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**Carcinoma of
Liver**

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I. CASE REPORTPRIMARY CARCINOMA OF LIVER
(Childhood Type)

Case is that of white female, 16 months of age, admitted to the University Hospitals 5-7-32 and expired 7-20-32 (76 days).

Normal Post-Natal Course

2-26-31 - Patient born. Weight - $8\frac{1}{2}$ lbs. Spontaneous delivery. Full term. Vertex presentation. Duration of labor - 2 hrs. 20 min. No cyanosis, convulsion or palsy. Held up head at 4 months of age and sat alone at 8 months. Some cervical adenitis at 9 months. On breast milk for two months every two and one-half hours, and then weaned. Fed cow's milk (Eagle's Brand).

Enlarged Liver at 6 Months

8-25-31 - Physician examined child. Diagnosis - rickets and enlargement of liver. Cod liver oil suggested.

Sudden Growth of Liver. Age 13 Months

4-7-32 - Again taken to a clinic. X-rays taken. Wassermann negative. Diagnosis probable malignancy involving liver. At no time was baby jaundiced. According to the mother, enlargement of abdomen had been present since birth, suddenly increasing at this time. Weakness always had been marked. At present time baby unable to sit up without support.

Large Liver, Anemia

5-7-32 - Admitted to University Hospitals. Physical examination - fairly well-nourished infant with marked pallor, marked enlargement of abdomen, and undersized extremities. Total length 70 cm. Head circumference - 45 cm., chest - 38cm. Very marked pallor of mucous membrane. Decreased turgor of skin. Patient too weak to stand. Has lower thoracic kyphosis. Reflexes - normal. Palpable axillary nodes present, as well as palpable inguinal nodes. Progress: Put on a 15 month diet. Temperature 100. Weight - 8000 grams. Laboratory: Urine - heavy cloud of albumen. Blood - Hb. 29%, rbc's 2,560,000, wbc's 13,650, Pmn's 37%, L 63%, marked hypochromasia, slight poikilocyto-

sis, polychromatophilia. Wassermann - negative.

Sarcomatous Type of Metastasis

5-8-32 - X-ray of chest - skull - abdomen - negative skull. Numerous large, rounded densities in right chest, and at least one in left chest, which are characteristic of metastatic tumors, probably sarcoma or embryoma. Intestinal loops are all crowded into left and lower portion of the abdomen, the appearance suggesting a very large liver. Kidney shadows cannot be definitely made out. Conclusions: Metastases to the lungs, probably from sarcoma or embryoma. Negative skull. Enlarged liver.

Thorotrast

5-14-32 - X-ray of abdomen - .8 gms. of thorotrast per kilogram body weight, given intravenously. Large mass made out in liver. Spleen well shown and is dense due to thorotrast. Mottled density shown in liver which suggests that majority of normal liver tissue has been displaced by tumor. Conclusion: Very massive tumor of liver. Urine - 3+ albumen. N.P.N. - 56.7. Temperature 102.1. Weight - 7700 grams. Deep X-ray treatment started.

Kidneys Negative

5-19-32 - Skiodan injection - Intravenous urography very unsatisfactory because of density of liver. Fairly distinct shadow of right kidney pelvis which is grossly normal. Left not well visualized. Slight cough. Temperature 102. Weight - 7550 grams.

Slight Response to X-ray Treatment

6-4-32 - X-ray of chest - There has been very slight reduction of size in metastatic nodules. Not as much change as one would expect however under x-ray therapy. Another deep x-ray treatment is given.

6-6-32 - Deep x-ray treatment. Temperature 102.8. Weight 6850 grams. Vomited about 25 c.c. after treatment. B.U.N. - 22.2 mgs. Icteric index - 20 units.

Losing Ground

6-15-32 - Very irritable and slowly losing weight. Weight - 6805 grams. Takes feedings fairly well. Taking mostly formula with little tomato juice and orange juice.

Lost 200 grams

6-24-32 -

7-8-32 - Blood - Hb. 33%, wbc's 6,000, Pmn's 67%, L 20%, E 2%, B 1%, M 4%.
Temperature 100.

7-19-32 - Weaker and more listless. Respiration labored and more rapid. Petechiae present. Skin jaundiced. Takes feedings poorly. Has had a hacking cough for last few days.

Exitus

7-20-32 - Very listless. 2:00 A.M. - Breathing very difficult. 4:30 A.M. - Expired.

AutopsyEmaciation, Jaundice, Large Liver

Body is well-developed but very markedly emaciated, white, female infant, 16 months of age, measuring 70 cm. in length and weighing approximately 6800 grams. Slight rigor present. Hypostasis purplish and posterior. No edema or jaundice. There is a 1+ jaundice. Pupils measure 3 mm. and are regular. On superficial examination the abdomen is very large and liver can be seen through the abdominal wall. It extends over entire abdomen and down to the region of pelvis. Numerous large nodules can be felt through the abdominal wall.

The Peritoneal Cavity contains some straw-colored fluid. No fat in the abdominal wall. No infection in peritoneal cavity. Diaphragm at 5th rib on both sides. The appendix is subcecal and free.

