HEMOGLOBIN PRODUCTION FACTORS IN THE HUMAN LIVER

II. LIVER DEGENERATION, CANCER, CIRRHOSIS AND HEPATIC INSUFFICIENCY

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When we first took up the study of the hemoglobin production factors in abnormal livers, we were surprised to find that the great majority of these cases showed normal or perhaps low normal human values. It is obvious from a glance at the tables below that only under conditions of grave injury does the liver cell give up the unknown substances which can be used to produce new hemoglobin and red cells. Even in fatal *liver insufficiency* (Table 25) the liver cells still contain some of the factors which go to form new hemoglobin although the amount of these hemoglobin production factors may be *reduced to 1/3 normal*. By way of contrast we observe in the next paper (Tables 31 and 32) that primary and aplastic anemias show a considerable *excess storage* of these same factors within the liver.

The same methods and experimental procedures were used in these experiments as described in the preceding paper—in fact all these experiments developed during the same period and the cases were assayed as material became available but the data are arranged according to the abnormal findings.

Table 21. *Diagnosis and histological description* of liver.

A-1105. Myocardial failure—passive congestion of liver—36 yrs.
Liver—autopsy weight 2150 gm.—laboratory specimen 1850 gm.
Histological specimen—typical picture of advanced passive congestion of liver lobules. The central one-half of the lobules shows atrophy of liver cells with fatty degeneration. The marginal half of each lobule shows relatively normal liver cells. Lipochrome pigment is not abundant.

A-1226. Heart disease—passive congestion of liver—hemoglobin 70 per cent—44 yrs.

Liver—autopsy weight 2200 gm.—laboratory specimen 1840 gm.

Histological specimen—liver lobules show central atrophy as usual. These cells show some fat droplets and lipochrome pigment. The liver cells in the periportal regions are normal. Kupffer cells not pigmented. A few bile canaliculi in center of lobules show brown colloid.

A-1249. Heart disease—passive congestion of liver—hemoglobin 93 per cent—53 yrs.

Liver—autopsy weight 1900 gm.—laboratory specimen 1100 gm.

Histological specimen—extreme passive congestion with complete central atrophy of liver cells here. In center of lobule phagocytes full of lipochrome pigment are numerous but mainly an empty reticulum is observed. In mid zone a few liver cells show fat droplets. The liver cells in the outer half of each lobule appear normal.

A-94. Old endocarditis of all valves—passive congestion of liver—41 yrs.

Liver—laboratory specimen 1240 gm.

Histological specimen—liver lobules show extreme passive congestion with central atrophy and some cell necrosis. Bile canaliculi conspicuous in mid zone of lobule. Portal tissue normal. About 1/3 liver parenchyma looks normal. Lipochrome present.

A-78. Rheumatic heart with decompensation—passive congestion of liver—41 yrs.

Liver—laboratory specimen 1370 gm.

Histological specimen—liver lobules show early acute passive congestion with atrophy and central necrosis, about 2/3 liver cells look normal. Little fat, no lipochrome. In some sections the liver lobules show necrosis involving almost 1/2 the liver cells.

A-60. Syphilitic aortitis—cardiac insufficiency—passive congestion—broncho-pneumonia—45 yrs.

Liver—laboratory specimen 1340 gm.

Histological specimen—liver cells very small. Central atrophy present, a good deal of fat, no necroses. Lipochrome abundant. Few leucocytes.

Table 21 shows typical instances of cardiac *passive congestion* with “red atrophy” of the liver. Biological assay of this liver tissue shows subnormal or low normal values and this may be explained by simple atrophy and disappearance of many liver cells.

Table 21 shows one very unusual case—the last one in the table—A-60. There was nothing unusual about this case clinically—a man

with syphilitic aortitis and cardiac failure lasting several years. A serious break in compensation was recorded 3 weeks before death. Patient came into the hospital and died in 24 hours. The liver showed the expected passive congestion. It so happened that this material was divided and tested on two dogs. The smaller amount might not be convincing but the larger amount, 120 gm. daily, gave no evidence of any hemoglobin producing factors in this material. Only one other case in all this series shows a zero test—see Table 35 (Paper III), case of eclampsia. We have no explanation to offer but believe that methods and experimental procedure can be excluded.

