The Geographical Pathology of Primary Liver Cancer

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SUMMARY

Recent epidemiological data on primary liver carcinoma are reviewed. The highest incidence is reported in African males, in whom the frequency rises rapidly until the 3d decade, after which it remains constant or may even decrease. There is evidence that the increase in liver cancer in Africa and Asia is dependent on an increase in the proportion of cirrhotic livers which become malignant rather than on increased incidence of cirrhosis. The pathogenesis of liver cancer in man is unknown, but there is circumstantial evidence that it may represent a two-stage process in which liver damage in childhood, possibly due to malnutrition, may predispose the organ to a carcinogenic stimulus in later life. Pathological evidence suggests that this stimulus may be viral hepatitis. The significance of this hypothesis is discussed in relation to pertinent experimental observations.

It is 100 years since Livingstone wrote that cancer was unknown in parts of Africa, and the first authentic report of liver cancer in the Southern Bantu was made only in 1905 (67). Today it is recognized that cancer is common in Africa, and it would be impossible to review briefly the extensive literature on liver cancer from this continent and elsewhere. Accordingly, the present paper will be limited to reviewing some of the more recent epidemiological studies on liver carcinoma and their influence on current hypotheses regarding its etiology and biological behavior.

GEOGRAPHICAL DISTRIBUTION

The map (Chart 1) is compiled from the most recent data available which, however, are of variable reliability, since in many parts of the world no rate studies are available, nor is the distinction always made between primary and secondary hepatic neoplasms.

There is consistent evidence that liver cancer is uncommon in North America, Western Europe, the U.S.S.R., and Australia (23, 26, 59, 71, 78, 85, 90, 91). No significant sex or racial differences have been observed in the United States and in Western Europe, and the incidence is of the same order on the two continents. With the possible exception of a few scattered areas (30, 98), liver cancer appears to be rare in Central and South America and in the Caribbean (15, 44, 62, 80).

In contrast, a very high relative incidence of primary cancer of the liver has been reported at autopsy among the indigenous peoples of Africa, south of the Sahara, and of Southeast Asia, especially in males (10, 12, 58, 87, 113). In Africa, incidence studies (43, 74) have confirmed that this relative increase is absolute (Tables 1, 2). The highest incidence of primary liver cancer is reported in Bantu males from Lourenço Marques, Mozambique, where, in the 25- to 34-year age group, the rate is nearly 500 times that in the United States and 15 times that in the South African Bantu male. In the 65-year age group, however, the rate is only twice that of the United States white and is of the same order as in the South African Bantu. Caution is required, however, in interpreting age-specific rates in Africa, owing to small numbers in each age group and the fact that, in the older age groups, there may be some under-reporting. A less marked but definite increase as compared with the United States is also observed in African females. In contrast to the Bantu population, no increase in liver cancer has been found in the white South African population (8, 101, 106).

In the United States, liver cancer forms only a very small proportion of all cancer in the younger age group, whereas in Mozambique the highest incidence is found in the younger age groups, and

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the incidence curve tends to flatten with age (Charts 2, 3). Since the earlier autopsy studies showed the same high relative frequency as reported today (10), it would appear unlikely that this flattening is a cohort effect due to the recent introduction of a carcinogenic stimulus, such as has been proposed to occur in lung cancer (22). In Johannesburg liver cancer has been reported to have a seasonal incidence (43), but this variation has not been reported elsewhere.

In Asia incidence surveys are not available, but all ratio studies from Malaya (58), Singapore (64, 87), Indonesia (14), the Philippines (5, 6), and Southern China (21, 45, 113) would strongly suggest an increase of liver cancer in these areas, especially in males, and this is supported by studies in immigrant communities (75, 90). The pathological picture is similar to that described in Africa.

It is usually believed that liver cancer is common in Japan, on the basis of autopsy studies (61), but the available morbidity and mortality studies suggest only a slight increase, as compared with that in the United States (84, 85).

In the Indian sub-continent liver cancer does

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**TABLE 1**

INCIDENCE OF PRIMARY LIVER CARCINOMA IN THE UNITED STATES AND AFRICA

(Rate/100,000)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>U.S. white</th>
<th>U.S. nonwhite</th>
<th>Johannesburg</th>
<th>Mozambique</th>
<th>Uganda</th>
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<tr>
<td>0–</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>15</td>
<td>1.6</td>
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<td>114</td>
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<tr>
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<td>10</td>
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<td>8.6</td>
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<tr>
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<tr>
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<td>15.0</td>
<td>57</td>
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<td>16.0</td>
<td>45</td>
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<td>32.4</td>
<td>59</td>
<td>13.9</td>
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</tr>
</tbody>
</table>

* * Private communication from Professor J. N. P. Davies of Kampala.