The Pleural Cavities contain no fluid. The mediastinum is free of tumors. The Pericardial Sac contains minimal amount of fluid.

The Heart weighs 30 grams. Valve edges and chambers normal. Myocardium

slightly pale but shows no evidence of disease. No congenital anomalies. The Root of the Aorta and coronaries are normal.

Greenish Metastasis in Lungs

The Right Lung weighs 200 grams, Left 75 grams. Numerous nodules throughout the lungs, varying from 1.0 cm. in diameter to about 3.0 cm. These are mainly subpleural and stand out as little knobs over both lungs. They are more numerous in the right lung. They are soft and fleshy, some have broken down and are necrotic. Some of the smaller nodules are greenish, suggesting liver tissue.

The Spleen weighs 20 grams. The capsule is grayish and the pulp dark red and firm in texture.

Tumor

The Liver extends 13.0 cm. below the costal margin in midsternal and midclavicular lines. Numerous nodules present on surface. There is one mass in midline below the sternum which is very soft and contains a great deal of hemorrhage. On cut section, the liver presents numerous nodules and in some areas it seems that there is regeneration of the liver tissue itself. Some of the nodules are very hemorrhagic and soft, presenting a fleshy appearance. The Liver weighs 1150 grams. (17% of body weight).

No Extra Hepatic Primary Tumor

The Gall-Bladder, Gastro-Intestinal Tract, Pancreas and Adrenals normal.

Each Kidney weighs 30 grams. The right is somewhat flattened by the mass in the liver pushing against it. Otherwise there is no particular change. The capsules strip easily revealing smooth surfaces. No evidence of infection or tumor within the kidney.

The Bladder is normal. The uterus and ovaries are normal.

Enlarged Nodes

There are some large lymph nodes along the aorta and some at the root of the mesentery. These are taken for

section (tumor).

Diagnoses

1. Primary hepatoma of liver.
2. Metastasis to lungs and aortic lymph nodes.
3. Emaciation, extreme.

Microscopic Report

Tumors in liver present considerable difficulty in interpretation. In a great many of the sections, it is difficult to determine whether the tumor nodule is regenerating adenoma, whether it is remains of a lobule of liver cut off by fibrous tissue, or whether it represents a portion of the tumor. The study of the tumor is most satisfactory in the nodules within the lung and lymph nodes. In these areas, the tumor cells are polyhedral or cuboidal, very much like a normal liver cell. The cytoplasm is abundant and takes a deep eosin stain similar to normal liver cells. The nucleus is round, centrally placed and possesses like normal liver cells a vacuolated chromatin arrangement. Many mitotic figures are present. The tumor cells arrange themselves into definite cords with sinusoidal spaces between them. In these sinusoidal spaces, it is difficult to find red blood cells although occasional cells can be seen. It is questionable, therefore, whether these sinusoidal spaces are actually connected with the blood stream. In most of the sections, the sinus appears to be filled with an amorphous substance like coagulated protein. There is an occasional projection of cytoplasm into these sinusoidal spaces. Occasionally, a nucleus of a cell is present in such a manner that it forms a projection into the sinusoid but no true Kupffer's cells can be found.

Thorotrast is not visible in the tumors within the lung. Sections from the liver itself, as stated previously, present difficulty in determining whether a single individual mass of cells is a liver adenoma, tumor or liver undergoing secondary change due to pressure. The arrangement of the cells and the appearance of the cells themselves are very similar in all three cases. The presence

of mitotic figures, however, usually identifies the tumor. In nodules which are definitely tumors, no Kupffer's cells and no thorotrast granules are seen. In the adenomas or in the remnants of liver tissue, thorotrast granules are prominent. The distortion of liver adjacent to the tumor is difficult to interpret. It probably represents secondary changes induced by the pressure of the growing tumor. In sections taken from liver where no tumor is present, the architecture of the liver is approximately normal.

II. CASE REPORT

PRIMARY CARCINOMA OF LIVER (Cholangioma Type).

Case is white female, 49 years old, admitted to Minnesota General Hospital 4-17-33, discharged 5-1-33 - (14 days). Returned to home under care of private physician and expired in July or August 1933. Autopsy performed by private physician.

Past History

Gall-bladder history? For about 28 years prior to admission had "weak" stomach. Could not eat beef because it caused lump in stomach; for 4 or 5 years had "gas" in stomach with nausea. During this period, could not eat fried foods, gravy or sweet foods as they gave gastric distress, consisting of distention and nausea.

Onset

November - 1932 - had "influenza." Ill one week. Never well after this illness. Gastric distress became more marked.

Worse

February 1933, indefinite symptoms which she previously had become worse. Sensation of weight in epigastrium, frequent belching, passage of abnormal amounts of gas by rectum, qualitative and quantitative food distress, weight loss of 10 lbs. She palpated mass in epigastric region. Physician consulted. Gastro-intestinal studies done. Diag-

nosis of tumor of abdomen made.

Tumor in Liver

4-17-33 - Admitted. Past Illnesses: frequent migraine, epigastric distress (noted above), measles, whooping cough, smallpox, mumps. Operation for suspension of uterus and appendicitis. Usually constipated, had hemorrhoids for years.

