size of the two groups this observation again may not be valid. Laidlaw & Read (1961b) suggested that more fluctuation occurred in patients with hepatic encephalopathy. Of the 7 hepatic patients tested, 2 were encephalopathy Group C, 2 Group B and 3 Group A. Despite the small numbers, the degree of fluctuation of MDF was, if anything, slightly less in the hepatic group than in the control (see Table 3A). This suggests that the presence of encephalopathy alone in a clinically stable patient does not lead to greater fluctuation of MDF. One patient with an undoubtedly severe latent encephalopathy (L68), when stabilised on a suitable diet etc, displayed a remarkably steady record (see fig. 4.5, days 87 - 95).

On the basis of the data in Table 3A, we would not consider significant in either group any day-to-day change in MDF of less than $+0.5$ c/s, This estimate is similar to those obtained by Brazier & Finesinger (1944); Read et al (1968), but is less than those of Engel et al (1947) and Rubin (1938) who both gave a figure of $+1.0$ c/s. Possibly this higher value was obtained because of inadequate attention to environmental conditions.
Interepoch variation.

The statistical analysis suggested that marked inter-epoch variability usually foretold marked day-to-day changes. In this we are in agreement with Laidlaw & Read (1961b) who stated that "if... a subject shows little inter-epoch fluctuation, significance can be attached to smaller inter-record changes". Strictly, our observations only held for the control group, but as there were so few in the hepatic group it is possible that in a larger series a similar result might be obtained.

We did not make an extensive analysis of inter-epoch frequency variation, but it was seldom that changes of more than $\pm 0.25$ c/s occurred.

Visual Tasks.

None of the three visual tasks resulted in greater stability assessed on a day-to-day basis. This was true for both groups. Nor did the order of presenting the tasks make any difference (control group only could be tested for this). Early on in the project the impression was gained that there was no difference of variability according to visual tasks and because of this the average was taken of the three values of each index obtained for each record. This approach has been vindicated.

Visual task order was examined to see if there was more fluctuation with a particular progression of tasks. Some sequences might have evoked less interest and hence allowed greater variance due to inattention. It was encouraging to find that visual task order was not an important factor and this implied that the subject's attention was probably at a constant level throughout the period of recording.

The above findings are in disagreement with those of Laidlaw & Read (1961b), who found less day-to-day fluctuation when the subject looked at a
pattern than when he did nothing. This observation was not supported by a statistical analysis, but their findings may still be valid as their recording technique differed slightly from ours. Laidlaw used the same progression of tasks on each occasion, whereas we always altered the order. Laidlaw argued that it was necessary to ensure that all recordings were obtained under exactly the same conditions (personal communication). We deliberately varied the task order to avoid a possible boredom-factor, that might have resulted from knowing exactly what was going to happen next. Furthermore, a pattern of illuminated lights was used by Laidlaw, whereas our pattern consisted of beads on pegboard. These differences of technique are indeed minor. It probably matters little which recording technique is adopted and it is thought likely that neither the order or the nature of the task affects E.E.G. fluctuation in a significant manner.

Whilst it is undoubtedly correct to obtain some measure of E.E.G variance for a defined population one will at the same time be losing information with regard to individual behaviour. Thus a patient who is known to have a highly stable day-to-day record which varies by say $+0.1$ c/s, may have a depression of MDF after protein loading of $-0.4$ c/s. As we have determined that for hepatic and control groups a shift must exceed $+0.5$ c/s to be significant, then the above value, which would not be significant in a general sense, is vastly different for the individual in question. In future it might be better to determine each subject's own variance and then to assess any drug effect in the light of this. Whilst a measurement of inter-epoch variability may give some indication of probable day-to-day fluctuation, it would be more informative, although time consuming, to assess an individual's variance over several days.
C. **DRUG TRIAL.**

In this section it is proposed to discuss the data relating to intravenous heroin and water, and oral lactose, neomycin and ammonium chloride. The other information obtained in this trial (intramuscular water and morphine) will be discussed later.

**Water and Heroin.**

Following water intravenously there were no important changes of mean values of MDF, LR, AMPO and AMPS (See fig. 3.12b and Table 3D). Surprisingly there was some depression of SWI mean values which was most pronounced at 120' (-5). The reason for this was not forthcoming. It may have been due to a reduction of eye movement and other artefact, as the subject became familiar with the surroundings and realised that the injection was not going to have any unpleasant effects! There were, however, some fairly large shifts of individual MDF values i.e. -0.66 to 0.92 c/s - see Table 3D. It was of interest that of those subjects showing fluctuations greater than ± 0.4 c/s were young females. The author is not aware of any literature stating that diurnal variation is more prominent in female subjects. For records performed over the course of 2 hours it would, therefore, be unwise to ascribe significance to values less than ± 0.5 c/s, a figure similar to our estimate of day-to-day fluctuation in healthy individuals receiving no medication.

The heroin test was implemented to see if it could replace the morphine test as a measure of encephalopathy. Several normal subjects felt quite unwell after small doses of morphine (e.g. 10 mg) and occasionally vomited. Also the test took 3 hours to complete. As heroin was stated (Goodman & Gillman 1965) to produce less gastric side effects
than morphine it was decided to try the former drug and further, to use the intravenous route of injection, as any E.E.G. changes might appear sooner.

The data for the heroin test appear in fig. 3.12a and Table 3D. The most striking effects were a reduction of MDF, and SWI with an increase of AMPS, similar to those obtained with morphine. Comparison with figure 3.12b in which the test was performed using water shows some differences which are most marked with respect to MDF and AMPS, but the differences are not large.

Although there were fewer side effects with heroin, it was abandoned as a possible test of encephalopathy because in normal subjects quite large and persistent shifts were observed in MDF (e.g. -0.7 c/s) and shifts of this magnitude were obtained with Group C patients in the morphine test. The initial impression was that indeed neither the morphine nor the heroin test was likely to be of clinical value, but as there were some claims to the contrary regarding morphine it was decided to pursue this test alone.

**Lactose, Ammonium Chloride and Neomycin.**

The object of performing these tests was to discover if the E.E.G. of normal people responded to a drug per se, whether active or not, and to see if any change resulted from the use of neomycin or ammonium chloride in normal subjects. Clearly, if there was MDF slowing with ammonium chloride or acceleration with neomycin, one would need to be cautious in the interpretation of similar shifts in cirrhotic individuals.

The data regarding these tests appear in figs. 3.13 and 3.14 and in Table 3E. With lactose, (fig.3.14) there were small changes of mean values affecting all indices which were of no consequence, but most striking was the wide range of values, especially with regard to MDF and SWI. Inspection of Table 3E reveals quite marked acceleration of MDF (up to 1.58 c/s) in three
subjects - L40, 41 and 34. All these were female and the marked fluctuation may well have been due to menstrual cycle effects, but not in the case of L41, who was post-menopausal. The fluctuations were just as large on the days off lactose, so that the changes are unlikely to be related to the subjects' knowledge that they might be 'drugged'.

No striking change was seen following Neomycin or Ammonium Chloride (fig. 3.13 and Table 3E). After neomycin there appeared to be a slight increase in mean values of AMPS which was not accompanied by any change in MDF mean values. Again there was considerable fluctuation of individual MDF values, in this instance unrelated to differences of sex. It was also significant that acceleration of MDF did occur which was greater than 0.5 c/s in four subjects. However, there was no overall difference between the neomycin and lactose MDF values and this makes it probable that the apparent acceleration of MDF after neomycin was simply an expression of random variation rather than a drug induced effect.