TABLE 21
Hemoglobin Production Factors in Abnormal Human Liver
Cardiac Passive Congestion—Red Atrophy of Liver

Number	Cause of death	Iron content human liver		Liver intake per day		Hemoglobin output per 7 days feeding		
		fresh tissue	daily intake	Human	Control	from Human	from Control	ratio Human to Control
		<i>mg. per cent</i>	<i>mg.</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>	<i>per cent</i>
A-1105	Myocarditis	18.6	50	260	300	40	53	87
A-1226	Cardiac	6.7	18	260	300	25	45	64
A-1249	Cardiac	6.9	11	155	300	44	41	210
A-94	Cardiac	—	—	177	300	25	33	132
A-78	Cardiac	—	—	181	225	19	33	70
A-60	Aortitis	—	—	70	300	0	35	0
A-60	Aortitis	—	—	120	160	0	30	0
Average.....				175				

If we exclude this last case A-60 from the average, we get an average of 112 per cent which practically coincides with the degenerations listed under Table 22. All cases listed in Table 21 show typical central atrophy of liver cells, in some cases with more or less central necrosis of liver cells. The usual mid zone of fat is found while the periportal liver cells are normal. It is not surprising that this type of liver atrophy (cardiac) should show some loss of these potent hemoglobin producing factors as a goodly percentage of liver parenchyma has vanished and its place is taken by reticulum, congested capillaries

and phagocytes. We may say that the normal liver parenchyma is "diluted" by this much inert tissue. We believe the remaining liver cells contain a normal amount of the substances which promote hemoglobin formation under experimental conditions.

Table 22. *Diagnosis and histological description of liver.*

A-580. Chronic pulmonary tuberculosis—amyloidosis—hemoglobin normal—23 yrs.

Liver—laboratory specimen 2700 gm.

Histological specimen—extreme amyloidosis, 2/3–3/4 of each liver lobule is amyloid. Liver cells show atrophy and fat droplets.

A-326. Chronic pulmonary tuberculosis—amyloidosis—41 yrs.

Liver—laboratory specimen 2380 gm.

Histological specimen—extreme amyloidosis, only about 1/4 of section is hepatic epithelium. Small atrophic threads of liver cells. Few tubercles. Lipochrome conspicuous in atrophic liver cells. Very little fat.

A-348. Chronic pulmonary tuberculosis and amyloidosis—43 yrs.

Liver—laboratory specimen 2550 gm.

Histological specimen—amyloid makes up about 1/2 of each lobule. Liver cells outside of this amyloid deposit are well preserved. No fat, no necrosis, little lipochrome.

A-226. Chronic pulmonary tuberculosis—amyloidosis—disseminated tubercles—20 yrs.

Liver—autopsy weight 1250 gm.—laboratory specimen 1220 gm.

Histological specimen—amyloid and stroma make up about 1/2 of each liver lobule, most of the amyloid appears in portal zone, small amount of lipochrome in central half of lobule. Liver cells atrophic, little fat.

A-293. Chronic pulmonary tuberculosis—slight amyloidosis—50–60 per cent hemoglobin—22 yrs.

Liver—laboratory specimen 950 gm.

Histological specimen—fat droplets conspicuous in peripheral half of lobule. Center liver cells are swollen. Little lipochrome. Few lobules show early amyloid deposit. Few tubercles, slight portal fibrosis. Mononuclears numerous in capillaries. Kupffer cells large.

A-1359. Alcoholism—pulmonary tuberculosis—hemoglobin 90 per cent—41 yrs.

Liver—autopsy weight 2580 gm.—laboratory specimen 2350 gm.

Histological specimen—practically all liver cells show large and small fat droplets.

Pigment is scanty. Occasional focal necroses. The portal stroma is slightly increased and contains many mononuclear cells. Icterus is indicated by some colloid casts in bile canaliculi.

A-42-28. Acute and chronic alcoholism—43 yrs.

Liver—laboratory specimen 1800 gm.

Histological specimen—liver shows extreme fatty degeneration. All liver cells full of large or small fat droplets. Lipochrome noted in some areas.

TABLE 22
Hemoglobin Production Factors in Abnormal Human Liver
Amyloid Liver (Tuberculosis), Fatty Liver (Alcoholism)

Number	Cause of death	Iron content human liver		Liver intake per day		Hemoglobin output per 7 days feeding		
		fresh tissue	daily intake	Human	Control	from Human	from Control	ratio Human to Control
		<i>mg. per cent</i>	<i>mg.</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>	<i>per cent</i>
A-580	Amyloid	—	—	380	150	49	54	72
A-326	Amyloid	—	—	340	300	43	30	127
A-348	Amyloid	—	—	365	142	46	38	47
A-226	Amyloid	—	—	174	300	12	30	71
A-293	Sl. amyloid	—	—	135	300	32	33	214
A-1359	Alcoholism	5.8	19	380	300	35	50	56
A-42-28	Alcoholism	—	—	260	300	38	30	146
X-510	Alcoholism	—	—	360	225	58	33	110
A-79	Alcoholism	—	—	195	300	43	34	196
X-185	Alcoholism	—	—	193	160	14	30	74
Average				278				111

X-510. Acute and chronic alcoholism—40 + yrs.

Liver—laboratory specimen 2520 gm.

Histological specimen—large and small fat droplets in all liver cells. Little lipochrome pigment.

A-79. Acute alcoholism—terminal bronchopneumonia—30 + yrs.

Liver—laboratory specimen 1375 gm.

