

THE ICTERUS INDEX

of the

BLOOD SERUM

as an aid to

DIAGNOSIS, TREATMENT, and PROGNOSIS.

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## INTRODUCTION.

At the present time clinicians are showing a markedly increased interest in the study of diagnostic methods meant to increase our knowledge of the functional activity of the liver.

Doubt has been cast on the value of liver function tests on the following grounds:

1. That they have failed in the diagnosis of early hepatic pathological conditions and dysfunction, owing to the liver's large factor of safety.
2. That they do not permit accurate correlation with pathological lesions.
3. That the liver has many functions, and that no one test is specific even for one function alone, and far less for the function of the liver as a whole.
4. That in some cases the tests are negative in clinically positive cases.

Whilst it must be admitted that these objections are not groundless, could not the very same objections be raised against, for example, the renal function tests? And yet we find the latter in daily use, and their results used as a basis for the formation of vital conclusions.

Probably the latest development in liver function tests/

tests is that described by Alice R. Bernheim, M.D., in the Journal of the American Medical Association in 1924, and called by her the Icterus Index.

This index is an estimation of the bilirubin content of the blood serum; not a true quantitative estimation, but an estimation by means of a colorimeter of the intensity of the staining of the serum as compared to an arbitrary standard of colour.

The liver is an extremely complex organ, having various functions, not all properly understood, but at present it is generally admitted that there are four main functions, viz.,

1. Bile Formation.
2. Destruction of Red Blood Corpuscles.
3. Glycogenic.
4. Detoxication of Proteins.

It is also stated by some writers to have internal secretion. It is, under the circumstances, unlikely that any test will be evolved which can check all these functions at once, but it seems that the simple test about to be described, which makes use of the bile pigments in the blood serum as a means for determining liver function, is of great value in certain diseases, both in diagnosis, treatment, and prognosis.

Bile pigments are essentially formed from the destruction of haemoglobin, probably in the liver, as/

as was shown in 1874 by Tarachanoff, who demonstrated that in dogs with biliary fistulae there was a rapid and marked increase in bile pigments in the blood after the intravenous injection of haemoglobin.

Since then it has been generally accepted that haemoglobin is the mother substance of biliary pigments.

In 1917, however, Whipple and Hooper<sup>1</sup> repeated these experiments, and found that the bile pigment output was generally but not always increased after injections of haemoglobin, and also observed a far greater output of pigment when the usual meat diet of dogs was changed to a carbohydrate one. They therefore suggested that the pigment metabolism might not be the simple mechanism it had been thought to be, but that other substances as well as haemoglobin might enter into the formation of bile pigments. This is supported by the fact that to supply the pigment excreted in the bile, at times it would be necessary to deplete entirely the serum of blood cells if all the pigment was formed from red corpuscles.

There must therefore be some additional source of pigment, but whether we believe that bilirubin is formed from haemoglobin wholly or only partly by the liver cells or by the reticulo-endothelial system in general, which is chiefly situate in the spleen and bone marrow, and includes the Kupffer cells of the liver, /

liver, it must be admitted that the liver plays the main part in the secretion of bilirubin and it is on that account that it is claimed that the bilirubin in the blood serum is of value as a guide to liver function.

Since the destruction of red blood corpuscles by the liver is a physiological occurrence, it is to be expected that there will be a small quantity of bilirubin present normally in the blood serum. That this is so has been shown by Conner and Roper<sup>2</sup> who using Gmelin's test proved its presence, and also showed the amount to be constant in the same individual.

This amount has been placed at one part of bilirubin to 500000 to 600000 parts of serum in the normal person, and when the concentration reaches one part in 50,000 or 60,000 the tissue cells become saturated with the pigments and clinical jaundice appears. The range of bilirubinaemia between the normal and that amount which causes clinical jaundice may be called the "range of latent jaundice".

The normal amount of bilirubin in the serum is increased by:

1. Disturbances of the biliary system, either by cholelithiasis, cholecystitis, cholangitis, adhesions round the gall bladder, and diseases affecting the liver itself, or growths pressing on the bile ducts.

