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Serum Bilirubin in Health and Disease

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1. INTRODUCTION.

During the past ten years particularly, our outlook on jaundice has been largely transferred from the color of the skin and presence or absence of bile pigment in the urine and feces to the changes occurring in the blood serum much in the same way as we have become concerned in cases of nephritis with the urea content of the blood, and in cases of diabetes mellitus with the blood sugar concentration. Responsible for this change of viewpoint is the introduction of new and more delicate methods for the detection and estimation of bilirubin in the blood serum, most notable among which has been that of Hijmans Van den Bergh, of Utrecht, Holland, whose monograph appearing in 1918, has been the inspiration for a great deal of work in various parts of the world. The popularization of his contributions has been largely accomplished among the English-speaking peoples by the publications of J. W. McNee, of the University College Hospital of London.

Ehrlich (1883-4) discovered that if a small amount of a diazonium salt in acid solution be added to an alcoholic solution of bilirubin, coupling occurred with the development of an azo dye (azo-bilirubin - a reddish violet colored dye). This dye was isolated and investigated both

chemically and spectroscopically by Proscher (1900) who pointed out even then that this apparently excellent reaction for bilirubin had not been made use of in clinical work. Thereafter the method appears to have been forgotten, until Van den Bergh applied it to blood serum. As regards the delicacy of the test, he found that a solution of 1 in 1,500,000 of pure bilirubin dissolved in alcohol still gives a positive result.

He next made the important discovery that the bilirubin in sera of cases of obstructive jaundice reacted promptly, (within one-half minute), with the diazo reagent, in contrast to that accumulating in sera in which it appeared to be hemolytic in origin. In the latter instances, a reaction occurred only after a delay, more or less long or after the protein of the serum was precipitated by two volumes of 96 per cent alcohol and the reagent was then added to the supernatant liquid, i.e. a reaction occurred "indirectly." The first or obstructive type of reaction he called direct, the second he called indirect.

The difference in this behavior of bilirubin has been attributed by various authors interested in the subject to absorption or non-absorption of the bilirubin to protein, to absorption by the lipoid constituents of the blood, to the presence or absence of bile salts in the serum, to the presence of bilirubin as an acid or in the form of the bilirubinate, et al.

The technique which has been found accurate by various authors and that used in this study is the original indirect quantitative method described by Van den Bergh and in cases of "direct" increase in the serum bilirubin, a slight modification of the method of Thannhauser and Andersen.

That the bilirubin in the blood must reach a certain concentration and be in contact with the tissues for a period of time before they take on a yellow color, has been repeatedly observed both at the bedside and in the laboratory. This fact was well known to Frerichs who in 1858 in his classical "Treatise on Diseases of the Liver," said: "When the impediment (to the outflow of bile from the liver) has its seat in the ductus choledochus, the bile first shows itself after three days by a yellow color of the conjunctivae. Its absorption into the blood takes place much earlier, but in order that the jaundiced color of the skin should become visible, a certain amount of concentration is necessary. The color makes its appearance in the renal secretion sooner than the skin, and the serous effusions in the various cavities of the body become tinged with pigment earlier than the urine. I have repeatedly found bilirubin ('cholepryrhin') in the serum of the blood, and in effusions into the abdominal and thoracic cavities, where no traces of a jaundiced tint had been present either in the urine or in the skin." Hence, it becomes at once manifest, that unless

serum bilirubin estimations be made, transient increases, having the diagnostic equivalence of actual jaundice, may be overlooked. That such transient increases in the serum bilirubin do occur unaccompanied by bilirubinuria or tissue icterus has been observed on numerous occasions during attacks of gallstone colic.

Van den Bergh has shown that there is a definite renal threshold value for the direct or obstructive type of serum bilirubin, viz. a concentration of 2 mg. per 100 c.c. serum. The threshhold value for the indirect type of serum bilirubin is as yet unknown but apparently considerably higher than 2 mg. per cent. When in a lesion tending to produce an obstructive type of jaundice, the serum bilirubin exceeds 2 mg. per cent, bilirubinuria occurs just as ordinarily glycosuria results when the concentration of sugar in the blood exceeds 180 mg. per cent. As the upper limit of normal may safely be considered as 1 mg. per cent, various observers have recognized the existence of so-called "latent jaundice" with values ordinarily between 1 and 2 mg. per cent bilirubin. A state of latent jaundice may exist for some time before actual clinical jaundice occurs. The recognition of such a state may be of considerable aid in diagnosis, and in cases receiving neo-arsephenamine an occasional fatal outcome due to arsenical hepatitis and jaundice may be averted by prompt cessation of treatment.

The intensity of tissue icterus is no measure of the degree of jaundice present. This is explained by the fact that the tissues hold the pigment when once they are stained with it for some time, even after the lesion producing jaundice has been removed, or the serum bilirubin has diminished for other reasons. In the case of the skin, Frerichs offered the explanation that the deepest layer of the epidermis is stained and the coloration disappears only after it has been shed as the outermost layer. In the case of other tissues of the body, the cause for this retention or absorption of the pigment is not known.

The color of the skin may be misleading in that its yellowish tint may be due to the increase in the circulation of pigments other than bilirubin. It is well known that some people normally have a yellowish skin which has been found in instances to correspond with an increase in the chromolipoid content of the blood, particularly as regards carotin, the yellow pigment present in carrots and many other vegetables and plants. In patients affected with diabetes mellitus, who have been on a high vegetable diet, carotinemia with its yellow skin discoloration is frequently seen, a condition originally called xanthosis diabetica by Umber and Von Noorden. Similarly, a waxy coloration of the skin may be present in cases of chronic nephritis in which the serum bilirubin is notoriously low. In certain cases of carcinoma with a low serum bilirubin value, a yellowish dis-

coloration of the skin may be noted which may be very difficult to differentiate clinically from cases of pernicious anemia in whom the serum bilirubin level is almost always high.

11. THE FORMATION OF BILIRUBIN.

In 1847, Virchow discovered in old hemorrhages a pigment which resembled bilirubin. He was unable to satisfy himself that this pigment was identical with bilirubin, and he therefore gave it the name haematoidin. He expressed the belief that the pigment was derived from the hemoglobin of disintegrated red blood cells. Many subsequent investigators have confirmed the observation that when red blood cells escape from the blood vessels into almost any tissue of the body, the pigment designated by Virchow as haemotoidin is formed. It has been found e.g. in hemorrhagic pleural, peritoneal and spinal fluids. It has been shown to form in the body following experimental injection of defibrinated blood or crystalline hemoglobin subcutaneously, intraperitoneally et al.

It has since been definitely shown that hematoidin is the same as bilirubin, recently particulary by Rich. Van den Bergh has by means of the diazo reaction shown bilirubin to be formed following the injection of blood beneath the scalp of a dog, and this author has recovered a concentration of 25 mg. per cent in fluid obtained from a traumatic

subdural hematoma - a concentration equivalent to the bilirubin content of the gall bladder.

The identity of bilirubin and hematoidin and their production from hemoglobin extrahepatically, suggest very strongly that the liver may not be necessary for the formation of bilirubin in the animal body. That such is the case has been shown by Mann and his co-workers at the Mayo Institute, who have found that bile pigment may accumulate to the point of producing bilirubinuria and staining the sclerotics and mucous membranes, after total extirpation of the liver in dogs. If solutions of hemoglobin are injected intravenously in such animals, there is a more rapid and greater accumulation of bile pigment. They have shown through the use of spectrophotometry that bilirubin is formed chiefly in the bone marrow and spleen, and to a very slight extent in the liver, the function of the latter being apparently chiefly one of excretion of bilirubin rather than formation, much like the excretion of urea by the kidneys. The formation of bilirubin from hemoglobin and its production in the bone marrow and spleen (and to a slight extent in the liver) suggests very strongly the reticulo-endothelial system as the actual site of bilirubin production.

That the spleen of man may produce bilirubin has been shown by a number of observers, and four such instances were met with in this study. Three were instances of hemolytic jaundice in which the splenic and peripheral

blood contained 6.2 mg. and 4 mg., 10.7 mg. and 6.2 mg., and 4.2 and 2.4 mg. % of bilirubin respectively. The other was a case of purpura hemorrhagica, the splenic artery and peripheral venous blood containing 0.25 mg. per-cent, while blood gently expressed from the spleen contained 0.6 mg. per cent.

111. METHOD USED

The bile pigment content of the blood in the following study was estimated by the Van den Bergh method, the original technic being employed in cases showing a delayed (more than one minute) or indirect reaction; the principle of Thannhauser and Andersen was employed in cases showing a prompt reaction, the original ferric thiocyanate solution of Van den Bergh being employed as a quantitative standard. That no difference in the quantitative readings in cases showing only an indirect or delayed reaction occurs whether Van den Bergh's original method or that of Thannhauser and Andersen is used was noted by the last named and was also determined in this study. The readings are designated in milligrams per hundred cubic centimeters of serum, as others have done, instead of the unit or 1 in 200,000 parts of serum originally designated by Van den Bergh, 0.5 mg. per hundred cubic centimeters being the equivalent of 1 unit. As some difficulty was experienced in making readings of less than 0.2 mg. per cent, these are all designated as - 0.2 mg. per cent. As

it has been found, as was emphasized by Lepehne, that serum bilirubin tends to diminish on standing, because of oxidation to biliverdin, estimations were made within from one to two hours after the blood was obtained. Specimens kept in the dark and on ice show practically no diminution over night. No differences in the readings were noted whether plasms or serum was used, as others have experienced.

Biphasic reactions described by Feigl and Querner have been included under the direct reactions for reasons similar to those of Andrewes (McNee and Keefer). It is felt that they represent quantitative transitions between the indirect and the direct reactions, having been encountered early in experimental ligation of the common duct and late in cases of catarrhal jaundice in the course of this study. Greene also does not consider such a reaction separately.

