in DNA from those parts of the world where the sickle genes are frequently associated with the 13-kb fragment.[12,19] These include Nigeria, Ghana, Algeria, Morocco, several Mediterranean countries (Sicily, Cyprus, Greece), and Jordan in the Middle East. However, in Gabon, Kenya, Saudi Arabia, and India, where the sickle genes are rarely linked to the 13-kb *Hpa* I polymorphism, the *Hpa* I assay is not useful. Linkage analysis with other restriction site polymorphisms such as *Hin* dIII, may detect some additional cases,[18,20] but large family studies are needed to establish the linkage phase. In contrast, direct DNA analysis of a lesion does not require extensive family studies. The enzyme *Dde* I detected the sickle mutation in all the populations we studied.

Since silent base substitutions affecting the third base of a codon are known to occur, in some races the normal codon for $\beta^{6\ Glu}$ could conceivably be GAA instead of GAG and the valine codon in the sickle mutation could then be GUA. In these cases, the nucleotide sequences of both the β^A and the β^S genes (CCTGAA and CCTGTA) would not be recognised by *Dde* I at this position. In the populations we studied, however, the β^A gene retained the *Dde* I site and produced the 180-bp fragment in every instance. The normal β^6 sequence in all these DNA samples must therefore be GAG.

At present, there are two limitations to this assay. First, *Dde* I analysis will not detect the β^C gene, as the $\beta^{6\ Glu \rightarrow Lys}$ mutation produces the sequence *CCTAAG* which is cleaved by *Dde* I, and therefore cannot be distinguished from the β^A genotype. The *Hpa* I polymorphism is more useful since over 95% of the β^C genes are associated with the 13-kb fragment.[17,19] Another drawback is that about 10 μg of DNA is required for analysis, since the small DNA fragments generated by *Dde* I produce weak hybridisation signals. This quantity can be obtained only by culturing the amniotic fluid cells. In contrast, *Hpa* I produces large fragments, thousands of basepairs long, which are easily detectable in DNA isolated from uncultured amniotic fluid. In many countries where sickle cell anaemia occurs frequently, cell culture would greatly increase the workload and might not be economically feasible. Hence, a more sensitive assay needs to be developed.

Our current approach to antenatal diagnosis of sickle cell anaemia runs as follows. If the *Hpa* I polymorphism is present and the linkage phase can be firmly established by study of a previous SS or AA child, we directly analyse uncultured amniotic fluid cell DNA. If these conditions are absent, we analyse cultured amniocytes with *Dde* I.

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肝細胞癌 PHC

HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS B肝

A Prospective Study of 22 707 Men in Taiwan

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假設：B肝病毒是PHC的病原學主要角色
前瞻性研究 B肝抗原帶原者的肝細胞癌發生率高

Summary A prospective general population study of 22 707 Chinese men in Taiwan has shown that the incidence of primary hepatocellular carcinoma (PHC) among carriers of hepatitis B surface antigen (HBsAg) is much higher than among non-carriers (1158/100 000 *vs* 5/100 000 during 75 000 man-years of follow-up). The relative risk is 223. PHC and cirrhosis accounted for 54·3% of the 105 deaths among HBsAg carriers but accounted for only 1·5% of the 202 deaths among non-carriers. These findings support the hypothesis that hepatitis B virus has a primary role in the aetiology of PHC.

RR=223

肝細胞癌和肝硬化在HBsAg帶原者死亡率中占54.3%

Introduction

PRIMARY hepatocellular carcinoma (PHC) is the most common malignant neoplasm in China, in much of Asia, and in Africa,[1–5] but it is uncommon in the U.S.A. and Europe. It ranks 22nd among malignancies in White men in the U.S.A., accounting for less than 1% of all malignancies.[3] Many possible aetiological factors have been implicated, but most of these (for instance, androgenic steroids or hepatic parasites) do not occur widely enough or do not show the same geographical distribution as PHC and can explain only a small proportion of cases. Two implicated factors, aflatoxins and hepatitis B virus (HBV), occur widely; it is possible that they may have major aetiological roles in PHC and macronodular cirrhosis, in which PHC arises.[1,6,7]

PHC在中國 亞洲 非洲常見 但美國 歐洲罕見
很多病原學因素都不夠廣泛分布 不然就沒有跟PHC一樣的地域分佈 只能解釋疾病一小部分
黃麴毒素和HBV廣泛出現 很有可能是主要病原