Physical examination: Appears anemic and seems to have lost weight. Slight icteric tinge to sclerae. Lungs - negative. Heart - blood pressure 120-80, negative. Abdomen - normal contour, scar in mid-suprapubic region, no tenderness except in region of gall-bladder; in this area, there is a mass about 9 cm. long, 5 cm. wide, extending into midline which moves on respiration and feels smooth; independently of this, liver is palpable at rib margin; spleen not palpable.

Laboratory

Urine - negative except for few wbc's in uncatheterized specimen. Blood - Hb. 86%, wbc's 5,100, Pmn's 66%, L 34%. Icteric index - 16 units. Blood Wassermann - negative. Gastric expression - maximum free Hcl acid 11°. Liver function - first $\frac{1}{2}$ hour 30% dye retained. Stool - benzidine test negative.

X-rays

Gastro-Intestinal Study - stomach filled out well and appeared entirely normal. Duodenal bulb somewhat spastic but shows no evidence of deformity. Dense shadow in right upper quadrant which is quite characteristic of a coral shaped gall-stone. Gall-bladder - fairly good function with several coral type of stones within it. Chest - no evidence of metastasis. There is a very small dense shadow at the left base, and two similar shadows in the right lung, which are very suggestive of primary calcified tubercles.

Thorotrast

Examination of liver and spleen following injection of thorotrast shows right lobe of liver to be within normal limits, the left lobe is fairly well visualized and appears to be somewhat larger than normal. Spleen shows moderate enlargement, extending slightly below

level of costal margin. It lies almost entirely laterally, and extends for only a very short distance medially. Re-examination - some slight areas of rarefaction in liver made out. These suggest small metastases. Left lobe of liver not visualized at all. This would suggest the possibility that it is entirely involved in tumor.

Pneumoperitoneum (carbon dioxide)

Liver and spleen well outlined and show same findings as previously reported. The large mass in mid-epigastrium is well outlined and well visualized. It appears to be connected with liver although a line of demarcation between left border of liver and mass can be made out. This line, however, does not completely separate them, and possibly represents division between right and left lobes of liver. Mass is clearly outlined below and possibly represents a large mass associated with liver. K.U.B. - Examination of urinary tract is unsatisfactory due to presence of barium in colon. Kidney shadows poorly visualized although right appears to be within normal limits. Re-examination of stomach - again shows marked pressure on greater curvature, due to enlargement of spleen. There is also evidence of pressure on the lesser curvature due to pressure from left lobe of liver. Barium enema - marked downward displacement of splenic flexure due to pressure from enlarged spleen.

Progress

During patient's stay in hospital, no significant change in condition. Exploratory operation suggested but thought to be of no particular benefit to give an exact diagnosis. Not performed.

5-1-33 - Discharged - to continue under care of own physician. Diagnosis - Carcinoma of left lobe of liver, primary undetermined.

Autopsy

Performed by patient's home physician. Summary of autopsy findings follows:

Very large tumor present involving

practically all of left lobe of liver with metastases to right lobe of liver, retroperitoneal lymph nodes, pancreas and both lungs. Only possible focus for tumor either in left lobe of liver or possibly in head of pancreas, although it seems that the pancreatic tumor is secondary mass.

Tissues

Sections made from various organs received from attending physician who performed autopsy. Gross examination shows tumor to have no characteristic appearance. It is composed of white stroma. No bile pigment seen in tumor. Tumor masses from lung, liver and pancreas recognized grossly. Microscopic sections show presence of tumor in lungs, liver, pancreas, lymph nodes and ovaries. Tumor in pancreas and ovaries appears to be secondary invasion in these organs rather than primary tumor. This, of course, is not certain from microscopic examination only. Tumor in all areas has approximately same appearance, being composed of cords and rudimentary tubules resembling to a remarkable degree the cords and tubules of regenerating bile ducts seen in cirrhosis of liver. Cells generally cuboidal and very deep staining. Numerous mitotic figures present. No arrangement into sinusoid formation. Giant nucleated cells seen in hepatoma not found. No visible bile production. Examination of material for presence of thorotrast negative. Liver tissue away from the tumor shows presence of cirrhosis.

Conclusions

1. Primary carcinoma of liver, cholangioma type.
2. Metastases to lungs, pancreas, local lymph nodes, right lobe of liver and ovaries.
3. Cirrhosis of liver.

III. ABSTRACT

CARCINOMA OF LIVER

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infants and young children.
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General

Originally (1850-1880) primary tumors of the liver were thought to be relatively common. However, as familiarity with various forms of malignancy developed, more and more of the liver carcinomas were found to be secondary. Numerous cases are reported in which the primary tumor was so small that it escaped notice in a superficial examination as the secondary growths were large or numerous. The belief developed that probably all "primary" liver tumors were of this type, that is, secondary to a small undiscovered primary elsewhere in the body. Today, one of the criteria for judging the liver as the primary focus is that there is no other possible primary lesion. This is applicable to a tumor of any organ but in case of the liver it is much more significant. However, various investigations in the past few years have put primary growths of the liver on a firm footing. The histological features are quite constant and a diagnosis (even on a biopsy of a lymph node) can be established in some instances. The criticism that a few millimeter sized carcinoma was overlooked in examining 20-odd feet of bowel can be more easily disregarded if the histological features of the tumor are those of primary liver carcinoma.