IV. NORMAL SERUM BILIRUBIN

The Van den Bergh reaction was applied to the blood of 202 "normals" of the following age groups:

From 5 months to 9 years	11
From 10 to 19 years	11
From 20 to 29 years	101
From 30 to 39 years	28
From 40 to 49 years	24
From 50 to 59 years	20
From 60 to 69 years	7

The group of normals was composed of 112 medical students, interns and nurses in good health (most of whom had had a recent physical examination); twenty-six individuals above 30 years of ago found tc be normal at the Pay-Health Clinic conducted under the auspices of The United Jewish Social Agencies; forty-six inmates of Longview Hospital for the Insane (twenty-seven males, nineteen females), normal physically but affected with a psychosis other than alcoholic; twelve children, five in the pediatrics service of the Cincinnati General Hospital for gonorrheal vaginitis, five at the Branch Hospital for Tuberculosis on account of a "contact history", and two examined in private life; and six relatives of the four individuals giving the highest values.

In 193, or 95.54 per cent of the normals, the value of serum bilirubin was less than 0.6 mg.; in six, or 2.97 per cent, it was between 0.6 and 0.9 mg., and in three, or 1.49 per cent, between 1.0 and 1.5 mg. The relative values in the two sexes and the total percentage frequency of any given value or less are illustrated in table 1.

Table 1. Relative Values and Total Percentage Frequency of Any Given Value or Less

Mg. Bilirubin*	Per cent Males	Per cent Females	Total per cent having given value or less
-0.2	28.2	47.0	34.15
0.2 - 0.29	30.4	26.5	63.36
0.3 - 0.39	19.0	14.0	80.69
0.4 - 0.49	8.7	8.0	89.1
0.5 - 0.59	8.7	1.5	95.54
0.6 - 0.69	0.0	1.5	96.03
0.7 - 0.79	2.1	1.5	98.01
0.8 - 0.89	0.72	0.0	98.51
0.9 - 0.99	0.0	0.0	.....
1.0 - 1.5	2.1	0.0	100.0

* Blood taken from one to four hours after a meal. The value of milligrams of bilirubin denotes the amount per hundred cubic centimeters of serum. The reactions were all indirect.

This table would indicate that the level of serum bilirubin is relatively higher in males than in females, for in thirty, or 47 per cent, of the females, the bilirubin value was less than 0.2 mg. in contrast to thirty-eight or 28.2 per cent of the males, and in three females, or 4.5 per cent, above 0.5 mg., in contrast to nineteen males, or 13.6 per cent above this level. The four values above 0.8 mg. were limited to the males. No distinct differences were observed in the various age groups. The blood from the umbilical cord of thirteen new-born infants was examined in addition, and the physiologic hyperbilirubinemia described by Van den Bergh and others was encountered, the readings being in the vicinity of 1 mg. or more.

That the value of the serum bilirubin is not absolutely constant was first shown by Gilbert and Herscher, who found it to increase somewhat during fasting. The blood of three of the normal individuals here studied was examined daily before breakfast for one week, a maximum variation of 0.2 mg. being noted. Förster and Förstner, who examined eighteen individuals with various diseases under the foregoing conditions, employing the technic of Ernst and Förster, found a variation generally between 0.1 and 0.3 mg. On examining twenty-one individuals before breakfast, two hours after the noon meal, and before the evening meal, they found the highest values generally, but not always, before breakfast. The fluctuations were generally from 0.1 to 0.2 mg. Broun et al. found a variation of as high as 0.5 mg. in a normal individual, the blood being taken before breakfast, before dinner (12:00) and at 4:00 P.M. According to Meyer and Knüpffer, the blood bilirubin diminished in quantity from two to five hours after meals, and increases after eight hours, apparently on the basis that during digestion bilirubin is excreted from the blood (Förster and Förstner).

As 98 per cent of the normal patients had a value of approximately 0.8 mg. or less, 1 mg. may be safely considered the upper limit of normal, thus allowing 0.2 mg. for fluctuation during the day and from day to day. As a value of 0.6 and 1 mg. was exceeded in only 4.5 per cent of the cases, any value between 0.6 and 1 mg. should be considered

as possibly indicative of an increase, particularly as the latter figure is approached. In his monograph, Van den Bergh states that in the vast majority of healthy individuals the values found are between 0.25 and 0.4 mg. (from 1 to 400,000 to 1 to 250,000). In a latter paper published in France, he gives figures for the bilirubin content of normal human serum of from 0.1 mg. to 0.25 mg. (1:1,000,000 to 1:400,000), which have been accepted by Lepehne, McNee, Ravdin et al. Lepehne found the average figure in a series of patients not suffering from jaundice to be 0.15 mg. McNee obtained similar results. Botzian and Wiemer also consider the upper limit of normal 0.75 mg., Mandelbaum, 0.62 mg. (1.25 units) and Haselhorst, 0.5 mg. (1 unit). Strauss and Buerlmann found values between 0.15 and 0.55 mg. in fifty normal patients, with an average of 0.3 mg. Förster and Förstner consider 1 mg. as the upper limit of normal. Greene and his co-workers at the Mayo Clinic consider 0.2 mg. as the maximum normal. This limit takes care of instances of familial cholemia.

Particular attention was paid to the four individuals (medical students) with the highest values of serum bilirubin - 0.8, 1.1, 1.25 and 1.5 mg., respectively - who represent what Gilbert and Lereboullet, in 1906, called simple familial cholemia and what Van den Bergh spoke of as physiologic hyperbilirubinemia. In all four there was a yellowish cast to the skin, and the periphery of the sclerae

was slightly icteric. In none was the liver or spleen felt. None had ever noticed or had ever been told that he was distinctly jaundiced, except patient 4, who on one occasion, two years ago, had been told that his skin was yellow. There was no instance of unexplained pruritis or definite bradycardia. The specimens of urine were entirely normal, except for the presence of urobilin in traces in two of the individuals and in marked excess in the other two. A questionable increase in erythrocytic fragility was noted in one. A relatively high red cell count was present in three. Van den Bergh has occasionally encountered a palpable spleen in addition to urobilinuria in similar cases and feels that such cases border on chronic hemolytic jaundice. He found the disease more common among the Jewish race and generally encountered values of 1.1 and 1.25 mg.

Table 2. Data of Four Patients Having Highest Serum Bilirubin

No.	Mg. Bil.	Icterus Index *	R.B.C.	Hb. %	Reticulated Cells %	Urobilinuria	Erythrocytic Fragility **	Retention of Bromsulphalein ‡
1	1.5	14	6,4	90	0.25	++	0.44 - 0.36	0
2x	1.25	11	6,0	85	0.2	Trace	0.44 - 0.38	0
3	1.1	12	5,6	90	1.0	++	0.42 - 0.36	0
4	0.8	9	6,0	85	0.1	Trace	0.44 - 0.36	0
							0.42 - 0.34 (control)	

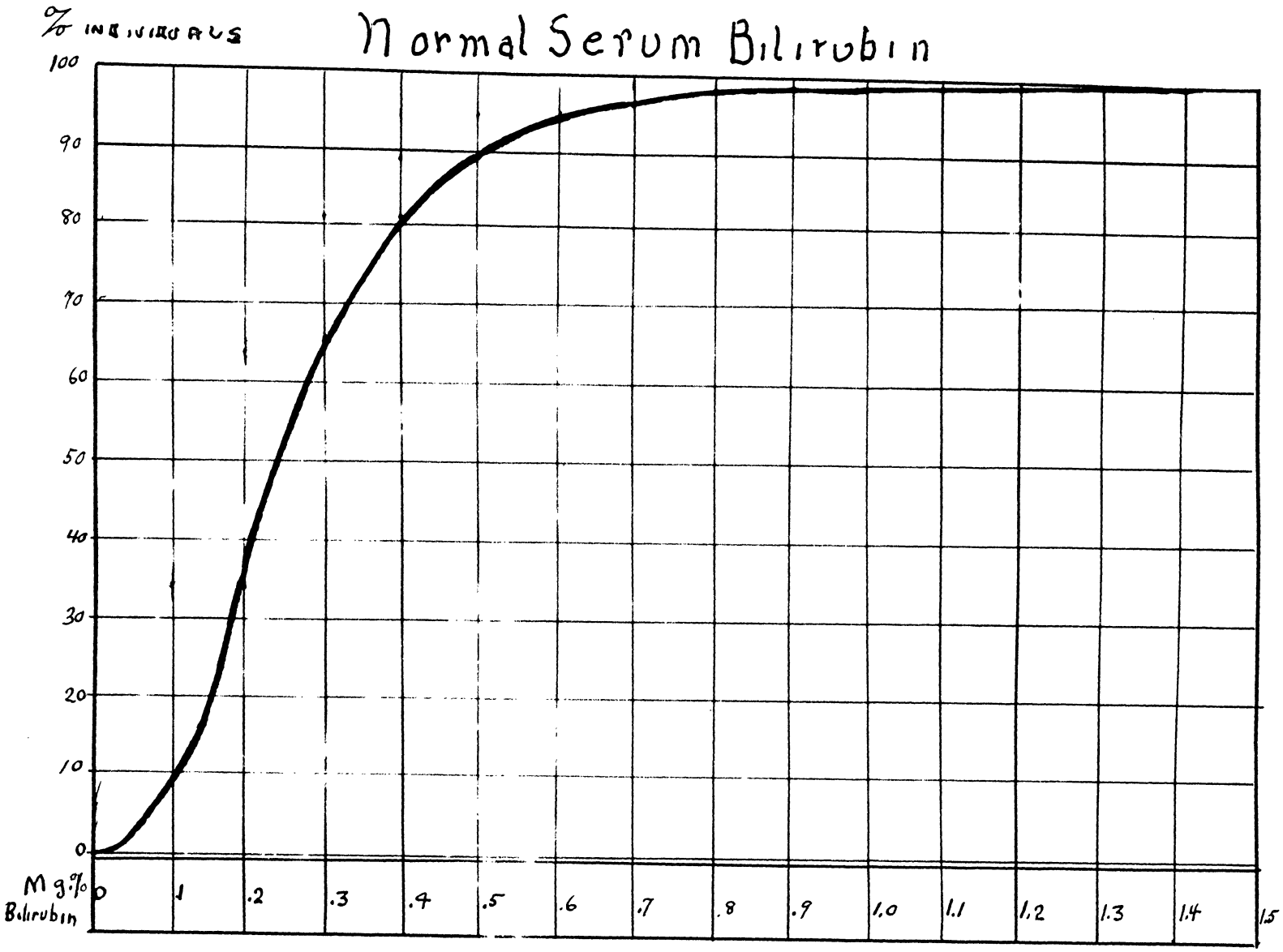
* Method of A. R. Bernheim (Icterus Index, J.A.M.A. 82:291, Jan. 26, 1924)

** Technic of Giffin and Sanford (J. Lab. & Clin. Med. 4:465, 1918-1919)

‡ Retention in one-half hour. Technic of Rosenthal and White (Clinical Application of Bromsulphalein Test for Hepatic Function, J.A.M.A. 84:1112, April 11, 1925)

x Jewish patient.