MS JUDY CHANG AND PROFESSOR YUET WAI KAN. REFERENCES *continued*

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1. 早期病例對照顯示PHC HBV弱相關
2. 後來更多敏感度高的偵測HBsAg科技 顯示其出現在PHC病人血清中的頻率顯著高於控制組

Early case-control studies showed poor correlation between PHC and HBV.[8,9] Later, more sensitive techniques for the detection of hepatitis B surface antigen (HBsAg) showed that HBsAg appeared in the serum of patients with PHC substantially more frequently than in serum from controls.[10–12] Epidemiological studies have revealed a very strong correlation between the geographical frequency of the HBsAg carrier state and prevalence of PHC.[1] Several other observations have strengthened the association between PHC and the chronic HBsAg-carrier state, and there is widespread awareness that HBV may have a major role in the aetiology of PHC.[13,14] Our large-scale cohort study started in 1974, when there was little awareness or acceptance of the possible association between HBV and PHC, in order to establish prospectively the incidence and the relative risk of PHC among HBsAg carriers and to determine whether the HBsAg-carrier state is antecedent to the development of PHC. This report is the first on this prospective general population study of 22 707 Chinese men. 15·2% of whom are HBsAg carriers.

該報告是這項針對22 707名中國男性進行的前瞻性總體研究的第一份報告，其中15.2%是HBsAg攜帶者。

Subjects and Methods

Study Population and Recruitment

The study is being conducted among male Chinese government employees (civil-servants) in Taiwan because their life and health insurance system provides almost total ascertainment of the fact of death with excellent determination of cause of death. The study was restricted to men for the following reasons: prevalence of PHC is three to four times higher in men than women; there are more male government employees; their average age is higher; and they stay in government service longer. Initially, enrolment was restricted to men aged 40 to 59 years; later, because of general popularity of the project, men of all ages were recruited. Study participants were recruited through two sources:

1. Government Employees' Clinic Centre (GECC) men were enrolled during routine free physical examinations or selected other clinics (e.g., dental, ear, nose, and throat, and ophthalmology) where it was considered likely that a sample unbiased for liver disease could be obtained.
2. Cardiovascular Disease Study (CVDS) men had been recruited from the GECC ten years earlier, when they were 40–59 years old, for a prospective study of cardiovascular disease risk factors; they had been kept under active surveillance since then.

Potential participants from the GECC group were given a written description of the study while they were waiting for their clinic appointment. Those willing to participate (99·99%) signed a consent form and completed a brief health questionnaire. A portion of serum from the sample taken as part of the subject's routine examination was procured for our study. We wrote to participants from the CVDS group, explaining the study and inviting those interested (89·6%) to come to our clinic, where a blood sample was obtained and a similar health questionnaire was completed. There were 1480 men in the CVDS group and 21 227 men in the GECC group. The CVDS and GECC groups are almost identical in most respects but the CVDS group is older. We believe the study participants are representative of male government employees in Taiwan as regards health but, compared with the general population, government employees have higher educational backgrounds and better health care, and enjoy better living conditions and health. The frequencies of HBV infections, cirrhosis, and PHC are similar in government employees to those in the general population. The HBsAg carrier rate is the same as that in other groups of men of the same age, and the mortality rate from PHC and cirrhosis is approximately the same as that in the general population.

Detection of PHC

PHC is detected through the health and life insurance which is mandatory for all government employees and is provided by a single large government bureau operating exclusively for this purpose. Insurance is usually retained after retirement and can be cancelled only at the request of the retired person. Substantial financial benefits are paid by the insurance system irrespective of cause of death and there are few, if any, deaths for which no claim is filed. Thus, all deaths of active government employees and deaths of most retired government employees are known to the insurance bureau: we receive from the bureau monthly lists of recent deaths and newly retiring employees who have cancelled their insurance. Each government employee has a unique number which is retained even after retirement and is never duplicated. Death and retirement lists are compared by computer with the study population and verified. We contacted by letter or telephone newly retired men who cancelled their insurance, to find out about their state of health. To date only 643 men have cancelled their insurance (2·8% of study subjects). To verify the completeness of the insurance system for the ascertainment of deaths, we actively followed all HBsAg-positive men and controls matched for age and province of origin with each HBsAg-positive man. Province of origin represents the historical origin of the man's family in China and in all but a few men corresponds to place of birth. This active surveillance involved annual completion of a health questionnaire and retesting for HBV markers. Adherence to follow-up has averaged 95% annually. The state of health of those who failed to return for follow-up was determined by telephone or home visit. We lost contact with only 74 men and could not verify that they were still alive. From this active surveillance we were able to verify that among men retaining their insurance all deaths are known to us. We contacted 569 of the 643 men who cancelled their insurance (88·5%) leaving only 0·3% of the original recruits whose possible deaths would not be known to us.