Histological specimen—liver cells show diffuse fat infiltration with tiny fat droplets. Slight portal cell increase. Much congestion.

X-185. Chronic alcoholism—terminal bronchopneumonia—about 40 yrs.

Liver—laboratory specimen 2700 gm.

Histological specimen—fatty liver cells contain large and small droplets. Moderate lipochrome, no fibrosis.

Table 22 shows typical cases of *amyloidosis* due to long continued tuberculosis. The cases are arranged in order of the extent of the amyloid deposit. The first two cases in histological sections show about two-thirds of the section made up of amyloid. If we allow for this "dilution" of the liver cells by this amyloid deposit we arrive at figures about 3 times those given in Table 22 or high normal values. If however on the basis of normal liver weights in tuberculosis we say that there is an excess weight of amyloid amounting to 1000 gm. in each instance we would find our calculations for the remaining liver cells at about the normal level. There is no evidence that amyloid contains any factors which favor hemoglobin regeneration although most of the amyloid probably is undigested and unabsorbed.

Table 22 also shows that acute and chronic *alcoholism* does not seriously deplete the store of hemoglobin producing factors in the liver. In fact if we allow for the abnormal liver weight due to fatty degeneration we arrive at values which are close to normal.

Table 23. *Diagnosis and histological description of liver.*

A-512. Primary liver cell cancer—hemoglobin 90 per cent—no icterus—54 yrs. Liver—autopsy weight 6000 + gm.—laboratory specimen 5135 gm. Histological specimen—pigmented tumor cells numerous, much necrosis. Liver cells are very rich in pigment which contains *iron*. Tumor cells show *iron* staining pigment.

A-54-31. Liver carcinoma with cirrhosis. Liver—autopsy weight 1760 gm.—laboratory specimen 1650 gm. Histological specimen—liver cancer originating probably from hepatic epithelium. Elsewhere the liver shows a moderate grade of annular cirrhosis. The liver cells are well preserved and appear relatively normal. Lipochrome pigment is present.

X-3788. Cancer of stomach—liver metastases—hemoglobin 100 per cent—60 yrs. Liver—autopsy weight 4690 gm.—laboratory specimen 4290 gm. Histological specimen—extensive replacement of liver cells by adeno-carcinoma. There appear to be more tumor than liver cells. Liver cells show a little atrophy especially in centers of lobules. No unusual pigment. Small amount of lipochrome pigment. Kupffer cells normal.

A-1741. Embryoma testis—liver metastases—hemoglobin 60 per cent—38 yrs. Liver—autopsy weight 1700 gm.—laboratory specimen 1460 gm.

Histological specimen—liver sections show a good deal of diffuse tumor infiltration of the liver lobules about the portal structures. Occasional bile canaliculi show hyaline brown casts. Lipochrome pigment is in evidence. Some Kupffer cells contain a little pigment which stains for iron.

A-367. Cancer of breast—liver metastases—53 yrs.

Liver—laboratory specimen 2400 gm.

Histological specimen—much cancer tissue. Some liver cells normal, but numerous central necroses near cancer areas, also atrophy and lipochrome pigmentation. Bile canaliculi plugged in some areas, probably a good deal of normal liver parenchyma.

TABLE 23
Hemoglobin Production Factors in Abnormal Human Liver
Liver Carcinoma—Primary and Secondary

Number	Cause of death	Iron content human liver		Liver intake per day		Hemoglobin output per 7 days feeding		
		fresh tissue	daily intake	Human	Control	from Human	from Control	ratio Human to Control
		mg. per cent	mg.	gm.	gm.	gm.	gm.	per cent
A-512	Liver—Ca.	—	—	733	225	50	30	51
A-54-31	Liver—Ca.	4.7	11	280	300	44	50	94
X-3788	Stomach Ca.	7.1	43	610	300	93	50	91
A-1741	Embryoma	38.7	80	208	300	80	74	157
A-367	Breast Ca.	—	—	343	300	15	41	32
A-129-29	Stomach Ca.	8.4	18	210	300	15	44	48
A-456	Prostate Ca.	13.8	76	555	300	27	34	43
A-359	Gall bladder Ca.	—	—	185	200	47	62	83
Average.....		14.5	46	391				75

A-129-29. Cancer of stomach with liver invasion—icterus—51 yrs.

Liver—laboratory specimen 1500 gm.

Histological specimen—much of the liver section shows tumor tissue or degenerating liver cells. Much fatty degeneration of liver cells found. Some normal liver cells are present. Lipochrome pigment is abundant. Kupffer cells show a yellow pigment.

A-456. Cancer of prostate—extensive liver metastases—78 yrs.

Liver—autopsy weight 4200 gm.—laboratory specimen 3900 gm.

Histological specimen—cancer tissue makes up much of sections. Liver cells show various degrees of atrophy and fatty degeneration plus lipochrome. Large Kupffer cells.