**TABLE 2**

INCIDENCE OF PRIMARY LIVER CARCINOMA IN THE UNITED STATES AND AFRICA

(Rate/100,000)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>U.S. white</th>
<th>U.S. nonwhite</th>
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<th>Mozambique</th>
<th>Uganda</th>
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<td>0.4</td>
<td>0</td>
<td>4</td>
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<tr>
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<td>0.7</td>
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<tr>
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<td>5.2</td>
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<tr>
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<td>75.3</td>
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<td>5.0</td>
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<td>20.8</td>
<td>8.7</td>
<td>40.7</td>
<td>55</td>
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<tr>
<td>75–</td>
<td>46.6</td>
<td>8.1</td>
<td>49.4</td>
<td></td>
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</tbody>
</table>

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not appear increased in the north and west (33, 56), but there may be some increase in the southern part (77, 96). No reliable data are available from the Middle East or Central Asia.

Histological characteristics.—In South Africa the increase in liver carcinoma is confined primarily to tumors of the hepatocellular type, and no significant increase in primary adenocarcinomas or tumors of the intra-hepatic bile ducts has been observed (40). This has been observed elsewhere whenever distinction is made between true adenocarcinomas and glandular liver-cell tumors (96).

Geographical variation has not been demonstrated in the incidence of embryonic liver cancers of children.

Relationship of cirrhosis and hepatocellular carcinoma.—Since 60–90 per cent of all liver cell cancers arise in cirrhotic livers, consideration of this rather an increase in the proportion of cirrhotic livers which become malignant. There are also differences in the frequency with which different morphologic types of cirrhosis undergo malignant change (40, 92); but, owing to semantic variations in classification and difficulties in determining the etiology of cirrhosis by morphology alone, it is unknown whether carcinoma arises with equal frequency in the same morphological type of cirrhosis in countries of high and low incidence—and, even further, whether it arises in the same etiological type.

It is generally considered that the relationship between cirrhosis and liver-cell carcinoma is not causal but represents different manifestations of the same stimulus (40, 91), and cirrhosis per se
would not appear intrinsically a precancerous lesion in either man or animals. For example, carbon tetrachloride, although a strong cirrhogenic agent in the rat, does not produce liver cancer in that species (39), and the cirrhogenic activity of the azo dyes can be separated from their carcinogenic effects.

PRESENT CONCEPTS REGARDING THE ETIOLOGY OF PRIMARY LIVER CANCER IN MAN

The data at present available are insufficient to permit conclusions whether the cause of liver carcinoma in areas of high and low incidence represents the same stimulus operating at different levels, or different stimuli, although the different age curves in Africa and the United States might suggest the latter possibility. The present discussion, accordingly, will be directed primarily toward the studies in Africa and Asia, in the light of current knowledge of experimental liver carcinogenesis.

The available evidence suggests that the carcinogenic stimulus in areas of high liver cancer incidence should be regarded as directly hepatocarcinogenic, since there is no associated, consistent increase in cancer of other sites. Hypotheses should also explain not only the high incidence in certain regions but also the differences in age distribution between Africa and the United States.

There is no evidence that racial or genetic differences are significant factors. Apart from the specific adenocarcinoma of the intra-hepatic ducts found in South China (46) associated with Clonorchis sinensis, neither protozoal nor bacterial infections appear of importance (40).

Trace elements.—The demonstration that iron deposits may be carcinogenic (36) has renewed interest in the massive visceral hemosiderin deposits, which may be more than 4 or 5 gm. per cent dry weight in the liver, found in the Southern Bantu of Africa. However, siderosis does not occur in many areas where liver cancer is common, and siderotic cirrhosis rarely becomes malignant (40). In carcinomatous liver tissue zinc and cobalt have been reported increased, and there is a marked decrease in molybdenum (17); but the significance of these isolated observations is unknown.