Following ammonium chloride there was little change of mean values for any index except SWI, which showed a small increase. The induction of slow activity has been noted previously following ammonium salts in both normal (Marossero et al 1957) and cirrhotic individuals (Tsukiyama et al, 1961). Again, the range of values for MDF was considerable (0.34 c/s to -0.81) but there was no association of variability with the female members. The range of values was similar to that with lactose, making it unlikely that ammonium chloride was producing any E.E.G. effect.

All the above findings with regard to the oral drugs were expected, in the sense that no mean change in the E.E.G. indices occurred, but what the tests do emphasise is the extraordinarily wide day-to-day fluctuations that may occur, irrespective of the sex of the individual.
D. TESTS OF HEPATIC ENCEPHALOPATHY.

The knowledge of the presence and degree of hepatic encephalopathy is of considerable value to the clinician confronted with a patient with cirrhosis who has a set of normal biochemical liver function tests. Such knowledge is useful for a) deciding whether a patient's protein tolerance is likely to be compromised, b) an index of one of many aspects of liver function, c) assessment of the future liability to episodes of encephalopathy especially in the context of a porta-caval shunt which carries with it (end to side) a 28% incidence of encephalopathy (Reynolds et al 1966).

Unfortunately, an isolated E.E.G. analysis does not allow one to assess the presence or absence of encephalopathy (Laidlaw & Read 1961b). If the MDF is less than 7.0 c/s there is little doubt that the E.E.G. is abnormal and that an encephalopathy is present. However, a test is needed to determine whether the abnormal reading is due to hepatic causes. One such test involves the administration of neomycin. If the MDF is above this value one still cannot be sure that encephalopathy is absent. The patient's optimum MDF may be higher than the obtained value, and unless an E.E.G. is available prior to the onset of hepatic disease, it may be difficult to discover the optimum level, without the aid of a test involving neomycin or a low protein diet. Furthermore, a patient who has experienced an episode of encephalopathy may, with effective treatment, return to his optimum MDF so that the finding of an optimum value by itself may not exclude an encephalopathy.

For all these situations there is an indication for some test of encephalopathy which will impose a temporary stress upon the liver and/or brain. The severity of E.E.G. change following the applied stress may then
be taken as an index of encephalopathy.

Some of these tests have been assessed and will now be discussed.

**Morphine and Water Injection.**

The results of these two tests appear in Tables 3B, C, F and G and are illustrated in figs. 3.8 - 3.11 and 3.15 - 3.20.

**Water.** With regard to the mean shifts, very little change was found following intramuscular water in either control or hepatic groups. The range of values was quite small in the control group, except for SWI which varied by ±12.

Conversely in the hepatic group the range was quite considerable and the fluctuation with almost every index was greater than in the control group (see fig. 3.8). Of the 6 hepatic patients who received water, one belonged to Group B and the rest to Group A. The variability of response cannot therefore be attributed to the presence of encephalopathy. The two tests performed on L28 both showed marked changes - (see Table 3G). This may have been because she suffered from chronic active cirrhosis, which may be associated with greater E.E.G lability. However, L27 had the same variety of cirrhosis, was of the same age and sex, and showed very little change after water. The extreme fluctuation in L28 may therefore be just a manifestation of individual lability.

In neither group did the MDF slow by more than ±0.4 c/s, so that in the assessment of significance of the morphine responses, this figure might be a useful guide.

**Morphine.**

The effect of morphine in both groups was to produce a decrease of MDF and SWI, an increase of LR and AMPS with little change in AMPO.
It has been mentioned that 8 subjects in the control group who received morphine were patients with duodenal ulceration. The mean shifts of MDF in this sub-group following morphine were -0.04 c/s with a range of -0.31 to 0.22 c/s. This response was slightly less than the mean MDF shift of the control group as a whole (-0.26 c/s) so that it is unlikely that any errors will result from the inclusion of the duodenal ulcer patient data.

**LR, AMPO and AMPS**

It is of particular interest that in many cases there was an increase of LR. This occurred in 20 (60%) of the hepatic group and 17 (77%) of the control. Such a change would at first sight indicate that the subjects were more alert after the morphine, a drug which is usually stated (Goodman & Gillman, 1965) to induce sedation or drowsiness. However, it was noted by Wikler (1954) that injections of 30 mg morphine in healthy people often made them transiently more alert. Andrews (1941) found that 20 mg morphine produced mild mental excitation, but only in subjects who had previously been addicted to this drug. Neither author made exact measurements of alpha reactivity, but presumably Andrew's statement regarding increased "occipital alpha blocking time" would be equivalent to an increase of LR.

In our data, LR increased because of the increase of AMPS associated with little or no change of AMPO. If a subject is drowsy one would find a low value for LR because of poor reactivity to eye opening, associated with a general lowering of E.E.G amplitude and hence a lowering of AMPO and AMPS. If the subject is then alerted, a decrease of AMPO with an increase or no change of AMPS would occur which would increase LR, as morphine did, but for different reasons. Assuming that in most individuals the effect of morphine is to induce mild sedation, then one might expect an increase of AMPS due to
a lessening of tension - the paradoxical alpha amplitude increase of early sleep (Davis et al 1938). (Many of our subjects indeed appeared tense at the time of the pre-injection recording). If the subject is then aroused by various visual tasks etc. there may be no change in AMPO, (compared with the pre-injection value of AMPO). This situation will undoubtedly increase LR but it cannot be assumed that a more alert condition has been achieved. We never observed an alerting effect after morphine and this was only noted in the early phases by Andrews (1941) and Wikler (1954), following much higher doses than ours.

A tentative conclusion is that morphine increases LR because of mild sedation due to a paradoxical increase of alpha amplitude when the eyes are shut.

It is, therefore, probable that the differing responses of LR are entirely dependent on the degree of sedation achieved. Mild sedation would be expected to result in an increase of LR. If the subject (whether healthy or cirrhotic) was sensitive to morphine, heavier sedation might be induced i.e. past the paradoxical phase, and cause a decrease of LR. Inspection of figs. 3.9 and 3.15 show that similar degrees of LR depression occur in both normal and hepatic individuals. Thus the LR response to morphine may have nothing to do with encephalopathy and may simply be a measure of the degree of sedation.

Before wholly accepting the above hypothesis, three further points should be mentioned:-

1) of the 5 patients in encephalopathy Group C, four showed a reduction of LR.

2) with advancing years the hepatic group as a whole showed progressively less increase in LR after morphine - see fig.30a.

It is usually stated that the risk of encephalopathy - in the context of porta-caval shunts - increases with age (Sherlock 1968).
In this sense the more commonly found LR reduction in the older age group is consistent.

3) both our data and those of Laidlaw & Read (1961b) indicate that with developing hepatic coma there is a reduction of LR.

It is virtually impossible to draw any worthwhile conclusion from the above. A good deal of the difficulty is that LR is a ratio, measuring two variables, and it would clearly be preferable to disregard this ratio and instead take account of AMPO and AMPS as separate entities.

**MDF** Inspection of the histogram in fig. 3.10 reveals an overall difference of MDF shift between the control and hepatic group. This was just significant ($P < 0.05$). From the data obtained by injection of water (intramuscular), all shifts should be disregarded unless worse than -0.4 c/s. Despite this, some members of the control group showed a slowing of magnitude comparable to the hepatic group. There was an impression that those in the control group with a marked slowing after morphine were all of a younger age group, but this observation did not withstand statistical examination.

Cirrhotic females showed a greater MDF shift than both cirrhotic males and control group females - see fig. 3.20b. The explanation of this was not obvious - perhaps this was because most of the female patients had cryptogenic cirrhosis, a condition which is associated with a higher incidence of encephalopathy (Summerskill et al, 1960). As discussed below, those with alcoholic cirrhosis were all male, and reacted much less than the other varieties of cirrhosis.