Diagnosis of Cause of Death

The causes of death of all study subjects are investigated through the records of preceding periods in hospital. Most deaths, other than sudden deaths, among government employees occur in hospital or very soon after discharge and most patients have been admitted to large well-equipped and well-staffed hospitals so that clinical parameters relating to cause of death are usually well established; necropsies, however, are not common. Among the 41 deaths due to PHC that we report, 19 (46·3%) were confirmed histologically. 19 of the remaining patients had had raised serum alpha fetoprotein (AFP) levels and changes on a liver scan, or angiography, or both, interpreted as PHC; 1 more patient had had scans interpreted as PHC but AFP was not measured, and the remaining 2 patients had had raised AFP levels and their clinical picture was interpreted as PHC. The clinical picture, liver scan, and angiographic patterns did not differ between histologically confirmed and unconfirmed cases. In fact, for the patients we report as having PHC the diagnoses were clear and there appeared no likely alternatives. Deaths attributed to cirrhosis all showed unequivocal clinical evidence of chronic hepatic failure in the presence of portal hypertension and other classical evidence of cirrhosis.

Laboratory Tests

All recruitment and follow-up specimens are tested for HBsAg, alanine aminotransferase, and AFP. Anti-HBs and anti-HBc (hepatitis B core antigen) testing were too expensive to undertake on all 19 253 HBsAg-negative subjects. All 1020 HBsAg-negative men from the CVDS group and controls matched for age and province of origin with each HBsAg-positive subject in the GECC group were selected from among the HBsAg-negative subjects for anti-HBs testing. 3661 men were tested for anti-HBs. From these, all the 615 who were anti-HBs-negative were tested for anti-HBc. The anti-HBs and anti-HBc rates derived from the above sample were then used to project the frequency of these markers for the entire study population. HBV markers are tested by radioimmunoassay (RIA) with standardised commercial kits ('AUSRIA', 'AUSAB', and 'CORAB', Abbott Diagnostics, North Chicago). AFP levels are also measured by RIA with a commercial kit, ('AFP-PEG', Dianabot, Tokyo).

Results

Between Nov. 3, 1975, and June 30, 1978, 22 707 men were enrolled in the study; 81·6% were aged between 40 and 59 years. Within this age range our sample constitutes 12·8% of male government employees and 1·4% of all males in Taiwan. Among the 22 707 men, 3454 were HBsAg-positive (15·2%), and 19 253 were HBsAg-negative (84·8%). From sample testing we estimate that 15 570 (68·6%) would be anti-HBs positive, 2248 (9·9%) would be anti-HBc positive only, 1272 (5·6%) would be negative for all three HBV markers, and in 163 (0·7%) the anti-HBc results would be borderline. By Dec. 31, 1980, 307 study subjects had died, and 74 had retired and cancelled their insurance and could not be traced (0·3%). We had carried out approximately 75 000 man years of follow-up, an average of 3·3 years per man.

Of the 307 deaths, 41 were due to PHC and 19 to cirrhosis. Thus, PHC and cirrhosis together accounted for 19·5% of all deaths. The next most common causes of death were accidents (11·4%), ischaemic heart disease (10·7%), and lung cancer (9·1%).

There was a very pronounced excess of deaths from PHC and cirrhosis in those who were HBsAg-positive on recruitment (table I). Of the 41 men who died of PHC, 40 were in the group of 3454 men who were HBsAg-positive and only 1 was in the group of 19 253 HBsAg-negative subjects, a relative risk of 223.

There was also a large excess mortality from cirrhosis among HBsAg-positive men. 17 of 19 men who died from cirrhosis were HBsAg-positive. PHC and cirrhosis together accounted for 57 of 105 deaths among the HBsAg-positive subjects (54·3%) compared with 3 of 202 deaths among the HBsAg-negative subjects (1·5%). There was a slight excess of mortality from other causes among the HBsAg-positive men, but the difference was not significant. Together PHC and cirrhosis accounted for 19·5% of all deaths in the total study population.

Of the 3 HBsAg-negative men who died of PHC (1) and cirrhosis (2), 1 of the cirrhosis patients was anti-HBs-positive and the others were positive for anti-HBc only. Thus, the risk of dying from PHC or cirrhosis was much lower in HBsAg-negative men even if they were positive for other HBV markers. If anti-HBc-positive men had the same risk of PHC as those who were HBsAg-positive, approximately 26 anti-HBc-positive men would have died instead of only 1 ($p<0·00001$).

