HEPATIC FIBROSIS AND CIRRHOSIS IN MAN IN RELATION TO MALNUTRITION *

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Since a deficiency of certain nutrients may cause hepatic damage in experimental animals,[1-3] the possibility has been considered that the high frequency of hepatic lesions in malnourished communities may be the direct result of similar deficiencies.[1-8] In view of the economic implications of this hypothesis, and since recent studies have cast doubt on such a simple relationship,[9-12] we are presenting our observations on the development of liver disease in a group of South African Bantu, whose diet is regarded as inadequate by orthodox standards. In general, our findings add support to the view that the rôle of diet in liver disease among adults is far from established in such communities.

MATERIAL AND METHODS

Our material was drawn from 876 consecutive necropsies on Bantu patients dying at Baragwanath Hospital (1,500 beds), the majority of whom were domiciled in Johannesburg or surrounding townships. An average of two sections from the liver were available for review in all but 20 cases (2.3 per cent). In these, however, the necropsy records stated that the organ was normal.

In addition, 215 specimens of liver were taken for biopsy. In general, these were derived from patients in whom liver disease was suspected.

All sections were stained routinely with hematoxylin and eosin. Additional stains used when desired were Masson's trichrome stain for collagen and a silver reticulin stain. Alcoholic hyalin was demonstrated by Mallory's stain, iron pigment by Perls's reaction, and fat by oil red O or Sudan IV on frozen sections.

To simplify the classification of liver disease, the following groupings were adopted:

Group I. Non-Fibrotic Livers. Livers which showed no increase in portal fibrosis, or only slightly increased collagen or reticulin in an occasional portal triad.

Group II. Slight Portal Fibrosis. Livers in which there was a slight

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but definite diffuse increase in fibrosis affecting the majority of the portal triads.

Group III. Moderate Portal Fibrosis. Livers similar to those in group II, but in which the portal tracts tended to be linked by fibrous tissue ("peri-portal fibrosis"). In groups II and III the normal lobular architecture was, in general, preserved as represented by the relationship of portal tract to central vein (Fig. 1).

Group IV. Severe Diffuse Septal Fibrosis. An advanced degree of group III fibrosis with intralobular fibrosis causing lobular distortion, but without significant parenchymal cell hyperplasia or formation of regenerative nodules ("mild cirrhosis") (Fig. 2).

Group V. Severe Cirrhosis. Livers with marked distortion of architecture due to scarring and the formation of regenerative and hyperplastic parenchymal nodules (Figs. 3, 9, and 10).

Group VI. All livers from patients in whom death was primarily due to hepatic necrosis. Scattered areas of focal necrosis such as are seen in enteric fever and generalized sepsis were not included, and such livers were classified according to the degree of fibrosis.

Group VII. Group VII included livers in which no satisfactory grouping could be attempted because of irregular fibrosis or massive tumor infiltration.

Focal fibrosis due to tuberculosis, bilharzial granulomas, or abscess formation was ignored, as was also centrilobular fibrosis.

Grading of Fatty Change. Livers were graded from 0 to 3 plus according to the proportion of cells containing fat droplets (i.e., 0, < 30 per cent, 30 to 60 per cent, and > 60 per cent).

Grading of Hepatic Siderosis. The grading of hemosiderin deposition (0 to 3 plus) was the same as that used previously.[13]

Development of Portal Fibrosis and Cirrhosis in the Bantu Liver

The age distribution of each type of hepatic lesion is shown in Tables I and II. For convenience, lesions will be discussed under the following headings:

Diffuse Portal Fibrosis (Groups II to IV)

Diffuse portal fibrosis was an incidental post-mortem finding and no evidence of portal hypertension was observed. In only 2 of the 15 livers with severe diffuse fibrosis (group IV) did the hepatic lesion appear related to the cause of death. While the frequency and severity of fibrosis increased with age in both sexes, it commenced earlier and was more severe in males than in females.

Many livers with moderate or severe fibrosis showed a fine surface granularity, with accentuation of the lobular markings on section. No constant relationship was apparent between weight of the liver and degree of fibrosis.

TABLE I

Percentage Distribution of Hepatic Lesions in Bantu Males According to Type and Age Groups *

Hepatic lesion	0–4 yrs.	5–14 yrs.	15–24 yrs.	25–34 yrs.	35–44 yrs.	45–54 yrs.	55–64 yrs.	65+ yrs.	All ages
	%	%	%	%	%	%	%	%	%
I No fibrosis	90.7	72.3	48.2	51.9	51.2	36.6	34.0	23.2	51.7
II Slight portal fibrosis	8.2	11.2	29.6	27.9	25.2	38.7	32.0	41.8	27.1
III Moderate portal fibrosis			3.7	5.1	9.4	11.8	20.7	25.6	9.5
IV Severe septal fibrosis				1.3	2.4	4.3	3.8		1.9
V Cirrhosis		11.2	11.1	10.1	10.2	6.5	7.6	7.0	7.4
VI Necrosis		5.5	3.7	1.3	0.8				0.8
VII Miscellaneous, unclassified	1.2		3.7	2.6	0.8	2.1	1.9	2.3	1.5
Number in each group	85	18	27	79	127	93	53	43	525

* The degree of siderosis and of fatty change was ignored in this classification.

TABLE II

Percentage Distribution of Hepatic Lesions in Bantu Females According to Type and Age Groups *

Hepatic lesion	0–4 yrs.	5–14 yrs.	15–24 yrs.	25–34 yrs.	35–44 yrs.	45–54 yrs.	55–64 yrs.	65+ yrs.	All ages
	%	%	%	%	%	%	%	%	%
I No fibrosis	89.9	83.4	83.8	83.9	73.8	54.5	57.1	57.6	74.1
II Slight portal fibrosis	10.1	8.3	13.5	10.7	13.1	27.1	32.1	12.1	15.7
III Moderate portal fibrosis		8.3†		1.8	6.6	7.3	3.6	18.2	4.8
IV Severe septal fibrosis					1.6	3.6	3.6	3.0	1.4
V Cirrhosis					3.3	7.3	3.6	6.1	2.6
VI Necrosis			2.7	1.8					0.6
VII Miscellaneous, unclassified				1.8	1.6			3.0	0.9
Total number in group	69	12	37	56	61	55	28	33	351

* The degree of siderosis and of fatty change was ignored in this classification.

† A case of rheumatic heart disease with well marked chronic venous congestion. Both central and portal fibrosis were present.