Normal Serum Bilirubin



The relative higher values of serum bilirubin in males than in females, as well as in the newborn, the fact that hemoglobin is apparently the mother substance of bilirubin, and the consistently low values encountered in secondary anemia, suggest a quantitative relationship between serum bilirubin and quantity of hemoglobin and number of red cells. A comparative study was accordingly undertaken between these factors in 110 individuals free of organic disease of the liver or biliary tract and in fairly good general health. The individuals were sent in for observation and study by the "Krankenkasse" of Munich to the medical service of Professor Von Mueller of the University of Munich ("Krankenhaus Links der Isar") and were diagnosed mostly as psychoneurosis or neurasthenia. The results obtained are thus tabulated:

Table 3. Hemoglobin and Serum Bilirubin

	No.	Av. HB.	Av. R.b.c.	Av. Serum Bilirubin (mg. %).	K= $\frac{\%\ \text{Bil.}}{\%\ \text{Hb.}}$
Males Fasting	11	76	4.5+	0.23 (var. ± 0.1)	0.3
Females Fasting	11	72	4.5	0.26 (var. ± 0.05)	0.36
Males Fasting	14	85	5.2	0.38 (var. ± 0.1)	0.45
Males Fasting	6	101	5.8+	0.47 (var. ± 0.1)	0.47
Males 2 1/2 - 3 1/2 hrs. p.c.	12	74.5	4.5+	0.16 (var. ± 0.05)	0.21
Females 2 1/2 t 3 1/2 hrs. p.c.	28	73.5	4.4+	0.14 (var. ± 0.06)	0.19
Males 2 1/2 to 3 1/2 hrs. p.c.	22	85	5.2	0.24 (var. ± 0.1)	0.28
Males 2 1/2 - 3 1/2 hrs. p.c.	6	98	5.8+	0.32 (var. ± 0.15)	0.33
TOTAL	110				

The figures suggest some quantitative relationship between hemoglobin and serum bilirubin and also substantiate the finding of Gilbert and Herscher of a higher serum bilirubin value during fasting.

It was also thought that the relationship should further be studied at a high altitude because of resultant polycythemia and accordingly a trip was made to the Jungfraujoch Hotel in Switzerland which is situated at an altitude of approximately 10,000 feet above sea level. (Unfortunately warning of high altitude studies only at 14,000 feet or higher was not known at the time the study was undertaken).

Jungfrau Results

No.	Time	Pt.	Hb. %	R.B.C.	Serum Bilirubin
1	3:10 P.M.	P.I.	72	3,9	0.12
2	4:00 P.M.	P.R.	76	4,2	0.1
3	8:30 A.M.	A.M.	99	6,3	0.70
4	9:10 A.M.	A.J.	88	5,6	0.36
5	9:50 A.M.	G.B.	70	4,3	0.10
6	10:00 A.M.	M.B.	89	5,5	0.46
7	12:15 P.M.	H.J.	87	5,7	0.22
8	12:45 P.M.	H.H.	83	5,0	0.25
9	1:10 P.M.	F.B.	88	5,5	0.10
10	1:20 P.M.	C.B.	88	5,6	0.52

As will be noted from the chart, a high degree of polycythemia was not encountered. This may be due to the fact that the individuals studied -- hotel or mountain railway employees -- are in the habit of going down to the valleys every two or three weeks and also because of the insufficiently high altitude at which the study was made. Professor Naegele of Zurich afterwards told the author that polycythemia at high altitudes is not as frequent as generally supposed. Interestingly enough, the highest serum bilirubin value was encountered in the individual with the highest hemoglobin value and greatest number of red cells, tho a direct relationship was not uniformly encountered.

V. PREGNANCY AND THE NEWBORN.

Observations were made on twenty-one pregnant women attending the pre-natal clinic of the Out-Patient Dispensary. The duration of pregnancy at the time the determinations were made ranged from five to nine months, while the highest value obtained, 0.4 mg. per cent, occurred at eight months of pregnancy. No constant relationship was noted between the height of the serum bilirubin and the duration of pregnancy.

Eufinger and Bader examined one hundred and twenty-three healthy pregnant women, (1) during their pregnancy, (2) during labor and (3) on the eighth day following delivery. They found during pregnancy, thirty-five or 28

per cent, a value exceeding 0.25 mg. per cent (0.5 unit, which they consider the upper limit of normal). In the twenty-one cases here studied, a value exceeding 0.25 mg. was encountered five times or in 23.8 per cent of the cases. They found that such a value becomes more frequent as the pregnancy is of longer duration; and that towards the end of pregnancy, is of over 0.5 mg. per cent (indirect only) is seen. They found a direct reaction present in 5 per cent of their cases during labor (one a case of associated cardiac decompensation), and feel therefore that the term "Geburtsleber" coined by Walthard is justifiable. They state that a rapid decline in the serum bilirubin occurs within a week after delivery. They feel that while a direct reaction may occur during labor with no prognostic significance, its occurrence previous to parturition is indicative of hepatic injury and that in eclampsia and hyperemesis the degree of bilirubinemia is a measure of the severity of the ailment.

Determinations were made on the cord blood of thirteen newborn infants normally delivered on the obstetrical service of the General Hospital. As Van den Bergh, Ada Hirsch, and Yippo have found, a distinct tendency towards hyperbilirubinemia was encountered. In eight, the value exceeded 1 mg. per cent, the highest reading being 1.8 mg. per cent, in four the value ranged between 0.6 and 0.9 mg. per cent and in one, the lowest reading, a value of 0.4

Pregnancy

No.	Age	Months duration pregnancy	Mg. bilirubin indirect
1	25	4	-0.2
2	21	5	-0.2
3	20	5	0.3
4	20	5	-0.2
5	20	5	0.3
6	18	6	-0.2
7	21	6	-0.2
8	34	6	0.2
9	16	6	-0.2
10	26	7	-0.2
11	31	7	-0.2
12	31	8	0.2
13	25	8	-0.2
14	19	8	-0.2
15	27	8	0.4
16	19	8	0.3
17	38	8	-0.2
18	16	8	-0.2
19	25	8	0.2
20	24	9	0.3
21	19	9	0.2

mg. per cent. Ada Hirsch found values between 1 and 3.3 mg. per cent. The lowest value met with by her was 0.62 mg. per cent (1:160,000). Van den Bergh and Westrienen found the serum of the newborn infant always to be more yellow than that of the mother or of normal adults, and felt therefore that the hyperbilirubinemia existing at birth was foetal in source. Ada Hirsch showed the bilirubin content of cord blood to be greater than that of the serum of normal adults and also that during the first twelve hours after birth the bilirubin content of the infant's blood rises quickly, reaching a maximum on the second or third day. After this period, the bilirubin content either sinks rapidly in which case no icterus develops, or remains elevated whence icterus neonatorum develops - (Van den Bergh). Yippo has confirmed the above observations with spectrophotometric methods.

Van den Bergh and Westrienen also found that after two weeks of life, the serum bilirubin content was the same as that of older children.

As bilirubin is formed from hemoglobin, and as a polycythemia exists at birth, the existence of a hyperbilirubinemia at birth may thus be accounted for. The increases during the first two days may be explained by the increased erythrocytic destruction occurring then.

Newborn Infants

No.	Sex	Color	Mg. Bilirubin Indirect
1	F	W	1.2
2	F	W	1.3
3	F	W	1.0
4	M	W	1.1
5	M	W	0.9
6	M	W	0.4
7	F	B	0.9
8	F	B	0.8
9	F	B	1.0
10	F	B	1.8
11	F	B	1.0
12	M	B	1.2
13	M	B	0.9

VI. DISEASES OF THE LIVER AND BILIARY TRACT

A. TERTIARY SYPHILIS OF THE LIVER.

The series included twenty four cases; the diagnoses being based on the criteria set forth by Rolleston and McCrae and Caven. Jaundice was encountered in eleven or 45% of the cases in agreement with McCrae's and Caven's experience of forty instances in their one hundred cases. In only one instance was a pure latent state of icterus encountered (No. 15). The jaundice present was of a mild degree, an average of 3.4 mg. % bilirubin .

Six of the thirteen patients without jaundice had experienced one or more hematemeses in the past and presented a severe degree of secondary anemia. In contrast, only one of the eleven jaundiced patients had had a hematemesis prior to the occurrence of the jaundice, and in only three (patient 17had vomited blood just prior to admission) did a severe secondary anemia exist. In nine of the thirteen cases not showing jaundice, a hyperbilirubinemia was absent, in spite of considerable enlargement of the liver.

B. PORTAL (ALCOHOLIC) CIRRHOSIS HEPATIS.

Three instances of this disease were encountered in contrast with the much more frequent cases of hepatic syphilis.