**SWI.** Before discussing the clinical correlations of the morphine test comment should be made about changes in SWI. This index tended to decrease in both groups. Two possibilities can be offered from this change 1) the
subjects were more sedated after injection and there was less movement artefact.

2) there was a positive correlation of shift of SWI with shift of MDF. SWI is a measure of delta activity with respect to the overall activity in the theta and alpha range. If there was slowing of MDF there would be an increase of its amplitude and thus a relative decrease of SWI. As long as there was no absolute change of delta activity, a slowing of MDF will result in an apparent reduction of SWI.

What is the significance of the large downward MDF shifts in normal people? They were unlikely to be the effects of diurnal variation. Changes after intramuscular water in the current work, rarely exceeded +0.3 c/s, and C. Thomson (personal communication) found changes of no more than this over 24 hours.

Morphine has numerous actions, both cerebral & peripheral, but the effects most relevant to the current problem are sedation, hypotension and respiratory depression. None of these parameters were measured, but it is clear that hypotension and/or respiratory depression could induce mild cerebral hypoxia, and hence a slowing of MDF. Thus hypoxia might account for the E.E.G. response of either controls or cirrhotics and it is possible that the E.E.G. is measuring merely an individual idiosyncrasy to morphine - just in the same way as some people vomit with the drug and others do not.

Clinical Correlations.

The five patients in encephalopathy Group C all showed fairly large shifts of MDF, with a mean change of -0.72 c/s - see fig. 3.16. Smaller shifts (mean -0.50 c/s) were displayed by Group A patients and smaller shifts still by the control group (mean -0.26 c/s). Superficially this suggests that the MDF measurements allow one to assess the degree of encephalopathy. Some overlap of Group A patients with gp.C is permissible because of the errors in
classification already discussed (p 275). Six out of 22 control subjects (27%) displayed shifts of more than -0.5 c/s and, therefore, reacted in the same way as Group C candidates. Whilst a shift in MDF worse than say -0.5 c/s may indicate an encephalopathy in a given patient with cirrhosis, perhaps once in every four tests (27%) this will be incorrect. Furthermore, we have occasionally observed widely different responses to the same dose of morphine (see Case 4 in the Case History Section). All this suggests that the morphine test is a poor detector of encephalopathy.

If it is accepted that the brain becomes sensitised by continued exposure to nitrogenous material from a collateral circulation, there would be a higher incidence of encephalopathy in those patients with varices than those without. Assuming that morphine detects encephalopathy there should be greater MDF slowing in those patients known to have varices. Fig. 3.16 clearly shows this association does not hold good.

It was of interest that after morphine a larger mean shift of MDF (-0.82 c/s) was displayed by the four patients with chronic active hepatitis. In this condition there is usually more derangement of hepatic function than in other varieties of cirrhosis, and hence they may be more sensitive to drugs such as morphine, which are metabolised by the liver. But three of the four patients with chronic active hepatitis were group A and the other group B. This again raises the difficulty of knowing the degree of encephalopathy present at the time of testing, so that no firm conclusions can be drawn regarding the behaviour of these patients.

The 19 alcoholic patients showed quite a small mean shift (-0.37 c/s) which was comparable to the mean shift of the control group. Are patients with alcoholic cirrhosis less at risk with regard to encephalophy? Summerskill et al (1960) observed that a progressive course and higher incidence of
encephalopathy were more common in cryptogenic and post-hepatitis cirrhosis than in the alcoholic variety; where arrest of the disease may follow abstention. Read et al (1961) commented on the lower incidence of encephalopathy following porta-caval shunts in alcoholic cirrhotics.

It is tempting to suggest that alcohol, a potent enzyme inducer (Figueroa & Klotz, 1962) facilitates the catabolism of morphine by the liver and hence lessens its cerebral action.

Several of the control and hepatic subjects who received morphine and were monitored for several days thereafter, displayed a persistent depression of MDF lasting from 1 - 4 days (see Case History Section - Cases 1, 3 and 7). There are two possible explanations of this response a) the slow breakdown of morphine. It has been shown by Lewis et al (1970) that heroin breakdown products may be detected in the urine for periods up to 12 days after injections of this drug (7.5 mg on three consecutive nights) b) the known tendency of the E.E.G to assume normality slowly following stress - as in the recovery phase of hepatic coma. Possibly both these factors are responsible. It was initially thought that measurements of the duration of the morphine lag effect might correlate with the degree of hepatic encephalopathy. Unfortunately such lag effects were also observed in normal subjects for periods similar to hepatic patients so that such an investigation would probably have been unrewarding.

How do these results compare with those of Laidlaw & Read (1961 a & b and 1963)? It is difficult to agree with them that morphine produced E.E.G changes similar to those of developing delirium, for reasons already enumerated. It is accepted that in all Group C cases there was a reduction of MDF, but not that there was always a reduction of LR. It cannot be confirmed that morphine produced only small MDF shifts in normal people, and because of the overlap of the control and hepatic groups it cannot be agreed that morphine reliably detected
the presence of encephalopathy.

The dose of morphine used by Laidlaw & Read was constant - either 8 mg or 16 mg - usually the former. Thus an under-weight subject would receive a relatively large dose and someone overweight relatively little. It is well known that patients with severe cirrhosis lose weight (Fagin & Thompson 1944) and such patients would thus receive a relatively high dose. Healthy subjects would be expected to have a higher mean body weight and therefore less response to morphine. Hence it is possible that the good separation of patients with and without encephalopathy from control subjects, obtained by Laidlaw & Read, was entirely due to differences of body weight.

Both the current work and that of Laidlaw and Read may be criticised for failing to take into account the time-gap between an episode of encephalopathy and the actual test. Perhaps this could be avoided in future research by selecting patients with recurrent attacks of encephalopathy. Unfortunately, it was common for such patients (in the author's experience) to have a theta dominant record even between attacks. It cannot be assumed that the E.E.G behaves in the same way to morphine when it is theta dominant as when it is alpha dominant. According to Laidlaw (personal communication) there is less slowing of MDF in the theta range when morphine is given because its chief effect is to produce an increase of delta activity. Furthermore, there is no point in administering morphine when the record is already abnormal. These difficulties might be overcome by giving such patients say, neomycin, so that the MDF returns to the alpha range, and then observing the action of morphine, but this in itself might abolish the previous encephalopathy. The most practicable solution would be to select patients all of whom had experienced an episode of encephalopathy at a defined, recent interval - say within the previous two months.
Our results with morphine are also at variance with those of Lods & Dupuy (1964) and Guggenheim (1964) who stated that morphine had no effect in normal people. Both these authors however relied on visual inspection which may not detect shifts less than 1.0 c/s (Gibbs & Gibbs (1947). It is agreed, as both researchers above have concluded, that morphine does not appear to be a good detector of encephalopathy. Guggenheim (1964) noted frontal delta activity on several occasions after morphine. No increase of delta activity was detected by us but this may have been due to the posteriorly located montage.

Is it ethical to give a known toxic and addictive drug to patients with cirrhosis? According to Pappworth (1957) such a test would be unethical unless the patient were made fully aware of the risks involved. Are the risks substantial? Lods & Dupuy (1964) induced hepatic coma after 10 mg morphine in a patient with previous encephalopathy. There were no such complications in our work, probably because the test was not done a) where the MDF was less than 7.0 c/s (when there is evidence of encephalopathy already) b) where there was evidence of severe hepato-cellular jaundice, whatever the MDF, as this condition is likely to be associated with impaired drug metabolism.

If these precautions are observed the risk of adverse effects is probably very small.

Protein.