PHC frequently coexists with cirrhosis, and patients with cirrhosis are at increased risk of PHC. The frequency of underlying cirrhosis in this study population is of course unknown. All 22 707 men were asked on recruitment if they had ever had liver disease and to give details of such disease. 70 reported they had previously been told they had cirrhosis; we were able to confirm this by examining their medical records. Of the 40 HBsAg-positive men with a history of cirrhosis on recruitment, 12 have died (table II), 5 from PHC and 7 from cirrhosis (30% combined). None of the 30 HBsAg-negative men with a history of cirrhosis on recruitment have died (table II).

1257 men gave a history of having had "hepatitis" on recruitment. 390 were HBsAg-positive (31%); 8 of the 390 men have subsequently died of PHC (2·1%), whereas there were no PHC deaths among 867 HBsAg-negative men with a history of "hepatitis" on recruitment.

The incidence of death from PHC during the study period was 181/100 000 for the entire group and for HBsAg-positive men only it was 1158/100 000. These figures convert to annual incidence figures of 55/100 000 and 351/100 000, respectively. Whether calculated for the whole group or for HBsAg-positive subjects only, the incidence of PHC deaths rose as a direct function of age (table III).

To verify that this prospective study is measuring the continuing incidence of new liver carcinomas (not subclinical tumours present at the time of enrolment) we analysed the PHC deaths according to time since recruitment. As expected, the incidence was almost constant over time (table IV).

There were subjects in the study who come from most of China's 35 provinces. The 16 most populated provinces were each represented by 100 or more subjects who made up 93% of the study participants. The prevalence of HBsAg varied from 4·7% to 20·1% in the subjects from these 16 provinces. There were cases of PHC among participants from 13 of the

TABLE I—DEATHS BY CAUSE AND HBsAg STATUS ON RECRUITMENT

HBsAg status on recruitment	Cause of death			Population at risk	PHC incidence*
	PHC	Cirrhosis	Other		
HBsAg-positive	40	17	48	3454	1158
HBsAg-negative	1	2	199	19 253	5
Total	41	19	247	22 707	181

*Incidence of death from PHC per 100 000 during the time of the study.

TABLE II—DEATHS BY CAUSE, PREVIOUS HISTORY OF CIRRHOSIS, AND HBsAg STATUS

Status on recruitment	Cause of death			Population at risk	PHC incidence*
	PHC	Cirrhosis	Other		
Previous cirrhosis:					
HBsAg-positive	5	7	0	40	12 500
HBsAg-negative	0	0	0	30	0
No cirrhosis:					
HBsAg-positive	35	10	48	3414	1025
HBsAg-negative	1	2	199	19 223	5
Total	41	19	247	22 707	181

*Incidence of death from PHC per 100 000 during the time of the study.

TABLE III—PHC INCIDENCE BY AGE AT RECRUITMENT

Age*	Subjects			PHC deaths	PHC incidence per 100 000†	
	Total	HBsAg-positive No.	(%)		Total	HBsAg-positive
20–29	647	130	(21·1)	0	0	0
30–39	1814	398	(21·9)	1	55	251
40–49	8338	1415	(17·0)	4+1‡	60	283
50–59	9949	1303	(13·1)	28	281	2149
60–69	1920	206	(10·7)	7	364	3398
>70	39	2	(5·1)	0	0	0
Total	22 707	3454	(15·2)	40+1‡	181	1158

*Age when HBsAg status first determined.
†Incidence of death from PHC per 100 000 during the time of the study.
‡HBsAg-negative.

TABLE IV—PHC INCIDENCE AND LENGTH OF FOLLOW-UP

Year of follow-up	HBsAg-positive		PHC incidence*
	Men in follow-up	PHC deaths	
1	3454	15	434
2	3426	11	321
3	3397	7	206
4	2275	6	264
5	309	1	324

*Incidence of death from PHC per 100 000 during the time of the study.

16 provinces. There were no significant differences in the incidence of deaths from PHC among HBsAg carriers by province.