Historical

The following have been particularly active in developing the field:

- Rokitansky 1849 - original descriptions.
Sabourin 1881
Hanot and Gilbert 1881 - criticisms and more authentic classification.
Eggel 1901
Goldzieher and Bokay 1911
Winternitz 1916
Snyders and Straub 1923

Counseller and McIndoe 1926
Strong and Pitts 1930
Wilson 1931
Tull 1932 (largest personal series:
134 cases).

Incidence and Geographic Distribution

The following table includes the various individual and collected series in which a particular geographic distribution is not present (? -- at least not stated).

| <u>Name</u> | <u>Num- ber</u> | <u>No. of Autop- sies</u> | <u>Per- cent- age</u> |
|---------------------------|---------------------|-----------------------------------|-------------------------------|
| Eggel | 164 | - | - |
| Goldzieher & von Bokay | 18 | 6,000 | .3 |
| Yamagiwa | 42 | - | - |
| Karsner | 9 | - | - |
| Winternitz | 3 | 3,700 | .08 |
| Hale-White | 25 | 18,500 | .15 |
| Fried | 4 | 1,200 | .33 |
| Clawson & Cabot | 1 | 5,100 | .05 |
| Von Glahn & Lamb | 6 | 1,800 | .33 |
| Mayo Clinic | 5 | 5,976 | .08 |

Total average percentage of incidence in the groups where it can be estimated is .14%. At the Minnesota General Hospital, there have been 3 cases in a period of 15 months (507 autopsies, .6% incidence). This is apparently an unusual coincidence? At the Massachusetts General Hospital, there were 5 cases in a group of 1000 autopsies (.5%). With a more firm background for diagnosis, the percentage incidence probably will be somewhat higher than .14%.

The incidence in certain regions is much different than the above. Strong and Pitts reported 12 cases; 2 in whites with an incidence of .109% and 10 in Chinese with an incidence of 7.19%. Pirie in Africa among natives, in 91 malignancies, found 36 (40%) primary in the liver. Tull has the largest personal group of primary liver carcinomas (134 cases). His work is done in the Tan Tock Sing Hospital in Singapore (all natives). In 17,664 autopsies, he found an incidence of .76%. While not as high as in the smaller group of Strong

and Pitts, there nevertheless is a much higher incidence than found in other localities.

| | <u>Number</u> | <u>Autopsies</u> | <u>%</u> |
|--------------|---------------|------------------|----------|
| White (all?) | 62 | 42,276 | .14 |
| Chinese | 134 | 17,664 | .76 |

Etiology

The above statistics suggest that some causative factor could be found to account for the difference in incidence. The presence of liver flukes is the causative agent commonly described. In the following arrangement of data, this is brought out effectively:

| <u>Source</u> | <u>% Incidence</u> | <u>Incidence of Liver Flukes</u> |
|--------------------------|--------------------|----------------------------------|
| White | .14 | rare |
| Chinese (Tull's cases) | .76 | "not endemic" |
| Chinese (Strong & Pitts) | 7.19 | 75% infection |

In the series by Tull, the following associated conditions were present:

| | |
|-----------------------------------------------|----------|
| Syphilis | 29 cases |
| Active pulmonary tuberculosis | 20 |
| Ankylostoma duodenale, or, Necator americanus | 12 |
| Ascaris | 11 |
| Trichocephalus dispar | 7 |
| Malaria (recent) | 6 |
| Anaebiasis | 6 |
| Cholelithiasis | 6 |
| Clonorchis sinensis | 2 |
| Gastric ulcer | 1 |

In this series, fluke (clonorchis sinensis, Oriental fluke) was found in only 2 cases. In 38 cases, some form of intestinal parasite was found. Tull states that the fluke is not endemic in the area from which he drew his cases. Strong and Pitts (Vancouver) however found 75% of the Chinese infected with the worm. Firie in Africa who found 40% primary liver tumors in 91 cases of

malignancies considered the Schistosomiasis (African fluke) to be an etiological factor.

The assumptions from these studies which are frequently quoted are:

1. Primary liver tumors are relatively infrequent in the general population.

2. In certain areas, the tumors are common: up to 7% of autopsies and 40% of all malignancies.

3. The largest single group of cases was collected in an area where individuals are notably infested with intestinal parasites.

4. In the groups in which the incidence of liver carcinoma is highest, the infestation is most severe (up to 75%). The particular parasite is the liver fluke.

The sequence described in these cases is (1) hepatitis due to the presence of the worm, (2) cirrhosis, (3) repeated infestation, (4) malignant change.