Native drugs and toxic agents.—In view of the numerous known experimental hepatocarcinogens, the role of such agents in human liver cancer has been of interest. It is as difficult to understand how a single agent could be so widespread in distribution as to explain the high frequency of liver cancer in communities of widely differing cultures in Asia and Africa. No such agent has been demonstrated, although hepatotoxic agents have been reported in specific areas, some of which have caused liver tumors experimentally (51). The senecio alkaloids have been implicated by Schoental and her co-workers (82), and it has been demonstrated that even a single dose of lasiocarpine in rats may lead to severe chronic liver damage several months later (83). However, in Jamaica where veno-occlusive liver disease due to these alkaloids is frequent, no increase in liver cancer has been found (15). Alcohol would appear of no significance outside North America and Western Europe (54), and liver cancer is common in the Moslem communities of West Africa.

CHART 4.—Bar diagram showing the proportion of cirrhotic livers at autopsy in which primary carcinoma is present as reported from areas of high and low frequency.

Consideration has been given to the possible role of industrial products and food additives as causative factors. Their almost complete absence in the African environment and the low incidence of liver cancer in Europe and North America would suggest that such factors are not major hepatocarcinogens in man.

Endogenous liver carcinogens.—Des Ligneris (25) in South Africa reported that mice painted with nonsaponifiable extracts from livers with primary carcinoma from Africans developed skin tumors, but not when painted with extracts of normal livers from white subjects. Later, Steiner (98) showed carcinogenic activity in a large variety of extracts from human and animal tissue. We have repeated Des Ligneris' experiments in our labo-
ratory by both painting and injection and have been unable to confirm his results (Table 3). It is possible that the differences previously described by Des Ligneris were dependent on the formation during preparation of oxidative products of cholesterol or similar compounds of the type described by Bischoff (13).

ROLE OF MALNUTRITION OR VIRUS INFECTION

Recent interest has been directed mostly to the possible role of chronic malnutrition and viral hepatitis.

TABLE 3

<table>
<thead>
<tr>
<th>Extract*</th>
<th>Solvent†</th>
<th>No. mice at start</th>
<th>Survivors at 18 mo.</th>
<th>No. sarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>White liver: &lt;1 day</td>
<td>S.O.</td>
<td>38</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>81 days</td>
<td>S.O.</td>
<td>39</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Bantu liver: &lt;1 day</td>
<td>S.O.</td>
<td>60</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>81 days</td>
<td>S.O.</td>
<td>49</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Bantu hepatoma: &lt;1 day</td>
<td>S.O.</td>
<td>59</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>81 days</td>
<td>S.O.</td>
<td>40</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>355 days</td>
<td>S.O.</td>
<td>50</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

* Period of days during which the extract was exposed to atmospheric air for auto-oxidation.
† S.O. = Sesame oil; T. = tricaprylin.

Malnutrition.—The role of certain diets inadequate in nutrients in modifying experimental tumors is recognized (99), and a choline-deficient diet alone can cause liver cancer in rodents (38). These facts, and the finding that liver carcinoma was frequent in communities with poor dietary backgrounds, suggested the possibility that in man also malnutrition per se could be a major cause of liver cancer. This hypothesis was strengthened by the observation that kwashiorkor, a disease of children due to protein deficiency, was widespread in many countries with a high incidence of liver carcinoma and that a severe fatty liver occurred in this condition. The concept thus developed of a sequence of fatty liver, cirrhosis, and cancer, based on the misconception that cirrhosis developed in kwashiorkor. However, several critical reviews have appeared, indicating that simple malnutrition in adults, apart from chronic alcoholism, is not a significant cause of cirrhosis in man, and also stressing the fact that the fatty liver of kwashiorkor has never been shown to become cirrhotic (15, 42, 70). In both Asia and Africa the fatty cirrhotic liver, the so-called “alcoholic or nutritional cirrhosis” of the United States, and the morphological type regarded as most typical of nutritional deficiency are exceedingly rare (1, 42, 70, 92). Furthermore, no geographical correlation, at least in adults, has been demonstrated between degree of nutrition, deficiency of a specific nutrient, and liver cancer. For example, liver cancer is rare in many parts of India and Latin America, although the diet is very inadequate in many areas.

Possible role of viruses.—In recent years there has been increasing interest among pathologists, especially in Africa, regarding the possibility that a virus may be implicated as a cause of primary liver carcinoma. Most attention has been focused on viral hepatitis, but the evidence is mainly circumstantial and speculative, being based on the following observations.