Discussion

This study shows that the risk of PHC is much higher in HBsAg carriers than in non-carriers. The results support the hypothesis that HBV has a role in the aetiology of PHC. In this large prospective study, the present relative risk estimate of PHC is 223 for HBsAg carriers compared with non-carriers. However, since all but 1 of the subjects who died from PHC were HBsAg-positive, the 95% confidence interval for the relative risk is quite wide (28 to 1479). Irrespective of the eventual value for the relative risk, it is clear that it is very high. This study establishes beyond any doubt that the HBsAg carrier state commonly precedes PHC in Chinese men. The primary contributions of a prospective study are to establish the prior occurrence of a factor or agent in relation to the disorder in question, to verify increased relative risk estimates made from case-control studies, and to establish or verify the incidence of the disease. Our study strongly supports the hypothesis that HBV has a role in the aetiology of PHC because it establishes a very much increased risk of PHC among persons who were HBsAg carriers before they developed PHC.

Although this study strengthens the argument that HBV may be a cause of PHC, it does not prove it. Alternative explanations of the very high relative risk among HBsAg carriers are that HBV is a cofactor with another aetiological agent or is simply a risk factor. The very high relative risk found in this study and many case-control studies in various parts of the world, however, suggests that HBV is closely associated with the process leading to PHC and is not simply a risk factor. This association is in fact the strongest ever established between a virus and a human neoplasm.

Case-control studies have repeatedly shown that PHC does occur in HBsAg-negative subjects. This finding can be taken to mean either that HBV is not sufficient to cause PHC or that there are several independent causes. The fact that some cases of PHC are not associated with HBV is a weak argument against its aetiological role, for many diseases have multiple independent aetiologies.

Before the strong association between HBV and PHC was established, aflatoxins in foodstuffs were thought to be the most probable cause of PHC. Aflatoxins are established hepatic carcinogens in many animal species,[6,15] and many studies have shown that aflatoxins are frequently present in human foods in areas of the world with high incidences of PHC.[16–19] A study in Africa showed a geographical correlation between the amount of aflatoxin in food and the incidence of PHC.[20] Aflatoxin-feeding experiments in monkeys, however, suggest that primates are much less sensitive to the carcinogenic effects than many other species.[21] Aflatoxins have been demonstrated in foodstuffs in Taiwan but there are insufficient data regarding distribution, frequency, or concentration.[2] No effort in this study was made to study aflatoxins mainly because there is no way to measure previous aflatoxin exposure; and because the Chinese diet is so complex, food sampling for aflatoxins is a formidable task. All we can say is that the currently available data are consistent with HBV having a role as an independent aetiological agent in PHC or as a cofactor with aflatoxin. The very high relative risk among HBsAg-positive men in this study, however, suggets that HBV is an almost essential factor, whereas the aflatoxin in the food in Taiwan is not likely to be an independent inducer of PHC among Chinese men.

PHC usually occurs in cirrhotic livers.[23,24] Prospective studies of patients with clinical cirrhosis have shown a considerably higher risk of PHC among HBsAg-positive than HBsAg-negative cirrhosis patients.[14] The data from our study also show a close relationship between PHC and cirrhosis; 30 of the 41 (73%) men who died of PHC also had cirrhosis. Since necropsies were not done, this figure might be considered an underestimate of cirrhosis in PHC; however, cirrhosis was found in a similar proportion (14 of 19; 74%) of histologically confirmed PHC cases. Thus, our study suggests that HBsAg carriers are at increased risk of PHC even if they do not have underlying cirrhosis. It is not possible to find out whether the risk of PHC is greater in HBsAg carriers with cirrhosis since most subclinical cirrhosis cannot be diagnosed in a population study. The data from this study, however, show that an HBsAg carrier with clinical cirrhosis is at considerably greater risk of dying from PHC than a carrier with no suspicion of liver disease. PHC did not develop in any of 30 HBsAg-negative men who were known to have cirrhosis when they joined the study but did develop in 5 of 40 HBsAg-positive men with clinical cirrhosis when they were recruited. This finding indicates that HBV rather than cirrhosis promotes PHC, as suggested by the prospective study by Klatskin[25] of subjects with chronic active hepatitis in the U.S.A.; among the 24 HBsAg-positive patients PHC developed in 3, whereas none of the 67 HBsAg-negative patients developed PHC.

Death-certificate data from Taiwan show that PHC is the most common malignant neoplasm, accounting for 20% of all malignancies for both sexes combined and for 25·4% of malignancies among men only. Our study, in which cause of death is generally well established and which is more reliable than figures derived from death certificates, suggests that the death-certificate data have underestimated the frequency of PHC in Taiwan. Together PHC and cirrhosis in this study accounted for 20% of all deaths and 54% of all deaths among HBsAg-positive male carriers. PHC accounted for 37% of malignancies in our study compared with 25·4% of malignancies in men from death-certificate data. The death-certificate data give the ratio of PHC deaths to cirrhosis deaths as 0·78%, whereas in our study the ratio is 2·6. This pronounced difference suggests that many deaths due to PHC are attributed to cirrhosis on death certificates.