Of/

Of these causes, in the cases where pure mechanical obstruction results, such as in obstruction of the common bile duct by a stone or in pressure on the bile ducts from without, the increased bilirubinaemia comes about through the rise in pressure in the bile passages above the obstruction, which causes stagnation of the bile with consequent re-adsorption into the circulation, either directly by the hepatic vascular capillaries, or, as seems more probable, by the lymphatics.

In the case of cholecystitis, it has been shown by E.A. Graham<sup>3</sup> that inflammatory changes are a constant accompaniment of cholecystitis. These inflammatory changes are essentially a pericholangitis, which often extends upwards to involve the smallest biliary capillaries. This inflammation, by causing swelling, and consequent blocking of the smaller bile capillaries, causes a certain amount of obstruction to the outflow of bile.

Whilst this is usually not enough to cause clinical jaundice, it is enough to give rise to some re-absorption of bile, with consequent hyperbilirubinaemia.

## 2. Haemolytic conditions.

Of these, perhaps, the best examples are pernicious anaemia and acholuric jaundice. In these conditions the hyperbilirubinaemia is caused either/

either by an abnormal fragility of the red blood corpuscles liberating an excess of haemoglobin from which the excess of bilirubin is formed, or, as seems more probable, by over activity of the reticulo-endothelial system, in support of which last statement one would advance the improvement which splenectomy causes in pernicious anaemia.<sup>4</sup> That this improvement is only temporary must be admitted, but the spleen is not the only situation of the reticulo-endothelial system, which is probably affected as a whole in this disease. Whichever is the agent for destruction of red blood corpuscles, the haemoglobin thus set free is broken down, and bilirubin formed by means of the endothelial cells of the spleen and the Kupffer endothelial cells of the liver, and once formed is reabsorbed into the blood. It will be seen then that the excess of bilirubin in the blood in these cases is formed entirely independently of the glandular cells of the liver. From the above arguments it will be understood that primary anaemias may be expected to produce a hyperbilirubinaemia on account of the haemolytic process which occurs; whilst those anaemias which are secondary in type will produce a hypobilirubinaemia as the rate of red blood cell destruction is lowered in these cases, and in consequence there/

there is not enough pigment formed to raise the bilirubinaemia to normal.

That this is borne out in practice will be shown later.

Other cases in which, arguing on the same lines, a hyperbilirubinaemia may be expected are cases of large haematomata, ruptured viscera with internal haemorrhage, and malaria.

In the last of these there is a definite haemolytic process taking place in the blood stream, whilst in the other examples the process is analogous to the normal formation of bilirubin from the senile red corpuscles destroyed in the liver. That is to say, the haemoglobin of the corpuscles in the blood clot present is broken up into its two component parts, protein and haematin, the latter being again broken up to form haematin, which is almost identical with bilirubin, and seems to be the source of this substance under normal conditions.

As examples of internal haemorrhage and haematomata causing a hyperbilirubinaemia, Bernheim<sup>5</sup> quotes the following cases:-

Two cases of ruptured ectopic gestation with intraperitoneal haemorrhage gave an icterus index of 10.

Fractures of the pelvis and the femur gave icterus indices ranging from 9 to 11.

A large popliteal haematoma gave an icterus index of 10.

As the highest normal icterus index, as will be shown later, is 6, it will be seen that in these cases there was a definite hyperbilirubinaemia.

### 3. Toxic Conditions.

Here we may take as an example the hyperbilirubinaemia found in pneumonia. In this condition an analogy may be drawn from the case of the kidney in nephritis where the injury to the kidney epithelium allows the passage of albumin into the urine; similarly in the liver when the epithelium of the biliary capillaries is damaged by the toxins circulating in the blood in pneumonia, the capillaries allow the passage of an albuminous coagulable substance, which plugs the capillaries, and the bile, becoming dammed up behind these plugs, bursts through the walls of the capillaries and enters the lymphatics, and is absorbed into the circulation, thus causing hyperbilirubinaemia.

Following up the work of Bernheim, the writer will endeavour to show in the following pages that the hyperbilirubinaemia caused by the above three main factors may be of use in diagnosis, treatment, and/

and prognosis.

Bernheim, however, was not the originator of bilirubin estimations as a test for liver function.

