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PRIMARY CARCINOMA OF THE LIVER*

Thirteenth James Ewing Memorial Lecture

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I WISH to thank Doctor L'Esperance and the James Ewing Memorial Committee for inviting me to deliver this, the Thirteenth James Ewing Memorial Lecture. I appreciate this honor all the more since I realize that I am perhaps the first colleague from outside the United States who has been afforded the privilege of paying tribute to the memory of one of America's greatest sons. For James Ewing's fame as a physician transcends all national boundaries and barriers: his outstanding contributions to cancer pathology were as well-known to his colleagues throughout the world in his own lifetime as they are to this day.

From my earliest student days I have admired his monumental work, "Neoplastic Diseases", for its erudition, lofty scholarship, and above all, for its clinical approach to a problem in pathology that is still so baffling. It was to this great work, therefore, that I turned at the beginning of my own researches into primary liver cancer.

In dedicating his life to the understanding of cancer, James Ewing helped found the great American Cancer Society and the world-famous

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New York Memorial Center for Cancer and Allied Diseases, and these will remain fitting and constant reminders of James Ewing's endeavours to ameliorate one of the greatest causes of human suffering.

Primary carcinoma of the liver is a remarkable form of malignancy. It is remarkable not only because of its demographic and geographic distribution, its early age incidence in African and some Oriental races, but also because of the ease with which it can be induced in experimental animals by specific environmental factors.

Tonight's lecture is based mainly on my book[1] and on my recent review of the subject[2]. It will be considered under four headings: (I) Incidence (II) Pathology (III) Clinical Manifestations (IV) Etiology.

I. Incidence

From a survey of the World's available postmortem statistics, it would seem that the incidence of primary liver cancer varies strikingly among the different races of mankind. Of rare occurrence among the peoples of Western Europe and America, it is by contrast remarkably common among the aboriginal inhabitants of Africa and certain parts of Asia.

Geographically, the areas of known or suspected high prevalence of the disease extend from the west African coast and central Africa south of the Sahara Desert, along eastern and southeastern portions of Africa and across eastern and southeastern Asia, including particularly Indonesia, the Philippines, China and Japan.

Western Races. Primary liver cancer is rare among all Western people irrespective of whether they live in Europe, America, Africa, Asia or elsewhere. The postmortem rate averaged 0.14 per cent in Europe and 0.27 per cent in the United States of America, and the relative frequency of this tumor among all malignancies was 1.2 per cent and 2.5 per cent respectively.

Oriental Races. Among Oriental people, on the other hand, the autopsy rate was approximately 0.8 per cent, and the relative frequency of primary liver cancer to all other cancers was almost 14 per cent. A very high incidence of the disease was noted in Indonesians (41.6 per cent of all cancers) followed by Chinese (33 per cent) and Filipinos (22 per cent). Relatively high frequencies have also been recorded in certain parts of India and in Japan.

African Races. The highest frequency of the disease, however, has been observed in Africa. Thus, primary liver cancer is extraordinarily common among the Bantu and other indigenous people inhabiting the vast territorial regions south of the Sahara Desert. According to recorded statistics, the postmortem rate varied between 0.7 per cent in Kenya and 2.4 per cent in South Africa (average 1.1 per cent), and the relative frequency of primary liver cancer to all carcinomata ranged between 17 per cent and 53 per cent.

In many parts of Africa, moreover, primary liver cancer has been found to be the most frequent form of internal cancer, especially in relatively young adult males.

In Le Dantec Hospital at Dakar, French West Africa, for example, 60 cases (representing 75 per cent of all cancers) are treated annually[3], and approximately 100 new primary liver cancers are sectioned every year at the Pasteur Institute of that city[4]. At the great Memorial Center of New York, on the other hand, not more than six cases are treated in any year[5].