1. The cirrhosis in which cancer develops most frequently in Africa and Asia shows many of the morphological characteristics regarded by pathologists as typical of “post-hepatitic” or “post-necrotic cirrhosis” (1, 18, 20, 42, 69, 70, 87, 92). Although such livers are generally regarded as being frequently the result of viral hepatitis on autopsy and biopsy evidence (4, 32), many cases do not give a history of jaundice. A similar pathological picture can arise in a fatty cirrhotic liver due to alcoholism (73). Viral hepatitis is endemic in Africa, and epidemics have occurred followed by the development of cirrhosis (8, 20, 70); but the sequence of acute hepatitis to cancer has not been demonstrated by serial liver biopsy during such epidemics. However, the morphological similarity between cirrhosis definitely due to a viral hepatitis and the usual type of cirrhosis with cancer in Africa strongly suggests a common denominator. Further, no other agents have been demonstrated as a probable cause of this type of cirrhosis in Africa or Asia (42, 92).

2. Originally, it was considered that “post-necrotic” cirrhosis was the result of a single episode of acute massive necrosis. However, the failure of experimental cirrhosis to develop readily following a single episode of massive necrosis and the evidence that such a cirrhosis can occur in man and animals as a result of a chronic progressive hepato-
titis have led to the view that this is the more common pathway, even if the initial attack has been subicteric (50, 55, 73, 97, 102, 112). This would support the view that the morphological pathways of primary liver cancer in man and experimental liver cancer are similar, although the etiological mechanisms may be entirely different. Such a chronic hepatitis would show both the epithelial inhibition and stimulation, described by experimental liver cancer are similar, although the pathways of primary liver cancer in man and

3. Ultrastructural studies have not demonstrated unequivocal virus particles in hepatoma cells, but neither have they demonstrated with certainty in the liver of patients with definite virus hepatitis (7, 48, 79). Theron et al. (100), however, have reported a peculiar granular material in one of three cases of liver cancer which they compared to the viroplasm of the Shope fibroma and also other virus-like particles. Although these observations have been confirmed by Svoboda in this department in a hepatoma from Africa, with the lack of further data conclusions are premature.

4. The early age of onset, the relatively constant age incidence in Africa, and seasonal variations described from Johannesburg would be consistent with a viral agent. Whereas the pathological evidence is suggestive, a major objection is the fact that hepatitis is common in countries where liver carcinoma is rare, although reports have ascribed isolated cases of liver cancer to virus hepatitis (47, 54, 89). Further, no variation in the incidence of cirrhosis and cancer has been observed in relation to seasonal variation in hepatitis in Denmark (23). Although strain differences in the hepatitis virus are possible, it would be difficult to explain the low incidence in other races in South Africa and Malaya on this basis. This fact argues equally against the existence of a specific liver cancer virus.

In animals, the only report of liver carcinoma following viral hepatitis has been in ducks (76).

Two-stage theory.—The absence of any satisfactory alternate hypothesis to the virus hepatitis theory to account for the high incidence of liver cancer in Africa, and the difficulties of reconciling the world-wide distribution of the hepatitis viruses with the regional distributions of liver carcinoma, have led to the development of a two-stage hypothesis to explain these facts. This theory suggests that in certain areas damage to the liver in childhood may cause excessive reactivity to a hepatotoxic agent in later life (11, 12, 42, 99, 105, 108, 110). However, confirmation of such a hypothesis rests on relatively tenuous evidence in man.

The stimulus which has received most attention as a possible cause of such damage is protein malnutrition in childhood, especially kwashiorkor. Although liver cancer is not necessarily increased in areas where kwashiorkor is common, the converse is not true; and a high incidence of liver cancer does not seem to occur in areas where kwashiorkor is definitely rare or infrequent (Chart 1).