A-359. Cancer of gall bladder—liver metastases—icterus—terminal endocarditis—78 yrs.

Liver—autopsy weight 1850 gm.—laboratory specimen 1300 gm.

Histological specimen—much tumor tissue. Much liver cell necrosis in places and post mortem change. Icterus and plugs in bile canaliculi in some areas.

Atrophy of liver cells elsewhere. Lipochrome abundant.

Table 23 shows various types of primary and secondary *cancer replacement* and invasion of the liver. There is no evidence that cancer cells even when originating from hepatic epithelium contain substances which promote hemoglobin regeneration. It appears that the largest liver specimens containing the largest mass of tumor cells give lower values per gram specimen weight. We may say these masses of cancer “dilute” the potency of the remaining liver cells just as is found with amyloid deposit (Table 22). There is no reason to suppose that the tumor material is not completely disintegrated and assimilated.

The first case (A-512) in Table 23 illustrates this “dilution” by tumor tissue. This liver weighed more than 3 times normal and we may safely assume that the liver cells made up less than the normal liver weight. If we take this fact into consideration the concentration of hemoglobin production factors instead of rating 51 per cent of control would read more than 150 per cent or normal.

The second case (A-54-31) in Table 23 shows a second instance of primary liver carcinoma where there was little increase in liver weight, yet the liver cell cancer did occupy a considerable ($1/5$ – $1/7$) bulk of the liver mass. If we allow for this “dilution” with inert tumor tissue we arrive at a figure within low normal values.

The liver cells closely associated with masses of tumor cells are usually supposed to suffer from hypothetical toxic material coming from tumor growth and disintegration. The liver cells actually show some atrophy and fatty degeneration and the tumor masses may interfere with bile circulation and blood flow through liver lobules. In spite of all this, the concentration of hemoglobin producing factors within the liver cells is not significantly reduced.

In one instance (A-456) the iron analysis shows high values for the total daily intake and this iron may account for more than half the actual hemoglobin production which would mean a low value for the liver cells even when allowance is made for the “dilution” with cancer tissue.

Another case (A-1741) Table 23, shows a high iron analysis and this iron intake undoubtedly is a factor in the production of hemoglobin. This will in a measure offset the "dilution" of the liver specimen by tumor tissue but in this instance the final figure would be close to 150 per cent or normal.

Table 24. *Diagnosis and histological description of liver.*

A-1589. Liver cirrhosis (hob-nail)—ascites—hemoglobin 75 per cent—74 yrs.
Liver—autopsy weight 1170 gm.—laboratory specimen 1000 gm.
Histological specimen—a typical annular fibrosis involving portal structures but not the islands of preserved liver cells which in some areas show fat but elsewhere may be normal. Very little pigment anywhere. Occasional focal necroses. Kupffer cells inconspicuous. Bile ducts inconspicuous.

A-1468. Liver cirrhosis (hob-nail)—ascites—pneumonia—61 yrs.
Liver—autopsy weight 1560 gm.—laboratory specimen 1480 gm.
Histological specimen—usual picture of hepatic cirrhosis with much scar tissue which contains numerous mononuclears. Many liver cells normal. New formed bile ducts not conspicuous. Post mortem autolysis is well marked. Large bile ducts normal. Pigment scanty. Kupffer cells normal.

A-615. Liver cirrhosis (hob-nail)—nephrosis—syphilis—hemoglobin 79 per cent—49 yrs.
Liver—autopsy weight 1450 gm.—laboratory specimen 1300 gm.
Histological specimen—considerable portal fibrosis with mononuclears and some new bile ducts. Liver lobules distorted but parenchyma looks normal except for cloudy swelling and little fat. No pigment. Kupffer cells normal.

A-1114. Liver cirrhosis (hob-nail)—icterus—hemoglobin 35 per cent—56 yrs.
Liver—autopsy weight 1950 gm.—laboratory specimen 1740 gm.
Histological specimen—typical annular periportal cirrhosis. The new scar tissue is full of mononuclears. Bile duct buds are not numerous. The hepatic epithelium is relatively normal except for icterus. Bile canaliculi conspicuous and filled with dark colloid. Kupffer cells contain a little pigment. Patient had been bleeding into gastro-intestinal tract, kidneys and body tissues, the last few weeks of life and this caused anemia. It is likely that some antistubstance was present in blood and responsible for the bleeding. Blood fibrinogen normal. Hepatic insufficiency seems unlikely.

A-788. Liver cirrhosis (hob-nail—alcoholic)—terminal pneumonia—hemoglobin 90 per cent—44 yrs.
Liver—laboratory specimen 1275 gm.
Histological specimen—much annular portal fibrosis, many lobules in part de-

stroyed with much bile duct proliferation. Fibrous tissue rich in mononuclears and polymorphonuclears. Perhaps half of section shows well preserved liver cells, little fat, much granular yellow pigment in liver cells. Iron granules stain abundantly in liver cells. Few colloid plugs in canaliculi. No hepatic insufficiency.