In whites, the relative frequency of parasites apparently has not been studied. The presence of cirrhosis has been found as follows (percentages given to closest whole number).

| <u>Author</u> | <u>No. of Cases</u> | <u>% in Hepatoma</u> | <u>% in Cholangioma</u> |
|------------------|---------------------|----------------------|-------------------------|
| Eggel | 164 | 86 | 63 |
| Yamagiwa | 42 | 75 | 47 |
| Karsner | 9 | 100 | 100 |
| Winternitz | 3 | 100 | 100 |
| Fried | 4 | 100 | 100 |
| Clawson & Cabot | 1 | 100 | - |
| Von Glahn & Lamb | 6 | 100 | 100 |
| Mayo Clinic | 5 | 100 | 100 |
| Strong & Pitts | 12 | 92 (of total) | - |
| Tull | 134 | 76 | 66 |

Approximately 75 to 80% of the cases are associated with cirrhosis. The inference which is commonly drawn is that

carcinoma of the liver usually is preceded by cirrhosis and in the Chinese and African cases, liver parasites are thought to be causative factor in the production of the cirrhosis. It is estimated that 3% of cases of cirrhosis turn into carcinoma.

Pathology

The liver tumors, both primary and secondary, have provided many interesting problems of purely pathological interest. It is surprising, however, how many of these have found clinical application. The purely academic question regarding presence or absence of reticulo-endothelial cells becomes an active clinical question in light of thorotrast injections (Rigler). The metabolism of tumors would appear to be of no particular clinical interest. Malignant growths absorb carbohydrate about 10 times more rapidly than normal tissue or benign growths. In the liver (a glycogen storehouse), the rate of growth of a tumor estimated by the number of mitotic figures is 2 to 4 times more rapid than in other organs (true of both primary and secondary growths in liver). This feature manifests itself in the clinical picture in the very fulminating course of liver tumors.

The general clinico-pathological features of the tumors is as follows: The masses may be single, multiple or diffuse giving rise to corresponding localized, diffuse or nodular enlargement. The liver need not always be enlarged. In 8 of 134 cases (6%), it was smaller than normal. The location of the tumor masses was:

| | |
|------------|------------|
| Right lobe | 69 |
| Left lobe | 11 |
| Hilus | 5 |
| Diffuse | 49 |
| | <u>134</u> |

The amount of apparently normal (i.e. not involved by tumor) liver tissue is:

| | | |
|-----|---|-----------|
| 50% | - | 17 cases |
| 30% | - | 45 |
| 15% | - | <u>15</u> |
| | | 77 cases |

Metastasis in 134 cases was as follows!

| | |
|--------------------------|------------------------|
| Diaphragm | 32 |
| One lung | 31 (bilat- eral 23) |
| Abdominal nodes | 24 |
| Kidney | 5 |
| Spleen | 5 |
| Cervical nodes | 4 |
| Pleura | 2 |
| Mediastinal nodes | 2 |
| Pancreas | 2 |
| Head (dura, skull, etc.) | 2 |
| Ribs | 1 |
| Dura (alone) | 1 |
| Heart | 1 |

Microscopic Appearance

On this basis, primary liver tumors have been divided into 2 types: Cholangioma and hepatoma. For the present, it appears that grossly or clinically the two types are indistinguishable. As noted above, there is a greater number of hepatoma than cholangioma associated with cirrhosis. As the names indicate, the one arises from the liver cells, the other from the biliary epithelium within the liver (carcinoma of gall-bladder and common duct are not called cholangiomata). In general, the histological appearance of the two tumors makes this division acceptable. Mixed tumors have been described. The characteristic microscopic features of hepatoma: arrangement of cells much like that in the "adenomas" of liver seen in cirrhosis, numerous huge giant cells with many nuclei, variability in size of cells; presence of sinus-like spaces lined by an endothelial-like layer and, frequently, bile granules in the cells. The cholangioma, on the other hand, are composed of regular, cuboidal or cylindrical cells arranged in branching cords without giant cells, sinusoids or bile granules. Cells, stated to be Kupffer cells, are described in the sinusoids of the hepatomata.

Physiology of Liver Tumors

By "function" or "physiology" in

reference to tumors is meant any influences they may exert on the body which are carried over from the original tissue of origin. Examples of such "functioning" tumors are those from the Islands of Langerhans, from ovarian cells (granulosa cell tumors or arhenoblastoma); from adrenal, etc. Many of the metastasis from hepatomas secrete bile. Grossly, they may be greenish color. In one case, the metal content of a liver tumor, although somewhat less than in the liver itself, was considerable. So-called Kupffer cells are described but their activity is not stated. No reference to the presence or absence of thorotrast within these cells was found.

In at least 3 cases, a condition of hypoglycemia has been associated with the tumors. The cause of the hypoglycemia has not been explained.

Clinical Features

Sex: In this respect, as well as in age incidence, the tumors must be divided into two groups: the infantile type and the adult type. It is assumed that the infantile type represents a maladjustment in the growth of the liver. These cases are unassociated as a rule with cirrhosis. In the infantile type, the sex distribution in 47 cases, collected by Pirie was:

| | |
|------------|-----------|
| Male | 21 |
| Female | 17 |
| Not stated | 9 |
| | <u>47</u> |

In the adult type, the tumors are found much more frequently in males:

| <u>Author</u> | <u>Number</u> | <u>Male</u> | <u>Female</u> |
|----------------------|---------------|-------------|---------------|
| Strong and Pitts | 12 | 12 | 0 |
| Counseller & McIndoe | 5 | 5 | 0 |
| --quoted by McIndoe | 19 | 15 | 4 |
| " " " | 32 | 31 | 1 |
| Tull | 134 | 134 | 0 |

Tull's cases, however, should not be included in a statistical study because there are only a few beds for females in

the hospital from which he draws his material.