The results regarding this test appear in Table 3H and fig. 3.21. There was little doubt that after protein loading, slowing of MDF occurred in patients with hepatic dysfunction and that the degree of slowing was often out with the level of spontaneous fluctuation that may be seen in unprovoked subjects (i.e. ± 0.5 c/s). The most marked degrees of slowing occurred in L3, L26 and L68. Patient L26 only reached -0.52 c/s at the 6th day but this was in the context of a 100G protein diet. The changes in E.E.G indices resembled those
of developing encephalopathy (see Case History Section - Case 1) and there was little doubt that L68 would have developed coma on as little as 30G protein had preventive therapy not been rapidly introduced. This suggested that protein loading is a specific toxic factor for hepatic disease. The only exception to this may occur in renal failure with 'uraemic encephalopathy' where protein loading might cause similar E.E.G. changes to those observed in hepatic encephalopathy.

The small number of patients prevented meaningful analysis of the protein results with respect to the variety of cirrhosis, but it was of interest that those with alcoholic cirrhosis showed least change (mean 0.04 c/s). The behaviour of this group was thus similar to that with morphine. Possibly, the explanation for their protein refractionness was not 'enzyme induction' and may be due to a fundamental difference of hepatic metabolism in the cirrhotic disorders secondary to alcoholism. Nevertheless it is theoretically possible that protein synthesising enzymes might also be induced by alcohol.

The patient with the largest change to protein was in encephalopathy Group C, the second largest, Group B and the third largest, Group A. This very superficially suggested that the degree of MDF slowing with protein loading was associated with the severity of encephalopathy. There were not enough observations to pursue this question further.

There appeared to be some association between the presence of varices and the severity of MDF slowing. Those patients with varices had a mean change of -0.56 c/s and those without had a mean change of 0.12 c/s. The value in the varices-present group was lowered by the -2.74 c/s change in L68 and if the shifts are recalculated without this value the mean change becomes -0.20 c/s, so that the apparent association may not be significant.
These results are in agreement with those of Laidlaw & Read (1961b and 1963) in that slowing of MDF occurs after protein loading. They found this change in 'nearly all' cases of Group C cases, and the trend of our results suggested that this situation would also have been found if more cases had been studied.

Horky et al, (1967) reported that the same patient may show varying tolerance to protein when tested on different occasions - presumably not separated by more than a few days - although they did not specify this. Two sets of observations were made on L3 with similar protein loads (5 months apart) and the resultant MDF slowing was remarkably similar on both occasions - see Table 3H.

Unfortunately very few studies were made of changes in normal people following protein loading. Three duodenal ulcer patients were given 120G protein per day for four days and this was combined with oral ammonium chloride (4G per day). None of these patients showed any E.E.G change but, in view of the small numbers and the short duration of the diet, these observations were not presented formally. It was interesting that Vojtechovsky & Horky (1966) found E.E.G changes of sleep 6 hours after a 100G protein breakfast. Clearly more work in this sphere will be required if protein loading is to be shown to be of value in detecting hepatic encephalopathy.

The advantage of a protein loading test is that it causes a natural increase in absorbed nitrogenous material as opposed to 'unnatural' tests involving ammonium salts and methionine etc. With protein loading one is probably mimicking the state of affairs after a porta-caval shunt, and theoretically the E.E.G. changes should give a good indication of the patient's tolerance to a shunt operation. It is stated that a high protein intake is
beneficial in cirrhosis especially where there is evidence of weight loss (Sherlock 1968) and it was claimed that such diets improved life expectancy (Patek et al 1948).

Thus, the higher a protein intake, the better, within the limits of encephalopathy. Normally the tolerance is determined empirically, using as an 'end-point' the appearance of overt encephalopathy, carrying with it the risk of frank coma. With E.E.G monitoring it should be possible to find the end-point without running such risks. It was clear that in L3 the MDF slowed steadily after 120G protein/day but that 70G/day was associated with a stable MDF (see fig. 4.11). Her limit of tolerance would probably be of the order of 1000G/day.

The other advantage of protein loading is that it carries little risk as long as the E.E.G is observed and provided it is not performed on patients with clinical or E.E.G. signs of encephalopathy.

The salient disadvantages are that a) it takes up to 7 days before definite changes emerge, b) patients may dislike too much meat and/or "Complan" c) the effects of protein loading have not been sufficiently well documented in normal people.

Neomycin.

The results of this test in the hepatic group appear in Table 3i and in Fig. 3.22. Despite considerable day-to-day fluctuation, it seemed that in four of the 8 cases studied (i.e. L68, 72, 90 and 146) there was an increase of MDF. The data on normal subjects who received neomycin suggested that accelerations of MDF up to 0.7 c/s may be found. This level was, in fact, exceeded, albeit intermittently, by all the above four patients, but not until seven days had elapsed.
In 3 of the 4 patients showing a neomycin response the initial MDF was less than 7.0 c/s and of the 4 showing no response, the MDF was greater than this. It was suggested by Laidlaw & Read (1961b and 1963) that a mild depression of MDF, suggesting an encephalopathy, could be shown to be due to hepatic causes if an improvement occurred with neomycin. This would be accepted provided a) there is no evidence of uraemia, as neomycin could improve a uraemic encephalopathy, b) neomycin is given for at least 7 days, c) the shift of MDF exceeds 0.7 c/s.

In our four subjects responding to neomycin these conditions were fulfilled. The fluctuant increase of MDF in L72 was of interest as the basal MDF (8.88 c/s) was within the normal alpha range (8.0 - 13.0 c/s). Thus, a MDF within the normal alpha distribution may not exclude encephalopathy. It is desirable to know a patient's optimum MDF, obtained at a time before the commencement of hepatic dysfunction, but as such information is rarely available the exhibition of neomycin may help to decide whether a MDF within alpha territory is the optimum value for the patient in question. A similar observation was made by Laidlaw & Read (1963).

The salient advantage of the neomycin test is that it carries no risk of inducing an encephalopathy, and may be performed simultaneously where neomycin is being given for therapeutic reasons. The main disadvantages are that it may take a week before definitive changes occur and that sometimes unpleasant gastrointestinal side effects may make it necessary to discontinue the drug. Furthermore, it is conceivable that a patient may have a MDF within the alpha range which does not improve with neomycin and yet evidence from other tests (e.g. protein loading) may provide definite evidence of encephalopathy.
Ammonium Acetate.

This test was used as a possible measure of hepatic encephalopathy because of an encouraging report by Tsukiyama et al (1963). They considered that ammonium chloride intravenously produced striking E.E.G changes which were obvious to visual inspection and definite enough to allow segregation between patients with and without hepatic dysfunction. The ammonium salt was delivered as a five minute intravenous infusion (see Historical Review). We were interested in testing the ammonia hypothesis of encephalopathy and in view of the acidosis known to be produced by ammonium chloride (Zintel et al, 1943) which could confuse the E.E.G interpretation, and the fact that Warren et al, (1960) had suggested acidosis would deter entry of ammonia into the brain, it was decided to use ammonium acetate. This substance had a pH of approximately 6.8 and is, therefore, unlikely to cause much acid-base disturbance.

It was in fact found that in the control group no change in arterial pH did occur, except for one subject (L56) who received a high dose (16 mg/Kg) resulting in a transient alkalosis (see Results Section) presumably due to the ammonium ion itself. In the other 4 controls in which pH was measured no change was detected and it was thought unlikely that the smaller doses subsequently used (8 - 10 mg/Kg) would affect pH in either group. It is perhaps worth mentioning that when L56 was alkalotic he was noted to be hyper-ventilating - which is perhaps an unexpected response. It is possible that the hyperammonaemia was stimulating his respiratory centre and such a mechanism has been postulated to account for the alkalosis often found in hepatic coma (Sherlock 1968).