In mild fibrosis, on microscopic examination, the portal triads showed an increase in reticulin and/or collagen fibers and membranes. Such triads were often infiltrated by lymphocytes, histiocytes, and

plasma cells; also by occasional neutrophils and eosinophils. In some livers, however, the picture was that of an inactive portal fibrous scar, cellular infiltration and fibroblastic activity being minimal or absent. In more marked portal fibrosis, the lamina limitans was often disrupted by radiating collagen septa surrounding isolated and degenerating liver cells. In a number of livers, newly formed bile ducts were seen in the portal triads, the appearances of which suggested cholangiolar proliferation. Although diffuse, fibrosis tended to be irregular and to involve the triads to a varying degree (Figs. 1 and 2).

A prominent feature in many livers was the presence of heavy hemosiderin deposits in the liver cells, Kupffer cells, and portal triads (Figs. 1 and 2). In these livers, fibrosis, new bile duct formation, and inflammation tended to be prominent. In addition, many showed foci of parenchymal cell degeneration, often in the region of the central vein associated with infiltration by hemosiderin-laden macrophages. Fibrous and reticulin membranes were observed in such foci, and by linking with the portal triads appeared to be the pathway by which the diffuse septal fibrosis seen in group IV livers developed (Figs. 4 and 5). However, the basic portal nature of the fibrosis usually could still be detected. Although architectural distortion was present in such livers (group IV), evidence of parenchymal regeneration or hyperplasia was slight, and the formation of pseudolobules was rare. Further, the absence of portal hypertension in such cases did not suggest widespread regeneration.

Severe Cirrhosis (Group V)

Hepatic carcinoma was observed in 21 (44 per cent) of the 48 livers in this group. Of the remaining 27, evidence of portal hypertension was present in 19. Cirrhosis of this type was found more frequently in males than in females, but the incidence was unrelated to age; or, if anything, was more common in the younger ages, in contrast to diffuse fibrosis.

While all livers in group V, by definition, showed cirrhosis with nodular hyperplasia, in some the lesions were more diffuse and less irregular than in others. Accordingly, an attempt was made to classify these livers morphologically. In 5 livers moderate fatty change (2 plus and 3 plus) with micro-cyst formation was present and the cirrhosis appeared to be of a diffuse septal type. In 2 of these, alcoholic hyalin was prominent. These 5 livers were, in general, similar to those described as "alcoholic cirrhosis" in white races. In one liver the his-

tologic picture suggested a group IV liver with diffuse parenchymal hyperplasia. For 3 livers no definite conclusion was reached.

In the remaining 39 livers, the hyperplastic nodules were more irregular in size and the surface showed greater nodularity. Of 18 non-neoplastic livers, 9 weighed 1,200 gm. or less, and only 3 more than 2,000 gm.

Microscopically, these livers showed hyperplastic parenchymal nodules, sometimes necrotic and bile stained, surrounded by bands of condensed stroma and fibrous membranes, often containing degenerating liver cells and numerous newly formed small bile ducts. In many livers these bands were of considerable width and suggested massive parenchymal collapse (Figs. 3 and 6). Infiltration of the stroma by lymphocytes and histiocytes was usually marked, but neutrophils, eosinophils, and plasma cells sometimes were observed. Fatty change and alcoholic hyalin were not evident. The most significant feature was the irregularity of the changes, since some areas were relatively unaffected by collapse or hyperplasia, the liver architecture being essentially normal. Using the criteria proposed by Mallory,[14] Himsworth,[1] and Goldblatt,[15] the general pathologic picture suggested post-necrotic cirrhosis.

Other Lesions

Hepatic Necrosis. Six livers showed acute or subacute necrosis. In 4, the necrosis was massive and the features were similar to those described in fulminating viral hepatitis[16] (Fig. 7). The remaining 2 showed diffuse central necrosis.

Fatty Change. Infants and Children. In this series fatty change was seen constantly only in infants suffering from kwashiorkor or severe gastro-enteritis. Of the 154 livers from patients under 5 years, 27 (17.5 per cent) were from cases of kwashiorkor. The histologic picture was similar to that described by others,[17] the organ showing marked fatty change with micro-cyst formation and cellular infiltration of portal triads (Fig. 8). Mild portal fibrosis, however, was seen in only 3 cases. In male infants between 1 and 2 years, only 1 of 13 kwashiorkor livers, but 3 of 12 non-kwashiorkor livers showed minimal fibrosis. In 2 livers from patients who had recovered from one or more previous attacks of kwashiorkor, no significant fibrosis or reticulin formation was noted. Not one kwashiorkor liver showed massive necrosis or post-necrotic scarring.

Adults. Fatty change was rare in adults and was not a feature of livers showing diffuse fibrosis. Slight fatty metamorphosis, usually

in females, was, however, found in chronic disease of extrahepatic origin, as in white people. Only 3 large fatty livers with fibrosis of the type described as "subacute portal cirrhosis" by Hall *et al.*[18] were observed, 2 being associated with generalized tuberculosis. Of the 215 liver specimens examined from adults, severe fatty metamorphosis (2 plus or 3 plus) was found in only 12, of which 9 were from women.

Siderosis. The histopathology of siderosis in the Bantu of Southern Africa has been discussed elsewhere.[13] In this series, the association of moderate and severe siderosis (2 plus and 3 plus) with portal fibrosis is shown in Table III; the proportion of siderotic livers in-

TABLE III

Relationship of Diffuse Portal Fibrosis to Other Pathologic Lesions

Associated disease or lesion	Degree of fibrosis					
	Males			Females		
	Mild II	Moderate III	Severe IV	Mild II	Moderate III	Severe IV
Moderate or severe siderosis	77	41	10	10	13	5
Miliary tuberculosis	18	1	1	3	4	1
Chronic venous congestion	48	15	2	22	6	
Chronic wasting disease	9	6		5	2	
Chronic gastro-intestinal disease	5	2		1		1
Chronic hepatitis or cholangiolitis	2	1	1	4		1
Amebic abscess or enteric fever	5	1		4		
Schistosome ova	4					
Kwashiorkor	2			1		
No obvious lesion or disease	16			9	2	
Total number of livers in group*	142	50	10	55	17	5

* This represents the total number of livers in the group, not the total number of lesions. When livers showed both siderosis and another lesion they have been entered for both.

creased with the severity of the fibrosis, siderosis being present in all livers with group IV lesions. But, as formerly reported,[13] siderosis was observed also in a small proportion of non-fibrotic livers. It is of interest that if livers with significant siderosis (2 plus or 3 plus) are excluded, the incidence of diffuse portal fibrosis in both sexes is similar (14.2 per cent in males and 13.9 per cent in females).

There was no demonstrable association between siderosis and severe cirrhosis.