In 1903, Gilbert, Herscher, and Posternak reported on a method of measuring bilirubin in the serum by an adaptation of the Gmelin Hayem reaction. Their method was not very satisfactory, owing to its being very complicated and rather inexact.

Later, in 1907, Posselt suggested a method of comparing the serum of suspected cases of hyperbilirubinaemia with a standard solution of bilirubin in an artificial serum, in capillary tubes; but he published no results of this method when used clinically.

In 1913, Hymans Van den Bergh devised the well known Van den Bergh reaction. This is still in extensive general use, and will be discussed in connection with the Icterus Index later.

In 1916, Hooper and Whipple described a colorimetric method of determining the amount of bilirubin in the blood by comparing acidified serum with a standard solution of copper sulphate.

Just previous to Bernheim's method, which she described in 1922, Meulengracht<sup>6</sup> experimented with a direct colorimetric method. He used the plasma obtained from 1 cc. of citrated blood, and compared it to a standard solution of one in ten thousand potassium/

potassium bichromate. He used test tubes of equal diameter and worked out the number of dilutions required to reduce the plasma to the colour of the standard.

Meulengracht's method, as was Bernheim's later modification, was based upon the assumption that bilirubin is practically the only yellow pigment in the blood, and that any other pigments present are only present in negligible quantities. Practically, the only exception to this assumption is the possible presence of a lipochrome pigment which may be derived from some foods.

Hess and Myers<sup>7</sup>, in 1919, showed that on a diet composed largely of green foods, carrots, oranges or eggs there was found to be a deeper yellow staining of the blood serum than normal.

That diet could influence the pigment metabolism of the body had previously been proved in 1914 by Palmer and Eckles<sup>8</sup> who showed that a diet rich in green foods given to cows increased the colour of the butter fat owing to a substance known as Carotin which accompanies the Chlorophyll in the green foods.

The Chlorophyll contains substances known as Carotin and Xanthophyll, the former of which may be extracted from the serum and even from the urine in some cases, by purified petroleum benzine, and the latter by 80% alcohol.

Palmer,<sup>9</sup> /

Palmer,<sup>9</sup> in a later article, showed that if hens were deprived of Xanthophyll in their food, the yolks of their eggs were colourless.

In their work on human beings, Hess and Myers found that the diet necessary to produce a condition which they named Carotinaemia must contain the following:-

2 oranges a day,

1 egg, or 2 ozs. of spinach,

this being continued for a period of two months.

Bernheim working on the same subject found that after a breakfast consisting of two eggs and an orange the yellow colour of the serum was not deeper than normal.

Excess of carrots, however, was found to cause an increase in the depth of colour. The effect was not lasting, for in the case of a man who had eaten two carrots, the icterus index rose to 15, and in another patient who had had one carrot it rose to 10, but in both cases fell to 5 the next day.

It would seem, therefore, that whilst the presence of carotin is evidently an additional factor in the staining of the blood serum, it does not seem likely that in normal adults under an average diet it will cause any serious fallacies in estimates of the colour of the blood serum.

It is possible that in the case of infants in whom/

whom the power of absorption of the intestinal mucosa is greater than in adults, and also in the case of adults who consume large quantities of green foods, for example, vegetarians and diabetics, it might become a more prominent factor.

It is of interest in showing that the blood and urine pigments are not formed solely from bile in all cases, but from the reports of other writers, and from the writer's own experience, its presence seems to be negligible as regards colorimetric estimation of the blood serum.

Having now discussed the theoretical standpoint of the icterus index as a clinical test, we come to the details of the technique.

The indicator on the scale of the standard coloration is selected a convenient figure, such as 15 or 20. The writer found ----- and moderately pigmented sera, 15 was the more convenient figure, whilst for more deeply pigmented sera 20 or even 30 was the figure used.

With the standard thus adjusted, a reading of the unknown is taken at the point on the scale at which the unknown and the standard match.

The icterus index is then calculated by dividing the reading of the unknown by that of the standard.

TECHNIQUE.

The technique used in the cases to be quoted later was essentially that of Bernheim<sup>10</sup> with certain slight modifications which experience showed to be helpful.