Tertiary Syphilis of the Liver

Number	Age	Hematemesis	Ascites	Liver (Rt. M.C.L.)	Spleen	Blood Wassermann	Pathological Diagnosis	R.B.C.	HB. %	Jaundice	Mg. Bilirubin Direct	Mg. Bilirubin Indirect
1	43	+	+	14 cm.	9 cm.	4+	-	2,1	35	-	-	0.4
2	34	+	0	5 cm.	4 cm.	4+	-	2,8	50	-	-	0.45
3	42	+	+	4 cm.	Edge	+	-	2,4	50	-	-	0.5
4	38	+	+	-	4 cm.	4+	-	2,2	30	-	-	0.65
5	42	+	+	-	-	4+	+	2,5		-	-	0.3
6	56	+		-	-	-	-	2,9	50	-	-	-0.2
7	43	0	0	8 cm.	Edge	..	+	4,7	90	-	-	-0.2
8	24	0	0	4 cm.	-	4+	-	4,8	87	-	-	-0.2
9	52	0	+	3 cm.	1 cm.	-	+	3,8	50	-	-	0.4
10	48	0	+	6 cm.	Edge	4+	-	4,5	85	-	-	0.6
11	27	0	0	2 cm.	-	-	-	4,3	70	-	-	0.3
12	30	0	0	5 cm.	-	+	-	4,4	75	-	-	-0.2
13	58	0	+	-	0	-	-	3,9	70	+	-	1.75
14	42	0	0	12 cm.	0	-	+	4,8	80	+	-	1.5
15	37	0	0	10 cm.	4 cm.	+	-	4,2	85	-	-	1.5
16	30	+	+	4 cm.	2 cm.	4+	-	2,3	35	+	+	...
17	44	0	+	8 cm.	-	4+	+	2,9	55	+	2.5	...
18	41	0	+	8 cm.	-	+	-	4,0	85	+	7.0	...
19	39	0	0	11 cm.	8 cm.	-	-	3,4	70	+	6.5	...
20	60	+	0	-	-	-	+	3,7	45	+	2.5	...
21	21	0	0	5 cm.	2 cm.	4+	-	4,6	80	+	6.0	...
22	53	0	+	3 cm.	Edge	-	-	3,8	68	+	2.5	...
23	60	0	+	5 cm.	Edge	4+	-	2,1	50	+	2.2	...
24	54	0	+	9 cm.	-	4+	+	3,1	70	+	1.9	...

Portal (Alcoholic) Cirrhosis Hepatis

Number	Age	Hematemesis	Ascites	Liver (Rt. M.C.L.)	Spleen	Blood Wassermann	Pathological Diagnosis	R.B.C.	HB. %	Jaundice	Mg. Bilirubin Direct	Mg. Bilirubin Indirect
1	54	0	+	8 cm.	4 cm.	-	-	4,1	70	-	-	0.5
2	55	0	++	-	-	-	++	4,0	70	++	-	1.5
3	45	0	+	Edge	-	-	+	2,2	..	+	4.3	...

C. MALIGNANT DISEASE OF THE LIVER.

There were nineteen cases, eight with jaundice and eleven without. Among those without jaundice, there were only two relatively high values, viz., 0.75 and 1 mg., the remainder being 0.6 mg. or less. In eleven cases of carcinoma of the liver without jaundice (diagnosis pathologically confirmed) Greene and his associates found two presenting bilirubin values above 2 mg. and three showing values between 0.9 and 1.6 mg. They feel that while the determination of serum bilirubin may not show any increase in some cases, it is nevertheless of definite value in the early diagnosis of carcinoma of the liver.

The absence of hyperbilirubinemia in the presence of hepatic malignant disease has also been noted by Lepehne, Meulengracht, and Andrewes. In the five cases showing the lowest readings in bilirubin, a severe secondary anemia was present. In four of Greene's eleven cases in which the values were 0.2 mg. or less, a severe secondary anemia existed in three. On the other hand, it is of interest to note that a severe secondary anemia was not present in five of the seven cases showing jaundice in which counts were recorded, and in all fourteen of such cases reported by Greene.

While it is realized "that more than three-fourths of the liver can be abruptly obstructed without

causing even a ripple on the clinical surface of things" (Rous and McMaster), , a relationship of the level of the serum bilirubin as well as the occurrence of jaundice in cases of malignant disease of the liver to the amount of circulating hemoglobin and blood cells appears to be suggested.

It is of great interest to note a fall in serum bilirubin in one of the cases (carcinoma), accompanying a drop in the hemoglobin and in the number of red cells. Greene has also seen the serum bilirubin fall in malignant disease of the liver.

Malignant Disease of the Liver.

No.	Age	Liver (Rt. M.C.L)	R.B.C.	HB %	Primary Site	Mg. Bilirubin Dir.	Indir.	Jaundice	Pathological Diagnosis
1	73	10 cm.	3,9	75	Stomach	-	0.3	-	+ (N)
2	65	4 cm.	4,8	80	Breast	-	0.3	-	- (N)
3	35	11 cm.	4,5	90	Pancreas	-	0.55	-	+ (N)
4	71	10 cm.	4,3	65	Stomach	-	0.75	-	-
5	81	4 cm.	4,1	90	Stomach	-	0.25	-	-
6	48	2 cm.	2,4	35	Stomach	-	0.25	-	+ (B)
7	26	4 cm.	2,6	35	Stomach	-	-0.2	-	+ (B)
8	57	15 cm.	4,5	80	Gall Bladder	-	-0.2	-	+ (N)
9	47	6 cm.	3,6	80	Liver	-	1.0	-	+ (N)
			1,3	30	(hepatoma)	-	-0.2	-	
10	4½ mos.		1,7	55	Liver (hepatoms)	-	0.6	-	+ (N)
11	67	10 cm.	4,0	85	Stomach	+	...	+	+ (N)
12	45	11 cm.	4,3	50	Pancreas	+	...	+	+ (N)
13	56	10 cm.	...	80	Undetermined	3.1	...	+	+ (B)
14	70	15 cm.	4,0	70	Bile Duct	19.5	...	+	+ (N)
15	69	4 cm.	3,2	70	Gall Bladder	15.0	...	+	+ (B)
16	68	2 cm.	...	75	Stomach	20.0	...	+	+ (B)
17	66	Nodular	3,9	60	Iris	4.6	-	+	+ (N)
18	71	2 cm.	5,2	70	Gall Bladder	40.0	...	+	+ (N)
19	43	6 cm.	2,0	40	Stomach	-	-.02	+	-

D. CHRONIC VENOUS ENGORGEMENT OF THE LIVER.

There were twenty-three cases of congestive heart failure - five rheumatic (four mitral lesions and one adherent pericardium); five syphilitic (aortic insufficiency); five hypertensive; six arteriosclerotic; one mitral and tricuspid insufficiency (etiology?) and one of auricular fibrillation associated with a toxic thyroid adenoma.

The higher values were more frequently encountered in the mitral lesions, an experience similar to that of Fishberg and of Meulengracht, the latter author using the icterus index. In eleven patients, the values were 0.65 mg. or below; of these, nine improved and two died. Of five with a value between 1.0 and 1.35 mg., two were improved and three died. The remaining readings were above 2.0 mg. (five direct increases and two indirect increases); both of the patients having indirect increases and three having direct increases died. The highest value obtained was 4.6 mg. in a case that proved fatal. No bilirubinuria was present in the two patients giving an indirect increase, while bilirubinuria was present in the five giving the direct reaction; there was thus a virtual hemolytic and obstructive type of jaundice present.

The two types of jaundice in circulatory failure have also been encountered by Meakins, Greene et al. The former author states that he has seen the direct type of bilirubin increase only in the presence of an associated tricuspid insufficiency.

Meakins has emphasized the distribution of the biliary pigmentation as being confined to the head and upper parts of the body and being absent over areas where oedema is present. He has further compared the bile pigment content of oedema fluid and serum in six cases showing the "direct" type of hyperbilirubinemia and found that there was either no or very little bilirubin in the oedema fluid though there was no difference in crystalloid content of the two fluids. He feels that two hypotheses present themselves by way of explanation "(1) that the permeable membrane between the capillary blood stream and tissue spaces is impermeable to bile pigments and (2) that there is such a gross interference with the blood flow through the tissues in circulatory failure that the contents of the tissue spaces remain uninfluenced by changes in the character of the blood plasma".

Sections of the livers of the two patients with the hemolytic type of jaundice and of two with the obstructive type were examined by Dr. Richard Austin, but

they did not reveal any especial difference in the pathologic picture. All presented a chronic passive congestion with hemorrhage. None of the cases showed demonstrable pulmonary infarcts; their relationship to the jaundice occurring in myocardial insufficiency has been noted by a number of authors (Eppinger, Libman, Keefer and Resnik and Rich and Resnik. In two instances of jaundice developing after pulmonary infarction, Keefer and Resnik obtained a direct reaction of 2.5 mg.

The mortality in the foregoing cases appears to be directly proportional to the height of the serum bilirubin, an experience similar to that of Bernheim and others, as shown in the table below.

Thus, in virtually one out of five cases with a value of less than 1.0 mg. the outcome was fatal, in contrast to two out of three with a value of 1.0 and more.

In nine of twelve cases showing definite hepatic enlargement, the value of the serum bilirubin was 1 mg. or over. However, the remaining three patients (two with the liver 10 cm. below the costal margin), who had a value of only 0.6 mg. or less, all recovered, thus illustrating the fact that hepatic enlargment does not necessarily signify retention of bilirubin; similar results have been noted by Fishberg and Andrews. There was no instance of definite hyperbilirubinemia in the

eight cases that did not show enlargement of the liver. Brule and Fishberg, however, have noted such an increase in the absence of hepatic enlargement in cases of cardiac decompensation. Lepehne and Fishberg have noted that the high values of blood bilirubin occurring in cardiac insufficiency are lowered with an improvement in compensation.