Primary Carcinoma of the Liver. There were 26 primary carcinomas of the liver in this series, 24 in males and 2 in females. All were of the liver-cell type, with the exception of one of bile-duct-cell type in

a female. In males, 21 (87 per cent) tumors arose in livers with severe cirrhosis (group V). While 54 per cent of these livers developed malignant change, none of the 9 such livers in females did so, which is significant ($P < 0.02$). The remaining tumors arose in livers with diffuse portal fibrosis. The histologic appearance in many cirrhotic livers with malignant change suggested that the carcinoma developed from hyperplastic parenchymal nodules, many of which showed marked atypicality and hyperplasia and at times appeared to merge with the tumor (Figs. 9 and 10).

Hepatic Disease and Biochemical Dysfunction

Local studies indicate that children who have recovered from kwashiorkor may be left with residual hepatic dysfunction as reflected by biochemical tests, despite normal histologic findings on liver biopsy.[19-21] Furthermore, children who have had no overt attack of kwashiorkor may also develop similar abnormalities.[20,22]

To what extent the biochemical changes persist into adult life is uncertain, but over two thirds of young adult Bantu reveal abnormalities[23,24] although we have found no significant hepatic lesion at biopsy in a number of such cases. It is clear, therefore, that a high proportion of livers in adults cannot be regarded as metabolically normal.

Discussion

Summary of Pathogenesis of Hepatic Disease in the Bantu

In infancy and early childhood, the most common hepatic lesion was the severe fatty change seen in kwashiorkor.

In adolescence and early adult life, most livers appeared relatively normal, apart from a small number showing mild portal fibrosis, usually associated with tuberculosis or chronic venous congestion. Isolated cases of acute hepatic necrosis and post-necrotic scarring were seen also.

In adults, hepatic lesions were of two major types: (1) A diffuse portal fibrosis which, in the more severe cases, was associated with well marked siderosis. The age distribution and histologic pattern in many livers suggested a low-grade progressive chronic cholangiohepatitis. (2) A severe cirrhosis which, in the majority of instances, suggested a post-necrotic origin and which occurred with approximately equal frequency throughout life. The different age distribution and pathologic patterns of these two lesions suggested that they were not related. Further, the age gap between the fatty liver of kwashiorkor and appearance of the more severe degrees of diffuse portal fibrosis indicated

that the latter was not a direct sequel of kwashiorkor. Too great reliance should not, however, be placed on the etiologic distinction made between the various types of severe cirrhosis (group V), in view of Dible's[25] caution on the frequent impossibility of determining the morphogenic pathway by the final picture.

Nutrition: General Remarks on Human Malnutrition

Animal Studies and Their Limitations. Liver disease in rats and other animals caused by dietary manipulation has been amply studied. Such experimental diets include those deficient in protein, in various amino-acids and vitamins, and also in certain lipotropic factors.[1,2] Excess of other nutrients such as cystine, riboflavin, and biotin, also may be harmful in certain dietary contexts.[2] It must be remembered, however, that a diet satisfactory for humans is apparently inadequate when fed to rats and monkeys.[26,27] In man deficiencies of nutrients almost invariably are multiple, and many other factors such as bacterial infection, parasitic infestation, and climatic stress may be of importance. Very little is known for man of the possible adaptations in metabolic activity and the physiologic requirements of nutrients which may develop in a specific dietary context, a fact of possible significance when discussing diets differing markedly from those of Western populations. The human requirements or even the need for such dietary factors as cystine, choline, inositol, biotin, and alpha-tocopherol are not yet established.

These considerations increase the difficulty of determining whether the Bantu diet is adequate in respect to particular nutrients. Nevertheless, in view of the misconceptions prevailing, it seems worthwhile to assess the adequacy of their diet in respect to certain nutrients in terms of orthodox beliefs in nutritional requirements.

Nutritional Consideration with Bantu Infants and Young Children. There is evidence that the composition of Bantu breast milk,[28,29] and the growth and general health of exclusively breast-fed Bantu babies compare favorably with their white counterparts.[30] At weaning, however, which is often sudden, babies are given a variety of foods, mainly cereal paps, but also proprietary cereal and dried-milk preparations, which are usually diluted excessively.[31] Such a diet, in comparison to breast milk, while adequate in methionine, is usually deficient in every other essential amino-acid as well as in total protein. In addition, when judged by amounts recommended for infants, the diet will be deficient in fat, calcium, vitamin A, riboflavin, niacin, possibly thiamine, and vitamins C and D. The amounts of choline, inositol, and

vitamin E will depend on the type of milling of the cereal; if the cereal is refined, the concentration of these nutrients will be very low. It is with this grossly inadequate dietary pattern that kwashiorkor so frequently occurs, and understandably the inadequacies are not remedied by supplements of single amino-acids, lipotropic substances, or vitamins.[17]

Nutritional Considerations with Bantu Adults. Information available from recent dietary surveys in Johannesburg and other areas[32-35] indicates that the adult Bantu diet, speaking generally, while markedly different in pattern from those of Europe and America, is seriously deficient in neither total protein nor amino-acids, in so far as the minimum requirements suggested by Rose[36] and associate workers are applicable, a conclusion reached also by Patwardhan[12] for tropical and subtropical peoples elsewhere. Unfortunately, dietary surveys usually provide average figures only for population groups and many individuals must consume much less than the mean figures reported. However, they do permit assessment of the probability of deficiencies of certain nutrients, the lack of which are known to lead to liver disease in various animals.

Etiology of Liver Lesions

Kwashiorkor

The possible etiologic factors causing kwashiorkor have been reviewed recently.[37] There is now general agreement that the syndrome is a manifestation of "protein malnutrition" in infants and young children. Recently, it has been demonstrated that cure may be initiated by a synthetic diet composed exclusively of eleven amino-acids.[38,39] While there is still uncertainty whether the liver changes are secondary to pancreatic damage, it appears justifiable to regard the fatty liver of kwashiorkor as a true example of human liver disease due to an inadequate diet. Yet, this series provides no evidence that progressive fibrosis, cirrhosis, or other sequelae develop directly in such livers, a conclusion similar to that reached in other local studies.[3,21]

Diffuse Portal Fibrosis

Diffuse portal cirrhosis in adults often has been called "nutritional or tropical cirrhosis" on the African continent. While fibrosis can scarcely be ascribed to the same cause in all livers, nevertheless, the histologic picture associated with the age trend (Tables I and II) suggests that a common morphogenic pathway is present in a large proportion. Notwithstanding, mild increased scarring and fibrosis of the portal triads may be observed occasionally in European subjects

dying without a history or other evidence of hepatic injury. It is probable that such lesions may result from non-specific hepatitis due to chronic intestinal disease, chronic bacterial infection, or heart failure.[40,41] The association of such diseases to portal fibrosis is shown in Table III and such possible factors cannot be ignored.