For French West Africa as a whole during the 16-year period 1940-1955, 1455 cases of primary liver cancer were documented[6]. These included 1227 cases in males and 228 cases in females, among whom primary liver cancer averaged 48.3 per cent and 14.7 per cent of all cancers, respectively, with annual ranges of 16 per cent to 65 per cent in males and 5 per cent to 18 per cent in females. These remarkable statistics from a single geographical region recorded over a relatively short period of time are in striking contrast with the total 1391 cases of primary liver cancer which up to 1950 Carnahan[7] was able to compile from the entire world's literature.

In South Africa, primary liver cancer is very prevalent among the migratory Bantu laborers of the gold mines, who are a specially selected and fit group of young men recruited from various tropical and subtropical regions of central and southern Africa. This tumor was responsible for 670 out of 772 cases (87 per cent) of all carcinomata. It is significant that the liver cancers were found almost six times more frequently in Bantu mine workers hailing from Portuguese East Africa than in those from South Africa.

Primary Liver Cancer in Animals and Birds. It is appropriate to mention that primary liver cancer is not unusual in lower animal life. Spontaneous liver cancers have been described in cattle and in most

domestic animals, including dogs, ducks, sheep, cats, horses, pigs, fowl, as well as in a few wild mammals and in birds.

Sex and Age Incidence. Primary liver cancer occurs predominantly in males, although there seems to be an enhanced frequency of the disease in female Africans when compared with those of other races.

Among Africans[1-3] and Indonesians[8, 9], the disease is pre-eminently one of youth, occurring mainly under the age of 40 years and very often before the age of 20 or 30 years.

In other races it is commonest at or after middle age, and is rare before the age of 40. No age, however, is exempt; for the tumor occurs also in the very old and has been discovered in children of all ages[10]. The youngest African case that I have seen was that of a boy aged nine years.

II. Pathology

Gross Pathology

The liver in primary hepatic cancer is always increased in size and weight. In my own series of cases, the maximum weight observed in any individual case was 7,100 gm., the minimum 1,900 gm., and the average, 3,870 gm. (The normal liver weight is 1,500 gm.)

For practical and descriptive purposes, primary liver cancer can be divided into two macroscopic groups: *nodular* carcinoma, a tumor formed of numerous discrete nodules of varying sizes, and *massive* cancer, consisting mainly of a single large dense mass. Both forms involve the right more than the left lobe of the liver, and the intervening liver tissue is usually the site of varying degrees of fibrosis or cirrhosis.

Nodular Cancer. The liver is large, hard, scarred, deformed and studded with closely grouped or irregular nodular masses. On section, much of its substance is seen to be replaced by firm, scattered or closely grouped nodules mostly white to grey in color, although they may also be reddish or soft and friable, when they are often found occupying portal or hepatic veins as tumor emboli.

Massive Cancer. The enlarged liver is distorted by a uniform smooth swelling with occasional secondary irregularities in its vicinity. On section, the tumor mass is found occupying practically the whole right lobe to which it is confined, but there may be additional smaller growths localised especially at the periphery. It may be soft, cystic, hemorrhagic or cartilagenous and its color may vary from white to grey.

A sharp demarcation between the two macroscopic groups is often not possible, for many tumors originally "nodular" in character tend to transform into "massive" cancers. It is then that the tumor may be so extensive that scarcely any normal liver remains.

HISTOPATHOLOGY

Primary liver cancer occurs in two forms, hepatocellular and cholangiocellular cancer. It is generally assumed, but not positively proved, that hepatocellular cancer originates from the cells of the liver lobules, and cholangiocellular cancer from the cell of the intrahepatic bile ducts. Mixed or hepatobiliary cancer may also occur.

Hepatocellular Cancer. This, the most frequent form of primary liver cancer, has a characteristic structure. The tumor cells are usually larger than normal liver cells, which they resemble: they are polygonal in shape with distinct borders, and when stained with hematoxylin and eosin show an abundant eosinophilic or moderately basophilic granular cytoplasm. The nuclei are bizarre, reach extraordinary dimensions and frequently occupy almost the whole cell: they are oval to spherical in shape, are markedly hyperchromatic, and although usually single, some cells may have two or more such nuclei containing purple-staining nucleoli. Mitotic figures in various phases are frequent, and giant cells containing single or multiple nuclei are often observed.

