AN INVESTIGATION

OF THE

INCIDENCE AND ETIOLOGY

OF

CIRRHOSIS OF THE LIVER

IN SINGAPORE

BY

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C O N T E N T S

F O R E W O R D

This thesis was commenced in 1934, when I had the opportunity of investigating a large number of cases of cirrhosis of the liver, all proved at post-mortem. During the three previous years my interest in the subject had been aroused, when I saw a considerable number of cases of the disease. I read a fair amount of the literature on cirrhosis, and was struck by the diverse arguments that had been advanced for its causation. I took the opportunity offered of investigating a large series of cases here. From the beginning it was obvious that the task was one of considerable magnitude.

I completed my original paper in 1936 when I went home on leave, and I had then submitted the essential conclusions that I have brought forward now. There were, however, numerous points that appeared to require further consideration, so I decided to await my return to Singapore and see if I could improve matters. Unfortunately time has been very limited during the last two years, and I have not the opportunity to do as much as I should have liked.

I have tried to discuss the subject from the point of view of the disease as seen locally, and the likely factors that are associated with it. In doing this I feel I may have presented some views from an unusual angle. At the same time I have endeavoured to keep before me the findings of the various workers

who have written on the subject of cirrhosis, particularly in the Tropics. The work has been done while engaged in a busy general practice.

I am indebted to several people for their assistance. The work was made possible by Dr. J. C. Tull, Government Pathologist, Singapore, who allowed me access to his clinic and his records. During the last two years his successor Dr. H. O. Hopkins has given me similar privileges. Dr. C. L. Park, Director of the League of Nations Health Bureau, Singapore, allowed me the use of the Library there. Major W.J.F. Craig, R.A.M.C. gave me considerable information and literature from Japan.

The photographs have been prepared from specimens kindly supplied by Drs. Tull and Hopkins from the Pathology Department, King Edward VII College of Medicine, Singapore. I am indebted to Messrs. Kodak and Nakajima, Singapore, and Messrs. Charles Baker, London, for preparing these.

Singapore, August 1938.

INTRODUCTORY.

Cirrhosis of the liver has long been recognised as a common condition in certain tropical countries, particularly in India, Java and Malaya. In Great Britain, when one sees a case of cirrhosis of the liver, the first thought is to associate the condition with an excessive consumption of alcohol over a considerable period of time. In the Tropics the disease is frequently seen amongst people who abstain from alcohol. This was pointed out in 1911 by Sir Leonard Rogers when he noted that the incidence was nearly as high amongst the Mohammedans, whose religion forbids them alcohol, as amongst the Hindus who have no such restrictions. Reports from other parts of India than those quoted by Rogers (1) and from Java (2), Siam (3), and Malaya (4) show that a fatal cirrhosis having no definite relationship to the consumption of alcohol is common in these places.

Various explanations have been put forward to account for the disease, but no theory appears to explain more than a limited number of cases. In studying the literature, one is struck by the complete failure to arrive at any definite conclusions, although there are several enthusiasts who are well satisfied with their own views, but at the same time are equally scathing of the other opinions. When I arrived in Singapore in 1932, I saw several cases of the disease in a short space of time and I was able later to see numerous examples in the post-mortem room. It might be well at this stage to quote a few

clinical cases which came under my observation.

Case 1. Chinese (Hokien) age 33, seen at Rengam Estate Hospital. He was employed as a labourer and had been in irregular employment in various parts of Malaya for the last ten years since he arrived from China. He had been ill for two to three months previously when he noted slight swelling of the abdomen. On examination he was fairly well nourished. There was well marked ascites and oedema of both ankles. Nothing abnormal was found in heart or lungs. The blood count was R.B.C. 3,800,000, Hb 60%, W.B.C. 5,400.

The abdomen was tapped and straw coloured fluid removed. The liver was then found to be enlarged to two inches below the costal margin. The spleen was just palpable. The Wasserman reaction was negative. He left hospital of his own accord, stating that he was returning to China.

Case 2. Indian (Malabari) age 40. He was employed at the Singapore Naval Base as a clerk for the past ten years. He had suffered from malaria three years previously, but had been treated efficiently. He had been a regular drinker of brandy since coming to Singapore, but stated that he had given up drinking during the past year. His illness commenced nine months before with a feeling of general weakness, and a flatulent dyspepsia. During the last four months he had lost a considerable amount of weight, but at the same time noticed

a gradual swelling of the abdomen and he complained of constant severe pain in the right hypochondrium.

Examination showed a very emaciated man with a distended and tense abdomen. Aspiration revealed a large quantity of bile-stained fluid. There was then found a large hard irregular mass just under the right costal margin and extending downwards for about four inches, while the spleen could not be felt. Blood examination showed R.B.C. 2,840,000, Hb 35%, W.B.C. 7,200. There was no abnormality in heart and lungs. His general condition became rapidly worse and he died after a further two weeks. Post-mortem examination showed an enlarged cirrhotic liver with extensive carcinomatous areas. No other lesions of importance were noted.

Case 3. Female Indian (Tamil), age 25. She complained of general weakness of one year's duration. Examination showed enlargement of both liver and spleen. The surface of the liver was regular and extended to two inches below the costal margin. The spleen was enlarged almost to the umbilicus. There was no sign of ascites. The blood count was R.B.C. 3,200,000, Hb 55%, W.B.C. 4,250 and blood Wasserman negative. She had been in Malaya for eighteen months only. She could give no history of any previous illness and she had never taken any alcohol. Splenic puncture was suggested by Dr. Tull, but revealed no evidence of kala-azar. She was given a course of antimony but without any benefit, and she returned to India three months after being first seen.

Case 4. Chinese (Hylam) coolie, age 40. He stated that he had vomited a cupful of blood. For the previous six months he had suffered from indigestion, but had never been sick before that. He was moderately well nourished. The liver was palpable just below the costal margin. The spleen was enlarged to midway between the costal margin and the umbilicus. The blood showed a considerable degree of anaemia, R.B.C. 2,530,000, Hb 35%, W.B.C. 6,700. He improved steadily with rest and had no further haemorrhages for another three months after the original attack, when he was lost sight of.

Case 5. Tamil male, age 45. He was seen at Rengam Estate Hospital. He had been employed on the estate since 1919 and an accurate account of his health was obtainable from the records. He had had numerous attacks of malaria from 1919 until 1930, but no other illness of any importance. He had consumed a moderate amount of "toddy" regularly. He complained of general weakness and had been unable to do his work as well as he did previously. Examination showed enlargement of the liver to two inches below the costal margin and of the spleen to within one inch of the umbilicus. His spleen had been enlarged since 1928 and had not been influenced by any anti-malarial treatment. The liver enlargement had not been noted previously. The general condition was moderately good. Blood examination showed R.B.C. 3,800,000, Hb 60%, W.B.C. 8,200. Examination otherwise was negative. Since the first examination in 1933 he has been

seen at regular intervals during the last two years. His condition has not showed any change and he continues to do light work.

Cases such as those are not uncommon in general practice in Malaya, and in hospital practice they are naturally much more frequent. I discussed the question of cirrhosis with Dr. J.C. Tull, Government Pathologist, Singapore, and through his courtesy I was able to see a considerable number of cases in the post-mortem room. He allowed me access to his records, and I decided to investigate a large series of cases and see if any definite conclusions could be arrived at. The small number of cases I had seen personally had presented a variety of conditions, and had not revealed anything etiological in the history or clinical examination, but it was hoped that a large number might show something more definite.

The patients belong to several different nationalities and in the case of the Chinese there are various sects. These sects differ considerably from each other in their native land in language, customs and habits, and in Malaya they tend to retain many of these characteristics. It was hoped that in the particular sects some factors might be noted which would throw light on the etiology of the disease. All the cases belong to the poorer classes, the majority being coolies who are employed as labourers in various trades. Their livelihood is precarious at the best of times, as wages are very low and do not permit of much more than mere existence. They do not seek medical advice readily, but in the event of prolonged sickness they are forced to obtain hospital

treatment. This is provided for them in the Tan Tock Seng Hospital, Singapore, which has accommodation for one thousand patients. The majority of these patients are male as it is only since 1929 that thirty beds have been allocated for females. Many of the patients are admitted to hospital in a really hopeless condition and so the death rate is very high. In addition to hospital post-mortems most of the medico-legal or Coroner's cases for Singapore Island are conducted in this clinic. These form quite a number of cases, as it will be seen easily that sudden deaths are common in a community that is not well nourished, and does not have reasonable medical attention for its various ailments. The total post-mortems vary from sixty to one hundred a month.

To obtain a sufficiently large series of cases for analysis, I have investigated the post-mortem reports for ten years from 1924 to 1933 inclusive. This series gives an uniformity of opinion as the pathological clinic has been under the charge of Dr. J.C. Tull, M.D., F.R.C.P. (Lond.), during the whole of this period. He has been very interested in the question of cirrhosis, and more particularly in primary carcinoma of the liver which frequently follows cirrhosis, and so the pathological changes have always been noted carefully.

The total number of cases investigated is 8,522. Chinese constitute 88%, Tamil 7.68% and Malays 1.02%. The last figure is rather striking. At first one would expect a higher incidence in the people of the country. The Malay population of Singapore

Island is equal to one-fifth that of the Chinese, but the Malay is very unwilling to accept European medicine and even when dying will not go to hospital, but prefers to remain amongst his relatives in his native village.

The Chinese are divided into various groups as follows:-

1. Hokkiens are people who come from the Southern part of Fukien Province and make their way to Malaya through the port of Amoy.

2. Hochews, also known or subdivided into Hochews, Hochias, Hockchews, live in the northern part of Fukien and through the capital and sea-port Foochow make their way to Malaya.

3. Hengwhas also come Fukien in the zone between the two preceding groups. Their exit from China is by way of Hengwhafu.

4. Teochews are people from south-east of Canton Province. Their sea-port is Swatow.

5. Cantonese are people from Kwangtang Province lying west and south of Hongkong.

6. Hylams are natives of the Island of Hainan in the extreme south of China.

7. Kwangsi and Leuchews. These people come from the mainland of South China. Their numbers are too few in the present series to provide any useful information.

8. Khehs or Hahkas are a nomadic race, who were driven out of the interior of China and finally settled on the borders of Kwangtang, Kiangsi and Fukien Provinces. They are a lazy race

SOUTH CHINA

SHOWING ORIGIN OF

VARIOUS CHINESE SECTS.

and are considered a poor type of Southern Chinese.

Some of the sects show preference for particular types of work. The Cantonese are often employed as cooks, while the Khehs form the bulk of the gardeners or weeders. Hochews constitute the majority of the rickshaw pullers in Singapore. The others are employed in various occupations as dock labourers, rubber estate workers, road coolies, gardeners, building trade labourers. Many of these Chinese have been in Malaya for a considerable number of years, but others have only been for a comparatively short time.

Apart from Chinese, Tamils are the only nationality whose numbers are sufficiently large to allow of any reasonable conclusion being drawn as to the frequency of cirrhosis. They are employed chiefly as rubber estate coolies and by the various Municipalities as town cleansers and road coolies. By arrangement with the Government of India, Tamil labourers are medically examined before leaving for Malaya, and so the incidence of ill-health amongst them in Malaya is considerably less than in their own country, since those suffering from obvious disease are not allowed to leave for Malaya.

The Chinese may be divided into two classes. Many of them have been in Malaya for a considerable number of years and have made it their home. They have produced families in Malaya and a considerable number of these Straits-born Chinese have adopted British nationality, preferring the prosperity, law and order of Malaya to the poverty and unrest of South China. The others come from China looking for work and their numbers fluctuate with the

MAP OF INDIA AND FAR EAST

SHOWING PLACES FROM WHICH

REPORTS IN TEXT

ARE OBTAINED


SHANGHAI
JAPAN
CHINA
FOOCHOW
AMOY
SWATOW
FORMOSA
CANTON
HONG-KONG
HAINAN
BURMA
SIAM
INDO CHINA
BANGKOK
BRITISH MALAYA
SINGAPORE
BORNEO
SUMATRA
BATAVIA
JAVA

state of Malaya's industries, particularly rubber and tin. They form a floating population never really settled for any length of time. They are not subjected to any special medical examination before coming here, and so quite a number of unfit people are admitted.

INCIDENCE OF CIRRHOSIS OF THE LIVER IN VARIOUS COUNTRIES.

To enable comparison to be made with other countries, reliable statistics of the incidence of cirrhosis of the liver confirmed by post-mortem examination have been analysed. Rogers (5) compares his series in Calcutta with those of St. Mary's Hospital, London and with the United Fruit Company's Hospitals in Central America. I have added to this list the results of similar series in Berlin, Holland and my own in Singapore. The following table shows the percentages of deaths from cirrhosis of the liver in these various places:-

	Percentage	Author
Calcutta	6.9	Rogers (5)
London	1.3	Quoted by Rogers
Central America	0.6	" " "
Berlin	1.0	" " "
Holland	1.1	Snijders (6)
Madras	9.3	Menon & Annamalai (7)
Java	7.5	Snijders (6)
Singapore	8.0	Present series

It will be observed that the percentage is very high among

all the places in the Far East. That the condition is not common to all tropical countries is shown by the low figure for the United Fruit Company's Hospitals in Cuba, Costa Rica, Jamaica, Columbia, Panama and Honduras, and I shall show later the disease is not at all common in tropical Africa.

II. ANALYSIS OF POST-MORTEMS IN SINGAPORE.

The total number of post-mortems studied shows a distribution among the various groups as follows:-

Hokkiens	2,357
Teochews	1,488
Hylams	767
Cantonese	748
Hochews	687
Tamils	648
Chinese (unclassified)	536
Khehs	526
Hengwhas	246
Malays (including Javanese)	204
Kwangsais	93
Shanghaiese	80
Indians (other than Tamils)	68
Others	104
	8,552

Roughly eighty-eight per cent of the cases are Chinese, which corresponds with the average percentage of Chinese patients admitted to Tan Tock Seng Hospital, the figure there being eighty-five. In some cases the sect was not noted, but in most of these the nationality was indicated, e.g. Chinese, Indian, etc. Some nationalities such as Europeans, Eurasians, Japanese, Arabs, etc. show such small numbers that no statistical value can be attached

to them, and again in some cases no note was made of the actual country of origin. All of these have been classified under the heading "Others".

ANALYSIS OF CASES SHOWING CIRRHOSIS.

The total number of cases showing evidence of cirrhosis is 687. There are distributed among the various groups as follows:-

Hokkiens	185
Teochews	114
Hylams	54
Cantonese	85
Hoohews	76
Tamils	30
Chinese (unclassified)	38
Khehs	44
Hengwhas	21
Malays	20
Kwangsais	7
Shanghaiese	4
Indians	3
Others	6
	687

SECTS.