Protein and Lipotropic Agents. Fatty metamorphosis induced by deficiency of lipotropic agents in the rat may cause diffuse hepatic fibrosis which is non-portal in distribution. The fibrosis in the Bantu livers was predominantly portal and did not appear related to the fatty liver of kwashiorkor. Reviewing the dietary data available, we believe that there is no clear-cut evidence of gross deficiencies of total protein or of amino-acids (including methionine) in the local adult Bantu diet, although the major part of the ingested protein is from vegetable sources. In these surveys the range of means for the groups studied was 63 to 112 gm. of gross protein per diem per man unit. While the significance of choline has not been satisfactorily demonstrated in human nutrition, we have calculated that the average adult Bantu ingests an amount well within the range reported for white groups. Finally, the uncommonness of significant fatty infiltration in the adult livers also militates against the view that this latter lesion and, accordingly, lipotropic deficiency, were direct etiologic factors.

Alcohol. Liberal consumption of fermented cereal foodstuffs is widespread in South Africa.[34,42] Although the alcohol concentration is inconsiderable, the large volumes consumed probably entail an alcohol consumption reaching or even exceeding that of the drinking population of the United States. Fatty change, a characteristic feature of "alcoholic cirrhosis" in white adults,[40,41] was rare in this series. Further, in a series of 15 liver biopsies on alcohol-conditioned pellagrins, no significant fatty change was found. We hesitate, therefore, to regard alcohol as a factor of significance in the etiology of liver disease as seen here. It is possible, however, that the response to alcohol, directly or indirectly, in the Bantu pattern of diet is not identical to that seen with the European dietary context. The absence of fatty change may be analogous to the relative rarity of atherosclerosis in the Bantu.

Vitamins. In experimental studies on animals, thiamine and other members of the vitamin B complex have been implicated in the development of fatty change in the liver.[1,2] In the Bantu diet, calculated intakes of thiamine and total niacin usually are adequate, although intake of riboflavin may be marginal. The mean intake for vitamin A and its precursors in the Johannesburg survey in 50 families was 6,000 i.u. per man unit.[34]

Siderosis. It has been postulated that the widespread siderosis among the Bantu in Southern Africa is the result of excessive iron intake, which may be up to 200 mg. per diem.[43] Originally we regarded this iron deposition as harmless,[13] bearing in mind failure to produce fibrosis by experimentally induced siderosis. But in the present series, excluding livers with severe cirrhosis, the association of siderosis with the more severe degrees of diffuse portal fibrosis was marked (Table III). In many livers, foci of liver cell degeneration associated with infiltration by hemosiderin-laden macrophages and early fibrosis were noted (Fig. 5). Diffuse fibrosis and siderosis were more marked in males than females, but the incidence of hepatic fibrosis without significant siderosis was the same for both sexes.

Walters and Waterlow[9] have suggested that diffuse portal fibrosis in infants and children in West Africa is the result of the combination of malnutrition and malaria, the former predisposing the liver substrate to the noxious influence of the latter. It is possible that hemosiderin in the Bantu may act in a similar manner, its toxic effect being dependent on previous damage to the liver.

To summarize, in Table III is tabulated the relationship of diffuse portal fibrosis to siderosis and diseases believed to cause mild portal fibrosis. If these are regarded as possible etiologic factors, there are few cases of diffuse fibrosis in this series for which no possible cause can be postulated.

Severe Cirrhosis

Since the age distribution and histologic pattern in the majority of the cases with severe cirrhosis suggested post-necrotic origin, discussion will be limited to this group.

Nutritional Background: Protein and Amino-Acid Deficiency. In experimental animals, acute hepatic necrosis has been produced by protein and cystine deficiency accentuated by lack of alpha-tocopherol and factor 3.[2] Evidence from local dietary surveys[32-35] suggests, however, that the Bantu do not suffer from gross protein deficiency; moreover, maize, the staple foodstuff, is not deficient in cystine. The latter is not an essential amino-acid for man, nor have the human requirements or even need of alpha-tocopherol been demonstrated. It would seem unwise, therefore, to attribute the hepatic necrosis observed in the Bantu as due solely to nutritional deficiences of the type described in animals, nor is there evidence of an excessive intake of those factors known to enhance experimental hepatic necrosis.

Condiments, Toxic Drugs, and Chemicals. It is believed that the widespread and excessive use of condiments in India and Ceylon may

be a factor in promoting hepatic necrosis.[16] However, condiments are not a feature of the South African Bantu diet. These people do, however, consume a wide variety of native medicines, the composition and effects of many of which are unknown. From Baragwanath Hospital, Grusin[44] has described 5 cases of liver poisoning due to potassium bichromate, the latter sometimes being used as a daily emetic, and it is possible that other hepatotoxic drugs may be implicated. In this series only one case of Chiari's syndrome was observed, but no livers with the features of acute senecio poisoning, or veno-occlusive disease[45] were found, although we have since observed 4 such cases in infants. Therefore, the etiologic rôle of hepatotoxic drugs requires further investigation.

Hepatotoxic Viruses. In the absence of a satisfactory test for hepatotoxic viruses, their significance is difficult to assess, the investigator being mainly dependent on the histologic appearance of the liver and on the clinical history. "Infective hepatitis" is endemic in Johannesburg and about 30 Bantu patients with this diagnosis are admitted each year to Baragwanath Hospital. The mortality is approximately 3 per cent. In a 3-year period, 48 patients diagnosed as having "acute yellow atrophy" were admitted, with a mortality of 54 per cent. Some of these patients almost certainly had fulminating viral hepatitis, and the histologic pattern of the 4 livers with massive necrosis in the present series was consistent with such a diagnosis.

Although in Europeans, examples of post-necrotic scarring and primary carcinoma are described as following viral hepatitis, reports indicate that such a sequence is more common in Africans,[46,47] Singalese,[16] and Indonesians,[48] some workers attributing the high frequency of such sequelae to previous liver damage.[47] In this series, the number of livers with hepatic necrosis is small, but the age distribution is consistent with a relationship to post-necrotic cirrhosis. Further, the age distribution of the latter suggests a factor acting constantly throughout life, a rôle which a virus could fill. The possibility of a virus as a major cause not only of post-necrotic cirrhosis but also of liver cancer in this country thus needs investigation.

Undernutrition. Gross deficiencies of calories and nutrients lead to atrophy of the liver, as well as of other organs,[41] but fibrosis and cirrhosis are not a feature. In any case, the Bantu diet is seldom seriously deficient in calories, and the livers in the present series were not atrophic.