PROPORTION OF MORTALITY TO HEIGHT OF SERUM BILIRUBIN

Mg. Bilirubin	No. Cases	Mortality
Less than 1.0	11	18.1%
1.0 and over	12	66.6%

Congestive Heart Failure
(Chronic Venous Engorgement of the Liver)

No.	Age	Liver	R.B.C.	HB %	Jaundice	Died	Mg. Bilirubin Direct	Mg. Bilirubin Indirect	Etiology
1	27	10 cm.	5,1	70	+	+	2.25	...	Rheumatic
2	30	6 cm.	4,4	90	+	+	2.8	...	Rheumatic
3	42	10 cm.	4,2	60	+	+	-	2.5	Rheumatic
4	16	4 cm.	4,4	70	+	+	-	2.5	Rheumatic
5	32	Edge	5,8	90	-	-	-	1.0	Rheumatic
6	48	10 cm.	4,1	70	-	-	-	0.5	Luetic
7	43		3,8	70	-	-	-	0.3	Luetic
8	48	10 cm.	5,3	70	-	-	-	0.25	Luetic
9	49	10 cm.	4,2	70	+	+	4.6	...	Luetic
10	32	4 cm.	4,0	80	+	-	3.0	...	Luetic
11	52	6 cm.	3,6	80	-	-	-	1.25	Hypertensive
12	64	8 cm.	4,1	70	-	+	-	1.0	Hypertensive
13	57	6 cm.	4,9	90	-	-	-	0.5	Hypertensive
14	56	-	5,0	80	-	+	-	0.65	Hypertensive
15	41	10 cm.	5,4	80	-	+	-	1.0	Hypertensive
16	60	-	5,4	80	-	-	-	0.5	Arterioscl.
17	61	-	3,9	70	-	-	-	-0.2	Arterioscl.
18	72	-	4,5	90	-	-	-	0.25	Arterioscl.
19	58	-	5,2	80	-	+	-	0.4	Arterioscl.
20	62	-	3,9	70	-	-	-	-0.2	Arterioscl.
21	65	4 cm.	4,7	94	+	-	2.5	...	Arterioscl.
22	43	10 cm.	5,7	80	-	+	-	1.35	Mitral and tri cusp. Insuff.
23	68	-	4,3	80	-	-	-	0.3	Toxic Goitre (Auricular Fibrillation)

2. [illegible] EFFECTIVE HEPATIC [illegible] IN [illegible].

Twenty-four cases of acute catarrhal jaundice were studied, serial estimations being made from day to day in five. The mean value during the first week of jaundice was approximately 17.2 mg., the second week, an average of approximately 10.3 mg., and during the third week an average of 4.9 mg. %. In the light of these estimations, the mechanism of acute catarrhal jaundice appears frequently to be one of sudden marked disablement of the liver in regard to the excretion of bilirubin with subsequent rapid resumption of function. This is in accord with the "two distinct phases" of the disease described by Jones and Minot in an extensive study of twenty-six cases, who also found the concentration of serum bilirubin during the disease to be a reciprocal of the concentration of bile pigment in the duodenum.

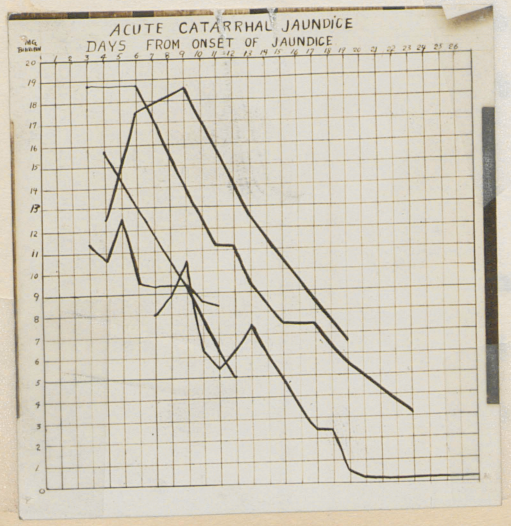
Thirteen cases were seen during the first week of jaundice; hepatic enlargement being detected in ten and splenic enlargement in five. The average value of bilirubin in the three cases showing only hepatic enlargement was 13.04 mg., while the average value in the four cases showing both splenic and hepatic enlargement was 17.09 mg. %. In sharp contrast to this is the average

of 7.10 mg.% in the five cases showing neither apparent hepatic nor splenic enlargement, in which determinations were also made during the first week of jaundice. This suggests that the swollen condition of the liver may indicate a greater degree of functional impairment in regard to the excretion of bilirubin.

While all the reactions in this series of cases were of the direct type, Schiff and Eliasberg, in studying a group of thirty cases occurring in children during the winter of 1921 and 1922, found that between October, 1921, and January, 1922, all the serums gave the delayed direct reaction only, whereas a prompt direct reaction was obtained in all subsequent cases, without the least apparent change in the clinical picture.

Acute Catarrhal Jaundice.

No.	Age	Liver (Rt. M.C.L.)	Spleen	Day of Jaundice	Mg. Bil. Direct
1	9	6 cm.	0	9	6.5
2	25	0	0	10	10.0
3	6	0	0	4	7.0
4	40	9 cm.	Edge on inspiration	21	4.0
5	37	1.5 cm.	0	6	15.6
				14	18.7
6	26	0	0	Day preceding	4.0
7	36	0	0	7	10.0
8	33	4 cm.	0	24	2.7
9	15	2 cm.	Edge	4	12.0
10	42	8 cm.	0	25	3.0
11	19	2 cm.	0	4	15.6
12	33	0	0	4	8.0
13	44	4 cm.	Edge	2	18.7
14	17	6 cm.	6 cm.	7	9.4
15	44	5 cm.	Edge	4	12.5
16	27	3 cm.	2 cm.	8	15.7
17	26	Edge	Edge	5	17.0
18	43	-	-	10	10.0
19	30	-	-	8	6.7
20	33	4 cm.	-	7	6.4
21	17	-	-	5	2.5
22	8	2 cm.	-	4	2.8
23	40	6 cm.	-	28	1.7
24	26	2 cm.	-	11	18.7



F. SECONDARY INFECTIOUS HEPATITIS.

1. Acute Lobar Pneumonia.

In fourteen cases of jaundice developing in the course of acute lobar pneumonia, the most striking observation was the involvement of one or more lobes of the right lung in thirteen cases, and while the left upper lobe was infiltrated at the time of the onset of jaundice in the fourteenth case, infiltration of the right upper lobe subsequently occurred (two weeks later). In the thirteen cases in which the right side was involved, there was associated involvement of the left lower lobe in two cases and slight infiltration of the left apex in the third. Of seven more patients having pneumonia with jaundice on whom estimations of serum bilirubin were not done, the process was limited to the right side in four; it was present on both sides in two, and in the seventh, while originally present on the left side (lower, then left upper), subsequently involved the right lower lobe twelve days later.

Thus, in 21 cases of acute lobar pneumonia showing jaundice, among a total of 826 patients having lobar pneumonia admitted to the hospital between 1923 and 1926, inclusive, the pneumonia process was present on the right side in all; in two of the cases (initially left-sided), the jaundice preceded recognizable infiltration of the right side. While the constant association of jaundice and pneumonia on the right side occurring in

this group of cases may be coincidental, it suggests the possibility of an anatomic basis as a factor in the production of secondary infectious hepatitis of pneumonia.

The earliest instance of marked hyperbilirubinemia was thirty hours after the onset of the disease (case 6), in which a value of 4.7 mg. was found approximately twenty-four hours prior to the occurrence of bilirubinuria.

2. Septicemia.

In four cases of septicemia with jaundice, there was a direct increase in serum bilirubin of relatively small degree. This substantiates the fact that the jaundice occurring in septicemia is obstructive and not hemolytic in origin; being due apparently to a secondary infectious hepatitis.

Lobar Pneumonia with Jaundice.

No.	Age	Lobes affected	W.B.C.	R.B.C.	Hb %	Day of Illness	Day of Jaundice	Mg. Bilirubin Direct
1	23	Rt. lung	63,0	3,6	70	9	?	8.0
2	33	Rt. middle and lower.	12,0	4,6	90	9	2	10.7
3	20	Rt. lung lt. lower.	17,0	3,0	80	8	?	6,3
4	31	Rt. upper	9,4	2,7	65	8	4	4.3
5	34	Rt. upper	25,0	-	40	7	4	10.0
6	20	Both lowers, esp. right; sl. lt. apex.	21,4	4,9	90	30 hrs.	?	4.7
7	39	Rt. lower	10,0	-	-	8	?	10.6
8	33	Rt. lower	18,6	4,1	70	6	?	11.0
9	19	Rt. lung and left lower	28,3	4,4	100	12	3	10.0
10	38	Rt. lung	16,4	-	-	7	?	3,7
11	31	Rt. lung	26,0	4,1	60	4	?	5.0
12	24	Rt. upper	29,0	4,5		8	?	5.0
13	22	Rt. lower	13,3	4,2	90	6	?	14.0
14	40	Lt. upper, later right upper	21,0	4,4	90	10	1	4.0

Septicemia

No.	Age	R.B.C.	HB. %	Mg. Bilirubin Direct	Blood Culture
1	24			4.8	Staphylococcus
2	49	4,3	90	3.3	Streptococcus viridans
3	26	2,6	30	4.7	Streptococcus hemolyticus
4	42			4.5	Streptococcus hemolyticus

G. TOXIC HEPATITIS (POST-ARSEPHENAMINE JAUNDICE)

In seven cases, a considerable degree of jaundice was generally encountered, an average of 15.3 mg.%. In No. 2, an associated old cirrhosis was found at necropsy. That serum bilirubin estimations may be of great value in detecting latent jaundice in patients receiving antiluetic therapy, and accordingly stopping treatment before the development of a full-blown jaundice has been emphasized by a number of authors.