Side effects from ammonium acetate were distinctly more frequent in the control group and usually consisted of faintness, associated with
blurred vision, nausea and occasional vomiting. Why so few adverse effects occurred in the hepatic group was interesting but hard to explain. It was not due to any difference of rates of removal of ammonia, as the rate was slower in the hepatic patients. The basal ammonia levels were all elevated in these patients, so that they would have received relatively less drug than the controls, and this may have partly accounted for the difference in side effects.

The dose of ammonium acetate had to be determined empirically, but 8 – 10 mg/kg seemed to be the lowest dose that would produce a substantial rise of venous ammonia without causing distressing side effects. We are in disagreement with Tsukiyama et al (1963) who admitted to no side effects in any of their patients, following doses equivalent to double those used by us, given in half the time. No doubt racial differences are important, but their findings are hard to accept.

**E.E.G. Changes.**

In both control and hepatic groups the most obvious mean change was a slowing of MDF, although at almost all intervals and with all indices there was a considerable range of values in both groups. These initial observations are in concordance with those of Tsukiyama et al (1963) – although the changes were not as marked, but differ from those of Cohn & Castell (1966) who found E.E.G changes in only 1 out of 19 cirrhotics following oral ammonium acetate. Yoshida (1968) was impressed with an increase of delta activity, but in our data this was seldom observed – more often there was a depression.

Consideration of Table 3L suggests that a normal subject may show changes of -0.3 to -0.5 c/s at almost all intervals but that the most severe depression is at 60 and 75 minutes. Comparison of these data with those obtained in healthy subjects following intravenous water (fig. 3.12b and Table 3D) shows that the MDF changes following water were a little less, but
that the range of values at each interval in both tests was considerable. This suggests that there is no overall difference between the effect of water and ammonium acetate in healthy individuals.

It is next pertinent to consider the changes in patients with cirrhosis following inert fluids intravenously - see fig. 3.28 and Table 3.P. Whilst considerable interepoch fluctuation was apparent, the MDF did not slow by more than -0.48 c/s.

In view of the above, it would again be wise not to accept as significant a MDF change following ammonium acetate in the hepatic group unless it exceeded -0.5 c/s. on two or more occasions. Implementing this criterion, only 4 of the 15 cirrhotics can be said to have a significant response. These are L68, 143, 156 and 164. In each case the maximum slowing occurred in the second hour.

Of these four patients, 3 belonged to Group C whereas L156 belonged to Group A. The latter patient had a porta-caval shunt and would be a candidate for latent encephalopathy. Furthermore, his basal MDF was suspiciously low - 8.07 c/s - suggesting that this was below his optimum and indicating the presence of a mild latent encephalopathy. In fact, the initial MDF of all four patients was less than 8.50 c/s.

So far these results are encouraging, but three Group C members showed virtually no change to ammonium acetate - (L120, 157 and 158). Inspection of Table 3K reveals that adequate elevations of venous ammonia were achieved (increases of 158 - 240 μg/m100 ml at 10 minutes). This apparent discrepancy may be due to the fact that the episodes of encephalopathy in these 3 were several years prior to the time of testing (L120 - 8 years; L157 - 4 years and L158 - 2 years). On the other hand L164, who experienced
an episode 2\(\frac{1}{2}\) years previously, showed a significant shift. Furthermore, this time factor does not appear relevant in the morphine test where all Group C candidates displayed a marked response (more than -0.5 c/s).

It is impossible to come to a firm conclusion on this problem, but clearly it merits further appraisal particularly with carefully selected Group C patients, as already discussed.

**E.E.G - Ammonia Association.**

All cirrhotic subjects had a pre-infusion MDF within the normal alpha range except for L68 (7.68 c/s) and L157 (7.74 c/s), whereas all the basal ammonia levels were abnormal. This immediately suggests that MDF has no relation to venous ammonia levels. As all of the patients who received ammonia were in a clinically stable condition regarding their cirrhosis, it can be deduced that the isolated basal ammonia values were indicative of chronic hyperammonaemia, and that this condition is by itself not associated with any change of MDF. This statement holds good for basal levels ranging from 124 to 419 µgm/100 ml, i.e. up to 7 times the upper limit of normal. (L145 had a basal value of 550 µgm/100 ml, but his E.E.G could not be analysed). It is not surprising to find a similar lack of correlation between shifts of MDF and shifts of venous ammonia levels (fig. 3.27) - despite changes of up to 300 µgm/100 ml. As the E.E.G is thought to be a sensitive index of encephalopathy, the above findings are strong evidence against the possibility of any direct connection between hyperammonaemia, whether acute or chronic, and hepatic encephalopathy. These observations are in agreement with the majority of workers (Abbott, 1959; Parsons-Smith 1957; Bogacz 1965; McFarland et al 1964; Cohn & Castell 1966).

As already mentioned in the Results section there was no correlation of MDF with varices. Theoretically there should be some association as those
patients with a collateral circulation are more likely to have a latent encephalopathy. Nevertheless, if hepatic function is good, there may be no encephalopathy despite the presence of varices and this may be a factor in our patients.

Ammonia - Clinical Association.

A statistical analysis of the ammonia results revealed a significant correlation of venous ammonia shift with encephalopathy, type A or C, especially at the 30 minute interval. There was an impression of an association between the presence of varices and shifts of ammonia, although this was not significant ($P < 0.05$). It is quite reasonable on theoretical grounds to find a connection between encephalopathy type and ammonia tolerance, although this association has not been previously documented. It is surprising that there was not a similar association between encephalopathy type and MDF shift and to explain this it was suggested that the encephalopathy-test interval was important. Nevertheless, it seems that if the ammonium acetate test is provoking encephalopathy, then the E.E.G is not as sensitive in its detection as measurements of venous ammonia.

Many authors have suggested a correlation between the presence of varices and an abnormal ammonia tolerance test (Kirk 1935; Stahl 1963; Conn 1967 and Grace et al 1969). According to Conn (1967) the result of an oral ammonia tolerance test represented the net effect of a number of factors which included gastro-intestinal absorption, hepatic blood flow, hepatic parenchymal function, portal-systemic shunting and ammonia uptake by the peripheral tissues. It is generally agreed that hepatic function per se is the least important. This comment stems from the finding of normal ammonia tolerance in "benign acute hepatitis, ... fatty liver and obstructive jaundice" where parenchymal function is considerably disturbed in the absence of a collateral circulation (Stahl 1963).
However, it has been pointed out by Grace et al (1969) that the metabolic defects in acute hepatitis etc. are not necessarily of the same severity as in cirrhosis.

Despite all this, most authors have been able to show a correlation of impaired ammonia tolerance and the presence of varices, and our results although not statistically valid, are superficially in agreement. The reason for failure to define a relationship with varices may partly be a result of using venous instead of arterial blood. The climate of opinion in Britain is still somewhat against arterial puncture unless there are valid therapeutic reasons, and we thought it unethical to insert an indwelling arterial cannula or to perform repeated arterial punctures. It has been made abundantly clear (Bassman & Bassman 1955; Stahl 1963) that venous ammonia levels may be widely different from arterial. This is due to peripheral metabolism especially in muscle, so that any regional variation of blood flow to the limb (e.g. heat or muscular activity) may cause an alteration of venous ammonia. We took steps to prevent muscular activity but did not take into account forearm temperature - which might have caused some errors.

The only positive conclusions on the ammonium acetate study that may now be drawn are that measurements of ammonia shifts at 30 minutes after infusion may assist the detection of encephalopathy or varices, but that the E.E.G. measurements do not help in these respects. It might be worthwhile pursuing the E.E.G test further, perhaps restricting the observations to before and one hour after infusion, provided that care is taken in the assignment of encephalopathy class.