Parasites. Malaria is not endemic in the Johannesburg region. Mild bilharzial (*Schistosoma haematobium*) infestation, however, is wide-

spread, particularly among males in this area, but no significant correlation has been demonstrated between this parasite and diffuse hepatic fibrosis, cirrhosis, or liver cancer.[49]

Conclusions

It would appear that in childhood, abnormalities of liver metabolism may arise in the Bantu which are not necessarily reflected by histologic liver damage.[19-22] There is some evidence that these abnormalities persist into adult life,[23,24] and are irreversible. Thus Wayburne and Bersohn[50] found no significant alteration in the tests for liver function of trainee Bantu nurses followed for 2 to 3 years, despite consumption of an adequate diet; and we have previously reported a similar frequency of hepatic dysfunction in both poorly fed and in adequately fed Bantu subjects.[23] Furthermore, from Tables 19A and 19D in the study of Gillman and Gillman,[3] it would appear that the pattern of liver disease seen in severe malnutrition (pellagra) is similar to that in healthy Bantu adults dying accidently.

There is evidence in man and animals that a healthy liver is less susceptible to hepatotoxic agents than a dysfunctioning organ.[40] Accordingly, it would appear reasonable to suggest that the significance of malnutrition in this locality is dependent mainly on the damage caused to the liver in infancy and early childhood, which renders the organ, in comparison to that of the European, more susceptible to stresses in adult life.

The nature of these stresses is not established, but the present observations suggest that siderosis, hepatotoxic viruses, and possibly toxic drugs may be of major importance. If this hypothesis is acceptable, there is little necessity to regard the diet of the adult Bantu as a major factor in the causation of liver disease. This does not imply that amino-acid imbalance, with concomitant changes in metabolic pathways, is not of significance, nor do we exclude the probability that isolated individuals may suffer from gross dietary deficiency. But we do maintain that the high incidence of liver disease in the Bantu is far from being explicable on the basis of clear-cut and widespread nutritional deficiencies in these people.

Summary

The results of pathologic examination of the livers from 876 consecutive necropsies and of specimens of liver from 215 biopsies on South African Bantu patients are reported.

Hepatic lesions were found to be of three major types: (a) A fatty liver occurring in infancy due mainly to kwashiorkor and rarely fol-

lowed by fibrosis and necrosis; (b) a fine symptomless portal fibrosis, most frequent in the second half of life and usually associated with heavy hemosiderin deposition; and (c) a severe cirrhosis, most frequently of post-necrotic origin and showing no specific age trend. More than half of the livers of the third group had developed primary malignant proliferation.

The causative rôle of dietary and non-dietary factors in the development of these lesions is discussed. Apart from severe malnutrition (kwashiorkor) in infancy, there is no adequate evidence that the nutritional factors which so readily induce hepatic damage in small animals are involved; in particular, it is doubted whether gross deficiencies of protein and amino-acids may be invoked as etiologic factors for the hepatic lesions so common among the Bantu.

In infancy, however, widespread liver damage, although not usually recognizable histologically, is demonstrable by various biochemical tests of liver function, and it is probably caused by malnutrition. It is suggested that such damage predisposes the liver to factors which, in adult life, precipitate liver damage. For the Bantu, it seems probable that such factors include siderosis, hepatotoxic viruses, and possibly toxic drugs.

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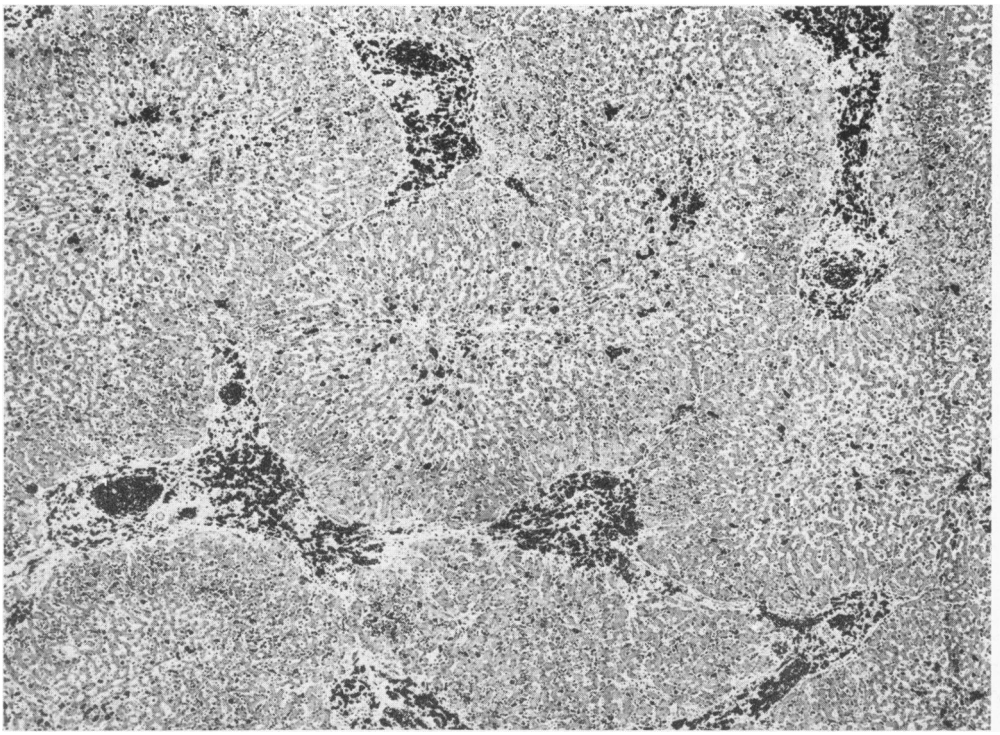
[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Liver (group III) from a 52-year-old man who died from lobar pneumonia. Moderate portal fibrosis with early linking up of the portal triads, but with preservation of the normal relationship of the portal triads and central veins. Heavy hemosiderin deposits also are present. Hematoxylin and eosin stain. × 40.

FIG. 2. Liver (group IV) from a 50-year-old woman who died of scurvy. Severe portal fibrosis with loss of the normal relationship of the portal tract to the central vein due to fibrosis. Marked hemosiderin deposits also are present. Hematoxylin and eosin stain. × 40.