Strauss and Buerkman found that hyperbilirubinemia in early lues may be encountered which drops under antiluetic therapy. They also found a rise in bilirubin of 0.2 to 0.45 mg. %, 20 to 24 hours, sometimes sooner, after an injection of salvarsan. They also found normal values in 48 individuals two to six months after intensive antiluetic therapy.

Schamberg and Brown found no relationship between the number of injections of the arsenicals and the incidence of hyperbilirubinemia which is borne out in this study. They feel that bilirubin estimations may also be of value in determining when a damaged liver will permit the resumption of arsenical treatment and the affect of such treatment on that organ. Gerrard, in a very extensive study, feels that the stopping of arsenical

treatment upon detection of latent jaundice and the free use of glucose may prevent the subsequent development of a much more grave disturbance of hepatic function. Routine serum bilirubin determinations in night clinics may also be of value in detecting actual jaundice, which may easily be overlooked in artificial light.

Toxic Hepatitis (Post-Arsephenamine Jaundice).

No.	Injections Arsephenamine	Last Injection	Onset Jaundice	Died	R.B.C.	HB. %	Mg. Bilirubin
1	10	18 days ago	5 days ago	-	4,8	90	15.0
2	17	6 weeks ago	3 weeks ago	+	4,0	75	31.0
3	11	4 weeks ago	1 week ago	-	3,2	60	6.3
4	6	6 weeks ago	6 weeks ago	-	5,7	90	12.0
5	3	5 weeks ago	4 weeks ago	+	5,6	105	18.7
6	6	11 weeks ago	10 days ago	+	...	70	16.0
7	5	2 weeks ago	2 weeks ago	-	6,0	80	8.0

H. CHRONIC CHOLECYSTITIS.

Twenty-three of the cases were not jaundiced, while nine were definitely icteric. Among the twenty-three, the serum bilirubin value was normal in nineteen, questionably increased in two, and definitely increased in two whose blood was examined during an attack of gall stone colic. In No. 13, the serum bilirubin was not increased during an acute attack; but no stones were present in this individual. There was a distinctly higher bilirubin value when the blood was examined within a few days after an acute attack than after a much longer interval. Van den Bergh mentioned the importance of an increase in the serum bilirubin during or very shortly after attacks of acute abdominal pain suggesting gall bladder disease, as indicating the presence of gall stones or at least some temporary obstruction to the outflow of bile, especially when the patient's normal value has been determined during a free interval. Meulengracht has stressed the occurrence of an increase in the icterus index during acute abdominal attacks as differentiating cholelithiasis from acute appendicitis and renal colic.

Among the cases with jaundice it is notable that the icterus was only of a relatively mild degree, an average of 3.4 mg. %.

It appears then that a serum bilirubin de-

termination is of little or no value in the diagnosis of gall bladder disease in the absence of jaundice unless it be made during or immediately after an acute attack, when it may be of very great value particularly if there be a co-existing cholelithiasis. It would appear advisable to determine the serum bilirubin in patients suspected of having gall bladder disease during free intervals as suggested by Van den Bergh for comparison with the value obtained during an acute attack.

A lack of any increase in the serum bilirubin in No. 3, with a stone present in the common duct is remarkable. The frequency of stone in the common duct without jaundice has been noted by Walters.

* All operative cases
a. Small stone in common duct
X Blood taken during attack

Chronic Cholecystitis

No.	Age	Sex	Stones in gall bladder	Days since attack of pain	Jaundice	G. Bilirubin Direct	G. Bilirubin Indirect
1	60	F	+	-	-	-	-0.2
2	53	[illegible]	+	-	-	-	-0.2
3	41	[illegible]	+	-	-	-	0.25
4	44	[illegible]	+	-	-	-	-0.2
5	52	[illegible]	+	-	-	-	-0.2
6	22	[illegible]	+	-	-	-	0.25
7	45	[illegible]	+	2	-	-	0.33
8	50	[illegible]	+	1	-	-	0.6
9	48	[illegible]	+	-	-	-	0.4
10	60	[illegible]	+	3	-	-	0.8
11	67	[illegible]	+	[illegible]	+	1.0	...
				7		-	0.4
12	25	[illegible]	-	7	-	-	0.35
13	33	[illegible]	-	[illegible]	-	-	-0.2
14	38	[illegible]	-	-	-	-	0.3
15	38	[illegible]	-	-	+	0.0	...
16	41	[illegible]	[illegible]	3	+	0.1	...
17	44	[illegible]	+	-	+	0.0	...
18	33	[illegible]	+	-	+	1.7	...
19	43	[illegible]	-	[illegible]	-	-	1.2
20	43	[illegible]	-	4	+	0.2	...
21	50	[illegible]	+	5	-	-	0.2
22	44	[illegible]	+	[illegible]	-	-	0.3
23	51	[illegible]	+	[illegible]	-	-	.9
24	18	[illegible]	+	4	+	3.0	...
25	38	[illegible]	+	2	-	-	0.2
26	31	[illegible]	+	0	+	0.0	-
27	38	[illegible]	+	-	-	-	0.2
28	50	[illegible]	+	7	-	-	-0.2
29	52	[illegible]	-	-	-	-	0.4
30	40	[illegible]	+	5	-	-	0.5

Chronic Cholecystitis*

No.	Age	Sex	Stones in gall bladder	Days since attack of pain	Jaundice	G. Bilirubin Direct	G. Bilirubin Indirect
1	60	F	+	-	-	-	-0.2
2	53	[illegible]	+	-	-	-	-0.2
3a	41	[illegible]	+	-	-	-	0.25
4	44	[illegible]	+	-	-	-	-0.2
5	52	[illegible]	+	-	-	-	-0.2
6	22	[illegible]	+	-	-	-	0.25
7	45	[illegible]	+	2	-	-	0.35
8	50	[illegible]	+	1	-	-	0.6
9	48	[illegible]	+	-	-	-	0.4
10	60	[illegible]	+	3	-	-	0.8
11	67	[illegible]	+	[illegible]	+	1.0	...
				7		-	0.4
12	23	[illegible]	-	7	-	-	0.35
13	23	[illegible]	-	[illegible]	-	-	-0.2
14	38	[illegible]	-	-	-	-	0.3
15	38	[illegible]	-	-	+	0.0	...
16	41	[illegible]	.	3	+	0.1	...
17	44	[illegible]	+	-	+	0.0	...
18	38	[illegible]	+	-	+	1.7	...
19	43	[illegible]	-	[illegible]	-	-	1.2
20	42	[illegible]	-	4	+	0.2	...
21	50	[illegible]	+	5	-	-	0.2
22	44	[illegible]	+	-	-	-	0.3
23	51	[illegible]	+	[illegible]	-	-	.0
24	10	[illegible]	+	4	+	2.0	...
25	33	[illegible]	+	2	-	-	0.2
26	21	[illegible]	+	[illegible]	+	2.0	-
27	38	[illegible]	+	-	-	-	0.2
28	36	[illegible]	+	7	-	-	-0.2
29	52	[illegible]	-	-	-	-	0.4
30	40	[illegible]	+	5	-	-	0.3
31	25	[illegible]	-	[illegible]	+	[illegible]	1.4
32	25	[illegible]	+	-	+	3.5	-

I. STONE OBSTRUCTING THE COMMON BILE DUCT.

Six cases of stone obstructing the common duct were studied. In four there was a marked "direct" increase in the serum bilirubin, while in one (#5) an instance of Charcot's intermittent hepatic fever, a transient slight increase during the attacks of pain and chills occurred. In this patient, the relation of bilirubinemia to temperature, chills, pain and number of leukocytes is noteworthy and is given in the accompanying table.

Walters has noted the frequency of stone in the common duct without jaundice. More remarkable is the fact that a stone may be present without even a distinct increase in the serum bilirubin, as in case 4 of this series (between attacks).

Stone Obstructing Common Duct.

No.	Age	Sex	Pathological Diagnosis	Clinical Jaundice	R.B.C.	HB %	Mg. Bilirubin Direct
1	72	M	+	+	4,7	80	15.0
2	45	F	+	5 weeks	4,4	75	9.4
3	36	F	-	7 weeks	...	85	26.0
4	42	M	+	+	...	75	16.0
5	43	F	+	-	...	75	1.8
6	45	M	+	3 days	...	85	2.8

Charcot's Intermittent Hepatic Fever (Case 4)

Time	Temp.	Leukocytes	Pain	Chill	Mg. Bilirubin Direct	Indirect.
1/3/27 4:00 P.M.	98.4	9,400	0	0	-	0.6
1/5/27 7:00 P.M.	103.2	17,800	+	+	1.8	...
1/6/27 5:30 P.M.	99.4	9,000	0	0	0	0.4

J. TUMOR OBSTRUCTING THE COMMON BILE DUCT.

Of particular interest in this series are two instances of a fall in serum bilirubin when a tumor obstructed the common bile duct. In one, a pathologic diagnosis of carcinoma of the pancreas was made, while in the second a firm tumor of the papilla of Vater, measuring 2 by 5 cm., and thought to be malignant, was encountered at operation. Word was received later from this patient's physician that the jaundice had completely disappeared.

It is of interest to note in case 3, a decline in the hemoglobin and red cell count accompanying the drop in the serum bilirubin, suggesting a possible cause for the latter. This is in accord with the experiments of Rous and Drury in ligation of the common duct, which Poer and I have had occasion to verify in a number of animals. The appearance of the skin on May 7 was one of mixed green and black jaundice, replacing the yellow tint noted February 4, and yet the bilirubinemia was at its lowest level. This, of course, is only another argument for the importance of the estimation of serum bilirubin. McNee mentions a similar experience.

In case 4, it was surprising to note a serum bilirubin value of only 4 mg. (determinations on

three successive days), with a jaundice of a month's duration. The tumor may have been of an inflammatory nature. It is unfortunate that autopsy was not obtained in this case.

Tumor Obstruction Common Bile Duct.