A-1530. Hepatitis and icterus—cardiac failure—alcoholism—hemoglobin 80 per cent—54 yrs.

Liver—autopsy weight 950 gm.—laboratory specimen 840 gm.

Histological specimen—liver does not show a characteristic cirrhosis. There is no striking distortion of liver architecture. Many liver lobules are normal except for icterus. Many lobules show extensive necroses which are healing with accumulation of mononuclears and scar tissue. There are some new formed bile ducts here. Bile canaliculi are conspicuous. Kupffer cells contain much granular pigment. There is yellow pigment in many liver cells. No pigment gives a stain for iron. This liver is not insufficient but has been subjected to focal injury in many lobules.

A-1238. Subacute hepatitis—icterus—hemoglobin 90 per cent—38 yrs.

Liver—autopsy weight 1340 gm.—laboratory specimen 1100 gm.

Histological specimen—portal tissue increased and infiltrated with mononuclears. Liver lobules not extremely distorted but show scattered necroses and diffuse cell infiltration and edema of stroma. Bile canaliculi in places conspicuous, filled with yellow colloid. Kupffer cells rich in pigment. Many liver cells, possibly 1/2 of each lobule, appear normal. This process may have begun as a cholangitis. Fibrinogen not reduced.

A-700. Liver cirrhosis—nephritis chronic—cardiac congestion—hemoglobin 75 per cent—79 yrs.

Liver—autopsy weight 2460 gm.—laboratory specimen 2180 gm.

Histological specimen—annular portal fibrosis with many mononuclears included. Little bile duct proliferation. Liver cells not disarranged but show granular degeneration and little fat. Some lobules show moderate lipochrome and others not. Kupffer cells normal.

X-835. Liver cirrhosis with hepatitis—icterus—esophageal hemorrhage—62 yrs.

Liver—autopsy weight 2670 gm.—laboratory specimen 2400 gm.

Histological specimen—advanced cirrhosis with great injury of hepatic epithelium, extreme fat, good deal of necrosis, diffuse fibrosis, much abortive bile duct proliferation—bile canaliculi all distended with colloid plugs—not much lipochrome. Severe parenchyma injury.

A-564. Liver cirrhosis (hob-nail)—syphilis—subacute nephritis—hemoglobin 80 per cent—56 yrs.

Liver—autopsy weight 930 gm.—laboratory specimen 770 gm.

Histological specimen—much portal scarring with mononuclears and new formed ducts and distortion of lobules, much liver parenchyma is normal but for much fatty degeneration and scattered large and small liver cell necroses. Kupffer cells large and contain no pigment.

A-789. Liver cirrhosis—lobar pneumonia—hemoglobin 85 per cent—45 yrs.

Liver—laboratory specimen 2775 gm.

Histological specimen—little portal fibrosis but many mononuclears and few polymorphonuclears. Occasional focal necroses in liver cells close to these portal areas. No pigment in liver cells but granular degeneration and little fat. Kupffer cells normal. Most of section shows normal liver cells.

A-29-77. Liver cirrhosis (hob-nail)—icterus.

Liver—laboratory specimen 940 gm.

Histological specimen—much scar tissue, possibly 1/3 of section, full of lymphocytes and new bile ducts, lipochrome abundant. Liver parenchyma hypertrophied, some diffuse fatty degeneration. Few necroses, some lobules show icterus plugs in canaliculi, some not. No hepatic insufficiency.

A-28-168. Liver cirrhosis (alcoholic)—terminal bronchopneumonia.

Liver—autopsy weight 2600 gm.—laboratory specimen 2590 gm.

Histological specimen—much post mortem change. Scars abundant and coarse, perhaps replacing 1/4 entire section, much bile duct proliferation. Liver cells show much fat, bile canaliculi show numerous colloid plugs. Lipochrome abundant.

A-27-160. Liver cirrhosis—cystitis—pyelonephritis.

Liver—laboratory specimen 910 gm.

Histological specimen—coarse scars, liver parenchyma looks well and makes up 4/5 of sections. Infectious biliary type? No bile duct regeneration, mononuclears found in scars. Few indefinite central necroses and little fat. No icterus. No hepatic insufficiency.

A-51-27. Liver cirrhosis.

Liver—laboratory specimen 750 gm.

Histological specimen—slight periportal fibrosis and clusters of mononuclears, like biliary cirrhosis in early stage. Few colloid bile plugs in canaliculi. Many large and small fat droplets in liver cells, few necroses of 1–2 cells. Few polymorphonuclears. Lipochrome inconspicuous.

X-334. Liver cirrhosis—syphilis—alcoholism—cerebral hemorrhage—42 yrs.

Liver—autopsy weight 2450 gm.—laboratory specimen 2340 gm.