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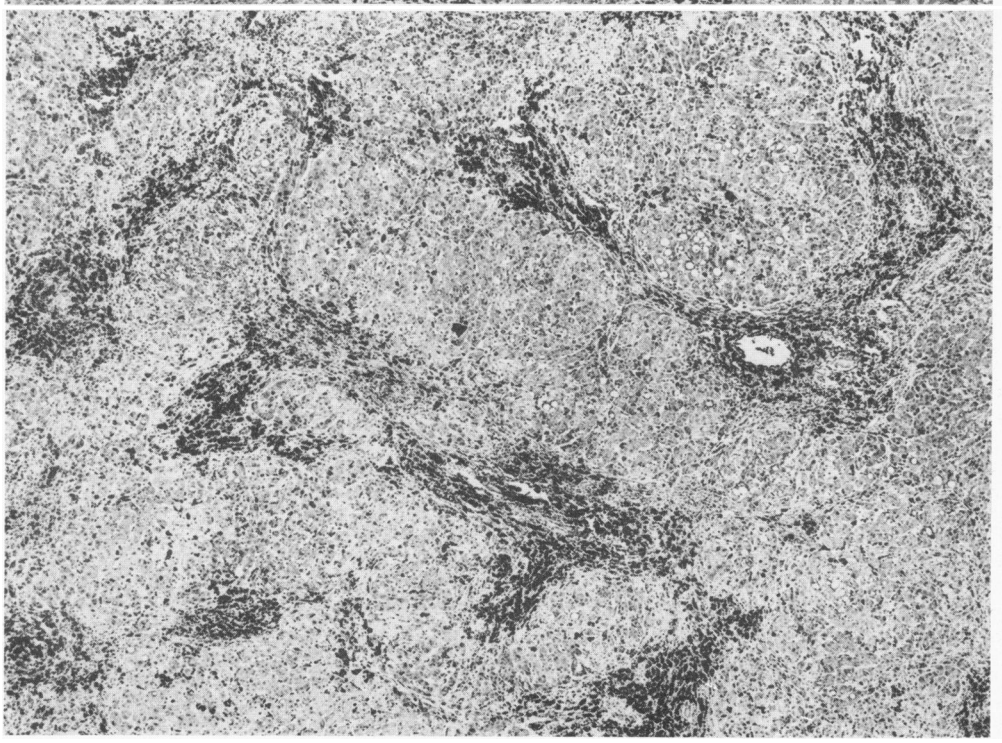

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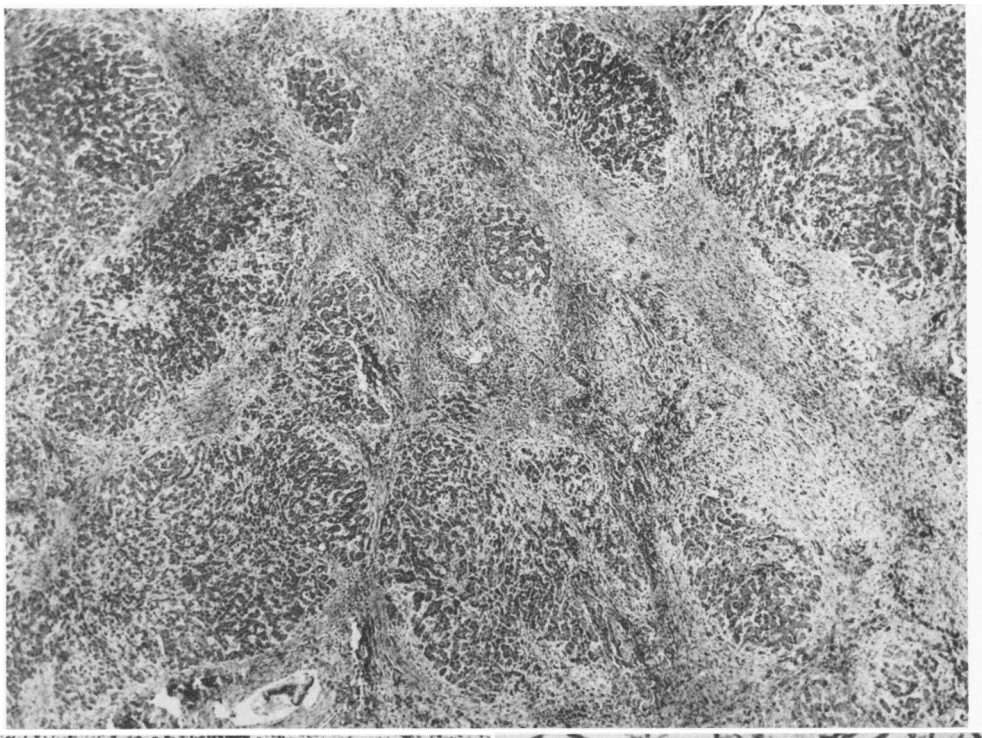
FIG. 3. Severe cirrhosis (group V) with large areas of condensed stroma and fibrosis in which degenerated and necrotic liver cells are present. Small islands of regenerating parenchymal cells also are present. Hematoxylin and eosin stain. × 30.

FIG. 4. Liver obtained for biopsy, showing large clumps of hemosiderin in the parenchyma associated with degeneration of liver cells. Reticulin stain. × 150.

FIG. 5. A focus of hemosiderin deposited in sinusoids, with increase in reticulin membranes due to degeneration of liver cells. Same liver as that seen in Figure 4. Reticulin stain. × 600.



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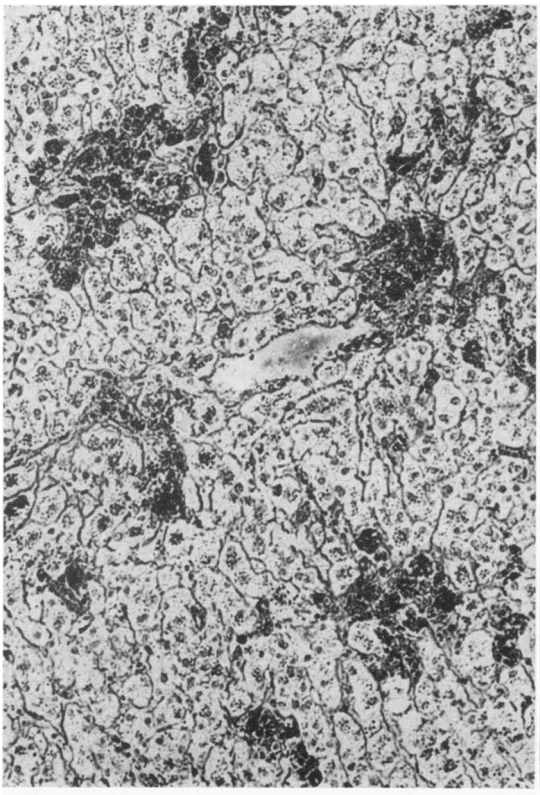