Table 3.2 gives some idea of the agreement between three tests of hepatic encephalopathy. Agreement was obtained in 12 of the 17 subjects (71%) who had two or more tests. This might mean that the tests were all equally
useless. It is possible, however, that an individual patient may be more sensitive to one form of provocation than another. The protein loading and ammonia tests are testing similar aspects of hepatic dysfunction, whereas morphine may be related to other factors e.g. no elevation of arterial ammonia was found by Laidlaw & Read (1961) after injections of morphine.

Four patients were of Group C in the inter-test analysis (L68, 120, 143 and 164). L68 showed a marked lack of correlation, whereas the other three showed some association. All these three showed only small responses to the relevant tests. It may be concluded that whilst there was some agreement between tests this was neither necessary nor meaningful, but that all three provocative procedures do not have a marked effect on patients in Group C, where large changes should occur, in some of the tests at least.

E. DISCUSSION OF CASE HISTORIES.

This topic will be reviewed under four headings:

1. The value of day-to-day monitoring.
2. The causes of post-operative E.E.G deterioration.
3. The predictive value of the morphine and ammonium acetate tests.
4. The paediatric data (Cases 9 and 10).

(1) The value of day-to-day monitoring.

The most striking case in this section was Case 1, which demonstrated more than any other, the value of day-to-day monitoring, where ordinary clinical and biochemical assessment gave little or no assistance.

In general, the changes indicative of E.E.G. deterioration based primarily on Case 1 were as follows:-

a) Slowing of MDF
b) Increase of AMPO and AMPS
c) Decrease of LR.
d) Increase of SWI.

E.E.G improvement was indicated by a reversal of these trends.

Most emphasis in this work has been laid upon changes in MDF, which was thought to be the most sensitive index. However, changes in AMPO and AMPS seemed equally good and negatively correlated with MDF (see RESULTS). LR tended to show no change or to lag behind the alterations of MDF. Only a few observations were made on SWI and in general this index appeared to give only approximate guidance, although where other indices were not available (Case 5) it seemed to make valid measurements of encephalopathy.

In general, the salient features of day-to-day monitoring were as follows:

a) As a means of assessing progress after a major operation.

Particularly in Case 1, coma was detected following the introduction of a 50G protein diet. Had the E.E.G analysis been rapidly available, the ensuing episode of pre-coma might have been prevented. Only slight changes were observed post-operatively in cases 2, 3 and 6, which were consistent with their well-being at the time.

The moderate and persistent degree of slowing shown in case 4 is more difficult to interpret but may indicate susceptibility to encephalopathy at a later date, as already discussed.

b) As a means of regulating dietary protein. Again this was well shown in Case 1 (fig. 4.1) where a 30/G protein diet was tolerated but a 50G intake was excessive. In Case 7 it was clear that protein loading on two separate occasions (120G and 130G) produced fairly large downward shifts of MDF. This information makes it
likely that neither diet could be tolerated on a long term basis - although we have never demonstrated that a prolonged dominant rhythm in the theta range has had any harmful effects. A slight degree of slowing on 100G protein occurred in Case 2 which again suggested the need for caution, but the same restrictions mentioned in the previous sentence apply here as well.

c) As a means of detecting incipient coma. Early signs of deterioration appeared twice in the graphs relating to Case 1. In one instance (day 25) the changes were followed by pre-coma and in the other, (day 40) the rapidity of the preceding changes suggested imminent coma but this event was prevented by the exhibition of neomycin. Case 5 appeared to be exceptional in that a minor change of SWI was detected only 24 hours prior to the development of coma. The reason for this was not clear, but may have been due to an extremely rapidly developing coma, or to the relative insensitivity of this index.

d) As a means of assessing the effect of therapeutic measures. Case 1 vividly demonstrated the combined effects of neomycin and protein withdrawal on MDF. When Lactulose was subsequently given in place of Neomycin, it was clear that it was equally effective in the prevention of encephalopathy. However, where neomycin was withdrawn in Case 5 (see fig. 4.9) lactulose and a low protein diet were clearly inadequate in preventing an episode of pre-coma.

Finally, it should be stressed that the presence of E.E.G. deterioration, which was consistently observed in the post-operative period, calls for the utmost vigilance if an episode of coma is to be avoided.
The causes of post-operative E.E.G. deterioration

It appeared to be a characteristic phenomenon to find a slowing of MDF in all cases following surgery for portal hypertension, sometimes by as much as 6 c/s. Varying degrees of depression then persisted for up to 3 weeks, and even beyond this in one case (Case 4). At least a partial explanation of these changes can be attempted.

(a) Operative Trauma

Part of the slowing is probably a non-specific effect of the trauma of the operation, irrespective of whether the amount of nitrogenous material reaching the brain is increased or not. For example, Case 3 had an oesophageal transection (which does not increase the amount of nitrogenous material by-passing the liver) and yet still showed some post-operative slowing (approximately -1.6 c/s), which persisted until his discharge, 2 weeks later.

Despite precautions, any major abdominal operation may be associated with cerebral hypoxia, due to varying combinations of blood loss, hypotension and anaesthetic agents. It is well known that hypoxia may produce slowing of the E.E.G. (Dawson & Greville 1963). The necessity of fasting prior to operation, of parenteral fluids and gastric suction may create temporary electrolyte imbalance, to which the E.E.G. is most sensitive (Read et al 1959). Furthermore, it is known that there is increased output of adrenal steroids post-operatively (Moore 1959) and this may be expected to induce a slowing of MDF (Woodbury 1958). In view of the known liability of patients with cirrhosis to stress, it is not surprising that some slowing of dominant frequency occurs.
Lehmann and Schmitz (1966) briefly reported the effects of abdominal and limb surgery on the E.E.G. in 23 patients (with unspecified illness) who received halothane and nitrous oxide anaesthesia. In four patients no change was observed in the post-operative period but in 19 cases, the alpha frequency was depressed by -0.5 to -1.5 c/s during the first week. In 10 cases there was no return to pre-operative levels within the first week, and in 6 of these an additional decrease of frequency was observed in the second post-operative week. They stated that the changes were not due to drugs. It was not mentioned whether the patients had any metabolic disorder before operation, but even so, it is unlikely that all 19 of them did, and that changes of 0 to -1.5 c/s due to major surgery per se, might therefore be expected.

(b) Increased shunting of nitrogenous material.

Where a porta-systemic anastomosis is constructed the brain is inevitably exposed to extra nitrogenous material. This is characteristically associated with a rise of blood ammonia (Sherlock 1968) a phenomenon confirmed in the present work (Cases 4 and 10). Whilst any slowing of MDF during the first two weeks after operation may be a non-specific reaction, as already discussed, a persistent slowing thereafter is more likely to be due to increased nitrogenous material reaching the brain. Persistent slowing up to 1½ months post-operatively, was observed in Case 4. Read et al (1961) in a description of neuro-psychiatric complications of 21 adult patients subject to porta-caval anastomosis, commented that 5 patients showed symptomless E.E.G. abnormalities, consisting of a theta dominant record in three of these. In a later study (Read et al 1966) it was suggested that this type of slowing was due to accumulated nitrogenous products, as an improvement
of MDF was often observed following neomycin therapy.

(c) **Protein intake.**

The protein tolerance may often be restricted after shunt procedures. This point was clearly shown in Case 1 where an increase of dietary protein from 30G to 50G/day was associated with a rapidly developing encephalopathy. There was also a suggestion of reduced protein tolerance in Case 2. A diet containing a slight excess of protein for a particular patient may result in a chronically depressed MDF (as in Case 4).

(d) **Biochemical disturbances.**

Abnormalities in electrolyte balance were not an important factor. Some correlation of MDF slowing with a raised bilirubin and to a lesser extent with urea, was found in Case 1. (See Results Section and fig. 3.30). As urea is formed in the liver as a result of protein breakdown, it is to be expected that in patients with encephalopathy, a reduction of protein intake will simultaneously improve the encephalopathy and reduce the amount of protein reaching the liver for breakdown. Hence a correlation of these two factors will arise.