No.	Age	Diagnosis	Duration Jaundice	Died	R.B.C.	Hb. %	Mg. Bilirubin Direct
1	72	Operative	?	+	4,8	65	9.3 (Sept. 3)
							13.8 (Sept. 9)
2	66	Pathological	5 weeks	+	...	60	2.0
3	67	Pathological	2 weeks	-	5,1	74	15.0 (Feb. 4)
					...	..	17.7 (Feb. 14)
4	51	Operative	4 weeks	+	3,4	50	5.0 (May 9)
5	88	Clinical	?	+	4,8	70	4.0 (Aug. 31)
6	59	Operative	?	-	5,0	70	9.4
					...	..	7.5 (Oct. 5)
							12.5 (Oct. 16)
							9.1 (Oct. 30)
							6.3 (Nov. 10)
7	68	Clinical	3 weeks	-	4,6	85	11.0
8	85	Pathological	?	-	5.0	77	16.1
9	62	Operative	4 weeks	-	4.2	85	29.0
10	49	Operative	11 weeks	-	...	65	22.2
11	70	Operative	6 weeks	-	4,0	60	18.2
12	75	Pathological	10 weeks	+	2,5	50	21.4
13	59	Clinical	3 weeks	-	...	70	9.1
14	53	Clinical	8 weeks	-	...	75	14.7

VII. MISCELLANEOUS DISEASES.

A. CHRONIC SPLENOMEGALIC HEMOLYTIC ICTERUS.

All of the cases presented a definite increase in the percentage of the reticulated cells, with marked urobilinuria (slight in case 4), and absence of bile salts and pigment from the urine.

Only an indirect reaction was obtained, as Van den Bergh first pointed out regardless of the degree of bilirubinemia. This is particularly illustrated by case nine with an indirect value of 25 mg. %.

That there is no direct relationship between the fragility of the red cells and bilirubinemia is borne out in cases 2 and 7, several simultaneous determinations being made in the latter. It is noteworthy that within seventy-two hours after splenectomy the serum bilirubin in this case dropped from a level of 4.2 to 0.35 mg., an experience similar to that reported by Rich and Rienhoff.

Evidence of disease of the gallbladder was present in five or fifty per cent of the series, a fact in harmony with the observations of W. J. Mayo in a large series of cases. The evidence in cases 1 and 2 consisted of attacks of severe pain in the right upper quadrant and vomiting, with temporary increase in the jaundice plus failure to visualize the gallbladder by Graham's method. Gallstones were found in cases 3,4 and 10.

The return of the hyperbilirubinemia in case 7 following splenectomy may be due to the existence of a simple familial cholemia, which Van den Bergh hints may in some instances possibly be the forerunner of a hemolytic jaundice. It may be added that the diagnosis in this case was substantiated at the Mayo Clinic. Since splenectomy was performed, the patient has regained his former energy and is able to perform the arduous tasks of a resident surgeon. There has been only a trace of urobilin in the urine on a number of examinations, and the reticulated cell count has remained normal. If nothing were known of the patient's previous history, his case might well be taken for one of simple familial cholemia. It should be added that he has achlorhydria.

Chronic Hemolytic Jaundice

No.	Duration Jaundice	Gall Bladder Disease	Spleen Enlarged	R.B.C.	Hb. %	Mg. Bilirubin Indirect
1	8 years	+	-	4,8	80	5.0
2	10 years	+	4 cm.	4,3	80	7.5
3	10 years	+	4 cm.	3,9	65	5.6
4	9 years	+	-	2,6	50	2.8
5	13 years	-	Below umbilicus	2,6	40	3.1
6	14 years	-	Below umbilicus	3,5	40	8.3
7	3 years	-	Edge	4,6	90	2.5
8	1 year	+	2 cm.	2,7	55	2.-
9	2 years	-	4 cm.	1,2	25	25.0
10	1 year	-	2 cm.	1,8	30	3.0

Case #7.

Date	Feb. 11	March 17	May 11	May 14	Splenectomy May 14	May 17	Sept. 3	March 14
Fragility	.42-.32	.48-.42	.44-.36	...		.48-.38	.44-.36	.40-.32
Control	.42-.32	.42-.32	.40-.32	...			.40-.32	.40-.32
Mg. Bil.	2.5	1.0	3.1	4.2		.35	1.7	2

B. PERNICIOUS ANEMIA.

The diagnosis was apparently certain in all the cases. All presented achlorhydria, the great majority either the characteristic glossitis or signs of spinal cord degeneration, or gastrointestinal disturbances particularly diarrhea, with negative X-Ray examination of the gastro-intestinal tract and repeated negative stool examinations. The later cases improved under liver therapy which was not used in the earlier cases. A point stressed recently by Minot, viz. that loss of weight occurs in some cases of pernicious anemia particularly where the gastrointestinal disturbances are prominent, was noted in eight of the cases to the extent of twenty to fifty pounds.

In the cases here studied hyperbilirubinemia (always of the "indirect" type) seems to correspond definitely to the presence of a lemon yellow tint to the skin, the bilirubin value exceeding 1 mg. % in twelve of the fourteen cases in which this coloration was present and reaching .8 mg. % and .5 mg. % in the remaining cases.

Four of the ten cases in whom no increase in serum bilirubin was demonstrated were apparently in a stage of remission. The fall of the serum bilirubin to normal during remissions in pernicious anemia has been noted by Scheel (Lepehne), Meulengracht et al. In the remaining six cases without hyperbilirubinemia in whom apparently active blood destruction was going on, a bilirubin value of .5 mg. % ---

higher than that encountered in secondary anemia of equal severity---was present in four, while very low values of 0.2 mg. or less were present in the remaining two.

It is interesting to note that the highest values were obtained in the eight cases in whom splenic enlargement was demonstrable. As the ability of the spleen to form bilirubin has been definitely established, its enlargement may be associated with increase in blood destruction and bilirubin formation. The associated hepatic enlargement in four of the cases suggest impairment of liver function as regards bilirubin excretion as an additional factor. (Liminished excretion of phenoltetrachlorphthalein was noted in two of eleven cases of pernicious anemia reported by Greene and Conner). It may be noted that in the three cases with splenic enlargement alone, the bilirubin values were 2.5, 2.2 and 2. mg. %., in contrast to three cases of hepatic enlargement alone in which the values were 1.75, .5 and .8 mg. % respectively; a fact in agreement with the mechanism of the disease as primarily one of increased bilirubinemia thru increased blood destruction.

The occurrence of hyperbilirubinemia in pernicious anemia was described by Syllaba 1906 (Van den Bergh) and by Scheel (1912, McNee)and was later confirmed

by Van den Bergh with the use of his own test. The figures obtained in this series are practically the same obtained in most of the published results which McNee stated to average between 1.5 and 2 mg. % (3-4 units). Van den Bergh encountered increases of 2.5 and 3.0 mg. % in severe cases. Brown and associates met with a value of 4 mg. % and Greene and Connor as high as 5 mg. %.

Pernicious Anemia

No.	Age	"Lemon-yellow skin	Liver	Spleen	R.B.C.	Hb. %	Regen-eration	Mg. Bilirubin Indirect
1	84	+	+	0	1,2	25	++	1.75
2	52	+	0	0	0,9	30	+	1.75
3	52	+	0	Edge	1,4	45	++	2.5
4	64	+	0	0	1,2	30	++	1.5
5	49	+	0	Edge	1,1	35	++	2.0
6	58	+	Edge	0	1,5	50	+	1.0
7	40	+	6 cm.	6 cm.	1,1	40	++	2.5
8	65	+	Edge	Edge	1,7	50	++	2.0
9	58	+	Edge	4 cm.	1,3	26	+	1.2
10	53	+	6 cm.	Edge	1,6	30	++	1.8
11	37	+	0	Edge	0,9	22	+	2.2
12	65	+	-	-	1,0	20	+	1.3
13	59	+	-	-	1,1	25	+	1.2
14	40	+	Edge	Edge	1,7	47	++	3.0
15	64	0	Edge	0	1,2	38	+-	0.5
16	55	0	0	0	3,1	55	-	0.5
17	62	0	0	0	2,1	40	-	0.5
18	40	+	0	0	1,8	32	-	0.5
19	34	-	-	-	1,0	16	-	0.5
20	55	0	0	0	3,0	80	-	-0.2
21	51	0	0	0	2,0	35	+	-0.2
22	55	0	0	0	3,3	60	-	0.3
23	50	-	-	-	2,8	45	+-	0.2
24	50	-	-	-	4,2	80	-	-0.2

C. SECONDARY ANEMIA.

The consistent hypobilirubinemia occurring in uncomplicated secondary anemia is a fact which has been noted by many authors. Van den Bergh pointed it out in sharp contrast to the hyperbilirubinemia occurring in pernicious anemia. He felt it to be of particular value in differentiating an occult carcinoma from a primary anemia in the absence of metastatic invasion or myocardial insufficiency. He also found a low bilirubin value in nephritis in the absence of an associated heart failure. This has been confirmed by Andrewes, Feigl and Querner, Beth etal. The last mentioned author would differentiate malignant nephrosclerosis from chronic nephritis by an elevated bilirubinemia in the former.

In applying the Van den Bergh test to the serum of cases of chronic nephritis with uremia, Andrewes noticed the slow development of an orange buff color gradually deepening over a period of 24 hours, and when the solution was made alkaline with caustic soda, a cherry pink color developed fading after a few minutes. In a case of bichloride poisoning whose blood was examined two days prior to death of uremia, this reaction was noted and has also been noted in a number of cases of chronic nephritis dying of uremia. The specificity of the test

Secondary Anemia.