Age: Again two types must be made: infantile and adult.

| <u>Children</u> | |
|-----------------|----------|
| Under 1 yr. | 14 |
| 1 to 5 | 9 |
| 6 to 10 | 8 |
| 10 to 16 | 14 |
| not stated | <u>2</u> |
| | 47 |

| <u>Adults (134 cases) (Tull)</u> | |
|----------------------------------|----|
| 28 - 30 | 3 |
| 30 - 40 | 38 |
| 40 - 50 | 40 |
| 50 - 60 | 34 |
| 60 and over | 19 |

In Counseller and McIndoe's group, the average age was 61.5 yr. In Strong and Pitts group, the average was 46.5 and the range, 21 yr. to 76 yr. The two Chinese groups have a lower average age incidence than the one white group.

Course: Two types of reaction have been observed, (a) a course typical of cirrhosis of 1 to 5 year duration with a sudden change and an acute termination (malignant change in a preceding cirrhosis is implied); (b) only the acute, rapidly fatal terminal picture. Almost all observers comment on the rapid progression to a fatal outcome. In Tull's 134 cases, the average duration of symptoms was 2 weeks. None had a course over 2 months. All came for hospitalization within 1 month after onset of symptoms. This feature probably is correlated with the rapid growth of tumors (either primary or secondary within the liver). Jackson in 11 cases in whites found that the average duration of symptoms was $9\frac{1}{2}$ weeks.

Symptoms and Signs: 134 Cases.

| | | |
|-------------------------------------|-----|-----|
| Weakness, emaciation | 119 | 89% |
| Edema of legs | 112 | 88 |
| Palpable tumor | 91 | 69 |
| Distention of superficial veins | 70 | 52 |
| Ascites | 63 | 47 |
| Upward enlargement of liver | 62 | 47 |
| Visible tumor - (before tapping) | 52 | 39 |
| (after tapping) | 71 | 53 |
| Jaundice | 46 | 34 |
| Fever (terminal) | 37 | 28 |
| Tenderness over liver | 20 | 15 |
| Pain | 12 | 9 |
| Vomiting | 3 | 2 |

Weakness, weight loss, edema, ascites and palpable tumor make up the chief symptoms noted in the other series:

Jackson lists gastric disturbances and diarrhea as prominent symptoms. Jaundice was noted in 61% of cases by Jackson and in 65% by Counsellor and McIndoe. Strong and Pitts state that it is "not constant". One point frequently emphasized is the high fixed position of the diaphragm. Strong and Pitts list this as a diagnostic point. Liver function tests in 9 cases (Tull) were of no value (see our case). The tests gave normal readings even in one case with only 15% liver substances remaining.

Treatment

Response to radiation apparently has not been determined. No references to this subject were found. Jackson gives an interesting account of the history of surgical attempts at liver resections. He states that Keen in 1899 reviewed 76 cases in which some type of excision had been done (type of cases?). Castle (1924) had a case that survived partial resection. Turner had a patient living after removal of 2 pounds 3 ounces of tissue. Jackson reports a personal case in which he resected the left lobe for a carcinoma. The patient is living and symptomatically cured. He ligated the left hepatic artery at the hilus before starting the resection. This was based

on Counsellor and McIndoe's work showing that each lobe had its own artery and that there was no anastomosis between the two.

Impressions

1. From 1850 to 1880, the diagnosis of primary liver tumor was frequently made. Later most of these were shown to be secondary. The fashion then swung to the idea that primary liver tumors were extremely rare and recovery from this notion has just begun.

2. In material dealing with the Caucasian race, the incidence is .14%. More recent data indicate that this percentage may rise.

3. Among Orientals and Africans, the incidence is much higher.

4. There is some evidence indicating that the incidence in these people is in proportion to the incidence of liver fluke infestation. In Chinese with only few fluke infestations the percentage is .76%; in other groups with 75% fluke infestation, the reported incidence is 7.19%.

5. In one group of Africans with fluke infestation, primary liver carcinoma formed 40% of all malignancies.

6. The sequence in these cases is as (a) repeated liver infestation, (b) cirrhosis, (c) malignant change.

7. Even in cases without flukes, cirrhosis is present in 75 to 100% in the various series.

8. Some purely academic questions in the pathology of the tumors have become of interest clinically. The presence or absence of reticulo-endothelial tissue becomes an important consideration in thorotrast injections. The rapid rate of growth of malignant cells in the liver, said to be caused by the high glycogen content, may explain the fulminating course of these cases.

9. The liver usually enlarges. In only 6% is it smaller than normal. In about one-third as little as 15% of liver substance remains. The right lobe is involved in 50%; left in 10% and the growth is diffuse in 36%.