If we compare the incidence of the sects in the total cases and cirrhosis cases, we find the results tabulated below:-

Sect	Percentage of Total Cases	Percentage of Cirrhosis Cases
Hokkiens	27.54	26.92
Teochews	17.40	16.59
Hylams	9.08	7.86
Cantonese	8.75	12.37
Hochews	8.03	11.06
Tamils	7.58	4.37
Chinese	6.28	5.53
Khehs	6.15	6.40
Hengwhas	2.88	3.06
Malays	2.50	2.91
Kwangsias	1.08	1.02
Shanghalese	0.93	0.58
Indians	0.80	0.44
Others	1.20	0.87

Cirrhosis of the liver is from these results an affliction common to all the poorer class Asiatics in Singapore. Tamils show the lowest comparative incidence of any group, but this does not represent the true state of affairs for these people in their own country. Tamil labour for Singapore has always been carefully recruited in India, as I have explained previously. The Tamil does not leave his own country to seek work on chance. In Malaya the Tamil population is healthy in the first instance, as unfit coolies are not permitted to leave India. As the majority find employment on Rubber Estates or under the various Municipalities, they are


%
25
20
15
10
5
INCIDENCE OF VARIOUS SECTS
IN TOTAL POST-MORTEMS
IN CIRRHOSIS POST-MORTEMS.
HOKKIENS
TEOCHEWS
HYLAMS
CANTONESE
HOCHEWS
TAMILS
CHINESE
KHEHS
HENGWHAS
MALAYS

subject to reasonable medical attention and for the most part they form a settled population. The Chinese coolies do not remain in such steady employment, but will always seek pastures new in the hope of improving their status in life. Tin and rubber are the basic industries of Malaya and are subject to extreme fluctuations. As a result the history of the country is one of slumps and booms. The Chinese population drift lightly from one occupation to another according to the state of the various industries. That the Tamil does suffer from cirrhosis to a marked degree is shown by the statistics from Madras already quoted.

Turning to the Chinese sects we find that the Cantonese and the Hochews show a higher incidence of cirrhosis than others, but in none of the sects is cirrhosis uncommon.

SEX.

As pointed out previously, Tan Tock Seng Hospital has very limited accommodation for female patients and for the first six years from which the present series of cases is drawn, there were no beds for females. Post-mortem evidence of the frequency of cirrhosis in the two sexes cannot then give us any information of value. Only twelve of the 678 are females. The statistics of the Medical Officer of Health for Singapore show that cirrhosis is much commoner in men than in women. This is the experience in India, Java and Siam.

AGE.

The age incidence has been determined accurately in 500 cases.

The youngest in the series is seventeen and the oldest is eighty-four. The majority are between forty and fifty, but the decades below and above show only a slightly lower figure.

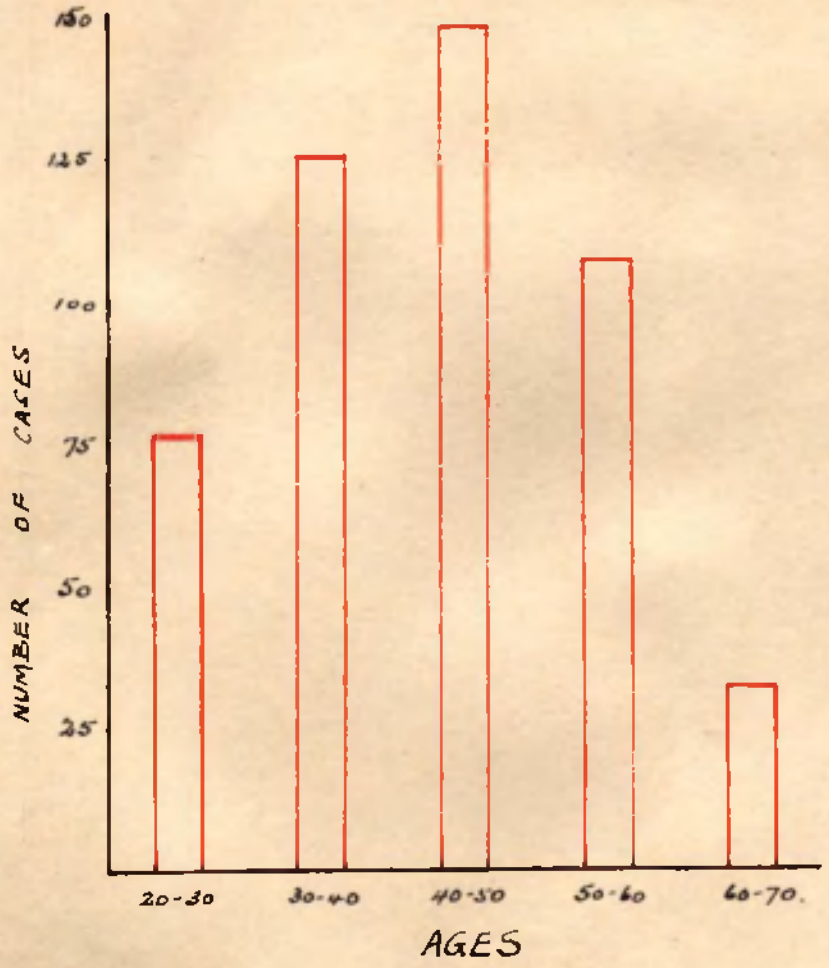
10 - 20	4
20 - 30	76
30 - 40	125
40 - 50	148
50 - 60	106
60 - 70	32
70 - 80	6
80 - 90	3

OCCUPATIONS.

All the patients are drawn from the labouring classes and hence the majority are classified as "coolies". Enquiry into five hundred cases reveals the occupations as follows:-

Coolies	220
Food Hawkers	50
Weeders	64
Rubber Estate coolies	48
Rickshaw Pullers	46
Sailors	18
Gardeners	18
"Boys" (house servants)	12
Carpenters	10
Clerks	5

AGE INCIDENCE OF CIRRHOSIS



Syces (chauffeurs)	3
Firemen	3
Masons	3

From these figures, it is impossible to draw any definite conclusion as to the frequency of cirrhosis in particular occupations. Cirrhosis has been observed to be more frequent in farmers or cultivators than in any other classes in India (8), Siam (3) and China (9, 10). On Singapore Island there is practically no farming. A few vegetable gardeners are found, but there is no cultivation of crops or farming on a large scale such as occurs in the other places.

III. PATHOLOGICAL FINDINGS.

1. LIVER.

The cirrhosis varies from a fine diffuse cirrhosis to a coarse multilobular cirrhosis. The organ varies in size. In some cases there is considerable enlargement and in others extreme atrophy. The common type is a portal cirrhosis similar to that found in Great Britain. For the purposes of this discussion, the cases are classified as portal, diffuse, biliary, carcinomatous, syphilitic, and cirrhosis with schistosomiasis.

(1) PORTAL CIRRHOSIS.

The liver may vary very much in size and weight. It may be much enlarged or it may be very small. The peritoneal surface is usually thickened and may be opaque due to chronic inflammatory changes in the capsule. Fibrous adhesions are often found binding the organ down to the diaphragm and to the anterior abdominal wall. Irregularity of the surface may be slight or marked. There may be a mere granularity or the presence of nodules whose size may be as large as an inch in diameter. These surface changes are generally wide-spread, but occasionally may be limited. The colour varies from yellow-brown to a dark red, but this is sometimes modified by bile-staining when a greenish colour predominates.

The larger type usually shows less nodularity and distortion than the smaller atrophic organ, and is frequently found in patients admitted for or dying from some other disease. Apart from enlargement of the liver there are often no other symptoms or signs to direct attention to that organ.

The cut surface is firm or hard. Bands of fibrous tissue are seen extending from the surface depressions throughout the organ, and dividing it into areas of irregular size enclosing the masses of liver cells. The fibrous tissue varies in colour and amount. It is generally greyish or cream coloured. The liver substance is paler than normal in appearance and in some cases, where there is an associated fatty change, is light yellow. Bile staining sometimes occurs. Microscopic examination shows connective tissue infiltration round the portal spaces, and extending from there throughout the parenchyma in an irregular manner, so that varying masses of liver tissue are isolated from each other. The fibrous tissue in early cases may be very vascular. Degenerative changes occur in the liver cells. This may take the nature of an increased granularity or actual fatty degeneration, and in malarial cases deposition of pigment occurs in the cells. In the acute cases the liver cells show most evidence of destruction, while the long-standing cases show little apparent change in the cells that remain.

Areas of hypertrophy of liver parenchyma may be seen, the cells arranged in thick columns, often taking the rounded outline of the superficial nodules. This hypertrophic process is sometimes very marked, and the liver cells may become altered into columns of large multinucleated cells, and adenomatous or carcinomatous changes supervene.

It appears that the enlarged liver is the result of a toxin

or toxins acting slowly on the tissues, and there is a ready reaction on the part of the liver cells which show considerable hypertrophy. Fatty changes often associated with tuberculosis, beri-beri, or malaria, tend to increase the size of the viscus.

In the atrophic type the intoxication is spread over a long period, and the liver tissue eventually fails to respond either because of the prolonged and constant poisoning, or perhaps because of the effects of some additional morbid factors.

(2) DIFFUSE CIRRHOSIS occurs with a normal or enlarged liver. The contour of the organ is not altered much unless in cases complicated by new growth. The surface is usually granular, but not very irregular. On section the granulation tissue is not very abundant, but is rather vascular. It is distributed mainly in the region of the portal tracts, but sometimes actually invades the lobules and penetrates between the liver cells, producing varying amounts of peri-cellular and monolobular cirrhosis as well as multilobular fibrosis. These changes appear in cases where the disease is rapidly advancing, and sometimes are seen in association with malignant disease. Rolleston and McNee (11) regard a similar type of cirrhosis in England as an acute manifestation of ordinary portal cirrhosis.

(3) BILIARY CIRRHOSIS. This type of cirrhosis is associated with biliary obstruction. Hanot's hypertrophic cirrhosis has not been diagnosed in this series. In biliary cirrhosis the liver is enlarged at first, but later it contracts and the surface becomes

rough. It is firm in consistence and is green in colour, due to bile-staining. The bile ducts are dilated, especially the larger ducts. Fibrous tissue extends out from the ducts and surrounds individual lobules of liver tissue and passes in between the liver cells, which are stained with bile and show degenerative changes. Acute inflammatory or necrotic changes are not uncommonly associated with this form of cirrhosis.

(4) CIRRHOSIS WITH PRIMARY CARCINOMA.

This group requires careful study on account of the frequency of its occurence in Singapore. Primary carcinoma of the liver is very uncommon in most parts of the world. Tull (12) has published a series of one hundred and thirty-four cases, which he has investigated in Singapore, and many of the cases of the present investigation are included in his paper. The incidence of primary cancer of liver in Singapore is 0.76 per cent of all autopsies. The neoplastic change is associated with cirrhosis in over seventy per cent of cases. The disease occurs in the following forms:-

1. A large single tumour mass frequently accompanied by small secondary nodules.

2. A diffuse infiltration of the whole liver by carcinomatous tissue - a carcinomatous cirrhosis.

3. Numerous nodules distinct from each other scattered through the liver tissue. These masses are usually soft and distinctly pale in colour and frequently show degenerative changes in their centres.

The first two varieties seem to be associated with cirrhosis more often than the last.

There is no doubt that primary cancer of the liver in Singapore is most often a condition arising in a previously cirrhotic liver, and in some instances the disease has been traced clinically in patients from the cirrhotic to the cancerous stages.

Almost all cases show definite enlargement of the liver and marked alteration in shape. The growth is most commonly found in the right lobe and causes upward extension of the liver. This is often seen with a large single tumour mass. The liver parenchyma may be extensively invaded although liver function tests do not indicate much disturbance of liver function. Cirrhosis of the remaining liver tissue may be fine or coarse.

Microscopic examination shows two types of tumour, the liver cell type or hepatoma, and the bile-duct or cholangioma type. The former is about three times as common as the latter. In the liver-cell type there are masses of cells of varying size, some multinucleated, invading the normal tissue. A fine stroma is almost always present in this type, but is uncommon in the bile-duct tumour. Invasion of the portal veins by cancer cells is common.

In the bile-duct type the liver is infiltrated by tumour tissue, and shows bile-staining. The condition is an adenocarcinoma, with cubical cells arranged in columnar or alveolar form and sometimes showing deposits of bile in the alveolar spaces. The cholangioma grows more quickly than the hepatoma.

In spite of the marked tendency to invade veins metastases are not very common. The commonest site for secondary deposits is in the lungs. The abdominal lymph glands are involved in only twenty per cent of cases.

(5) SYPHILITIC CIRRHOSIS.

Syphilis is a common disease among the Asiatics and few are adequately treated. The average coolie does not appreciate the importance of prolonged treatment, and is quite content with the disappearance of obvious manifestations of the disease. The commoner lesions seen in Singapore as a result of syphilis of the liver are peri-hepatitis, gummata formation, and diffuse fibrosis. A condition of syphilitic cirrhosis due to the combined effects of capsular and interstitial fibrosis is not uncommon. The fibrous tissue strands extend throughout the liver substance dividing it into irregular lobules - the hepar lobatum. This type of disease produces marked alteration in the size and shape of the liver, and the cut surface shows great variation in the distribution of the fibrous trabeculae, and as a result varying effects on the liver tissue. In Java this condition has been noted to be less frequent in the Javanese than in the Chinese.

(6) CIRRHOSIS FROM SCHISTOSOMIASIS.

The infecting agent is in all cases the Schistosma Japonicum, which reaches the liver by way of the portal veins. It produces a definite peri-portal fibrosis. The liver becomes shrunken and atrophic as the disease advances. The surface may show little alteration or marked granularity. On section areas of infiltration

with a peculiar white fibrous tissue are seen surrounding the portal veins through the organ. The colour of the newly-formed fibrous tissue and its distribution have earned the name "pipe-stem" cirrhosis. Microscopic examination shows the eggs of the parasite surrounded by fibrous tissue in the portal regions.

These various types of cirrhosis are seen in the following frequency:--

Portal and Diffuse	483
Biliary	42
Carcinoma	70
Syphilis	68
Schistosomiasis	24

II. ASSOCIATED PATHOLOGICAL FINDINGS.

Many cases show changes in the liver and spleen, but little else of note, except where other morbid conditions have produced a fatal result and so obscured the primary liver disease. In cases of decompensated cirrhosis there are signs of portal obstruction. Ascites is noted in one hundred and seventy-five cases in the present series. It varies in amount and nature. It may be clear, bile-stained, haemorrhagic or chylous. Jaundice is not a prominent feature, being seen in sixty-four of the non-malignant cases. Enlargement of the liver occurs in thirty per cent, diminution in size in twenty-five per cent, and the remainder show no marked alteration in size. The spleen is not enlarged in tropical cirrhosis as frequently as it appears to be in cirrhosis in Great Britain. In some cases it is actually small and fibrotic.