The correlation of bilirubin with MDF is quite striking — see fig. 3.30. At days 21 and 22 the bilirubin values almost doubled and appeared to anticipate the clinical deterioration at day 26 even before MDF. A similar case might be made out for the transitions over days 9 - 14 where again the bilirubin appeared to anticipate the E.E.G. change.

It would be difficult on the basis of one example to postulate that bilirubin is a primary factor in the genesis of hepatic encephalopathy. For example, it was noted that when Case 10 showed definite signs of encephalopathy the liver function tests, apart from ammonia, were all normal. It has been repeatedly observed (Zieve 1966) that patients in
hepatic coma may have bilirubin values ranging from near normal to grossly elevated. However, the correlations in Case 1 are such that it is tempting to suggest that at least the problem should be rethought. All bilirubin measurements in this work were total values, but it remains possible that a better correlation might be obtained if the unconjugated fraction were examined.

Estimations of venous plasma ammonia were performed only on a limited scale and on the whole showed no correlation with changes in MDF. Following operation there was a marked rise of venous ammonia in cases 4 and 10 (50 - 17\textmu g/100 ml and 52 - 208 \textmu g/100 ml) - an expected change - but whether the rise was responsible for the persistent slowing of MDF in Case 4 is not certain. A poor correlation of venous ammonia and MDF was obtained in Case 9. In Case 8, who had a persistent hyperammonaemia, the MDF was constantly normal. It is impossible to be dogmatic but it seems unlikely that hyperammonaemia alone is able to account for the post-operative slowing of MDF.

Frequent measurements of blood glucose were not made. Patients with hepatic cirrhosis may only very rarely show hypoglycaemia. It was shown by Zimmerman et al (1953) that levels below 50 mg/100 ml were only obtained twice in 256 measurements in 156 cirrhotic patients, some of whom were in terminal hepatic coma. According to Gibbs et al (1940) hypoglycaemia caused a gradual increase of delta activity, but this increase was not definite until the internal jugular blood level was 30 mg/100 ml. It has been noted by others that the alpha rhythm may change little (Dawson and Grenville 1963). Thus, it is unlikely that hypoglycaemia would have been observed either pre- or post-operatively and even if it had, any E.E.G. change would probably be unrelated to this biochemical abnormality.
(e) **Opiates.**

It has been shown that morphine induced a slowing of MDF three hours after injection and that this change often persisted for one to four days after a single injection - see Cases 1, 3 and 7. It is more than probable that where several injections of opiates are given to cirrhotic patients in the post-operative period (especially those patients who have shown a pre-operative slowing to morphine) there will be a persistent depression of MDF. Although Case 2 does not show a pre-operative depression following morphine it is pertinent that his MDF did not improve post-operatively until opiates were stopped.

(f) **Deterioration of liver function.**

It has been shown that hepatic blood flow is reduced after shunt operations (Leevy et al 1960; Redeker et al 1960). Consequently a worsening of hepatic function may occur after the operation (Read et al 1961) and this may partly account for depression of MDF.

In summary there seem to be so many factors that could account for post-operative E.E.G deterioration, that it is perhaps surprising that more severe changes do not occur. However, most patients subjected to porta-systemic shunts are carefully selected and those who were in the present series (i.e. Cases 2, 4 and 6) had a small depression of MDF after operation. The lieno-renal anastomosis performed in Case 1 was a life saving measure, and the development of post-operative pre-coma was not unexpected.

(3) **The predictive value of the morphine and ammonium acetate tests.**

Five subjects (Cases 1, 2, 3, 4 and 6) had morphine pre-operatively and one (Case 10) had heroin. Only Case 1 had post-operative encephalopathy whereas the change with morphine was small
Two patients developed persistent post-operative slowing (Cases 4 and 6) and both these had fairly marked morphine changes (-0.70 c/s and -1.05 c/s respectively). The value of the change in Case 4 was offset by a small response to morphine whilst on a high protein diet (-0.16 c/s). Case 2 showed no response to morphine (-0.05 c/s) and did not develop persistent post-operative slowing, although a slight reduction of MDF occurred on a 100G protein intake.

Cases 3 and 10 showed only a small response to morphine and heroin respectively and post-operatively showed no persistent slowing. Heroin given intravenously to adults in the current work produced changes similar to those observed with intramuscular morphine. There is no reason therefore to suppose that Case 10 should behave differently whether heroin or morphine were given.

Case 9 received morphine approximately 4½ months after the operation, when a large change was observed (-1.26 c/s) and this may have anticipated the development of coma some 10 months afterwards.

Clearly the morphine results are not always consistent and can only be taken as a general guide to future developments. The finding of widely differing shifts following morphine in the same patient (Case 4) casts considerable doubt on the reliability of the test.

Only two ammonium acetate tests were performed (Cases 3 and 6) in the pre-operative period. Case 3 showed a depression of -0.51 c/s in the second hour of the test compared to a change with morphine of -0.26 c/s. Case 6 showed a fluctuant response to ammonia, initially a depression of approximately -0.40 c/s, compared with a large morphine change of -1.05 c/s. The first case showed no persistent post-operative slowing and thus the morphine test was marginally more accurate.
The second case showed persistent slight post-operative slowing and presumably the morphine test was more correct again here. These small number of observations suggest that the ammonium acetate test is not valuable in the predictive sense.

(4) **The Paediatric data.**

It is very difficult to draw any significant conclusions from the paediatric data but certain general observations may be enumerated -

1) As with adults there seemed to be a general lack of correlation of biochemical determinations with the E.E.G. and the clinical situation. The plasma ammonia displayed a crude association with the E.E.G changes in Case 9, but this was far from striking.

2) The morphine and heroin results are difficult to interpret. Case 9 showed a marked slowing with morphine which may have anticipated the episode of fatal encephalopathy 10 months later. Case 10 showed no slowing with heroin on two separate occasions and was very well one year afterwards. Superficially this is encouraging. However, Case 10 had experienced an episode of encephalopathy and the heroin test which should have detected this, clearly did not. There is no reason to suspect that heroin should be any less provocative than morphine, and the present work in normal adults showed a similar pattern of response to both opiates. Perhaps the failure of Case 10 to respond to heroin was a manifestation of resistance to stress, which might have to be very severe before an encephalopathy could be induced.

3) Considerable day-to-day variation was shown by Case 9, but not by Case 10. The fluctuations in the former case were somewhat greater than those shown by clinically stable adult cirrhotics in the present work.
Case 9 was clinically unchanged between days 21 and 119 (see fig. 4.13) so that the E.E.G changes during this period must have been due to either a fluctuating latent encephalopathy or to the lability said to be characteristic of children's E.E.G's (Pond 1963). The changes were not related to plasma ammonia.

4) A delta dominant E.E.G correlated with pre-coma in Case 10, as it did in the adult group. A delta dominant record was obtained on two occasions in Case 9 but only the first of these was associated with pre-coma. One cannot be sure that a MDF of 3.0 c/s or less will necessarily mean overt encephalopathy in a child, as it normally would in an adult. It is likely, however, that a persistently delta dominant record in a child would indicate overt encephalopathy.

5) Both cases showed post-operative slowing:

Case 9 reached 3.0 c/s and Case 10 reached 5.87 c/s.

The pattern of slowing was similar to that shown in the adult group after shunt operations. Part of the slowing in Case 10 may have been due to repeated injections of heroin in the post-operative period.

The above results suggest that day-to-day E.E.G measurements are of some value in the detection of hepatic encephalopathy, in children but the results are not clear-cut and their nature suggests that further observations in this sphere should be made.