10. Most of the metastasis appear to be extensions. The local nodes and the lungs are most frequently involved by true metastasis.

11. Microscopically, there are two types: hepatomata and cholangiomata. The former reproduce liver structure; the latter ductal epithelium. Mixed types occur. The division is based on microscopic appearance and the veracity of the distinction is not certain.

12. The cells of the tumors sometimes "function". Bile is formed and there is some evidence that the tumors, like normal liver cells, can pick up metals from the circulation. The reaction to thoro-trast is not yet known. Some cases have been associated with spontaneous hypoglycemia.

13. On the basis of age, two types of tumors occur. In the infantile group, the tumors are thought to be developmental errors. In the adult types, they are said to be caused by (associated with) cirrhosis. In the childhood type, the greatest incidence is under one year and again during the period of adolescence. In the adult type, the age incidence is somewhat less than for the general cancer group.

14. The childhood group occur about equally in males and females; in the adult type, there is marked predominance of males. Only 6 cases in females were found.

15. The course is a very rapid one. In 134 cases, the entire period of symptoms in no case was over 2 months. In other groups in a few cases, a 1 - 5 year period of symptoms suggesting cirrhosis precedes the symptoms of malignancy.

16. The symptoms themselves are not characteristic. Chief among these are

weakness and weight-loss (90%), edema of legs (90%), ascites (50%) and palpable tumor (70%). Jaundice is variable (34% - 61% - 65%). A finding stressed by several is the upwardly displaced, fixed diaphragm. Liver function tests in 9 cases have given normal readings in spite of severe liver damage.

17. Results of radiation of the tumors apparently has not been described.

18. One case of successful resection of a lobe of the liver for tumor has been recently described.

Rudolph Koucky.

IV. ANNOUNCEMENTS

1. EXHIBIT

The Scientific Exhibit of the American Medical Association will be held in conjunction with the Cleveland Session, June 11 - 15, 1934. All applicants for space must fill out the regular application blank. Applications close on February 26, 1934. Assignment of space will be made about March 21, 1934. Further information may be obtained from Thomas G. Hull, Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago, Illinois.

2. SPEAKS

Dr. Morris Fishbein, editor of the Journal of the American Medical Association, will address the faculty and students of the Medical School in the Medical Science Amphitheater tomorrow (Friday), November 24, at 4:30 P.M. He will speak on "Changes in Medical Practice." If you have never heard him this is your chance; if you have, you will be there.

3. HOLIDAY

There will be no meeting of the General Staff next Thursday, November 30, on account of the Thanksgiving Holiday. Meetings will resume

the following Thursday and continue until the Christmas Holidays. Each department is urged to avail themselves of a general staff interest in departmental meetings. Plan your program now.

4. DYSENTERY

Interest in "amebic dysentery" should be displayed by every member of our group. Several local cases have been discovered and everyone is urged to be on the lookout for this disease. Further information can be obtained by reading the last issue of the Journal of the American Medical Association, published November 18, 1933.

5. PERMISSION

It is possible in many instances to obtain permission for examination of patients out in the state by working through local Funeral Directors. The majority are graduates of our own School of Embalming and are favorable to such procedures. We frequently are able to secure permission through them which could not be obtained in any other way. They also appreciate your recognition of their ability to help.

6. COOPERATION

We are endeavoring to maintain good laboratory service in spite of increased service demands, smaller force and increased number of students to instruct. Will you please help among other ways by limiting night requests to emergency procedures, bringing in spinal fluids earlier in the afternoon, and attempting to get in prospective donors for next day's operative list as early as possible. During the first 15 days of November, 276 patients were tested for blood transfusions.

V. MEETING

Date: November 16, 1933.

Place: Recreation Room,
Nurses' Hall.

Time: 12:15 to 1:22

Attendance: 117

Program: Hypertension

Discussion: Rudolph W. Koucky
Leo G. Rigler
Macnider Wetherby
Harold S. Diehl
John F. Briggs
E. T. Bell
George Fahr

Theme: R.W.K.: Correction -
"arch of aorta", not
"root of aorta", under autopsy.
Postmortem examination findings were presented. Microscopic studies show changes not only in the small vessels of the kidney but in the large.

L.G.R.: Films on this patient are here but cannot be shown very well. I will illustrate the type of change seen by some lantern slides. It is difficult to distinguish cardiac enlargement due to disease of the aortic valve from hypertensive disease. Slight differences are present but as a rule they are not diagnostic. There are 3 general types of change in hypertension. In the first stage we usually see hypertrophy alone which manifests itself merely as a rounding off of the left ventricle with no particular increase in size. In the second stage, the left ventricle is dilated, producing a boot-shaped type of heart. The left concavity is marked and there is marked and there is an increase in the ML. In the third stage, there is dilation of all chambers, enormous enlargement of the heart with increased ML and MR. The concavity of the left border is diminished although the left ventricle remains more prominent. There may be encroachment on the barium filled esophagus by a general increase in heart size. Additional signs are pulmonary congestion.