No.	Cause of Anemia	Pathological Diagnosis	R.B.C.	HB. %	Mg. Bilirubin Indirect
1	Gastric Ulcer	+	3,2	50	-0.2
2	Duodenal Ulcer	+	1,8	40	-0.2
3	Duodenal Ulcer	-	2,0	45	-0.2
4	Gastric Ulcer	+	2,5	45	-0.2
5	Duodenal Ulcer	-	2,4	27	-0.2
6	Chr. Nephritis	-	2,1	40	-0.2
7	Chr. Nephritis	+	3,0	40	-0.2
8	Chr. Nephritis	-	2,6	50	-0.2
9	Chr. Nephritis	+	3,4	60	-0.2
10	Chr. Nephritis	-	1,2	35	-0.2
11	Endometritis	-	3,3	50	-0.2
12	Fibroid Uterus	+	2,0	40	-0.2
13	Malaena	-	1,9	38	-0.2
14	Banti's Disease	+	0,6	10	-0.2
15	Hemophilia	-	1,7	30	0.2
16*	Endocarditis	-	2,3	40	0.25
17*	Endocarditis	-	2,9	50	-0.2
18*	Endocarditis	+	3,1	50	0.25

in uremia and prognostic importance in cases of chronic nephritis has recently been stressed by Blotner and Fitz.

D. SICKLE CELL ANEMIA.

An indirect increase in the serum bilirubin, similar to that in chronic hemolytic jaundice and pernicious anemia as directly opposed to the results in most secondary anemias, would indicate that the anemia in this disease is hemolytic in character. In case 2, which showed the highest value in the series, bilirubinuria was not present but marked urobilinuria was found.

Splenectomy in one case did not effect a disappearance of the hyperbilirubinemia, nor of the "sickling" of the red cells. The latter is perhaps comparable to the persistence of increased erythrocytic fragility following splenectomy in chronic hemolytic jaundice.

The first two of my cases were reported by Alden, while a report of the third has been made by Mitchell and his associates.

Sickle Cell Anemia

No.	Age	Sex	Color	R.B.C.	HB. %	Mg. Bilirubin Indirect	Remarks
1	4	M	B	2,5	69	1.0	
2	18	M	B	2,0	45	4.0	
3	2½	M	B	3,0	40	1.4 (Oct. 13)	Splenectomy (Oct. 30)
				2,7 (Oct. 13)	80	0.65 (Nov. 13)	
				4,0		1.0 (Dec. 13)	
4	14	F	B	1,7	30	1.3	

E. HEREDITARY HEMORRHAGIC TELANGIECTASIA.

In six patients who had hereditary hemorrhagic telangiectasia (mother and five children) a low value of serum bilirubin, similar to that obtained in ordinary secondary anemia, was present. Apparently, only mechanical loss of blood occurs in this disease.

F. ACUTE ALCOHOLISM.

In twelve cases of acute alcoholism, an increase in the serum bilirubin was not encountered, but, on the contrary, a tendency toward hypobilirubinemia was noted. In four of the cases (5,6,7 and 8), blood counts and determinations of volume index were made to exclude hydremia and anemia. In cases 5 and 7, the determinations were repeated twelve hours later, with virtually the same results. Whether the patients' levels of serum bilirubin were low before the ingestion of alcohol or whether alcohol stimulates the liver to increased excretion of bilirubin is not known.

Hereditary Hemorrhagic Telengiectasis*

No.	R.B.C.	HB. %	Mg. Bilirubin Indirect
1	1,8	35	0.3
2	4,4	..	0.2
3	3,6	50	-0.2
4	3,8	65	0.3
5	4,2	75	0.2
6	4,8	70	-0.2

* Mother and 5 affected children.

Acute Alcoholism

No.	Mg. Alcohol per c.c. urine	Coma	Mg. Bilirubin
1	4.2	+	-0.2
2	3.9	+-	-0.2
3	4.3	+	0.2
4	2.0	+	-0.2
5	3.0	+	0.4
6	5.0	+	-0.2
7	4.5	+	0.25
8	5.0	+	-0.2
9	...	+	-0.2
10	3.9	+	-0.2
11	5.0	+	-0.2
12	3.0	-	-0.2

G. TUBERCULOSIS.

Among twenty cases of chronic, far advanced pulmonary tuberculosis, a distinct tendency towards hypobilirubinemia is noted regardless of the degree of activity present. The highly active cases were all negroes, whereas those with relatively little activity (with or without cavitation) were older white men. The patients were residing at the Branch Hospital for Tuberculosis.

In three cases of acute tuberculous pneumonia, a hypobilirubinemia was present in two, with a relative hyperbilirubinemia in the third. Sections of the liver of the last case revealed an acute engorgement which Dr. Richard Austin feels is probably not tuberculous in character.

In three cases of miliary tuberculosis (all autopsied), a hypobilirubinemia was found.

In one case of disseminated hepatic tuberculosis - (biopsy diagnosis), no increase in the serum bilirubin occurred. The preoperative diagnosis in this case was possible chronic cholecystitis. No evidence of a tuberculous infection elsewhere in the body has as yet been recognizable.

While simultaneous red counts and hemoglobin estimations were not done on the cases here reported, it is suggested that the hypobilirubinemia present in tuberculous may be related to the anemia encountered in this disease.

Tuberculosis

No.	Age	Far advanced pulmonary lesions	Activity	Mg. Bilirubin Indirect
1	24	+	++	-0.2
2	19	+	++	-0.2
3	23	+	++	-0.2
4	53	+	++	-0.2
5	44	+	++	-0.2
6	36	+	++	-0.2
7	45	+	++	0.3
8	36	+	++	0.4
9	27	+	++	0.2
10	62	+	+-	-0.2
11	54	+	+-	-0.2
12	57	+	+-	-0.2
13	68	+	+-	-0.2
14	69	+	+-	-0.2
15	63	+	+-	-0.2
16	66	+	+-	-0.2
17	73	+	+-	-0.2
18	58	+	+-	0.2
19	55	+	+-	0.2
20	71	+	+-	-0.2
21[a]	32	-	-	0.2
22[b]	17	+	++	-0.2
23[b]	28	+	++	-0.2
24[c]	26	+	++	1.0
25[d]	57	+	++	-0.2
26[d]	26	+	++	-0.2
27[d]	32	+	++	-0.2

a. Disseminated hepatic t.b.c.
b. T.b.c. pneumonia.
c. T.b.c. pneumonia with acute hepatic engorgement - cause?
d. Miliary T.b.

H. DISEASE OF THE THYROID GLAND.

In ten cases of thyroid disease, the serum bilirubin was found to be practically unaffected. There appears to be no definite relationship between the basal metabolism and the degree of bilirubinemia. The average value in four cases of toxic adenoma was found to be somewhat higher than in three of exophthalmic goitre. In five cases of Basedow's disease, Forster and Forstner found a maximum serum bilirubin value of .8 mg. % by the method of Ernst and forster.

I. TYPHOID FEVER.

No distinct hyperbilirubinemia was encountered in eleven cases studied at various times after the beginning of the second week of the disease. In only one instance No. 3, was a relatively high serum bilirubin level encountered, .75 mg. %. This case died during its second week of severe toxemia and circulatory collapse. The diagnosis was verified at autopsy. Forster and Forstner in a study of four cases reported a maximum value of .6 mg. % in two instances.

Disease of the Thyroid Gland.

No.	Age	Basal Metabolism	Mg. Bilirubin Indirect	Pathological Diagnosis
1	14	+3	0.3	Puberty Hypertrophy
2	65	+5	0.6	Multiple Adenomata
3	33	+3	0.25	Benigh Thyroid Adenomata (Clinical Diagnosis)
4	38	+?	0.33	Multiple Adenomata
5	25	+24	-0.2	Multiple Adenomata
6	37	+28	0.35	Cystic Adenoma with Hemorrhage
7	43	+78	0.35	Diffuse Adenomata
8	27	+44	-0.2	Exophthalmic Goitre
9	30	+96	-0.2	Exophthalmic Goitre
10	42	+60	0.2	Exophthalmic Goitre

Typhoid Fever

No.	Week of Disease	R.B.C.	HB %	Mg. Bilirubin Indirect
1	2	4,1	85	-0.2
	3	...	..	0.3
2	2	3,6	80	0.32
3	2	4,0	80	0.75
4	2	5,3	90	0.33
5	3	4,1	75	0.35
6	2	4,1	60	0.3
7	4	3,9	85	0.43
8	5	3,5	70	0.3
9	6	4,3	80	-0.2
10	2 (Relapse)	4,6	85	-0.2
11	2 (Relapse)	4,1	80	0.3

J. DIABETES MELLITUS.

The normal icterus index is generally stated to be less than five and not above eight. If icterus index determinations alone had been done on the serum of these patients, the information obtained might have been misleading in the first six cases where high readings were found. The occurrence of carotinemia has been noted in the past and the importance of the diazo reaction in distinguishing bilirubin from other yellow substances which may circulate in the blood (e.g. lutein) was particularly emphasized by Van den Bergh. The presence of carotin was determined spectroscopically in four of the cases and by the method suggested by Palmer in Nos. five and six.

The serum bilirubin in diabetes mellitus is apparently not increased.

K. TABES DORSALIS.

No increase was noted in the serum bilirubin during gastric crisis in three cases of tabes dorsalis. This observation should be of value in differentiating such a crisis from an attack of gallstone colic. According to Meulengracht, there is also not any rise in the serum bilirubin during attacks of renal colic or acute appendicitis.

Diabetes Mellitus

No.	Age	High Vegetable Diet	Icteric Index	Mg. Bilirubin Indirect	Remarks
1	28	1 year	10	-0.2	Carotinemia
2	61	3 years	15	-0.2	Carotinemia
3	24	2 years	10	0.25	Carotinemia
4	44	4 years	16	0.2	Carotinemia
5	38	1 year	8	-0.2	Carotinemia
6	50	2 years	9	-0.2	Carotinemia
7	30	No special diet previously			
8	63	No special diet previously	2	-0.2	Associated Cystitis
9	24	No special diet previously	2	-0.2	Impending coma; recovery
10	60	No special diet previously	4	0.3	

Tabes Dorsalis with Gastric Crisis

No.	Mg. Bilirubin Indirect	Remarks
1	-0.2	During crisis
2	-0.2	During crisis
3	-0.2	During crisis

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