Histological specimen—liver presents the usual picture of a diffuse cirrhosis. The

liver epithelium shows a good deal of fat and very little pigment—no icterus. Scar tissue is abundant within the lobules and mononuclears are numerous. Bile duct sprouts are present. Liver cell function would seem to be impaired.

TABLE 24
Hemoglobin Production Factors in Abnormal Human Liver
Liver Cirrhosis—No Evidence of Liver Insufficiency

Number	Cause of death	Iron content human liver		Liver intake per day		Hemoglobin output per 7 days feeding		
		fresh tissue	daily intake	Human	Control	from Human	from Control	ratio Human to Control
		mg. per cent	mg.	gm.	gm.	gm.	gm.	per cent
A-1589	Cirrhosis	12.3	17	140	300	51	58	190
A-1468	Cirrhosis	8.1	17	210	300	50	52	139
A-615	Cirrhosis	18.5	34	185	300	49	54	148
A-1114	Cirrhosis	3.2	8	245	300	23	45	62
A-788	Cirrhosis	16.5	30	167	142	58	38	129
A-1530	Hepatitis	4.7	6	115	300	47	46	261
A-1238	Hepatitis	5.4	8	157	300	52	54	186
A-700	Cirrhosis	3.6	11	310	300	45	43	102
X-835	Hepatitis	—	—	340	300	41	40	91
A-564	Cirrhosis	6.5	7	103	300	26	53	145
A-789	Cirrhosis	—	—	396	300	71	54	100
A-29-77	Cirrhosis	17.3	23	130	300	48	35	320
A-28-168	Cirrhosis	—	—	370	300	53	54	79
A-27-160	Cirrhosis	—	—	130	300	63	53	274
A-51-27	Cirrhosis	—	—	107	300	59	53	310
X-3334	Cirrhosis	2.6	9	320	300	65	67	90
A-197	Sl. cirrhosis	—	—	190	300	36	28	200
A-205	Sl. cirrhosis	—	—	290	300	55	53	108
A-730	Sl. cirrhosis	14.5	29	200	300	50	35	218
A-1024	Sl. cirrhosis	8.3	18	210	105	71	30	118
Average.....		9.3	17	216				164

A-197. Liver cirrhosis (hob-nail)—subacute colitis—46 yrs.

Liver—laboratory specimen 1350 gm.

Histological specimen—moderate biliary cirrhosis. Mononuclears very numerous in thick portal tissue. Moderate bile duct regeneration in places. Liver cells show scattered small fat droplets, no necroses. Few colloid plugs in bile canaliculi. Bulk of liver cells are normal.

A-205. Liver cirrhosis (slight)—organizing pneumonia—43 yrs.
Liver—autopsy weight 2540 gm.—laboratory specimen 2050 gm.
Histological specimen—moderate to slight portal fibrosis, few new bile ducts.
Good deal of fat in central 3/5 of lobule, some degeneration with lipochrome pigment deposit in liver cells.

A-730. Liver cirrhosis (slight)—pneumonia lobar—46 yrs.
Liver—autopsy weight 1500 gm.—laboratory specimen 1400 gm.
Histological specimen—slight annular fibrosis with no new bile duct proliferation.
Many mononuclears, slight lobule distortion, little lipochrome. Liver parenchyma looks normal but for little fat. Occasional tiny hyaline necroses.

A-1024. Liver cirrhosis—icterus—carcinoma pancreas—53 yrs.
Liver—autopsy weight 1550 gm.—laboratory specimen 1500 gm.
Histological specimen—there is moderate portal cirrhosis and duct proliferation.
The liver cells are well preserved and approximate a normal appearance. There are no necroses. Bile canaliculi often contain yellow colloid. Pigment is abundant in hepatic epithelium and Kupffer cells.

Table 24 shows a considerable variety of *liver cirrhosis* and hepatitis without any evidence of hepatic insufficiency. These cases died from terminal infections, hemorrhage or alcoholism and presented more or less severe passive congestion of the abdominal viscera with all grades of icterus. It is obvious from a glance at Table 24 that the concentration of the hemoglobin production factors is not abnormal in these liver specimens. There are considerable individual variations but from the average of 164 per cent we see the low values rarely below 100 per cent and the high values rarely above 200 per cent.

Case A-1114, Table 24, presents the lowest value for the hemoglobin production factors and there are some points which indicate a possible hepatic insufficiency (see Table 25). A-1114 showed bleeding into the intestinal tract and body tissues but a normal fibrinogen. The liver cells did not appear seriously abnormal histologically. It seemed safest to place this case in the group of cirrhoses without convincing evidence of severe liver injury and insufficiency.

The iron analyses show an average value which is a trifle below the normal averages. The lowest values appear in association with secondary anemia—compare Table 33 (Paper III).

Icterus was present in varying degrees in this group of cases and we see no reason to suspect that bile pigment stasis influences the concentration of hemoglobin producing factors in the liver cells.