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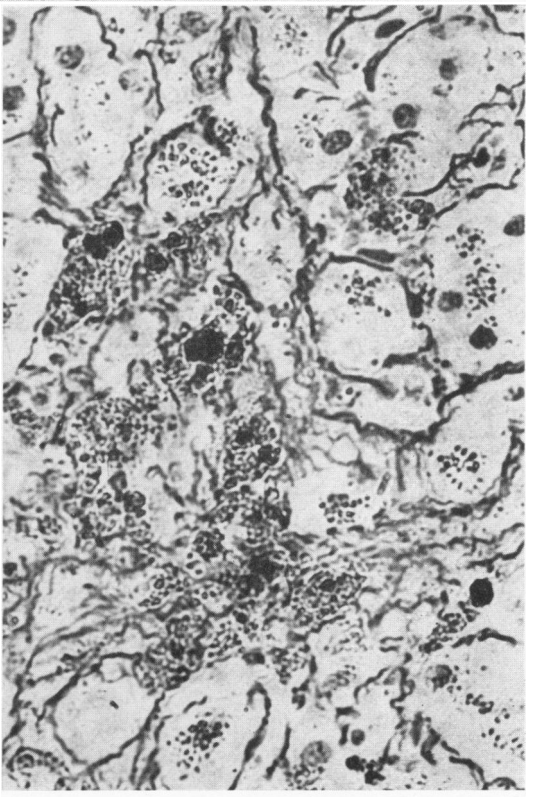

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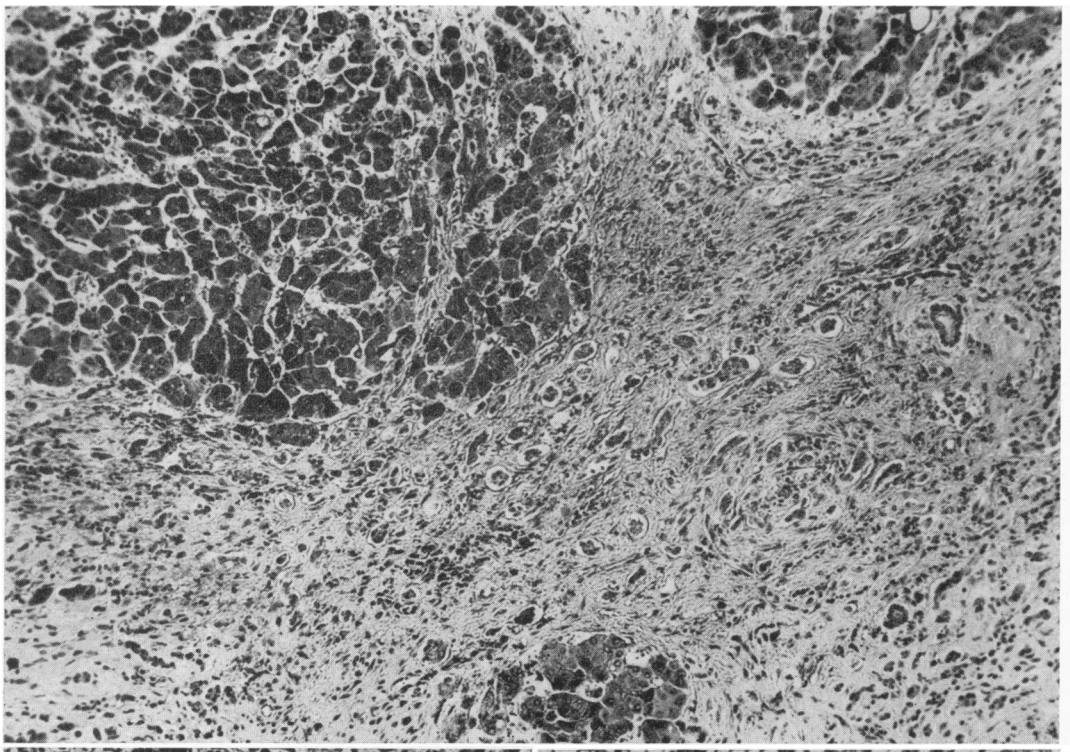
FIG. 6. Liver with severe cirrhosis, showing regenerating parenchymal nodules, some cells of which contain polyploid, bizarre nuclei. There is infiltration of the stroma by lymphocytes and histiocytes. Many newly formed bile ducts are present also. Hematoxylin and eosin stain. × 120.

FIG. 7. Liver with recent massive necrosis, showing collapse and degeneration of the parenchyma with condensation of the stroma in which there is mononuclear cell and lymphocytic infiltration. Many of the parenchymal cells are degenerated and bizarre. In addition, newly formed bile ducts are present. Hematoxylin and eosin stain. × 120.

FIG. 8. Liver from a child dying of kwashiorkor, showing marked fatty change and formation of "fatty cysts." The portal triad shows scanty cellular infiltration. Hematoxylin and eosin stain. × 120.



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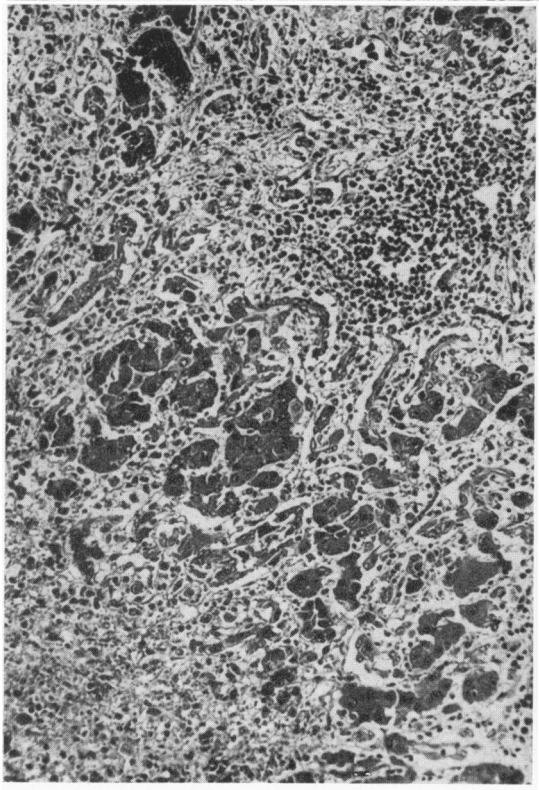