The tumor cells are characteristically arranged as compact trabeculae varying from 2 to 30 cells in thickness and devoid of intercellular stroma. These cell columns either anastomose with one another or are arranged as long parallel columns, which terminate freely as blunt, rounded extremities. Their margins are bordered by a single layer of endothelium resembling Kupffer cells, which adhere closely to the peripheral tumor cells, forming in this way a pronounced vascular stroma containing reticulum: numerous vascular spaces between adjacent cancer columns are thus formed varying in width—some containing much blood. Bile pigment is often seen in the tumor cords. In the more anaplastic tumors, however, this trabecular arrangement is less evident or even absent. The rest of the liver is usually the seat of cirrhosis.

Apart from fatty and scirrhous changes in the tumor cells, necrosis often occurs, affecting particularly the most central parts of the tumor columns. These necrotic areas are liable to hemorrhage, and if such

tumor nodules are superficially placed, alarming intraperitoneal hemorrhage may occur, often with rapidly fatal results.

Cholangiocellular Cancer. Cholangiocellular carcinoma occurs far less frequently than hepatocellular cancer. It is characterised by a glandular structure and an alveolar pattern of arrangement.

The tumor cells are columnar to cuboidal in shape and show some resemblance to bile-duct epithelium. The cytoplasm is nongranular and faintly acidophilic or basophilic. Their prominent nuclei are round, oval or spindleshaped, are proximally situated, and at times extend along the whole axis of the cell: they are particularly hyperchromatic, stain intensely with hematoxylin and contain single large nucleoli. Mitotic figures are frequent, but giant cells are rare.

In cholangiocellular cancer the cells are arranged in alveoli of varying shapes and sizes – a characteristic which distinguishes them from the solid trabecular formation of the hepatocellular cancers. The tubules are irregular or multiloculated cystic spaces lying in a pronounced fibrous tissue stroma, or they may be separated from each other by open spaces. The lumina of the tubules may be clear or contain degenerating tumor cells and mucus. Reticulum is scanty or absent.

METASTASES

Primary liver cancer possesses vigorous metastatic powers and dispersal may often be widespread.

a) *Intrahepatic Metastases.* Metastases within the liver commence at an early stage when individual tumor cells spread along the sinusoids to become organized as proliferating tumor nodules; or they characteristically penetrate the wall of a portal vein, which then becomes filled with proliferating groups of tumor cells that grow steadily, until the whole vessel and its branches (best seen in the vessels of the cirrhotic tracts) become occluded by a continuous tumor thrombus. With the invasion of the portal system, dissemination to other parts of the liver readily occurs. In this way, a single primary focus may give rise to widespread intrahepatic metastases.

b) *Extrahepatic Metastases.* Secondary deposits outside the liver occur in 50 to 75 per cent of cases. They are often multiple and may arise at a stage when the primary hepatic growth is still symptomless. Extrahepatic metastases begin with the invasion of the hepatic or portal veins. Dislodged tumor cells and cancerous thrombi reach the inferior

vena cava (which often escapes infiltration) and are conveyed via the heart to the terminal arterioles in the lungs. Here they proliferate, invade the surrounding lung tissue, and by penetrating the pulmonary veins become the source of systemic dissemination, although in exceptional cases the tumor cells pass directly into the general circulation without involving the lungs. The lungs are the most common sites for metastases. To a lesser extent, metastatic spread occurs also by way of the lymphatic vessels. In this way metastases may be found in any part of the body.

There is a close resemblance in histological structure between the metastases and the parent hepatocellular and cholangiocellular liver tumors. The metastatic deposits may become highly organized and even show unmistakable bile production in such distant situations as the lungs, bone, etc.