(F) CONCLUDING REMARKS

A technique for measuring the mean dominant frequency and associated indices of the E.E.G has been described which has been shown to produce accurate results of clinical value. The recording technique
was simple, took no more than 20 minutes to complete and required little adaptation for use in the wards. The analytical technique which took approximately 30 minutes, gave results accurate to within 0.1 c/s in the alpha range. Although the computer hardware represented considerable capital outlay, it required very little maintenance or calibration and gave highly repeatable results.

The range of day-to-day variation of MDF was found to be surprisingly high for both hepatic and control groups (± 0.5 c/s). If it is accepted that changes of ± 1.0 c/s may be detected visually then does automatic analysis justify the additional resolution of a mere half cycle? Furthermore, a change of reactivity can usually be detected by visual inspection. However methods of visual analysis are time consuming and prone to subjective errors (Dawson & Walter, 1944), although Laidlaw (1959) described a simple visual method which produced results similar to those of a 3NI wave form analyser, and gave results of practical clinical value.

It is possibly more rewarding to study individual rather than collective variation. A small shift in a stable individual may have significance for that patient and here automatic frequency analysis would be invaluable.

Within the range of day-to-day variation defined in the current work (± 0.5 c/s), no significant effect in normal people was found by the oral administration of lactose, neomycin or ammonium chloride. In the control group significantly greater changes were observed following heroin and morphine than after water administered in place of both these drugs.

No firm conclusions could be drawn regarding the tests of
hepatic encephalopathy. The morphine test, which was frequently distressing and potentially harmful to the patient, gave results in the hepatic group which were not clearly demarcated from the results of the control group. No obviously misleading result was obtained following protein loading. This test perhaps was the most promising because it imitates the patho-physiology of hepatic encephalopathy better than most other provocative tests hitherto described. However, in our data a week's testing was required before a clear response was obtained. There was a small risk of hepatic coma, the diet was often unpalatable and little is known of the E.E.G response of normal people to high protein regimes. Neomycin appeared to assist the elucidation of a borderline slowing of MDF and helped to decide whether an encephalopathy was hepatic in origin. No misleading results were obtained, but the number of patients examined was small. The test carried no risk to hepatic function but again took about 7 days to produce a definitive E.E.G. response. The ammonium acetate test did not appear to be a good measure of hepatic encephalopathy. No correlation could be found between the presence of encephalopathy or the detecting varices and the E.E.G response. The failure of an E.E.G/encephalopathy correlation may have been due to a lack of homogeneity in Group C. A good correlation was obtained between venous ammonia shift at 30 minutes and Group C patients, and there was an impression of association between ammonia shift and the detection of varices. All these observations were based on a small sample and require further verification. The association of ammonia shifts and varices has at least been previously documented. (Conn 1967).
The most striking advantage of E.E.G. measurements was in day-to-day monitoring especially in patients subject to operation. This allowed the early detection of impending coma and regulation of protein intake on an accurate basis. The measurements allowed the assessment of a new preparation 'Lactulose'. This was shown (case 1) to be effective in replacing neomycin in the prevention of encephalopathy, and there is no reason why any new drug (or operation) could not be assessed in a similar manner.

Day-to-day E.E.G monitoring may also have a place in paediatric hepatic disease, but more studies are needed in this sphere.

**FUTURE RESEARCH.**

Clearly there is a need for a suitable test to detect hepatic encephalopathy, and in the author's view none has yet been described. The fundamental difficulty is the large fluctuation shown by normal people so that any provocative drug needs to be given in high dosage, without causing harmful effects, and without influencing the normal person's E.E.G. There are numerous substances yet to be tried in association to E.E.G. monitoring - e.g. Methionine, Choline, Butyric Acid, Aminosol, Chlorpromazine etc. but it is possible that some simple biochemical test of encephalopathy may be found beforehand.

It is most important that any control group should be completely healthy. Our use of patients with duodenal ulceration was not entirely satisfactory but fortunately their responses seemed 'normal'. Many previous workers have used as a control group, Hospital patients "without evidence of hepatic disease" without actually specifying what they were suffering from. Particular care should be taken in selection of patients
on the basis of previous encephalopathy. It is suggested that in any future study only patients who have had an episode within 2 months of testing would be likely to have present hepatic encephalopathy. In this context it would be interesting to perform a selected provocative test at, say, monthly intervals from the episode of coma and to observe if there is a diminishing response with time.

Although the present system of automatic analysis was highly satisfactory, it did take 30 minutes for each record and especially where computer time is expensive, the more rapid the result, the better. The most useful index was undoubtedly MDF so that it would be valuable to perfect some form of electronic filtering mechanism which would give a continuous reading of MDF - based on say, successive 20 second samples. Such a device might have a place in continuous monitoring of patients liable to develop, or recovering from hepatic coma.
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APPENDIX I.

Normal Range of biochemical values.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Serum bilirubin</td>
<td>0.1 - 1.0</td>
<td>0.2 - 0.8</td>
</tr>
<tr>
<td>Serum Alkaline Phosphatase (KA units)</td>
<td>3 - 13</td>
<td>20 - 85</td>
</tr>
<tr>
<td>Serum alanine-aminotransferase (Units/ml)</td>
<td>less than 35</td>
<td>2 - 17</td>
</tr>
<tr>
<td>Thymol turbidity.</td>
<td>0 - 4</td>
<td>0 - 4</td>
</tr>
<tr>
<td>Serum urea (mg/100 ml)</td>
<td></td>
<td>20 - 40</td>
</tr>
<tr>
<td>&quot; sodium Meq/Litre</td>
<td></td>
<td>135 - 145</td>
</tr>
<tr>
<td>&quot; potassium &quot;</td>
<td></td>
<td>3.5 - 5.0</td>
</tr>
<tr>
<td>&quot; bicarbonate&quot;</td>
<td></td>
<td>21 - 26</td>
</tr>
<tr>
<td>Venous plasma ammonia (μg/m/100 ml)</td>
<td></td>
<td>20 - 60</td>
</tr>
<tr>
<td>Total Serum proteins G/100 ml</td>
<td></td>
<td>6.0 - 8.0</td>
</tr>
<tr>
<td>Serum albumen G/100 ml</td>
<td></td>
<td>3.6 - 4.7</td>
</tr>
</tbody>
</table>

Note - different range for liver function tests but not with other values.
### APPENDIX II.

#### List of Abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>Analog-digital convertor.</td>
</tr>
<tr>
<td>AMPO</td>
<td>'Amplitude' eyes open.</td>
</tr>
<tr>
<td>AMPS</td>
<td>'Amplitude' eyes shut.</td>
</tr>
<tr>
<td>BNI</td>
<td>Burden Neurological Institute.</td>
</tr>
<tr>
<td>DF</td>
<td>Dominant Frequency.</td>
</tr>
<tr>
<td>LR</td>
<td>Log reactivity.</td>
</tr>
<tr>
<td>MDF</td>
<td>Mean Dominant Frequency.</td>
</tr>
<tr>
<td>RAO</td>
<td>'Rhythmic Activity' eyes open. (equivalent to AMPO)</td>
</tr>
<tr>
<td>RAS</td>
<td>'Rhythmic Activity' eyes shut. (equivalent to AMPS).</td>
</tr>
<tr>
<td>SWI</td>
<td>Slow wave index.</td>
</tr>
</tbody>
</table>

#### E.E.G Definitions.

<table>
<thead>
<tr>
<th>Range Type</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha Range</td>
<td>8.0</td>
<td>13.0 c/s</td>
</tr>
<tr>
<td>Theta Range</td>
<td>4.0</td>
<td>7.9 c/s</td>
</tr>
<tr>
<td>Delta Range</td>
<td>1.0</td>
<td>3.9 c/s</td>
</tr>
</tbody>
</table>