The nature of the splenic enlargement depends of course on the presence of conditions other than cirrhosis, such as malaria or thrombosis of the splenic vein. Enlargement of the spleen is seen in thirty per cent of the cases. Gastro-intestinal haemorrhage is not very frequent, occurring in fifty-two cases, but this is the post-mortem incidence only, so it is not a true indication of the frequency of the haemorrhage during the course of the disease. Oedema of the bowel occurs mostly in cases of portal obstruction and is seen in thirty-four instances.

III. DISEASES OCCURRING WITH CIRRHOSIS.

We find a considerable variety of infections and chronic morbid conditions in association with the cirrhosis.

MALARIA.

Evidence of chronic malaria is to be seen in twenty per cent. Acute malaria is noted as a terminal event in ten per cent of cases.

BERI-BERI.

Signs of definite beri-beri are present in eighty cases. This does not represent the real amount of beri-beri occurring amongst these people, but only indicates the post-mortem frequency. As will be shown later, almost all of these people are subjects of deficiency disease at some time or another during their lives.

AMOEBIC DYSENTERY.

Careful search has been made for all cases showing signs of amoebiasis, since Rogers lays emphasis on the frequency of this

disease in his series. Only fifty cases show signs of active or chronic amoebic infection. This must be a fairly close index of the actual pathology of amoebic dysentery, as it is unlikely that any lesions of this nature would not be revealed by pathological changes in the intestinal tract or in the liver.

BACILLARY DYSENTERY.

Particular attention to this disease is also necessary as Megaw regards it as an important factor in the etiology of tropical cirrhosis. Forty-seven cases show signs of bacillary dysentery, but twenty-one of these are acute terminal cases. Bacillary dysentery appears from clinical and pathological findings to be more uncommon in Singapore than in India or China.

INTESTINAL WORMS.

Ankylostomiasis is the most severe of these infestations in Singapore and appears in one hundred and twenty-two cases. Ascariasis is also frequently seen and eighty-six show the presence of this round worm. Trichocephalus dispar is noted in seventy-four cases, but as this parasite is very common here and is not regarded as being particularly harmful it is probable that its incidence is under-estimated. Clonorchis sinensis is seen in fourteen. Schistosomiasis is not very common, but it does give rise to definite cirrhosis and twenty-four examples of this type are included here. The particular worm is the Schistosma Japonicum, and as will be shown later, it is imported to Singapore from one localised area in China.

SYPHILIS.

This is very commonly seen in the post-mortem room in Tan Tock Seng Hospital. Thirty per cent of all post-mortems show evidence of chronic syphilis, and forty per cent of the cirrhosis cases have signs of it.

TUBERCULOSIS.

This is one of the major problems seen in practice among the labouring classes of Malaya. Pulmonary, abdominal, glandular, and surgical cases are all common. It is widely recognised that pulmonary tuberculosis often complicates cirrhosis of the liver and in this series active lung lesions are present in ninety-six cases. Intestinal and peritoneal infections are noted in twenty-five.

LEPROSY.

This is seen in three cases only and is obviously of no pathological significance.

GALL-BLADDER.

The incidence of gall-bladder disease is not great. Gall-stones are seen in twenty-five cases, and septic cholangitis in fourteen. One might expect more disease of the biliary passages, when the incidence of liver disease is high as in this series.

PANCREAS.

Chronic pancreatitis sometimes accompanies cirrhosis, and twenty cases show naked-eye evidence of it.

KIDNEY.

Parenchymatous renal changes seem to occur rather more often in cirrhotic than in non-cirrhotic cases. One hundred and three

show signs of degeneration of the renal parenchyma. Hawes and Vardy (13) have reported from the same clinic a series of cases of nephrosis and the nephrotic syndrome, and it seems possible that there is some common factor responsible for the liver and kidney changes in these people. Chronic intersitial nephritis is a fairly common condition in the elderly Asiatic and occurs with arterio-sclerosis, so it will be considered under that heading.

DISEASES OF THE BLOOD VESSELS.

Arterio-sclerosis and atheroma are commonly seen in all the labouring classes of Asiatics. There is little doubt that the average coolie is liable to degenerative changes in his blood vessels at a particularly early age. I conduct regular examinations of Malays, Chinese and Indians as to their fitness for work in various occupations such as estate coolies, sailors and general labourers. I have been struck by the frequency of the thickening of the blood vessels which is seen in these people about the age of forty. In this series marked disease of the blood vessels is seen in one hundred and nine cases.

STOMACH DISEASES.

Definite pathological changes are not observed frequently. Dilatation of the gastric and oesophageal veins is seen commonly in cases showing portal obstruction. The stomach does not appear to be affected by disease very often in these people. Gastric ulcer is seen in nine cases and carcinoma in two only.

IV. CAUSES OF DEATH.

I have endeavoured to determine the causes of death in those

cases where cirrhosis is obviously well established and not complicated by the presence of other severe organic diseases, which in themselves would be sufficient to overshadow the liver changes as producing the fatal issue. The table below shows the more common causes of death in two hundred and fifty cases:-

Acute Pneumonia	43
Acute Pulmonary Tuberculosis	35
Beri-beri (terminal)	21
Bacillary Dysentery	14
Amoebic Dysentery	5
Septicaemia	15
Septic Cholangitis	14
Acute Malaria	10
Haemorrhage	12

The remainder of the cases die of the effects of cirrhosis or general ill-health rather than of any super-added infection.

DURATION OF THE DISEASE.

The surprisingly short history given by most patients is striking. The malignant cases must be considered separately from the other cirrhosis cases, as the former practically all date the onset of symptoms to less than one month before admission to hospital, and none of them live more than two months after that. In the non-malignant cases the average length of the illness is about four months. The shortest period is three weeks and the longest twenty-seven months. Hughes in India gives figure of one to seven months, and the Bangkok series averages three months with extremes of one to twenty-four months. Allowances must be made for the fact that these

people probably suffer gradual failure in health for some months at least before seeking medical advice, or before some acute illness or emergency causes them to be removed to hospital.

CLINICAL LABORATORY FINDINGS.

Anaemia of moderate severity is usual and in general of the microcytic type. The haemoglobin in established cases is commonly reduced to about fifty per cent. During the last few months I have had under my care a patient showing considerable enlargement of both liver and spleen, and with a definite macrocytic anaemia. His R.B.C. on first examination were 1,350,000 and his haemoglobin 40 per cent. His stools showed the presence of ankylostoma ova, but otherwise no abnormality was found. His diet was purely vegetarian and was of very poor quality. Treatment consisted in balancing the diet particularly with the addition of vitamin B, and he was given injections of campolon. His blood showed a rapid improvement, and after three weeks he was given treatment for the hookworm infection. This responded to two treatments with chenopodium. The liver and spleen showed a gradual reduction in size. The former is now just palpable whereas when first seen there was enlargement to two fingers below the costal margin, while the spleen which was enlarged to within two inches of the umbilicus is now palpable about one inch below the ribs. These changes have taken place within three months. Occasionally cases showing definite macrocytic anaemia have been found in this clinic but they are not at all common.

The blood proteins are practically always diminished and this

accounts for some of the oedema. It has also been observed that ascites tends to appear more quickly in cirrhosis after occurrence of haemorrhage, and it is likely that a reduction of blood proteins is a factor in producing this. The calcium, chlorides, and sugar of the blood all show a moderate reduction. The Van den Bergh reaction shows a direct or indirect positive. The Wassermann reaction is positive in forty per cent of cases.

Liver function tests often give disappointing results. The galactose tolerance test sometimes indicates a disturbance of liver function, but in many cases with extensive destruction of liver tissue such as occurs in primary carcinoma, this test may give normal readings. The Mayo Clinic workers (14) believe that the Bromsulphthalein test is the most helpful, and in cases where decompensation has not yet taken place, they have found it helpful in giving an indication of disturbed liver function.

Gastric analysis commonly shows a reduction of hydrochloric acid and from the reports of various workers, about thirty per cent of cases of established cirrhosis cases show complete achlorhydria. The renal efficiency is lowered in about twenty per cent of cases. There may be an associated renal lesion in some of these cases as nephrosis has been found common in the same clinic (13). It is possible that the kidney condition is degenerative and due to the same cause affecting both kidney and liver. The ascitic fluid has a specific gravity of 1004 to 1012 and a protein content of not more 1.5 per cent, and usually under 1 per cent.

IV. DISCUSSION OF POSSIBLE CAUSES OF CIRRHOSIS

Before attempting any discussion of the possible causes it is necessary to consider what conditions may cause damage to the liver. The following classification is modified from Willcox (15) and Rowntree (16), who have described the possible causes of liver damage in toxic jaundice and cirrhosis respectively.

1. Chemical Poisons.

Alcohol, arsenic, copper, lead, opium, quinine derivatives etc.

2. Bacterial Poisons.

Coli-typhoid group, the pyogenic cocci, the tubercle bacillus etc.

3. Protozoal and Parasitic.

Malaria, amoebiasis, spirochaetal infections, kala-azar, worms and flukes.

4. Poisons derived from Dietetic, Metabolic and Deficiency Disorders.

1. Poisons from food-stuffs -- spices, mushrooms, fungi, vegetables etc.
2. Metabolic and deficiency diseases -- nutritional oedema, beri-beri, pellagra, scurvy, acidosis, uraemia, hyperthyroidism etc.

This classification is obviously incomplete as a list of all possible causes of liver damage, but it will serve as a basis for considering the more important factors at greater length.

In the literature many causes have been suggested for cirrhosis, but practically all have been found wanting except in explaining a few cases. The disease occurs among many different

races of people and at varying ages. The only common factor in most of the cases reported from the tropics is that the disease is one of the poorer classes. Can we find something common to these various sects that may render them more liable to cirrhosis of the liver?

I. CHEMICAL POISONS.

ALCOHOL. It is reasonable to commence this discussion with the subject of alcohol, since this is recognised as a common source of poisoning in cases of cirrhosis in non-tropical countries. The alcohol consumption of the labouring classes is for the most part low. The Southern Chinese probably drink less than the Northern. Even among the better classes, drinking of alcohol is frequently confined to festive occasions. The coolie class cannot afford much in the way of imported spirits although brandy is quite a popular drink with some of the Chinese. The common alcoholic beverages consumed by the Chinese are as follows:-

1. Rice wine is brewed by the people themselves by mixing rice and yeast. After fermentation has taken place the juice is extracted and used as beverage. It has a low alcoholic content.

2. Distilled or native white wine is prepared from fermented molasses and has a considerable alcoholic content. This spirit is used mainly in the Province of Canton where it is known as "sam sui".

3. Shou Shin Wine or Chinese beer is brewed from wheat or barley and is a weak beverage. It originated in the Chekiang Province but is widely used by all classes in China.

4. Kau Liang is a cereal similar to maize grown mainly in North China and from it a liquor with high spirit content is distilled. Various medicated wines are prepared from it by the addition of native herbs. It is more expensive than the other types previously mentioned, but the medicated type is consumed frequently as a general tonic.

The Siamese produce two types of native wine. One spirit is made by brewing rice with yeast and cane sugar and the other is prepared from palm juice and various vegetable bitters. The Tamil drinks a spirit called "Toddy" which is also prepared from palm juice.

As the consumption of wines in the people under review is not very high, it is unlikely that this can be of great importance in producing liver damage, especially when we remember that cirrhosis occurs frequently in some sects whose religion forbids them taking any alcohol. In this series of cases it has been noted that the incidence of cirrhosis is higher amongst the Cantonese than any other group. They are rather more fond of wines than the other Chinese and possibly this may be a reason for the increased frequency of the disease in them.

OPIUM.

Opium is used by the Chinese to a considerable extent, but in Malaya Government controls the sale very strictly and only issues it on licence. The other nationalities do not use opium to any extent so that it cannot be looked upon as a source of liver damage in more than a small proportion of the total cases.

Again no increase has been noted in the incidence of cirrhosis amongst opium addicts compared with the others.

Apart from alcohol and opium it is difficult to trace any chemical compounds used to any extent or with which these people might come in contact. Mallory (17) has described an increased content of copper in cirrhotic livers, but this has not been the experience of the Dutch Pathologists in Java, who investigated a considerable number of cases. The other chemical poisons must be dismissed without further consideration, since they cannot possibly enter into the etiology in more than an occasional case.

II. BACTERIAL POISONS.

(a) Coli-Typhoid Group.

Coliform infections are very often met with in Singapore and I believe are definitely more common than in Great Britain. Urinary tract infections are most frequent and all classes of the community are subject to them. Mallory (17) describes a type of colon bacillus cirrhosis which generally complicates obstructive biliary cirrhosis. The bacilli spread to the liver by way of the bile-ducts producing an inflammatory reaction with necrosis of the liver cells. This condition has not been recognised amongst the Singapore cases, although bacillus coli has been found in a few instances of infective cholangitis.

Typhoid and paratyphoid infections are commoner in South China and India than in Malaya, where these diseases occur only sporadically. The incidence of definite pathological lesions

indicating previous typhoid fever is very small, but there is no indication of any greater frequency in the cirrhotic cases compared with the others.

(b) Bacillary Dysentery and Infections with Allied Organisms.

In India bacillary dysentery has been looked on by Megaw as a frequent cause of chronic peritonitis. He suggests that many such cases are diagnosed as cirrhosis wrongly. He finds that a large number of his cases give a history of recent diarrhoea or dysentery, and that many patients show a higher titre of agglutination against the Flexner bacillus than the controls do.

Diarrhoea is however frequently seen in cirrhosis in all countries, and a history of looseness of the bowels is not of much value as an indication of previous dysentery. The Mayo clinic cases give a history of diarrhoea in thirty per cent, but not one shows any evidence of dysentery clinically or in the past history.

Rao (12) finds that many of his patients give positive agglutination tests for various types of bacillus dysenteriae, but he does not consider that this is sufficient to justify a diagnosis of active dysentery, and he points out that many authorities in India disagree that Megaw in regarding these cases as endemic ascites instead of cirrhosis. It seems to me that the agglutination reactions cannot be regarded as sufficient evidence of the presence of an active toxaemia. A positive reaction may merely indicate a carrier. In cirrhosis there is frequently disturbance of bowel function which will be followed by changes in the flora, and so will produce altered agglutination reactions.