III. Clinical Manifestations

The clinical course of primary liver cancer is not constant. Symptomatology is dependent upon the degree of associated cirrhosis, the rate of tumor growth, upon complications, and upon the development of metastases.

Mode of Onset

The disease usually makes steady, silent progress over an indefinite period of time and the patient is generally unaware of his condition until the malignant liver has reached alarming proportions.

Owing to the insidious nature of the condition, the disease:

1. May be ushered in with dramatic suddenness as an acute abdominal catastrophe following rupture of a necrotic nodule or erosion of a blood vessel on the free surface of the liver. This happens in about 8 per cent of cases.

2. May first manifest itself equally abruptly as a rapidly growing and necrotic tender liver accompanied by fever, and these symptoms may simulate an amebic abscess, from which it may be difficult to distinguish it — 5 per cent of cases.

3. Again, also in about 5 per cent of cases, symptoms due to extrahepatic metastases in remote organs or parts may be the first to direct attention to what may prove to be a symptomless primary liver cancer—e.g., tumors of the skull, spine, ribs, clavicle, etc.

4. The liver tumor, on the other hand, may remain latent until discovered accidentally during a clinical "work up", or even only at autopsy: this occurs in about 16 per cent of cases.

SYMPTOMATOLOGY

In established liver cancer, the prodromal signs are usually vague and indefinite and are most often attributed to gastro-intestinal disturbances. When present, they may include lack of appetite, nausea, vomiting, diarrhoea, abdominal pressure and a sense of fullness in the upper abdomen after meals.

The most constant symptoms are: progressive muscular weakness (86 per cent of cases); loss of weight and emaciation (83 per cent of cases); and abdominal pain of a dull character localized to the right hypochondrium and unrelated to food (90 per cent of cases).

The liver is always enlarged, often to a remarkable degree. Its surface is usually nodular and tender; and its firm lower outline may be visible as well as palpable, and may extend upwards into the thorax and downwards to the level of the umbilicus or even lower.

Jaundice develops at a late stage of the disease in approximately half the cases; as also does ascites, with straw-colored or blood-stained fluid. Secondary anemia is almost invariably present. Signs pointing to portal hypertension, including dilatation of the superficial abdominal veins and edema of the lower extremities, occur in approximately one third of cases. Occasionally there is hematemesis from rupture of esophageal or gastric varices, and this may terminate fatally. The temperature is normal or moderately elevated, but the pulse may be raised even in cases without fever.

DIAGNOSIS

Regarding a patient with an enlarged liver in whom cancer is suspected, the following questions must be answered:—

1. Is the tumor part of the liver, or is it part of a neighbouring organ, e.g., stomach, kidney?

2. If the organ involved is considered to be the liver, is the enlargement due to local or to general causes?

3. If malignancy is suspected, does the neoplasm arise primarily in the liver or is it a metastasis secondary to cancer in a remote organ, e.g., stomach, colon, rectum, etc.?

Certain diagnosis of primary liver cancer is made only after consideration of the clinical manifestations and evaluation of the tumor material obtained by biopsy or at operation.

Aids to the Diagnosis of Primary Liver Cancer

1. *Liver puncture biopsy* is invaluable for determining the nature of obscure liver enlargements. The procedure, however, is not without danger, for hemorrhage or biliary peritonitis may occur. The tumor itself, moreover, may be missed.

2. *Liver function tests* are useful only insofar as they indicate the presence of general diffuse liver damage. They are not capable of pointing to the actual cause of the disease[11], as they cannot differentiate primary from secondary liver cancer or from cirrhosis.

3. *Roentgenography* will define the shape and size of the liver, elevation of the diaphragm and restriction of its movements, as well as localisation of pulmonary metastases. Examination by barium swallow for esophageal varices secondary to the associated cirrhosis, and evidence pointing to displacement and distortion of the stomach and duodenum by the liver tumor are also helpful in making the diagnosis[12].