Table 25. *Diagnosis and histological description of liver.*

A-956. Cirrhosis and hepatitis—liver insufficiency—hemoglobin 40 per cent—33 yrs.

Liver—autopsy weight 2160 gm.—laboratory specimen 2050 gm.

Histological specimen—the general picture is that of a coarse annular type of cirrhosis in which scar tissue makes up more than half of all liver sections. This scar tissue is full of mononuclear and a few polymorphonuclear cells. Only an occasional island of liver cells is normal. As a rule the islands of liver cells show focal injury and infiltration with wandering cells in large numbers. The picture throughout the liver sections is that of a diffuse subacute inflammatory reaction involving stroma and hepatic epithelium as well as bile ducts—a true diffuse hepatitis. Lipochrome pigment is scanty. No pigment observed in Kupffer cells. Occasional liver cells show bile canaliculi filled with yellow colloid (icterus). Many liver cells show fat droplets. The blood fibrinogen was subnormal during the last weeks of life and we may safely assume a true hepatic insufficiency.

A-982. Cirrhosis and hepatitis—alcoholism—hemoglobin 30 per cent—40 yrs.

Liver—autopsy weight 2700 gm.—laboratory specimen 2580 gm.

Histological specimen—no normal liver tissue anywhere. Remarkably diffuse increase in stroma both in portal region and throughout all parts of lobules. Lobules are full of tiny focal necroses in which wandering cells are numerous. Liver cells are of every type, some large and hydropic, others showing fat, others hyaline necrosis. Pigment is scanty. The regular architecture of the lobule is completely destroyed. New bile ducts are inconspicuous. Blood fibrinogen 0.452 per cent and normal blood clots at autopsy.

A-905. Acute hepatitis—icterus—delirium—soft clots and hemorrhages—hemoglobin 75 per cent—14 yrs.

Liver—autopsy weight 1350 gm.—laboratory specimen 720 gm.

Histological specimen—no normal liver cells, slight portal fibrosis with mononuclears. Central 1/2 of lobules shows extreme fat and even necrosis. Fatty degeneration noted in marginal 1/3 of liver lobule. Here abortive bile duct reaction seen. No pigment. Slight regeneration of liver epithelium, probable hepatic insufficiency.

A-1628. Subacute hepatitis with cirrhosis—icterus—hemoglobin 58 per cent—45 yrs.

Liver—autopsy weight 3590 gm.—laboratory specimen 3170 gm.

Histological specimen—liver lobulation completely destroyed by a diffuse reaction of cells and new formed stroma and bile ducts. There are focal injuries, acute and chronic. The liver cells are much degenerated and show abundant pigment and in places bile canaliculi filled with brown hyaline casts. Pigment is abundant

in phagocytes in the stroma. Pigment is seen in the epithelium of the new formed bile ducts. Mononuclears and polymorphonuclears are abundant in all parts of the section. This liver appears insufficient yet the blood fibrinogen was normal. The pigment in phagocytes gives an iron stain—only a part of the pigment in hepatic epithelium gives an iron stain.

A-976. Liver cirrhosis—alcoholism—syphilis—hemoglobin 100 per cent—41 yrs. Liver—autopsy weight 800 gm.—laboratory specimen 700 gm. Histological specimen—a coarse annular cirrhosis of moderate grade. The stroma between lobules is dense and filled with mononuclear cells and bile duct sprouts. Much liver parenchyma appears but slightly injured but there is much fatty degeneration and occasional focal necroses. The fibrinogen was subnormal (0.21 per cent) so that the liver was probably functionally subnormal.

A-709. Liver cirrhosis with fat—alcoholism—icterus—syphilis—soft blood clots—hemoglobin 92 per cent—54 yrs. Liver—autopsy weight 5280 gm.—laboratory specimen 3500 gm. Histological specimen—moderate annular portal fibrosis with some bile duct proliferation and scanty mononuclears. Pigment abundant in some cells; bile canaliculi are distended with colloid. Liver cells much injured, great amounts of fat. Some central necroses, many focal necroses. Hepatic insufficiency? The blood clots in this case were quite soft.

A-27-28. Liver cirrhosis—ascites—bronchopneumonia—46 yrs. Liver—autopsy weight 1530 gm.—laboratory specimen 1460 gm. Histological specimen—more than 1/2 of section is new bile ducts and scar tissue. Much icterus. Many leucocytes. Islands of liver parenchyma make up less than 1/2 of the section. Much necrosis of remaining liver cells. Hepatic insufficiency?

X-293. Liver cirrhosis and icterus. Liver—autopsy weight 840 gm.—laboratory specimen 825 gm. Histological specimen—portal fibrosis and duct regeneration conspicuous, possibly 3/5 of liver parenchyma in fair condition but for icteric casts in bile canaliculi. Leucocytes and polymorphonuclears in portal stroma.