In Singapore, Shanmugaratnam (86) found that liver cancer occurred almost entirely in Chinese immigrants born on the mainland, although approximately 80 per cent of such persons with liver carcinoma had spent over 20 years on the island. This suggested that the earliest changes preceding malignant transformation had occurred at a very young age. Similar observations have been made regarding lung carcinoma (89). In Africa there is evidence that kwashiorkor may cause metabolic liver damage, although it may still appear histologically normal. Kwashiorkor itself does not lead to cirrhosis, and the liver of the young African adult is histologically normal (16, 42, 105); yet the plasma proteins which become abnormal during the acute attack may remain so and may persist for many years (9, 3, 69, 105, 111). Similar prolonged serum protein changes have been produced in monkeys by a low protein diet. Such abnormalities, although not carcinogenic per se, suggest the possibility that more significant metabolic changes could also occur, and further work along these lines as indicated by Waterlow is necessary (110). Whether, in such a situation, an infective virus could act as a promoting or initiating agent for cancer remains to be determined. However, whatever the reason, there is evidence that the sequelae of viral hepatitis, such as massive necrosis, chronic hepatitis, and cirrhosis are more common in Africans than in Europeans and North Americans (9, 20, 42, 81, 114). Similar variations have been reported in sequelae of viral hepatitis in other racial groups, which have been related to malnutrition (24, 31, 95).

There is reasonable experimental evidence that "acquired errors of metabolism" occur at the organ level as in two-stage experimental skin carcinogenesis, and, in fact, such an error is implied in any multi-stage theory of carcinogenesis. The implications in carcinogenesis of mutational and nonmutational alterations in the cell have been reviewed by Walker (107), and King (49) has
discussed some aspects of the production of localized cell damage.

In the classical two-stage theory the initiating agent is in itself carcinogenic, but there is no theoretical reason why a noncarcinogenic permanent alteration in metabolism should not occur which could predispose the cell to a carcinogen or act synergistically with a second noncarcinogenic agent to produce cancer. Carbon tetrachloride, which is not carcinogenic in the rat, can expedite the production of liver tumors by dimethylaminoazobenzene (DAB) when the latter is given later (57), and partial hepatectomy prior to the administration of 2-acetylaminofluorene also expedites tumor production (58). Carter et al. (19) have produced a defective prothrombin in dogs, which was synthesized by the animal for nearly 8 years4 with a single dose of pentane dithiol. That diet may also act in this way, especially on young tissue, is suggested by the mutagenic effect of certain vitamin deficiencies as has been demonstrated in the fetus (66, 109), and clearly irreversible changes occur in the liver in the case of hepatomas produced by choline deficiency. Pietra et al. (72) have also demonstrated the increased susceptibility of young animals to experimental carcinogens. Expressed in terms of the protein (enzyme) deletion theory (60), the hypothesis would imply deletions which could not be produced in toto by either the childhood stimulus or adult stimulus alone, but only by the two acting in combination. Further work is desirable to determine the role of noncarcinogenic agents in experimental carcinogenesis in the liver.

If, on the other hand, the hypothetical stimuli—i.e., kwashiorkor or viral hepatitis—are regarded as low-grade carcinogens per se, the “summation theory” (65) would appear applicable. However, knowledge of the summation effect of two chemically different carcinogens on the liver is limited. Tannic acid has been shown to be synergistic with 2-acetylaminofluorene (83) but not with DAB (57). No synergistic effect in the liver between radiation and DAB was found by Lacassagne (52), and we have confirmed his results.

The possibility is not too remote that previous tissue damage could result in neoplasia by an infective virus, and this is suggested by the work of Duran-Reynals et al. (27, 28), who produced skin cancer by the vaccinia virus in mice previously treated with methicholanthrene and cortisone. Moreover, the Adenovirus 12 has been found to be carcinogenic in hamsters (103), and the SV 40 virus has caused reproducible epithelial changes suggestive of malignancy in human cells in tissue culture (88). In our laboratory, however, we have failed to produce an increase in cirrhosis or liver tumors in mice by the MH V8 virus despite prolonged pretreatment with thioacetamide, carbon tetrachloride, or a choline-deficient diet. A further possibility is that hepatitis may act as a nonspecific agent causing simple regeneration following necrosis and thus expedite tumor production in a damaged liver as in the case of DAB followed by partial hepatectomy (34).

In conclusion, although the two-stage theory is attractive and in accord with many of the pathological and epidemiological data, there are several inconsistencies. Further systemic investigations are necessary to amplify and confirm on a wider basis the limited metabolic and pathological studies available regarding the sequelae of malnutrition and hepatitis in man. However, further studies in the role of viral hepatitis will be handicapped until a suitable technic can be developed to demonstrate the virus.

ADDENDUM


REFERENCES

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25. DES LIONIERS, M. J. A. The Production of Benign Malig

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