4. *Portal-splenic venography*: Injection of radiopaque "Diodone" percutaneously into the spleen, followed by immediate roentgenography of the liver, will show the portal vein and its branches clearly outlined in unaffected portions of the liver, but in cancerous areas these are distorted or devoid of contrast medium[13].

5. *Abdominal aortography*: Injection into the aorta of a contrast medium, e.g., "Urokon", followed by rapid roentgenography, will show primary and secondary liver cancers as areas of diminished vascular density[14, 15].

PROGNOSIS

The outlook of primary liver cancer is hopeless, for it is generally a rapidly fatal disease. In my own series of cases, the duration of the disease was never longer than four months from the first appearance of symptoms, and the stay in hospital varied from one to 81 days, the average being 21 days.

TREATMENT

1. *Medical Treatment.* Owing to the hopelessness of the disease, medical treatment is essentially palliative and is directed towards the

relief of pain and discomfort. Sedatives are always required in increasingly frequent doses. In the terminal stages of the disease the condition can be ameliorated by means of steroids; and in the treatment of ammonia toxicity, which often occurs, the administration of glutamic acid derivatives, antibiotics and colonic irrigations may be helpful.

2. *Chemotherapy*. Chemotherapeutic agents have not proved beneficial as yet for the treatment of the disease. Nitrogen mustard (HN_2) and allied compounds have been tried to control diffuse and inoperable cancers of the liver, but the results have not been encouraging[16].

3. *Radiotherapy*. It is possible that radiotherapy may be of value in treating early stages of the disease but more information is necessary. Recent observations have indicated that the liver appears to tolerate large doses of radiation delivered by super-voltage machines and that the lives of patients with liver cancer are somewhat prolonged thereby, although the effect seems temporary[17-19].

4. *Radioactive Isotopes*. Little is known about the effects of isotopes on primary liver cancer. At the New York Memorial Center for Cancer and Allied Diseases, however, radioactive iridium implanted by means of long needles directly into extensive and inoperable liver cancer is currently being used, and the results are awaited with interest.

5. *Surgical Treatment*. The experience of treating primary liver cancer by surgical excision has generally been disappointing, mainly because of the onset of recurrences, the presence of latent intrahepatic or extrahepatic metastases at the time of operation, and also because of the associated cirrhosis in the unaffected portions of the liver.

Surgical treatment must be considered if at laparotomy the tumor is found to be small, circumscribed, solitary, and particularly if it involves only the left lobe of the liver. The tumor is then excised by partial lobectomy, due care being taken to control hemorrhage, which may be alarming. Removal of the more frequently involved right lobe of the liver by total right hepatic lobectomy has been regarded in the past as too hazardous an undertaking. This attitude, however, has now changed. Thanks to the current advances in surgical and anesthetic techniques, a number of successful total right hepatic lobectomies for primary liver carcinoma have been carried out[20-23].

The essential requirements for total right hepatic lobectomy include:

a) *Choice of case*: The right lobe of the liver alone is involved by the tumor, there being in the opinion of the operator no intrahepatic

metastases to the left lobe, no extrahepatic metastases, and minimal cirrhosis.

b) *Absolute control of hemorrhage*: To effect this the surgical approach should be wide, preferably by means of an abdominothoracic incision. Before any attempt is made to remove the right lobe of the liver, it is essential to isolate and ligate the right hepatic artery, the right bile duct, and the right hepatic veins. It is important that the operation sites should be adequately drained.

IV. Etiology

The true cause of primary liver cancer, like that of cancer in general, is unknown. From experimental and clinical evidence, however, it is becoming apparent that environmental factors may play a vital role in the etiology.