In Singapore we do not see much dysentery in any class of patient and the autopsy results show that an acute bacillary dysentery is often a terminal affair in many chronic diseases, and hence is probably more often the result of cirrhosis rather than an active factor in the production of liver disease. It seems that a toxaemia of sufficient duration to induce fibrotic changes in the liver, should manifest itself by some definite changes in the bowel in addition to alteration in the intestinal flora. Against Megaw's arguments it may be noted that dysentery is commoner in North China than in South China or Japan, but cirrhosis is very much less frequent in the former area than in either of the latter two. In Java the Dutch Pathologists state that bowel disease and intestinal toxaemia cannot be regarded with any certainty as probable causes of cirrhosis. Reviewing the evidence, we cannot agree with Megaw's conclusions that bacillary dysentery is responsible for many cases.

(c) Tuberculosis.

Tuberculosis is common amongst the class of patient under discussion, but active tuberculous lesions of the liver are not common. Generalised miliary tuberculosis may involve the liver and produce numerous small tubercles. Other cases show evidence of degeneration or amyloid changes in the hepatic tissues, but most of these changes are the result of chronic mixed infections lasting over a considerable period of time. Pulmonary disease is the commonest form of tuberculosis seen in Singapore and many of the coolie classes suffer from chronic lung disease. Intestinal

tuberculosis is also not uncommon. Since tubercle commonly reaches the liver by way of the blood stream, other tisses are exposed to the organism and so generalised infection is more likely than local disease of the liver. Prolonged malnutrition associated with chronic tuberculosis is a likely cause of damage to the liver cell apart from the effects of tuberculous toxins. These cases show a high incidence of tuberculosis in its various forms, and the cirrhotic cases show about eight per cent more tuberculosis than the others. This figure is not unduly high, however, when one takes into consideration the fact that tuberculosis frequently follows cirrhosis. One can only say that tuberculosis by producing a state of chronic ill-health must predispose to damage to the liver tissue, but it cannot be regarded as a factor of great importance in the production of cirrhosis.

(d) Other Bacterial Infections.

No other infections occur with any frequency in these people. Muir (18) has referred to the possibility of cirrhosis being post-infective in origin and suggests scarlet fever as a possible precursor. In Singapore all streptococcal infections are uncommon. Scarlet fever is almost unknown, puerperal fever uncommon, and erysipelas tends to be a localised mild infection instead of a severe spreading disease. Streptococci are found less commonly in throat and respiratory secretions in the tropics than in temperate zones, and this suggests that tropical climatic conditions inhibit the growth of these organisms. In this connection it is interesting to trace the distribution of scarlet fever in the Far East. In

Singapore and South China the disease is unknown, as we go north towards Shanghai there is a gradual increase in the incidence, and when we reach North China and Japan we find the disease occurs in regular epidemics of considerable severity. We have then no evidence that scarlet fever or streptococcal infections are associated with the production of cirrhosis here.

No other bacterial infections occur with any frequency in these cases and this is the experience of others in the tropics. We cannot then incriminate bacterial infections as being of great importance in the production of cirrhosis.

III. PROTOZOAL & PARASITIC.

These infections are common in Singapore and several of them have been suggested as likely causes of cirrhosis so that we must consider them in detail.

(a) Malaria.

Malaria has for long been a source of controversy. From India, Rogers and Fairley (19) are convinced that it never produces cirrhosis, while Hughes (20) is equally dogmatic that it is a very important exciting cause, and Rao regards it as an important predisposing cause. Reports from Java and Siam also suggest that it is a factor of some importance. Hurst (21) considers it likely that other factors such as gastro-intestinal toxaemia may produce cirrhosis in the liver damaged by malaria. It is difficult to believe that repeated attacks of malaria producing damage to liver tissues cannot be followed by cirrhosis. In chronic malaria the liver cells show evidence of cloudy

swelling and pigmentation and the periportal tissues are swollen and infiltrated with round cells. According to Weiss (22) this may develop into a nodular hypertrophy of the liver or it may progress to an intersititial hepatitis, and from overgrowth of the fibrous tissue cirrhosis develops. Hughes asserts that malaria is a frequent cause of cirrhosis because all his patients have suffered from malaria previously, and malaria is generally admitted to cause damage to the liver cell, and at post-mortem evidences of malaria are often found in the liver and spleen. He believes that malarial cirrhosis is of somewhat similar nature to Banti's disease, in that the initial disease of the liver and spleen leads to an increased portal pressure, and the constant supply of toxins to the liver by way of the splenic vein eventually induces fibrotic changes.

Most of the papers published show a high incidence of malaria in the previous history of the patients. The following table gives an indication of the frequency in various countries:-

South India	(Rao)	47%	(8)
Siam	(Vilaya)	60%	(3)
China	(Wang)	40%	(10)
U.S.A.	(Mayo Clinic)	12%	(14)

In Singapore many of the labouring classes have suffered from malaria because they live in areas where malaria has been endemic, and their occupations often entail working in districts where malaria is common and where epidemics are often produced by excavation of new ground. Twenty per cent of post-mortems show

signs of malaria, but the actual number who have suffered from malaria at one time or another must be considerably higher, because acute attacks and relapsing malaria of moderate severity may not leave very obvious pathological lesions. Summing up all the evidence it seems that malaria is often associated with cirrhosis and this cannot be regarded as a mere coincidence, but it is probably an active agent in producing the disease in some cases.

(b) Amoebiasis.

Rogers states that all the evidence points to chronic amoebic dysentery as the most likely cause of the excessive amount of cirrhosis of the liver of the Indians in Calcutta. He bases his argument on the fact that the cirrhosis post-mortems show a very high incidence of past dysentery. Evidences of old dysentery were found in twenty-five per cent to thirty per cent of the cirrhosis cases while in the general run of cases it was less than half that. He believes that frequent attacks of amoebic hepatitis tend to lead to fibrosis. Menon and Amanamalai (7) also report a rather similar incidence of amoebic lesions in their cases from South India. They point out however, that the fibrosis in typical amoebic lesions of the liver tends to be localised and not generalised. They suggest also that the bowel dysentery may be a complication of cirrhosis as this is known to lower the resistence to infections. In Siam over thirty per cent of the cases gave a history of dysentery previously, but this includes both the amoebic and bacillary types and the author has

attempted to differentiate them. Hughes finds only an occasional case of amoebiasis in his series from the Punjab. In Singapore amoebic lesions were found in only seven per cent of the cirrhosis cases and among the total post-mortems in 6.2 per cent. Compared with India or China the incidence of amoebic dysentery is low in this country. Again the frequency of dysentery in North China is considerably greater than that of South China and yet the incidence of cirrhosis is exactly the reverse. While it must be admitted that hepatitis is commonly induced by an amoebic infection, it seems that the end-result is more likely to be abscess formation rather than cirrhosis. From the figures in this series it is unlikely that amoebiasis can be responsible for many cases.

(c) Kala-Azar.

Kala-azar is very uncommon in Singapore and no case of the disease has been observed in any of this series. One might have expected an occasional case among Indians since they form a considerable percentage of the cases, and kala-azar is common in their country.

(d) Spirochaetal Infections.

Syphilis is the only spirochaetal infection occurring with any frequency in these cases. Spirochaetal jaundice, relapsing fever and yaws are seldom seen in this part of Malaya, and they are not very common in South China.

The frequency of tertiary syphilis in the patients of this series is high, and is in accordance with the reports from

South India, Siam and Java. Syphilis must be regarded as an important cause of liver damage since we find evidence of perihepatitis and gummata formation very frequently. Generalised visceral syphilis is not uncommon in these post-mortems. In the cirrhotic cases forty per cent show signs of chronic syphilis, while in the total post-mortems the incidence is thirty per cent.

There are therefore many cases which show no evidence of syphilis. In Java it has been noted that the incidence of syphilis among the Chinese is higher than among the Javanese, but both are affected with cirrhosis to a similar degree. While syphilis does produce a certain amount of cirrhosis, and is a potent cause of liver damage, it does not explain more than a limited number of the present series.

(e) Intestinal Worms.

Intestinal worms are considered by some people to be capable of inducing cirrhosis. The commonest worms met with in Singapore are Ankylostoma duodenale and Ascaris lumbricoides. It is conceivable that severe anaemia seen in hookworm disease lowers the resistance of the liver cells, so that they degenerate more quickly and are unduly susceptible to the effects of other poisons. Ascariasis seems to produce clinical symptoms mainly by mechanical effects. Although the actual worms in the bowel do produce some general toxic signs, they do not appear to have any special poisonous action on the liver. It is likely however, that the presence of worms in the bowel will be responsible for the

production of various toxic substances which may well cause liver damage. The incidence of intestinal worms is just as high in the whole series of post-mortems as in the cirrhotic cases, so that one cannot attach great importance to the effects of worms in the production of cirrhosis.

(f) Flukes.

Amongst the Chinese particularly, the frequency of liver fluke infections has often been commented on and at times accepted apparently as a reason for the frequency of cirrhosis (23). The only two flukes found in these cases are the Clonorchis Sinensis and the Schistosoma Japonicum. The former occurs in fourteen cases and the latter in twenty-four. An incidence of 5.5 per cent such as this does not incriminate these parasites very strongly. The schistosomasis cases form an interesting group in their distribution among the various sects:-

Hochews	18
Hokkiens	4
Cantonese	1
Chinese	1
	24

Two-thirds of the patients are Hochews and this explains the high incidence of cirrhosis in these people compared with the general average. On deducting the schistosomasis cases from the total number among Hochews, we reduce the percentage from 11.06 to 7.56 which approximates closely to their figures for total post-mortems of 8.03 per cent. The Hochews come from the

Province of Fukien which has long been recognised as a badly infected area for schistosoma japonicum. The disease has never been known to occur locally in Malaya, but these people arrive here already infected. The pathology of the disease is interesting in the long interval that occurs from the time of infection, till the onset of symptoms of a chronic nature.

Clonorchiasis is found almost entirely amongst the Cantonese and the Teochews (24). The infections are derived from eating raw or partially cooked fish. The cysts are digested by the gastric juices and liberate their larve in the duodenum from where they ascend the bile ducts. They produce a general thickening of the walls of the bile ducts and the fibrosis extends into the interlobular and intralobular tissues. As a result cirrhosis may eventually result. This infection is derived entirely from fresh water fish and must be brought by the Cantonese and the Teochews from China. Fresh water fish in Malaya have never been found to harbour the infection.

While there is no doubt that these flukes have produced definite cirrhosis, the frequency in this series of cases is so small that they do not account for more than a few cases.

POISONS DERIVED FROM DIETETIC, METABOLIC, AND DEFICIENCY DISORDERS

Attention has often been drawn to the possibility of the highly spiced food of the Asiatic being a possible factor in producing cirrhosis. This allegation has been made against the diet of some of the Indian sects in particular. As the majority of my cases are Chinese I have endeavoured to obtain accurate

details of the main diets of the Chinese. It is surprising that there is no published literature on this subject. In Singapore there is a Chinese Protectorate which looks after the affairs of the Chinese and particularly of the poorer classes, but they could not provide me with any subject matter.

I have, however, obtained considerable assistance from the European and Chinese members of the staff of the Protectorate, and also from several European and Chinese friends in Singapore.

Generally speaking the staple diet of the Chinese is rice. This is prepared in various ways by the different people:-

1. The rice is boiled with an excess of water for some hours and then removed by means of a bamboo utensil, and the fluid is kept until after the meal and consumed as a beverage. This method is adopted by most of the Teochews, Hokkiens, Hylams and Khehs.

2. Rice mixed with just sufficient water to cover it and cooked till there is little water left. This is known as "hard rice". The Cantonese prefer this form.

3. "Congee". Rice is cooked with an abundance of water, about one part to seven, and as a result a thin gruel is prepared which is consumed as the chief part of the meal. This method is adopted by the poorer classes of many sects.

Sweet potatoes are even cheaper than rice and are often boiled with the congee, and at times may substitute rice completely in the diet of a very poor. Wheat does not enter

into the diet of the Southern Chinese to any great extent, but north of Shanghai it replaces rice as the basic food.

Vegetables are nearly always boiled, very few are eaten fresh. The commoner vegetables are cabbage, celery, turnip, spinach, onion, bamboo shoots, beans, cucumber.

Fruits. The commonest are limes, bananas, oranges, durians, papayas, melons, plums. The average coolie does not consume very much fresh fruit.

Milk is not drunk or used in cooking to any marked degree, except that it is frequently taken with coffee. There is practically no fresh milk in Malaya and the natives depend on tinned milk. The poorer classes prefer sweetened condensed milk to any other form.

Meat. The Chinese are fond of meat, but the coolie cannot afford much, and probably does not eat a reasonable amount more than once a week. Pork is the favourite meat. The better classes eat beef and mutton. The Khehs are very partial to dog and cat meat.

Spices. The favourite spice is pepper which is used to a considerable extent by all classes. Chillies prepared from capsicum, and various curry powders consisting of ginger, turmeric and other strong spices are also used, but not to the same extent by the Chinese as by the Indian or Malay. Other condiments are prepared from beans and nuts fermented with malt, after which various fruit juices and jellies derived from limes and plums are added.

Fish. Dried fish is commonly eaten by the coolie classes and certainly much more so than fresh fish. The Cantonese and Teochews are fond of raw fish, which the other sects do not eat to any extent. This accounts for the infection with clonorchis amongst these two sects noted previously.

Eggs do not enter into the diet of more than forty per cent of the people.

With the coolie class boiling is the chief method of cooking. Where grilling or frying is done a cheap vegetable oil is used.

The daily routine is usually a morning meal and an evening meal of rice and vegetables, and perhaps a midday meal of coffee with a little rice.

The diets of Southern Indians and Malays are rather similar. Nicholls (25) has investigated the former rather fully. Rice is the basic food. Meat, eggs, milk and butter are hardly ever used. Fish is the only animal protein used. Spices are taken with each meal to dispel the anorexia arising from a tasteless diet. Tea is used by the majority, its absence indicating real poverty. Comparing his results with those obtained by Ochsb in Java in 1934, Nicholls states that there is little difference in the amounts of fats, proteins, and carbohydrates consumed. He concludes that the fat and protein are sufficient to support life, but they are not optimum for the production of good growth in children or good health in adults.

Burgess (26) and Vickers and Strahan (27) working in Malaya find a rather similar state of affairs. The staple cereal is

polished rice. Fish is the only comestible of animal origin to figure largely in the diets, and it is almost entirely dried fish that is eaten. Eggs are eaten by about thirty per cent, fruit by twenty-five and meat and milk by ten. Coffee is consumed by almost all and usually at least twice daily. Condiments and spices are also used by practically all. They conclude that proteins, fats and vitamin B are very deficient.