M.W.: Studies made are single readings. It has been quite a job to tabulate the 10,000 cases. We have started some followup studies and we hope to continue them. Records include cases from childhood to old age. In general, both sexes show about the same

pressure up to 35 to 40; over 40, there is a significant increase. We have compared our records with those of Bell and Clawson's autopsy studies. They use the size of the heart as their criteria, we use the elevation of blood pressure. You will note the large number of women with elevated pressures; almost twice that of men. In Bell and Clawson's figures, the incidence is 1.5 : 1 in favor of the men. When the group is corrected, throwing out coronary cases, the ratio is almost equal. Apparently, coronary disease is much more of a problem in men than women. Women may have a more labile blood pressure than men but this is not certain. It is very difficult for me to determine the normal level of blood pressure. When are we going to say that there is hypertension and when is the condition normal? Insurance companies have shown that above certain levels there is an increased mortality rate. Unfortunately, insurance figures deal primarily with men.

H.S.D.: The incidence of high blood pressure in various age groups has been very thoroughly studied in recent years. It is perfectly clear when you begin to follow these that a large portion of the individuals who show an elevated blood pressure on an initial reading will not have a persistent elevation (Palmer's figures are single readings). We have studied this problem in students. Elevations above 140 at the initial reading show only a relatively small percentage retaining this figure throughout the year. Does the individual who shows this elevation develop hypertension later on? This is a speculative matter. Some writers believe that this is not significant, others suggest that it is the beginning of hypertension.

Our recent studies will appear in the December issue of the Archives of Internal Medicine. Readings made 5 and 10 years ago are now being checked. In the previous paper, I stated that I doubted that these minor elevations of pressure had any significance. Follow-up study, however, makes us change this opinion somewhat. Dr. Diehl then dis-

cussed the chances of such elevated pressures being significant. In some cases, elevated readings are not maintained or become fixed at high level. The factor of heredity is generally assumed and reported on from various angles. We are now studying the parents of students who have persistent elevation of blood pressure. We have found that the parents of the control groups are older and have relatively low pressures. The cases we have designated as true hypertension show pressures in the parents which are much higher and the groups are younger.

J.F.: Clinical studies of hypertension are handicapped by suitable standard stimuli. Cold test consists of immersing the hand of an individual in ice bath and maintaining it for 3 minutes. The pressures are read on the opposite arm at half minute intervals until returned to normal. Patients with hypertension respond with much more of elevation and show, as a general rule, a plateau type of curve. We are studying this problem from several different angles. Old cardiac cases, thought to be hypertensives, although now showing no elevation of pressure, frequently give this reaction. In the previous reported cases of cerebrospinal syphilis, we were wrong in our interpretation because most of these patients also had hypertension. The children of hypertensive patients are being studied and may show the reaction. The ordinary drugs used in the management of hypertension do not abolish the reflex. There is only one exception and that is the exhibition of enormous doses of iodide. This seems to cause a lower pressure and the reaction to disappear. There is a theory at the present time that perhaps this entire problem is centered in the abdominal sympathetics. Surgical obliteration of the connections of trunks within the body result in the abolition of the reflex in hypertensive subjects; the effect of iodide may be similar.

E.T.B.: One of the questions that comes up all the time in study of hypertension is whether or not it is a specific disease such as tuberculosis,

typhoid fever, or whether what we see at postmortem is simply the end-result of the process. Problem has been studied from many angles. It is apparently not a special disease but an over-active physiologic mechanism. We find the greatest number of deaths in hypertension in persons over the age of 40. 90% of them occur in this age group. About 50% of all hypertensive deaths are due to heart failure (by our standard), about 15% to cerebral hemorrhage or infarct, about 15% to coronary occlusion and about 10% to uremia. A certain percentage dies from other causes. Illustrations were then made of the arteriole changes in hypertension in the kidney.

They apparently represent an exaggeration of the ordinary senile change and are similar in some ways to those seen in diabetes. Of particular interest are the kidney changes in the glomeruli. Changes in the basement membrane occur, such as thickening. These are usually associated with narrowing of the arterioles. About 15% of all deaths are due to the effect of hypertension. In some unusual extreme types, actual necrosis may be seen in the kidney.

G.F.: I wish to challenge Dr. Wetherby's contention that essential hypertension is more frequent in females than males. According to Bell's autopsy statistics, there are as many females as males dying of hypertension. When a woman reaches the age of 40 or 50, life is pretty nearly over for her. She has no worries, no great activity and her life is not nearly as absorbing as it was when she was raising her children. She begins to notice little changes and consults her doctor frequently for minor complaints. In other words, slight symptoms bring women to the doctor's office. More severe symptoms for the men will. I am not convinced that the incidence of hypertension is twice as great in females as in men.

M.W.: The figures include all patients coming to the Out-Patient Department as all go through Admission Clinic. Many of these patients are symptom-free and come for various minor complaints or

injuries. I wish to call your attention to the fact that I have never called these elevated readings hypertension but spoke of them only in terms of elevated blood pressures. You will note from our records that we have good samples in each sex and that the figures are based on percentage.

Gertrude Gunn,
Record Librarian.