Induced Liver Cancer in Experimental Animals. Few fields of experimental cancer research have yielded more striking results than the production of primary liver cancer in laboratory animals with compounds of known chemical composition, which, moreover, are specifically carcinogenic for the liver. Outstanding examples of these are the azo-compounds, o-aminoazotoluene[24] and p-dimethylaminoazobenzene ("butter yellow")[25], the essential effects of which are fatty and destructive changes in the liver parenchyma followed by cirrhosis, progressive hyperplasia of the regenerating liver and bile duct cells, leading ultimately to hepatocellular, cholangiocellular, or "mixed" cancer.

The induced liver cancers are easily transplantable and production of the tumors can be modified by diet[26]. A low protein – high fat or rice diet, or one deficient in methionine, riboflavin, or cystine increases the incidence of the tumor, whereas a high protein diet or one containing methionine, vitamin B complex or yeast has the opposite effect. It is interesting to note in this connection that factors which modify the incidence of experimental liver cancer have the same effects in experimental nutritional liver cirrhosis.

Cancer development, however, is not necessarily connected with the seriousness of the existing liver cirrhosis, and although cirrhosis usually precedes a liver tumor, it is not necessarily a predecessor of the lesion. Nevertheless, all are agreed that the liver tumors appear earlier in rats fed on a cirrhosis-producing diet.

Sex hormones seem to influence the development of experimental

liver tumors: androgens stimulate, and estrogens appear to inhibit carcinogenesis. In spontaneous mouse liver tumors and in rat liver tumors induced with "butter yellow", the incidence is much higher in males, but with castration is lowered to approximately the incidence level in females.

Other carcinogenic compounds used to induce liver tumors include: dibenzcarbazole, methylcholanthrene, acetylaminofluorene (which induces at the same time tumors of the bladder, renal pelvis, pancreas and lungs), selenium, carbon tetrachloride, ethylurethane, tannic acid and senecio alkaloids.

Carcinogenic factors from Human Livers, Tissues and Excretions. The discovery that the carcinogenic hydrocarbon, methylcholanthrene, is chemically related to naturally occurring biological products, e.g., bile acids and sterols, has given rise to the speculation whether carcinogenic compounds may actually be formed in the human body.

Investigations for such compounds in cancerous and non-cancerous livers and in other organs have resulted in the isolation of nonsaponifiable lipid extracts which, when tested in the subcutaneous tissues of mice, have yielded malignant tumors at the site of injection as well as in distant organs.

The carcinogenic factor of the nonsaponifiable fractions has been found to be a crystalline material consisting chiefly of cholesterol[27].

Primary Liver Cancer in Man. It is highly improbable that a common genetic factor is responsible for the enhanced incidence of the disease among such diverse and widely separated people as the indigenous races of Africa and the Orient. The Negroes of North America are no more subject to the disease than the American white population[28]. Moreover, there is strong presumptive evidence that frequency of the disease varies with environment even in the same race, since primary liver cancer appears to affect the Portuguese East African Bantu six times more frequently than the Bantu of South Africa, although there is little, if any, genetic difference between them[1].

Hepatic Cirrhosis and Primary Liver Cancer. Most observers regard the frequent coincidence of cirrhosis with primary liver cancer as an important intermediate stage in the carcinogenic process. Cirrhosis has been discovered in a large proportion of liver cancers throughout the world. In Africa and Asia, moreover, it is exceptional to encounter liver cancer without cirrhosis.

Cirrhosis appears to be associated more frequently with hepatocellular cancer than with cholangiocellular cancer. According to Ewing[29], cirrhosis is present in 85 per cent of hepatocellular cancers and in 50 per cent of cholangiocellular cancers. For both tumor forms, the association between the two diseases averaged 67 per cent, there being a range of 53 per cent to 100 per cent in a large series of cases compiled from the literature.

Postmortem Incidence of Cirrhosis. Where primary liver cancer is infrequent, hepatic cirrhosis is likewise relatively uncommon. In Europe and America the postmortem rate of cirrhosis is between 2 per cent and 3 per cent. Among the peoples of Africa and Asia, on the other hand, cirrhosis is found in 6 per cent to 10 per cent of all autopsies.