The diet of Chinese, Indians and Malays is thus deficient in quality and lacks good protein, fat and vitamins. It provides for the immediate source of energy by its high carbohydrate content, but the other elements are so deficient that they barely maintain ordinary wear and tear of the tissues, and certainly do not provide any reserve. In all Asiatics in Malaya as has been noted in India, the diet improves with the social scale in its fat and protein content.

POISONS DERIVED FROM FOOD-STUFFS.

Highly spiced foods undoubtedly cause portal congestion. Some authors believe that these condiments have a direct toxic action on the liver, and mustard oil has been incriminated particularly in this respect (28). It is probable, however, that the liver disease or oedema depends more on the presence of other diseases or deficiencies than on the poisonous effect of the oil. Some samples of oil do appear to have a toxic action, as occasionally several patients in the same household have developed signs of gastro-intestinal upset with oedema and dermatitis.

Its relation to cirrhosis does not appear to be very great as its use is confined to Indians, who do not show more cirrhosis than the Chinese. The effect of spices in inducing portal congestion seems to be of some importance. It is extremely common to find haemorrhoids in all the Asiatics whom we are considering, and it is well-known to them that the first essential in treatment is to stop taking condiments. There seems to be little doubt that the dilatation of the haemorrhoidal veins is secondary to portal congestion, but we cannot go further than this and invoke a specific toxic effect on the liver cells.

Mushrooms and other fungi have been known to cause toxic jaundice, and plants of the senecio and lupin groups have been alleged as causes of cirrhosis in animals (29). The former group are found to such a small extent in the diet of the Asiatic that they cannot enter into the etiology in more than a few cases. I have made enquiries from the local Botanical authorities, as to the possibility of foods derived from the senecio and lupin series being used here, but they have been unable to trace anything of this nature in local diets.

It seems from these findings that toxic products, obtained directly from foods, cannot cause much liver damage in Singapore.

POISONS RESULTING FROM METABOLIC AND DEFICIENCY DISORDERS.

In considering this subject many factors must be taken into consideration. To begin with we are dealing with a class of people whose livelihood is uncertain, and as a result their nutrition is in many cases poor. At best the food is generally of inferior

quality, and at times starvation is a very real and established fact. To maintain health, the actual calorie value must vary with the nature of work done. Many of these people have to do hard manual labour, and that at irregular intervals according to whether work is available or not. After periods of unemployment many are physically unfit to perform hard work, and their employers are not slow in getting rid of them. A considerable amount of labour in Malaya is employed by Asiatic contractors, who engage and dismiss coolies according to requirements from time to time. These contractors seldom make provision for medical attention, and simply leave the sick to fend for themselves. Where labour conditions are better, as is seen with Municipal and Government services, and with Rubber Estates who have built up permanent labour forces, one does not see the same amount of ill-health.

Many coolies arriving from China and India are not physically fit for hard work for some months after arrival. Two years ago I had occasion to examine several hundred new Tamil coolies, who had just arrived from India for employment at Rengam Rubber Estate, Johore. This estate has always looked after its labour force well, and has established a healthy, settled and contented community. About one-third of the new arrivals were poor specimens physically. It was found that they were unable to do more than half a day's work as done by the average coolie. Little organic disease was found among them, their unfitness being simply a question of poor nutrition.

They were given light work, their diets brought up to the level of the other coolies, and within three months practically all were fit to carry out routine work.

With supervision of labour forces the coolie can and does remain fit, but a large number are unable to obtain regular employment. In some places where malaria is endemic, owing to lack of efficient anti-malarial measures, the labour is never healthy and in consequence never settled. In the same way other fevers, bowel disorders, and anaemias all lead to disturbance in health and nutrition. It is to be noted that very few cases of cirrhosis are seen among coolies in permanent employment on rubber estates.

As to the general effect of poor diet, it is difficult to know what factors upset health in the early stages. Our knowledge of metabolic derangements and deficiencies is confined to the more gross disturbances, because we cannot recognise early manifestations.

It has been suggested that the largely vegetarian diet of the coolie class increases ammonia formation in the bowel, and this augments the work of the liver. As a result of the prolonged strain on liver function, its cells degenerate at an early age. Again a diet consisting largely of carbohydrate must impose extra work on both liver and pancreas. This is probably the reason for a mild diabetes, commonly seen in all the various Asiatic races here, at about forty years of age.

While there are many speculations as to the effects of

faulty diets, there are however two very definite disease conditions in these people arising from deficiency or faulty metabolism. One is a form of nutritional oedema and the other is beri-beri. We shall now consider them in detail.

NUTRITIONAL OEDEMA.

Nutritional oedema occurs amongst the poor classes in Malaya and Java and is known to the natives as "sakit abu". In this condition, there is a generalised oedema accompanied by cachexia. Emaciation is marked due to the extreme loss of subcutaneous fat. There is usually a moderate anaemia with a soft small pulse sometimes irregular and quickened. The heart is never enlarged in uncomplicated cases, while the liver is reduced slightly in size and has a paler appearance than normal in fatal cases. The appetite is poor. Periodic attacks of diarrhoea occur with soft frothy stools, which show a large amount of undigested carbohydrate, and lesser amounts of fat and protein also not properly digested.

The urine contains acetone in most cases. In severe cases the general course is slowly downwards and death results from the cachexia, not as in beri-beri from cardiac paralysis. The blood shows a diminution in fat, protein, calcium, and phosphorus content. This disease resembles epidemic dropsy, war oedema and famine oedema, which are met with in various countries from time to time.

De Langen and Lichenstein (30) have studied the condition

fully in Java and they regard their type of disease as due to general shortage of good food. It requires under-nutrition for one to two years to produce symptoms of the disease. Following on the initial disturbance in health due to lack of protein and fat in the diet, there is a secondary disturbance in carbohydrate metabolism. This is probably the result of atrophy of the gastro-intestinal mucous membrane which occurs in all cases. In addition to the deficiency of fats and proteins, the diets contain too little calcium and vitamins and the quality of the carbohydrate is poor. This condition interfering as it does that the metabolism of the body generally, produces its principal pathological effects on the digestive system. In some cases these effects may be sufficient cause for cirrhosis, since the catarrhal condition of the bowel will permit of toxic products being absorbed into the portal circulation or may prevent the absorption of some essential factors. Toxins may result from the incomplete digestion of food as a result of fermentation or putrefaction, or bacterial poisons may be more readily produced in the bowel than they would be normally. It has been suggested that epidemic dropsy may result from the use of mustard oil in cooking, but not many cases can result from this. Most cases of nutritional oedema show no evidence of cirrhosis but there are fatty changes in the liver, so it seems that other factors must be necessary to bring about fibrotic changes in the liver.

BERI-BERI.

This is a common disease in Singapore. It is responsible for a considerable amount of ill-health and causes a fair mortality. The report of the Medical Officer of Health for Singapore shows an average of two hundred deaths per one hundred thousand of population from beri-beri for the years 1924-1933. The disease shows itself in various forms. Mild cases showing slight oedema and neuritis are extremely common among the poorer classes, to whom it is a well-known condition and for which they take various medicines mostly containing vitamin B in some form.

The chronic oedematous type also occurs frequently and gives these patients an appearance of being well nourished, although in reality they are often very emaciated. The acute cardiac type is still seen very frequently and is often noticed after some serious illness or severe bodily strain. The disease has been one of the scourges of Malaya, and although very definite improvement has resulted from adjusting the diets of labour forces and educating the people generally, it may be considered that a large proportion of the population to-day suffer from the disease from time to time.

As we know it, beri-beri is a very well established clinical condition which takes weeks or more probably months to respond to treatment, although recently massive doses of vitamin B1 extracts by injection do produce very rapid improvement, particularly in the acute cardiac failure type of case. The fact that many cases

come on suddenly and without any warning must indicate that, a considerable number of this class of patient are potential beri-beri subjects. The disease is very liable to appear in the puerperium and often after an acute fever such as malaria. The pathological changes in beri-beri have been studied fully by Cannon in Hongkong (31). He describes the general oedema of the body tissues. The gastro-intestinal tract shows general congestion and swelling from the increased fluid content. The liver is congested and shows a peri-vascular infiltration of round cells, and in chronic cases cirrhosis accompanied by fatty changes in the cells. Fukuda (32) shows that in Japan the common post-mortem changes are degenerative cloudy swelling accompanied by fat precipitation in the liver and kidneys. The typical changes seen in Singapore are, in the acute cases cloudy swelling of the liver cells, and in chronic cases a fatty degeneration accompanied by chronic venous congestion, and in some of those definite signs of cirrhosis. I have not been able to find any reference to beri-beri being considered as a likely cause of cirrhosis, but there appear to be several arguments in favour of its being of considerable importance in the etiology. While studying the incidence of cirrhosis in various tropical countries, I have been impressed by the fact that the disease is uncommon in Central and South America (1), and also in our own East and West African Colonies (33), (34), (35). In many ways cirrhosis appears to have a world distribution similar to that

of beri-beri. We find also, the incidence in Japan (36) which is not tropical is twice as great as in Great Britain, and no particular explanation has been offered as to the etiology in Japan. Having spent three years in practice in Japan I have puzzled over this question, and I have tried to obtain some information as to possible causes of the disease.

I am indebted to Major W.F.J. Craig, R.A.M.C. for some details of the diets of the Japanese. While attached to the Japanese Army Medical Corps in Tokio, he investigated the diets of the working classes there. Contrary to popular opinion he found that the cost of living in Japan was only slightly below that of England. Rice forms the basic food. Compared with Malaya the diet shows a much higher fat and protein content. The Japanese Health Authorities realize that ordinarily the diets of the Army and the working classes have been deficient in fat, and in the Army an extra ration of fat has been added in recent years, while the Public Health Services have been encouraging the people to consume fatty foods. Compared with Malaya the diet of the labouring classes is very much better from all points of view, but compared with England there is a very definite deficiency of vitamins due to the high consumption of polished rice. As a race the Japanese do not consume much alcohol. Beer is quite a popular drink. It is a light chemical beer brewed in Japan. Sake, the national drink, is a white wine distilled from rice and has a low alcohol content. It is not consumed regularly by any class in Japan and the poorer people only have

it on special occasions. The only other factor which might account for cirrhosis in Japan is schistosomiasis, but this occurs in very scattered parts of the country and does not cause cirrhosis in more than a small percentage of cases.

The type of diet and frequency of beri-beri may well account for the greater incidence of cirrhosis in Japan as compared with England, while the better living conditions of the Japanese labouring classes generally, may explain the infrequency compared with the tropical regions of the Far East. It is also possible that climatic conditions may help to reduce the incidence in Japan. Tropical congestion of the liver is common, and by the French has even been recognised as a disease in itself. It may possibly predispose to cirrhosis in Malaya and India, but in Japan it cannot be of much importance, because the climate of Japan is very similar to that of Great Britain.

Investigating further the incidence of tropical cirrhosis we note that it is uncommon in tropical America. The United Fruit Company's report shows a lower incidence of cirrhosis than does Great Britain.

	Percentage of death from cirrhosis.
United Fruit Co.	0.6
London	1.3
Calcutta	6.9

I have obtained statistics from some of the African Colonies, but as these do not deal with autopsy records it is

necessary to compare the results on a population basis.

	Deaths from cirrhosis per 100,000 population	
Sierra Leone	4	(33)
Nigeria	1	(34)
East Africa	1.5	(35)
Great Britain	3.3	(37)
Japan	6.7	(36)
Singapore	13	(38)

It is interesting to note that the highest incidence amongst the various African Colonies is in Sierra Leone which has more beri-beri than the other places, but this is still little compared with the Far East.

It is thus evident that cirrhosis is not a common condition in tropical America or Africa, although these countries have many of the alleged causal factors such as dysentery, malaria, fluke and worm infections, syphilis, tubercle, etc.

Some indication of the frequency of liver diseases and beri-beri in China may help in this discussion. Figures from China have been very difficult to obtain until recently, when the incidence of various diseases in most of the large hospitals has been analysed by Chinese Medical Association (39). Beri-beri is much commoner in South China than in the North, and the incidence of diseases of the liver and biliary apparatus is also considerably more in South China than in North China. The total deaths from diseases of the liver and biliary apparatus average 4.8 per 100,000 population in Shanghai (40). This figure including all

diseases of the liver is still considerably lower than the figures for cirrhosis for Singapore or Japan. The hospital statistics show that beri-beri is three times as frequent in the South as it is in the North, while liver diseases are twice as frequent in the South.

Dysentery of both amoebic and bacillary types is very common in Shanghai and fluke infections are also frequent. Malaria occurs to a considerable extent in the summer months and is just as common as it is in the South. The climate of Shanghai shows extremes of heat and cold, being somewhat more severe in these respects than Japan, but otherwise showing similar seasons. It is difficult to understand why cirrhosis is much less frequent in Northern Chinese than Southern Chinese or in Japanese unless diet plays a part. Maxwell (41) has commented on the frequency of cirrhosis in Southern China and in Formosa, and believes it to be infective in origin, but he is unable to suggest any particular etiology. He is very opposed to the suggestion that malaria plays any real part in the production of the disease. It is interesting to note that in South China and Japan the staple diet is rice, while in North China rice as a food stuff is of secondary importance.

From a review of these statistics it is impossible to incriminate climate or infective conditions as potent factors in producing cirrhosis. The chief differences between the countries whether cirrhosis is common and those whether it is uncommon, are

in the diets and the resulting deficiency diseases. In Africa and America rice is not used to any extent and beri-beri is uncommon, although a form of nutritional oedema occurs. In North China we have people living under similar climatic conditions to those in Japan, and yet they have much less liver disease.

There are various ways in which beri-beri may cause liver damage. From recent work it appears that the metabolism of carbohydrates is upset when vitamin B_1 is deficient. Peters (42) believes that the disturbance is of the following nature:

			Vitamin B
Glucon			
	Lactic acid	Pyruvic acid	degradation products
Glycogen			O_2 & CO_2

Platt (43) has shown that fever, muscular effort and increased consumption of carbohydrates all lead to an accumulation of pyruvic acid in the blood when vitamin B is deficient. It is of course well recognised that the liver is more easily damaged when its store of glycogen is reduced, and this must be a constant feature of beri-beri even in its early stages. In the latter stages other influences tend to upset liver function. There is always some congestion and later atrophy of the gastro-intestinal mucous membrane, and this must interfere with digestion and absorption of food and it is conceivable that toxic products will form as a result. In established beri-beri the vascular mechanism of the liver is upset by the high venous pressure, and hence the liver cells will be damaged by the anoxaemia. There is little doubt that accentuating factors contribute greatly

to the various clinical types of beri-beri, and are of more importance than the amount of deficiency of vitamin B1. An acute fever or a severe strain such as a difficult pregnancy may precipitate the acute cardiac type of the disease, whereas a more chronic disease or prolonged but not severe bodily strain will produce the chronic neuritic form of the disease. It has been observed in Kedah (27) that Malays have developed definite beri-beri, when given work demanding more than the amount of exertion to which they have been accustomed. This was seen when a number of recruits were taken from various villages, where they had done light work such as cultivators or weeders on estates, and put to work making roads. Within a few weeks many of them showed signs of beri-beri. Their diets were obviously deficient in vitamin B, and the small amount stored in the body was exhausted rapidly by increased muscular work. I believe that a similar state of affairs is seen in liver disease. In the people whom we are considering there are many accentuating factors acting slowly but over a prolonged period, and as a result the liver function is always seriously handicapped and the cells cannot withstand such influences indefinitely.