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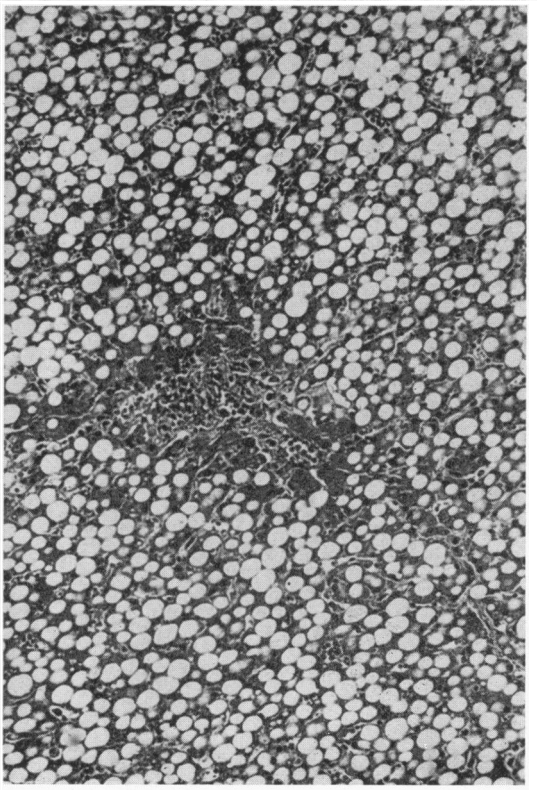

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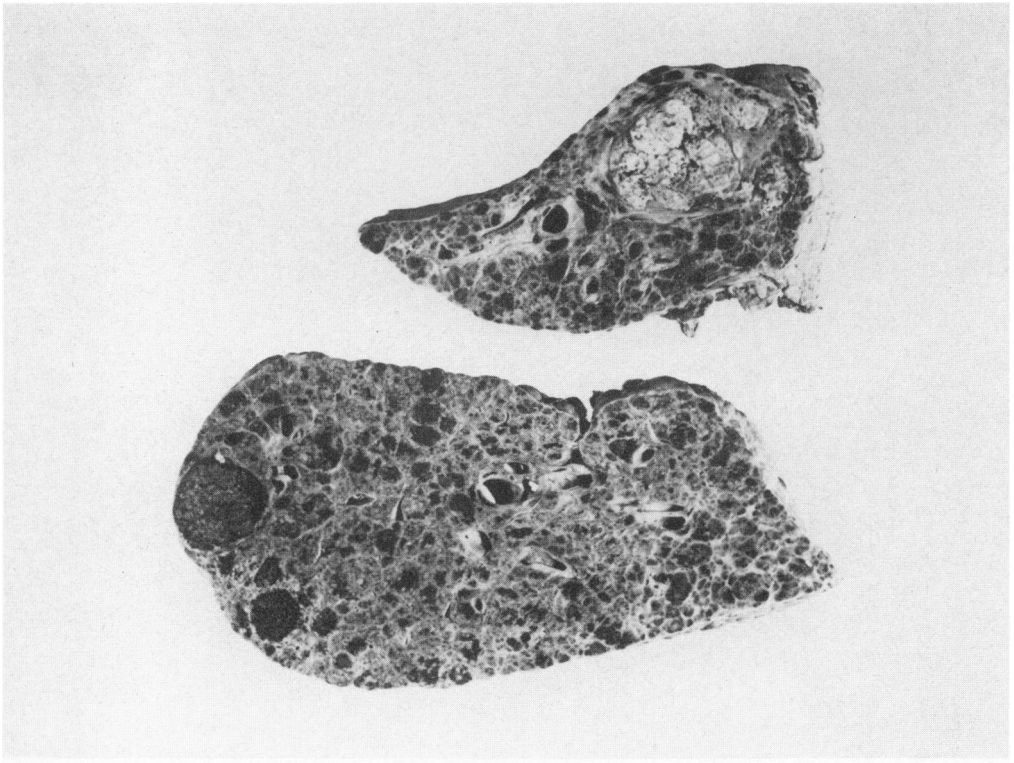
FIG. 9. Primary cancer arising in a liver with well marked nodular hyperplasia, probably of post-necrotic origin. Hyperplastic non-malignant nodules are present. × ½.

FIG. 10. Nodules of hepatocellular carcinoma arising in a liver with severe cirrhosis, probably of post-necrotic origin. Hematoxylin and eosin stain. × 30.



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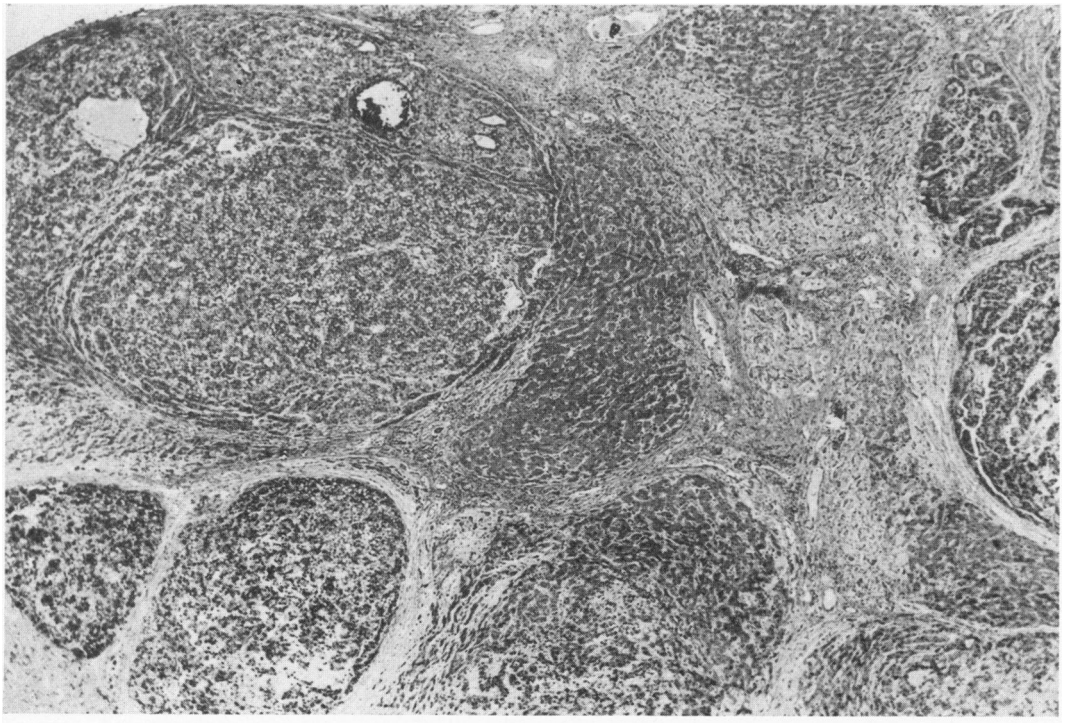

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