This relationship, however, is not absolute, for although a high incidence of infantile cirrhosis has been reported in certain parts of India, Ceylon, and Jamaica, liver cancer is relatively uncommon in these localities.

Hepatic Cirrhosis Developing Into Carcinoma. Most observers agree that cirrhosis precedes the onset of liver cancer. Malignant transformation appears to occur more readily in Africans and Orientals than in Western people.

In Europe and America primary liver cancer has been found in 3 per cent to 10 per cent of deaths from cirrhosis. In Africa the corresponding figures are 17 per cent to 43 per cent, whilst in Asia they are 12 per cent to 25 per cent.

Cirrhosis-Producing Agents and Liver Cancer. Because of its frequent association with primary liver cancer and its high incidence among the very races known to be prone to this tumor, cirrhosis is commonly regarded as an important precursor of the malignant process. On this account, a number of known cirrhosis-producing factors sometimes found in close association with human liver cancer have at different times been credited with possessing carcinogenic properties or acting as co-carcinogens on already damaged livers.

These factors include: 1) Intestinal parasites 2) liver flukes, which are said to elaborate substances that are toxic for the liver 3) schistosomiasis, which produces fibrosis around embolized schistosome ova 4) hydatid cysts 5) hepatic syphilis 6) infectious hepatitis 7) hemochromatosis and siderosis 8) alcohol 9) spiced foods 10) a keloid diathesis in Negroid races, among whom there is often a tendency towards

excessive connective tissue hyperplasia even after seemingly unimportant wounds.

Not one of these factors, however, is common to all communities known for their high incidence of primary liver cancer. Thus, liver fluke infestation, though common in China, Japan and other Oriental countries, is unusual in Africa; and although schistosomiasis is prevalent in many parts of Africa and Asia, primary liver cancer is rare in Egypt, where schistosomiasis is stated to affect 70 to 90 per cent of the Nile population, and is rare also among Western people living in bilharzia-infested areas. Moreover, infectious hepatitis appears to be no more frequent among Africans and Orientals than in Europeans or Americans. Africans do not, as a rule, eat highly spiced foods; on the other hand, the incidence of primary liver cancer is relatively low in Mexicans, yet their dietaries are rich in condiments.

Malnutrition and Cirrhosis. From clinical and experimental observations it would appear that chronic malnutrition, prevalent in parts of Africa and Asia, may be one of the more important causes of cirrhosis and perhaps also of primary liver cancer. Conversely, the general good state of nutrition prevailing in Europe and North America may perhaps account for the relative infrequency of these liver lesions. The diet of the African is often a deficient one. Depending upon geographic and climatic conditions, the staple foods are maize (corn) in southern Africa, and plantains, yams, potatoes and cassava in tropical Africa. Cattle, as a rule, do not thrive in central Africa, and are seldom slaughtered in southern Africa because they represent wealth to the rural Bantu,—also, their milk yield is poor. Moreover, among many African tribes, the consumption of fish, eggs and other protein-rich foods are forbidden by age-old tribal superstitions, traditions and customs.

In Indonesia and other parts of Asia known for their high liver cancer rates, the staple diet is rice; and the supply of meat, milk and other animal products is inadequate, because most of the available soil is used for the production of rice and other predominantly carbohydrate foodstuffs which offer a more generous caloric yield.

The common defects of all these high starch staple African and Asian foods are deficiencies in animal and other first-class proteins, in fats and in vitamins, especially of the vitamin B complex group. Carbohydrates are in excess.

For this reason, and also because of the seasonal fluctuations in food

supplies among Africans during the dry winter and early summer months, chronic malnutrition occurs and may manifest itself as an acute and sometimes fatal form of "kwashiorkor". This syndrome has been described in many parts of the world under different means. It is currently referred to as "protein malnutrition"[30].