OTHER DEFICIENCIES.

Other deficiency diseases are uncommon in Malaya. Scurvy is seen occasionally only. Rosedale (44) suggests that there is a considerable lack of vitamin C in most cases of beri-beri, and believes that a multiple deficiency is essential for the production of the disease. Likewise vitamin A has been found wanting in many

of the native diets. Various minor epithelial disturbances such as xerophthalmia and some forms of dermatitis, have been found to respond to addition of the vitamin, usually given here as Red Palm oil. So far as I know, however, lack of vitamin A has not been known to produce damage to the gastro-intestinal tract or liver.

Pellagra is seldom seen in Malaya. A few cases do occur from time to time, but the disease is not seen in the severe form that occurs in other tropical countries. Landor and Pallister (45) have reported some cases of this syndrome in Singapore, but the incidence is so small that it cannot be of much importance in our discussion.

Hyperthyroidism has been noted frequently in America and Switzerland in association with cirrhosis (16). It is of rare occurrence in Singapore and I cannot trace any cases in the present series.

I do not think there are any other conditions occurring with sufficient frequency to merit further consideration. I have dealt with the commoner diseases seen in these people in Singapore, as a result of faults in diet or assimilation. At the same time I have refrained from discussions of complex biochemical problems, which are almost entirely of a speculative nature, but have endeavoured to elucidate what common basic disturbances are found in these people.

V. FINAL CONCLUSIONS.

After reviewing all the evidence obtained from pathological examination and investigation of dietetic and social conditions, we do not find a ready answer as to the causes of cirrhosis. None of the alleged causes advanced by others in the Far East or in Europe or America supply an adequate explanation of the disease as seen in Singapore. It appears that most authors have been obsessed with the idea of accounting for cirrhosis on a single pathological basis, and have not considered the possibility that there is a diminished resistance of the poorer classes to liver disease, in which case many infections or toxaemias may produce the same end result in cirrhosis.

It has been shown in India, Siam and also here that the incidence of cirrhosis becomes less as the social scale improves. If an infection be the cause of cirrhosis, we must then find a high incidence of it among the poorer classes compared with the better classes, and also a greater frequency in the cirrhosis post-mortems than in the others. No one infection can be accused in more than a limited number of cases. Alcohol cannot account for much cirrhosis in Singapore, since most of the poorer classes consume little and that at irregular intervals.

Investigation of the various sects does not help us much in finding any definite etiological factors. Only two groups show a higher frequency of the disease than the others. In the case of the Hochews an explanation is forthcoming readily when

one notes the high incidence of Schistosomiasis, which has been known for long to be a definite cause of cirrhosis. The Cantonese do not show any such specific disease, and it is difficult to decide what is the reason for the frequency amongst them. They do consume more alcohol than the other sects, and their spirit "sam sui" has a high alcohol content. It is possible that this may be the reason for the increased disease in their case.

Syphilis is common to all groups but commoner in the Chinese than in Indians, Javanese or Malays. It is a potent cause of liver damage and must act in a considerable number of cases, but it is probably as common in other parts of the world where cirrhosis does not show the frequency it does here.

There is no doubt that cirrhosis in the Far East is largely a poverty disease, and so the chief predisposing causes are probably those associated with defective nutrition. Examination of the ordinary diets of these people shows that in their case, the liver is always working at a disadvantage compared with people whose standard of living is better. The quality of the food is bad, and almost the whole needs of the body have to be supplied from inferior carbohydrates because of the serious lack of proteins and fats. As a result of the poor diet, nutritional and deficiency diseases make their appearance. These are for the most part chronic well-established conditions which have taken some years to produce. The only acute deficiency is acute beri-beri which appears to be precipitated by some condition producing a rapid reduction of

the essential factor. It is the one type of deficiency which shows a dramatic response to substitution therapy.

One is forced to recognise that almost all of the coolie class are living a precarious existence and are potential cases of deficiency disease, and as a result their resistance to disease is much less. This is borne out by the fact that the average expectation of life is considerably less among them than among Europeans.

There is very good reason for an increased frequency of liver disease in these people. The liver is very much concerned in carbohydrate metabolism, and since these people live almost entirely on carbohydrate, the work of the organ is increased. This state of affairs exists from childhood and since almost the whole demands of the body have to be satisfied by carbohydrate, it is unlikely that the liver can support a sufficiency of glycogen for its own use for any length of time. It is well recognised that liver cells deprived of glycogen are much less resistant to disease, and their life must tend to be shorter. While the capacity for regeneration is great this cannot continue indefinitely. There is an absence of first class protein in the diet to make good ordinary wear and tear, and the other essentials such as fats, vitamins and minerals are also lacking seriously.

We find that the chief deficiency diseases, nutritional oedema and beri-beri, seen in the poorer classes are both associated with a marked upset in the metabolism of carbohydrate. In nutritional oedema there appears to be a serious disturbance in the

utilisation of all foods. In beri-beri sugars are incompletely oxidised, and the effects on the gastro-intestinal tract and liver are marked.

We have here a condition which appears to me to be capable of causing the initial upset in the liver, and predisposes to cirrhosis. I believe that the lack of vitamin B_1 combined with a diet of poor quality is the essential factor in producing degeneration of the liver cells. Just as lack of vitamin B_1 (46) is capable of producing degeneration of nervous tissue, I believe a similar state of affairs is possible in the case of liver tissue. It may not be that the complex is essential for the health of the liver itself, but when it is deficient, the disturbance of carbohydrate metabolism may be the reason for damage to the hepatic parenchyma. The acid products resulting from failure to break down carbohydrates completely may well damage the liver. When carbohydrate metabolism is upset there must follow a failure to utilise fats and possibly also proteins. Added to these we must remember that the diet as a whole is almost always of poor quality, and at periodic intervals really at starvation level.

The liver is more or less always handicapped and it cannot stand the strain indefinitely. It is subjected to an excessive demand on its function more or less continuously. As a result repair cannot keep pace with damage, and eventually fibrous tissue is utilised to replace the damaged, liver cells. This steady damage to the liver takes years to produce serious effects in most cases, and so cirrhosis is commonest in middle life.

While it is likely that nutritional disturbances may be sufficient to cause cirrhosis, there are many other conditions which must hasten or accentuate the disease in these people. Bowel diseases such as dysentery and the various unclassified diarrhoeas will prevent absorption of food, and at the same time supply poisonous products to the portal circulation. Anaemia is common in malaria, ankylostomiasis, and as a result of lack of essentials in the food or a failure to absorb them from the bowel. The resulting anoxaemia must interfere with normal liver function. Chronic debilitating diseases, such as tuberculosis, syphilis, and some of the others previously mentioned, maintain a state of general ill-health which will show its effects on any tissues already damaged.

My contention is that the majority of cases of cirrhosis of the liver in Singapore result from deficiency of vitamin B_1 and a poor diet in the first place, and that various infections add to the liver damage either directly or by increasing its demands. In this way I think we can explain the main incidence of cirrhosis in middle life as due to a slow but steady degeneration of liver cells, but in the presence of active diseases causing damage to the hepatic tissue, cirrhosis may occur much earlier in life.

May we not explain cirrhosis of the liver in Great Britain on similar grounds? The initial factor may be the lack of vitamin B_1 in the diet, or it may be a failure to absorb it. It has been shown that the diet of the average person in Great Britain

has only a bare minimum of the B_1 complex (47). There must be a considerable number of people who have a definite lack of this factor in their diets, and as a result are more liable to liver damage. Alcohol has long been known to be closely associated with cirrhosis. The alcoholic cirrhotic is a chronic alcoholic, and his diet is often deficient because his alcohol replaces his food. In this way his diet shows a serious lack of essentials. The effect of alcohol in producing liver damage may also be brought about by causing a gastritis whereby vitamin B_1 is not absorbed, and at the same time poisonous products are formed and circulated through the liver. Further, alcohol has been shown to interfere with carbohydrate metabolism. It lowers the blood sugar probably by stimulation of the pancreas to produce more insulin (48). The liver must then mobilise glycogen and convert it into glucose, and must try to make good the resulting deficiency of glycogen. In the chronic alcoholic there may be insufficient carbohydrate or protein in the diet to allow of the glycogen deficiency being made up easily. In addition vitamin B_1 may not be present in sufficient amount to permit of oxidation of what carbohydrate there is, and so the lack of glucose is intensified.

I suggest then that cirrhosis of the liver is the result of a disturbance of metabolism of carbohydrate associated with a lack of vitamin B_1. In the tropics the disease is due to a diet deficient in essentials particularly the vitamin B_1 complex, but

lacking also good protein. In Great Britain the cases associated with excessive consumption of alcohol show an upset in carbohydrate metabolism from the first, and there is a lack of essentials in the diet, because alcohol has replaced basic foods. Vitamin B_1 is either lacking in the diet, or is not absorbed from the gastro-intestinal tract because of the catarrhal changes induced by alcohol.

I believe the primary cause is food deficiency and disturbed carbohydrate metabolism. The liver is forced to work at a disadvantage and its cells have a shorter life than normal, and are more easily injured. The various infections and intoxications, which are common in the poorer classes in the Tropics, can then produce severe effects on the liver tissue. They are however, secondary factors in the production of cirrhosis, and act on liver tissue whose vitality is already reduced.

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SECTION VI

I L L U S T R A T I O N S

PLATE 1.

Cirrhosis of Liver - surface of the liver shows very marked nodularity.

PLATE 2.

Cirrhosis of Liver - surface of liver showing generalised irregularity. The left lobe has been cut in section, showing thrombosis of portal vein and this is also seen at the portal fissure.

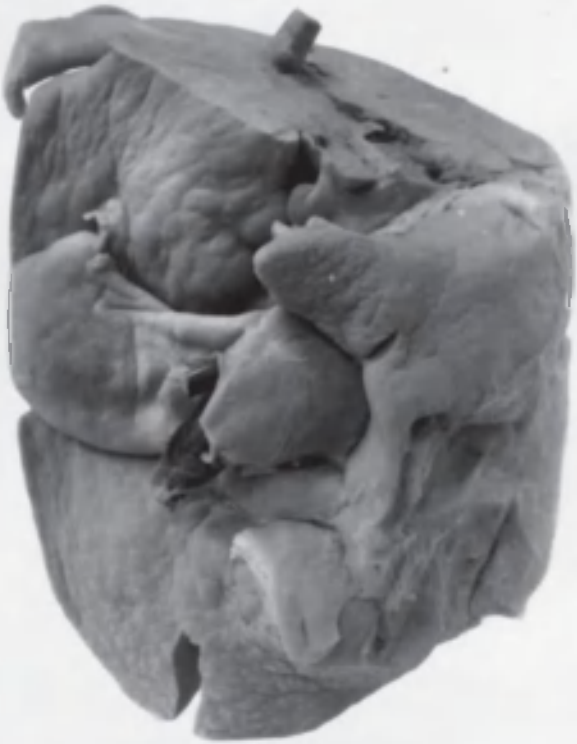


PLATE 3.

Cirrhosis of Liver - cut surface of liver showing a generalised coarse cirrhosis.

PLATE 4.

Cirrhosis of Liver - the outer surface of the liver shows marked irregularity. The cut surface shows numerous cyst - like spaces, due to degeneration and liquefaction of liver tissue.

PLATE 5.

Cirrhosis of Liver - liver showing little in the way of changes of the capsular surface, but early cirrhotic changes are seen on the cut surface, particularly in the left lobe.

PLATE 6.

Schistosomiasis - cut surface of liver from a case of Schistosomiasis. There is distinct fibrous tissue overgrowth surrounding the portal tracts, and the liver substance shows cirrhotic changes.

PLATE 7.

Syphilis - liver from a case of syphilitic cirrhosis showing the organ divided into irregular areas by strands of fibrous tissue. This is the condition known as hepar lobatum.

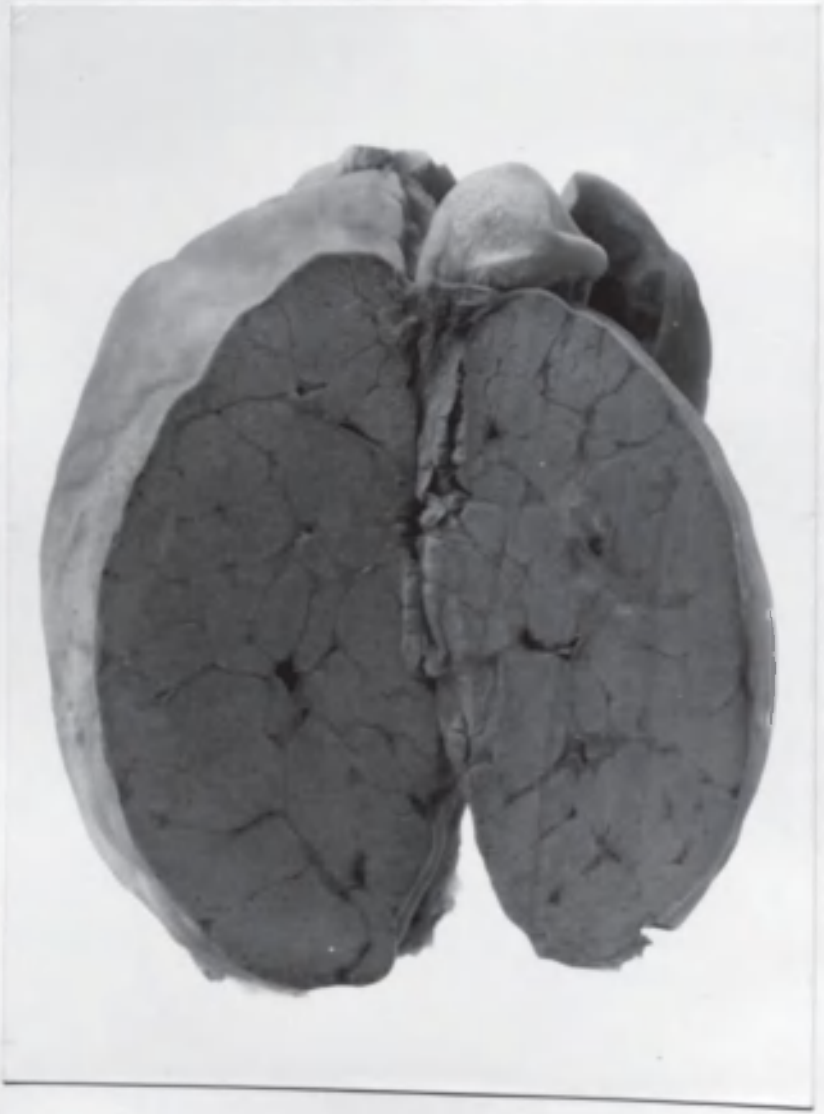


PLATE 8.