Although this study contributes substantially to the understanding of the relation between HBV and PHC, it leaves many unsolved questions: what is the role of cirrhosis in the aetiology and pathogenesis of PHC; do HBV carriers of other races and in other places have the same risk of PHC as Chinese men in Taiwan; and what factors determine which HBV-infected persons will develop PHC? Where feasible, prospective studies should be carried out in other populations.

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LUMBAR PUNCTURE HEADACHE: CONTROLLED STUDY ON THE PREVENTIVE EFFECT OF 24 HOURS' BED REST

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Summary Lumbar puncture was performed on 100 neurological patients by one investigator, using one needle size. 50 patients were kept ambulant and the other 50, who were comparable in age, sex, and neuroticism, were given 24 hours' bed rest. The incidence of post-lumbar-puncture headache did not differ significantly between the two groups.

Introduction

LUMBAR puncture (LP) is often followed by headache, which may be accompanied by nausea and vomiting or giddiness, and sometimes by neck stiffness. Characteristically, these complaints are posture-dependent: they arise when the patient is upright and subside when the patient lies down.[1]

LP headache is usually explained in terms of cerebrospinal fluid (CSF) hypotension: after-leakage of CSF through the dural needle-hole leads to compensatory dilation of cerebral veins, increased brain volume, and downward brain sagging when the patient is upright, with traction on pain-sensitive structures.[2-5] According to Wolff, LP headache has all the characteristics of CSF drainage headache.[5] There may also be psychogenic factors.[6,7]

The average incidence of LP headache is 33%. It varies with the size of the needle and perhaps other factors such as the patient's age and sex.[1] An effect of the technique of LP (e.g., the number of dural punctures) seems possible but has not been shown. The volume of CSF removed at the time of puncture, up to 12 ml, has no effect on the incidence of LP headache;[8] nor does the neurological diagnosis.[1]

Various methods are used to prevent LP headache, but only the use of a very thin needle (26 G) is of proven efficacy.[9] The preventive effect of the prone position for 3 h[10] has not been substantiated;[1] the head-down position is being studied.[11]

Bed rest for 24 h to prevent LP headache was recommended in 1902 by Sicard[12] and is still used widely.[13,14] However, the reports on its efficacy are contradictory.[1] To our knowledge no controlled studies on the preventive effect of 24 hours' bed rest are available. Therefore we conducted a controlled study of the incidence, time of onset, duration, and severity of LP headache in 100 neurological patients.

Patients and Methods

LP was performed for diagnostic reasons in 100 neurological patients by one investigator (P. A. T. C.). 50 patients were mobilised immediately afterwards and 50 after 24 hours' bed rest with one pillow; no particular posture in bed was prescribed. Excluded from the study were patients who (1) could not be mobilised, (2) could not be interviewed, (3) were expected to have an abnormal CSF pressure, (4) had had an LP within the past month, and (5) were less than 13 years old.

LP was done with the patient in the lateral recumbent position, always with an 18 G needle. This size was chosen because it is used most commonly in clinical practice[14] and does not preclude Queckenstedt's test. Pressure was measured before and after withdrawal of 12 ml CSF. The number of dural punctures was estimated and noted.

To eliminate a possible effect caused by improvement in LP technique, the first 25 patients were mobilised, the next 50 were given bed rest, and the last 25 were mobilised. Randomisation was rejected because the patients would have found it difficult to accept since they often discuss LP. LP was explained in a standard manner and patients were invited "to record their experiences". The purpose of the whole study was not mentioned. No patient refused.

If patients had typical LP headache in the opinion of the physician in charge, bed rest was prescribed until the next morning; if it then recurred on mobilisation, bed rest was prescribed again until the next day, and so on. No other measures to prevent LP headache (e.g., analgesics, extra fluid, or head-down position) were used.

Follow-up was for 7 days. On the 7th day the patients were interviewed by a member of the neuropsychological department. The interview consisted of: (1) a standard list of questions worded so as to avoid suggestion and related to post-puncture complaints, mixed with unrelated questions; (2) a personality questionnaire which rates neuroticism (the Dutch Personality Questionnaire) modified for neurological patients.[15]

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