Kwashiorkor is mainly due to lack in the diet of animal proteins and vitamins of the B complex group. It affects children during the breast-feeding, weaning or post-weaning periods, i.e., between the ages of six months and three or four years. The main clinical features include edema, ascites, retardation in growth and muscular wasting, lethargy, irritability, diarrhoea, various dermatoses, depigmentation of the skin, depigmentation and loss of texture of the hair, atrophy of the pancreas (in certain areas), and enlarged fatty livers which, in later life, may become fibrotic and culminate as a profound form of portal cirrhosis.

The histologic appearances of the fatty and fibrotic livers associated with kwashiorkor generally resemble those of experimental rats fed on the staple Bantu diet of corn meal and sour milk[31], and also those of rats fed on experimental diets deficient in the lipotropic factors, methionine or choline[32, 33]. Moreover, liver cancers have been induced in experimental animals by the sole means of choline-deficient diets unsupplemented by carcinogenic agents[34], and also by ethionine, the synthetic analog of methionine[35, 36].

It will be apparent, therefore, that primary liver cancer, so frequent among the populations of Africa and Asia, originates largely in an organ that is the seat of pre-existing hepatic fibrosis or cirrhosis and that the geographic and demographic distribution of both diseases is, to a large extent, identical, although there are notable exceptions.

The relevance of these observations lies in the influence of dietary factors upon the production of cirrhosis and primary liver cancers in experimental animals. Diets low in protein or in riboflavin not only induce cirrhosis, but also facilitate hepatic tumor formation in rats fed on these diets supplemented with dimethylaminoazobenzene ("butter yellow"), whereas high protein or riboflavin diets under similar conditions have the opposite effect.

If the results obtained in animals can be paralleled in man, it is reasonable to assume that human populations existing on deficient diets responsible for kwashiorkor can develop cirrhosis and other liver lesions

similar to those induced in animals under somewhat identical dietary deficiencies, and that accessory hepatotoxic or carcinogenic agents may likewise produce liver cancer.

However, no known external agents (e.g., similar to "butter yellow") have yet been isolated to account for human liver cancer. It must be remembered also that much of the evidence pertaining to etiology in human liver cancer is circumstantial, and that the actual cause of the remarkable sensitivity of the liver to cancer in African and Asian races has not yet been established. Neither the evolution of cirrhosis from kwashiorkor nor the exact mode of neoplastic transformation from active cirrhosis is as yet understood. A great deal of research is obviously necessary.

In cirrhosis and other liver damage, environmental factors additional to malnutrition are perhaps required to effect carcinogenesis, for there is as yet only scanty evidence that primary liver cancer can be induced by the sole means of a deficient diet. In Africa and Asia, it is possible that a susceptible liver already deranged by malnutrition may in this way become more vulnerable to other external stimuli, which may then have the effect of initiating the cancerous process. These adventitious agents may include endemic parasitic infestation, acute hepatic infections, tropical diseases, and irritation by known toxic substances or perhaps by some as yet undiscovered compounds with carcinogenic potentialities.

Absence of one or other such additional toxic factor may possibly explain the lack of correspondence between cirrhosis and liver cancer on the one hand, and malnutrition on the other, in Jamaica, Central America, and in other localities where kwashiorkor-like syndromes are present.

To determine whether primary liver cancer is a preventable disease (as seems likely) and in order to search for naturally occurring carcinogenic substances analogous to the azo-compounds or other chemical substances used in the experimental induction of liver cancers, local research should be conducted into the dietaries, customs and habits of those African and Asian populations showing the highest susceptibilities to liver cancer. Present day knowledge indicates that French West Africa, Portuguese East Africa, South Africa and Indonesia are perhaps the more likely regions for these investigations.

The possibility that environmental factors may cause cancer has

aroused considerable interest in many parts of the world, and has been a main topic of deliberation at recent international cancer conferences[37, 38]. Intensive research into the various facets of primary liver cancer in Africa and Asia is essential, for it is felt that the solution of the mystery surrounding this unique tumor will have profound effects on the whole problem of cancer.

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