Amoebiasis - abscess of liver.

This is the typical lesion produced by amoebiasis. It is almost always a solitary abscess, and the surrounding tissue shows little change.

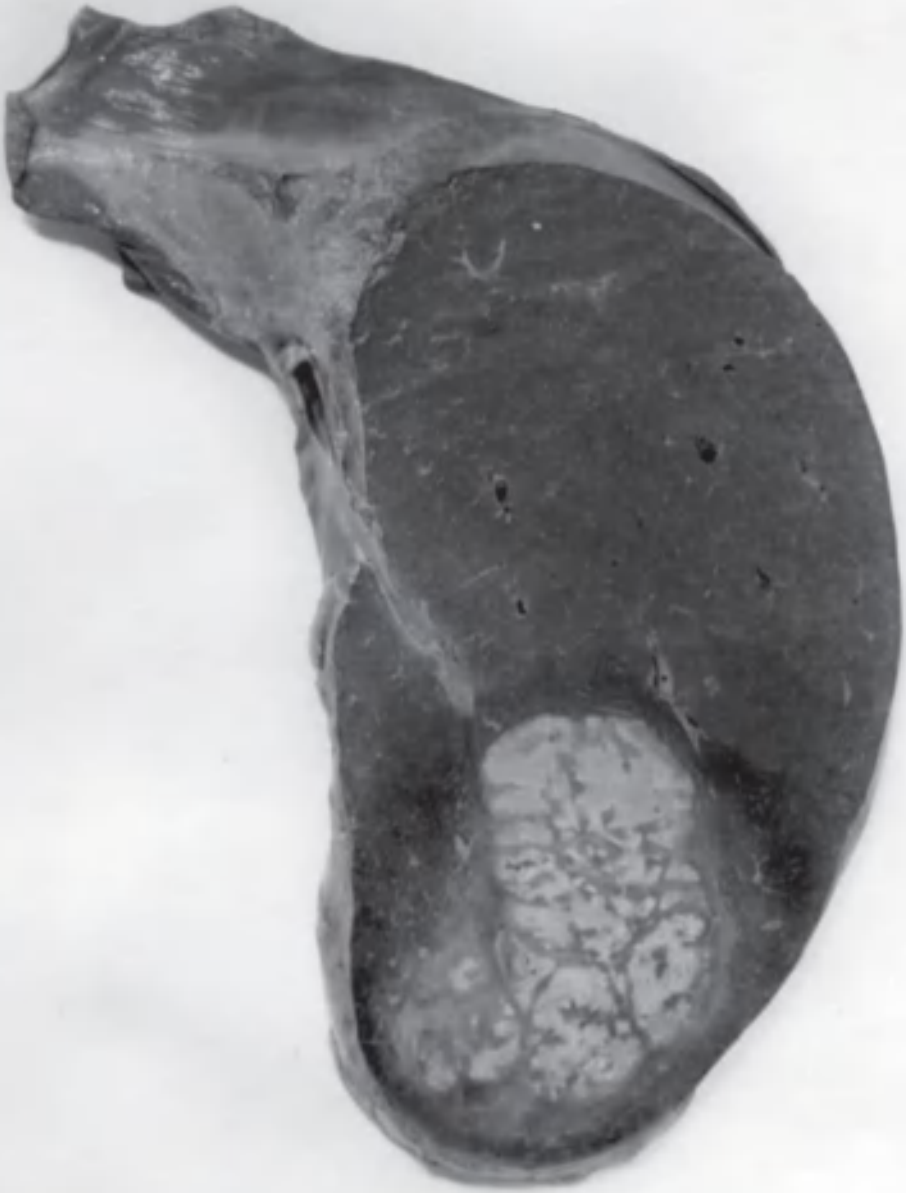


PLATE 9.

Chronic Venous Congestion - liver showing chronic venous congestion with marked fatty changes. This occurs in chronic beri-beri.

PLATE 10.

Primary Cancer - primary cancer of liver-cell or hepatoma type. There are several tumour masses showing some degree of encapsulation, and with necrosis and haemorrhage in the substance of the tumour. The remainder of the liver shows a coarse cirrhosis.

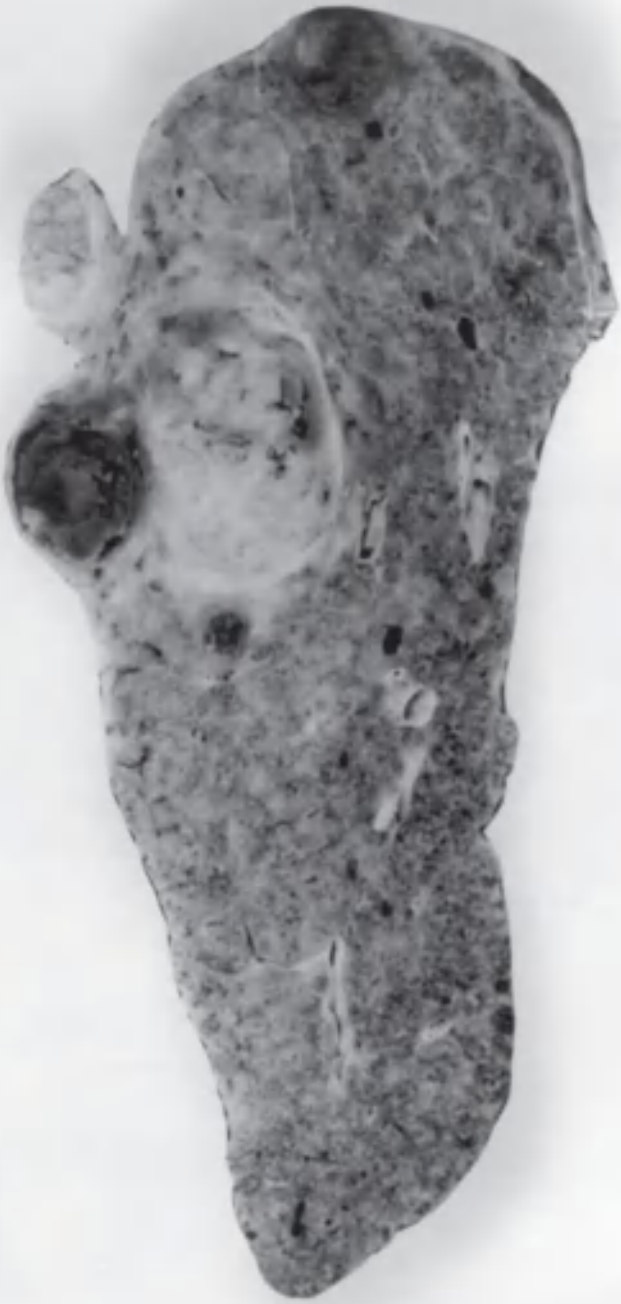


PLATE 11.

Primary Cancer - primary cancer of the bile-duct type invading the whole of the right lobe of the liver. The left lobe shows a granular cirrhosis.

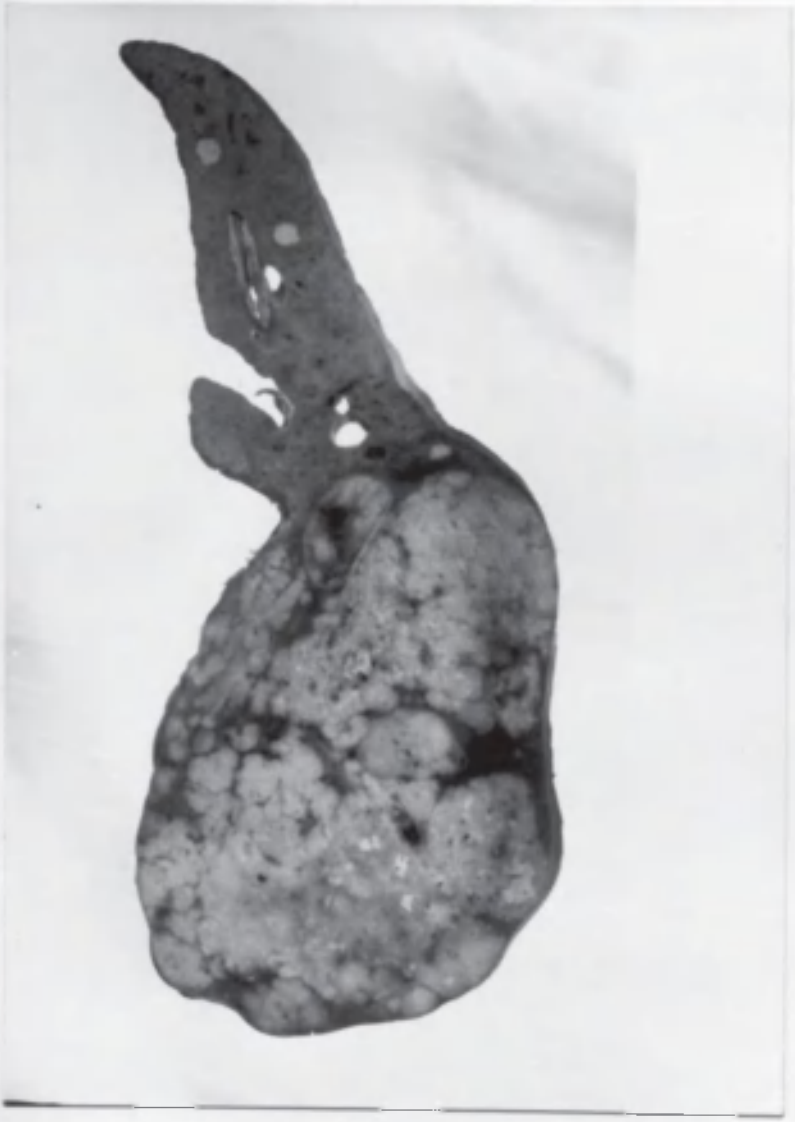


PLATE 12.

Primary Cancer - primary cancer of liver showing several tumour masses causing distortion of the organ. The liver is markedly bile-stained and shows a diffuse cirrhosis.

PLATE 13.

Primary Cancer - primary cancer showing almost the whole liver infiltrated with tumour growth. The remaining liver tissue is cirrhotic.

PLATE 14.

A. Portal Cirrhosis -- showing newly formed fibrous tissue surrounding liver lobules, and some infiltration between the liver cells. X 50.

B. Early Cirrhosis - showing cellular infiltration at periphery of lobules and invasion of liver tissue. X 120.

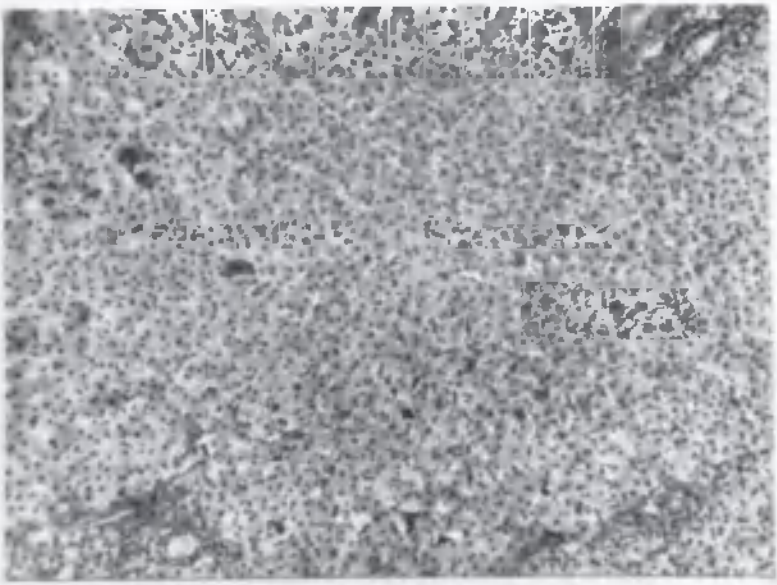
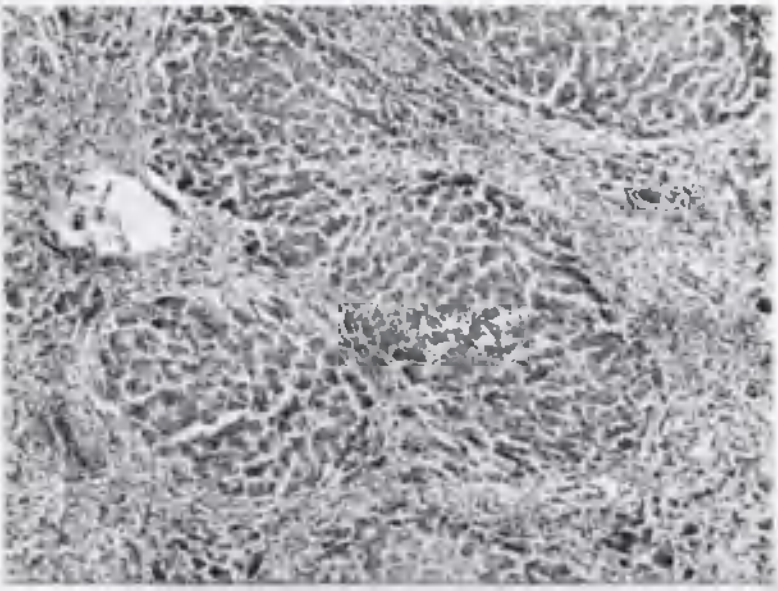


PLATE 15.