A-821. Liver cirrhosis (hob-nail)—ascites—icterus—bronchopneumonia—hemoglobin 40 per cent—81 yrs. Liver—autopsy weight 1060 gm.—laboratory specimen 990 gm. Histological specimen—moderate portal fibrosis with many mononuclears; here too black granular pigment in phagocytes (malarial or coal). Iron stain negative in all cells. Some deformity of liver lobules, much of section shows hypertrophied liver lobules with good epithelium, some granular degeneration and post mortem change. Giant nuclei, much lipochrome.

X-2353. Suppurative cholangitis—portal cirrhosis—cancer of bile ducts—icterus—38 yrs.

Liver—autopsy weight 1720 gm.—laboratory specimen 1300 gm.

Histological specimen—inflammatory reaction about bile ducts and portal tissue, occasional small abscesses. Central part of lobule may show necrosis or extreme stasis of bile in bile canaliculi. Some liver epithelium fairly well preserved.

Table 25 presents a group of cases in which *severe liver injury* is present and in some instances liver insufficiency is obvious. In this liver material the hemoglobin producing factors are obviously reduced

TABLE 25
*Hemoglobin Production Factors in Abnormal Human Liver
Hepatitis and Functional Liver Insufficiency*

Number	Cause of death	Iron content human liver		Liver intake per day		Hemoglobin output per 7 days feeding		
		fresh tissue	daily intake	Human	Control	from Human	from Control	ratio Human to Control
		<i>mg. per cent</i>	<i>mg.</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>	<i>per cent</i>
A-956	Hepatitis	1.7	5	290	300	13	53	26
A-982	Hepatitis	1.8	7	360	142	27	38	28
A-905	Hepatitis	—	—	100	150	36	59	92
A-1628	Hepatitis	24.0	109	450	300	74	58	85
A-976	Cirrhosis	2.4	2	100	300	8	30	80
A-709	Cirrhosis	10.9	55	500	142	29	38	22
A-27-28	Cirrhosis	—	—	187	142	26	38	52
X-293	Cirrhosis	—	—	118	300	4	35	29
A-821	Cirrhosis	24.5	35	141	142	13	38	34
X-2353	Cholangitis	1.8	3	186	200	20	62	35
Average.....		9.6	31	243				48

below normal. The average figure is 48 per cent as compared with the normal of 162 per cent. Most of these abnormal livers are below normal weight so that if calculated for normal weight the figures would be still lower.

In one case (A-1628) the iron analyses show a high figure and a daily intake of 109 mg. Fe. This would account for about half the reaction noted in this case which is higher than the average. It is probable that there was blood destruction during the last days of life with excess storage of iron in the phagocytes and hepatic epithelium as noted in sections.

Cases of severe liver injury with anemia give the lowest values by biological assay. The concentration of hemoglobin producing factors may be less than one-fourth of normal. This invites speculation. We may say that anemia alone does not appreciably reduce these hemoglobin production factors (Table 33, Paper III). It may be argued that the anemia is due to infections or tissue or intestinal bleeding some time before death. This may in fact explain much of the anemia but we would suggest that a factor may be introduced relating to liver function. There is some evidence to indicate that the liver participates in active fashion in the preparation of parent substances for hemoglobin production. Given a serious liver dysfunction in these cases we have another cause for the anemia.

SUMMARY

Biological assay of human liver material shows various concentrations of hemoglobin producing material in various diseased states.

Cardiac congestion with red atrophy of the liver shows values (Table 21) somewhat below the human normal—94 per cent compared to 162 per cent. It is probable that this is due to atrophy and destruction of the liver cells in the centers of the liver lobules. We believe the remaining liver cells have a normal content of hemoglobin producing factors.

Amyloid (tuberculosis) and fatty (alcoholic) degeneration show (Table 22) subnormal values—111 per cent compared to 162 per cent. If we allow for the “dilution” of liver cell weight by the amyloid and fat we observe normal values for the concentration of hemoglobin producing factors.

Carcinoma growth in the liver whether primary or secondary shows net figures (Table 23) which are low—75 per cent compared to normal 162 per cent. It appears that cancer tissue, even tumor cells originating from hepatic epithelium, contains no hemoglobin producing factors. If we allow for the “dilution” of the remaining liver cells by the cancer tissue the figures are within normal limits.

Cirrhosis and hepatitis (Table 24) with no signs of true hepatic insufficiency or severe hepatic injury but death supervening from secondary infection or hemorrhage will give average normal values—164 per cent compared to normal human of 162 per cent. Icterus is not a factor.

Cirrhosis or hepatitis with severe parenchyma injury and signs of hepatic insufficiency give low values (Table 25) in biological assay—48 per cent compared to normal human 162 per cent. It may be surprising that the liver cells hold so tenaciously to these unknown factors influencing hemoglobin production but obviously only in severe liver injury is this concentration seriously reduced.