A. Portal Cirrhosis - showing marked formation of fibrous tissue dividing the liver into lobules of varying sizes. X 65.

B. Cirrhosis of less marked degree than the above. X 65.



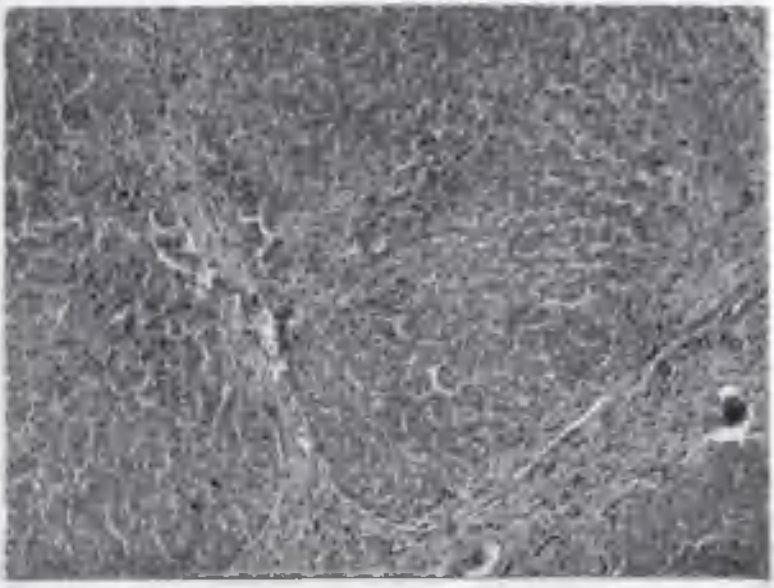


PLATE 16.

A. Biliary Cirrhosis - section of liver showing considerable formation of new fibrous tissue, in which marked proliferation of bile-ducts can be seen. X 50.

B. Biliary Cirrhosis - the same section as above under higher magnification showing fibrous tissue with incompletely formed bile-ducts. X 250.

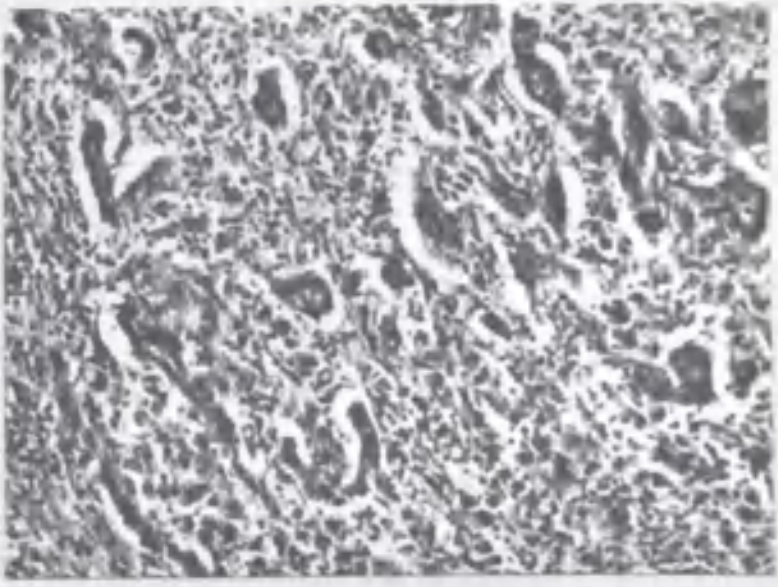


PLATE 17.

A. Schistosomiasis - section of liver showing (a) liver tissue on the left infiltrated with fibrous tissue, (b) ova of Schistosoma Japonicum in the centre, (c) primary carcinoma of liver on the right. X 65.

B. Schistosomiasis - section of liver showing ova of Schistosoma Japonicum surrounded by fibrous tissue. X 250.

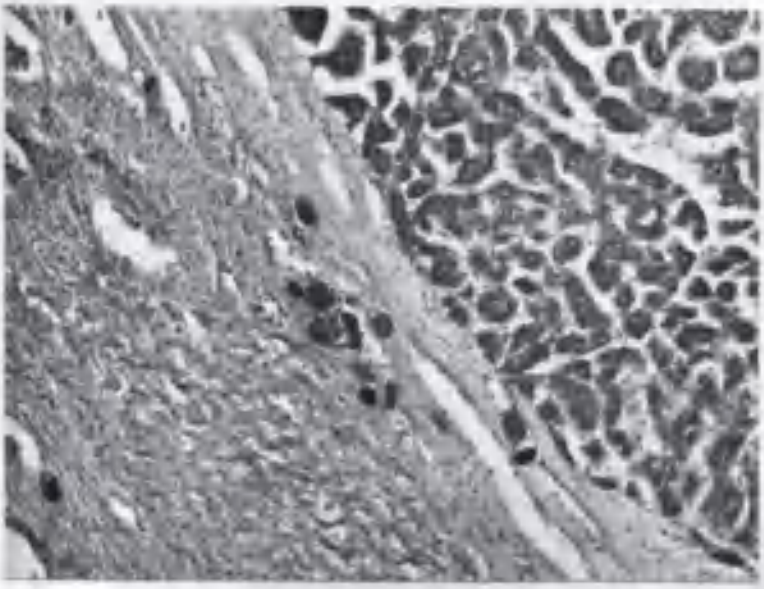
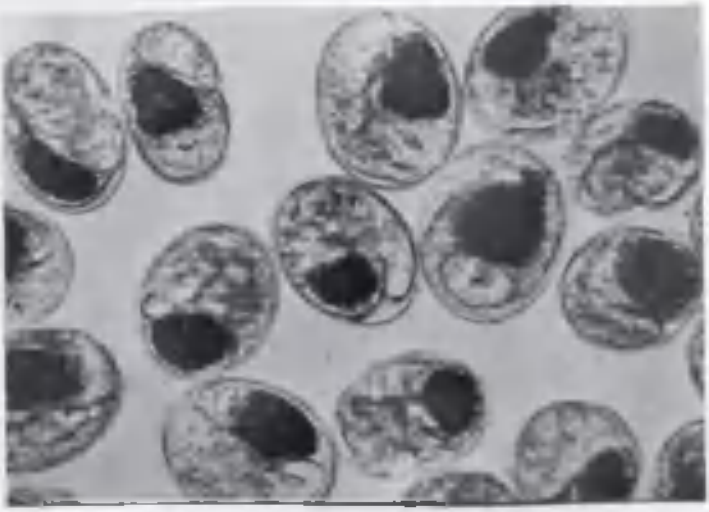


PLATE 18.

A. Clonorchiasis - cysts of Clonorchis sinensis. These cysts are swallowed in badly-cooked fish. The larvae are liberated in stomach and duodenum, and from there ascend the bile-ducts to the liver.

B. Clonorchiasis - section of liver showing marked proliferation of bile-ducts with surrounding fibrosis.



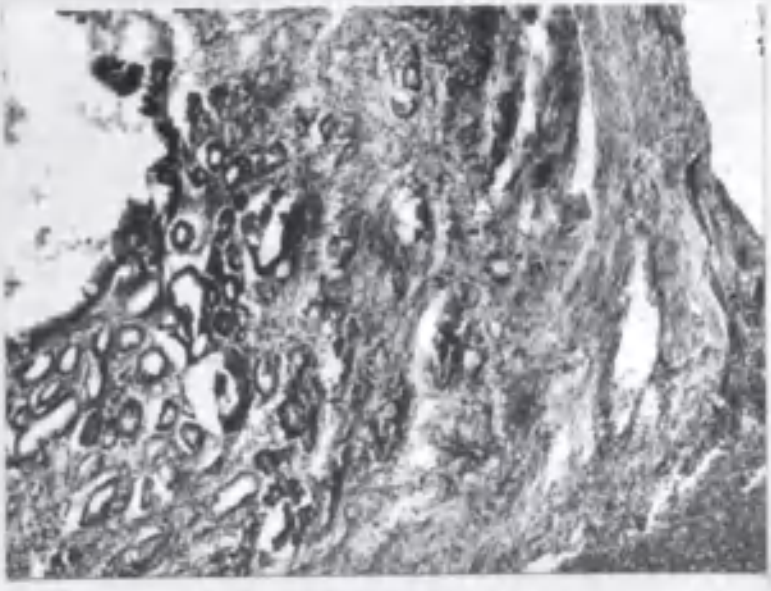
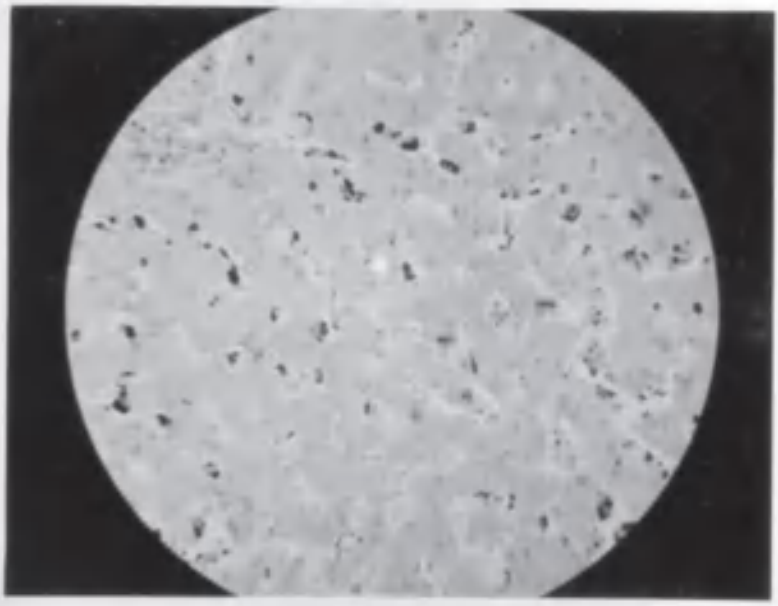


PLATE 19.

Malaria - sections of liver showing considerable deposit of malarial pigment. The outline of the liver cells is obscured, and in the first section numerous fatty droplets can be seen.



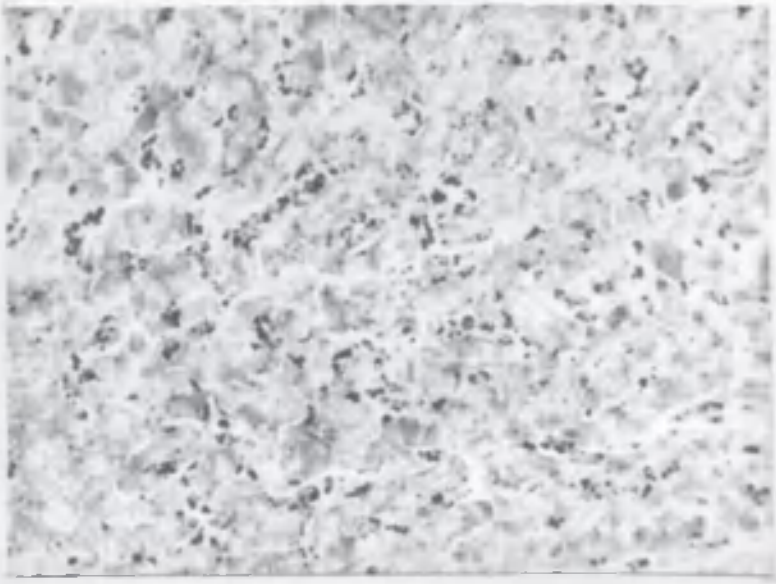
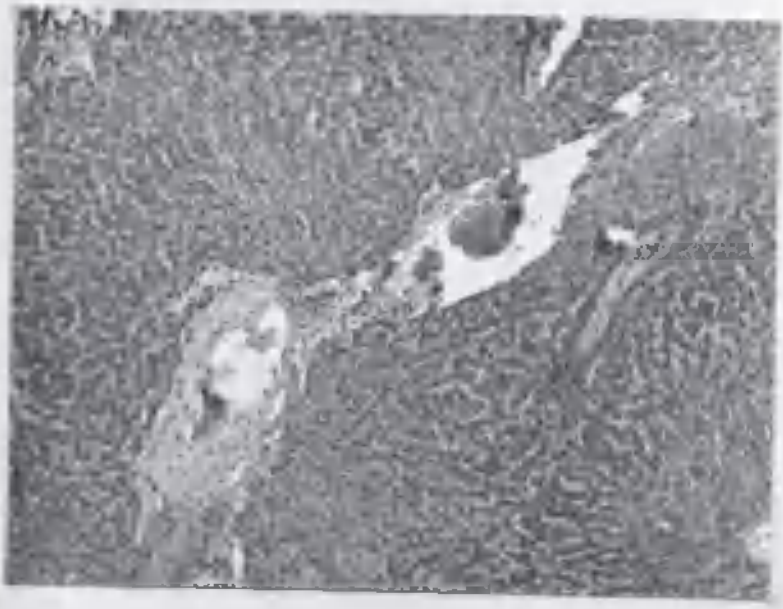


PLATE 20.

A. Chronic venous congestion of liver.
This occurs commonly in chronic beri-beri.

B. Fatty Degeneration of Liver - section of liver showing advanced fatty changes. The patient had a severe anaemia. He was suffering from ankylostomiasis and pulmonary tuberculosis.



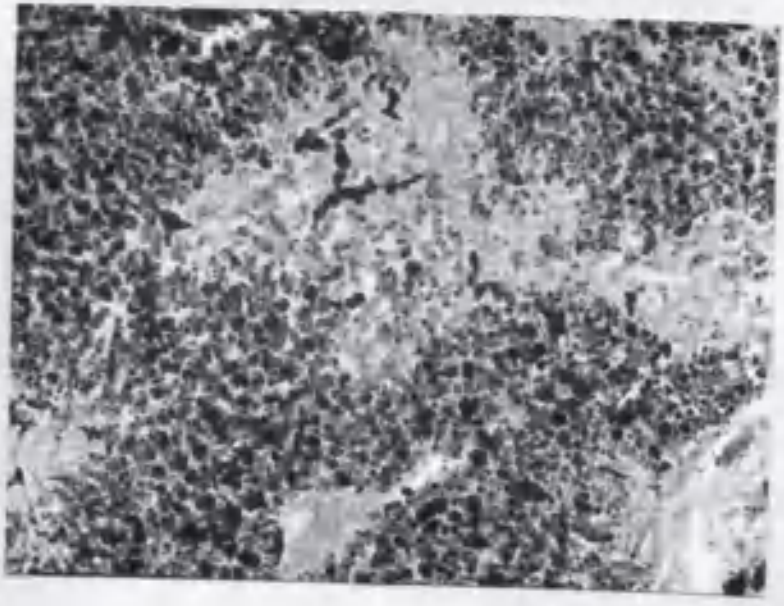


PLATE 21.

A. Primary Carcinoma of the liver-cell type. The carcinomatous tissue shows a resemblance to normal liver tissue. Several multi-nucleated cells common in this type of tumour are seen, and there is a well-defined connective tissue stroma.

B. Primary carcinoma of the bile-duct type showing attempted formation of alveoli. This type of tumour shows no stroma.