The broad outline of the technique is as follows: venous blood is withdrawn from the median basilic vein in the usual manner. This blood is allowed to clot and the supernatant serum is pipetted off and centrifuged till quite clear. It is then compared in a Dubosc colorimeter with an arbitrary standard solution of 1 in 10,000 potassium dichromate (This being equivalent to .05 Gms. in 500 ccs. of distilled water, and giving a solution slightly paler than normal serum).

The indicator on the scale of the standard solution is set at a convenient figure, such as 15 or 20. The writer found that for normal cases and moderately pigmented sera, 15 was the more convenient figure, whilst for more deeply pigmented sera 20 or even 30 was the figure used.

With the standard thus adjusted, a reading of the unknown is taken at the point on the scale at which the unknown and the standard match.

The icterus index is then calculated by dividing the reading of the standard by that of the unknown.

In/

In cases where the serum is very deeply pigmented it may be necessary to dilute it in order to obtain an accurate reading. This dilution must be made with normal saline; and when the calculation is made, the figure obtained as above must be multiplied by the number of dilutions of the serum.

The calculation may therefore be worked out in the following formula:

$$\text{Icterus Index} = \frac{\text{Reading of Standard}}{\text{Reading of Unknown}} \times \text{Number of Dilutions.}$$

Thus we find that the deeper the colour of the serum, the higher the icterus index.

With regard to details of technique: Bernheim used in her experiments a Bock Benedict colorimeter, which apparently requires less serum than the Dubosc model, and therefore recommends that only 5 ccs. of blood should be used. The writer found, however, when working with a Dubosc colorimeter that whilst the test could be carried out with the serum yielded by 5 ccs. of blood, it was more convenient to withdraw 10 ccs. of blood where possible. This amount of blood will yield 4 - 5 ccs. of serum, and this amount is sufficient to allow of a direct reading being taken with a Dubosc colorimeter. If less serum is used, it is necessary to dilute it before a reading can be obtained, and it was found to be difficult to match the resultant very pale serum with the standard.

In/

In all cases unnecessary dilution should be avoided, as the consequent multiplication required in the calculation of the index will multiply any error made in the original reading.

The writer also found that some sera became cloudy even when diluted with normal saline.

The following addition to the technique was moreover found to be of great assistance in the easy performance of the test. As soon as possible after withdrawal, the blood was placed in an incubator at 37 degrees Centigrade for a few hours. This caused a firm clot to form, and gave the maximum yield of serum. In addition to the above, it was found that if, after the clot had formed, it was separated from the sides of the tube with a wire, it fell to the bottom of the tube, and allowed the serum to rise to the top, which greatly facilitated the pipetting off of the same without contamination with blood corpuscles.

#### Errors and Fallacies in Technique.

1. The standard solution of potassium dichromate becomes paler on exposure to light. It should therefore be kept in the dark. It is said that the addition of two drops of sulphuric acid per 500 cc. of standard will preserve the colour.

2./

2. The serum must be clear when the reading is taken, cloudy or lipaemic serum giving high faulty readings. Serum usually becomes opaque if allowed to stand for more than twenty-four hours, and readings should be taken within that time.

During the ingestion periods the serum is also cloudy and should be discarded. This fallacy can be avoided by withdrawing the blood from the patient in the fasting state, or immediately before food.

3. A third common and important cause of discolouration of the serum is haemolysis. This imparts a reddish tinge to the serum, which makes accurate readings impossible.

Haemolysis must be avoided by using dry sterilised needles to withdraw the blood, and it is advantageous to allow the blood to run directly into the centrifuge tubes, which must also be carefully cleaned and dried. This obviates any possibility of contamination by moisture whilst transposing the serum from tube to tube. The slightest trace of moisture will give rise to some haemolysis, and render the test valueless.

If dry sterilised needles are not available, or if it is desired to withdraw the blood into a syringe, haemolysis may be avoided by washing out the syringe and needle beforehand with normal saline, /

saline, but if this is done, care must be taken that the serum is not diluted in any way. Care must also be taken that any pipettes used are either dried or washed out with saline before use.

4. The readings should be made by daylight, artificial light making accurate matching of the solutions difficult if not impossible.
5. The possibility of carotinaemia as a fallacy has already been discussed. This would appear to be more of a theoretical objection than a practical one. Bernheim recognises the possibility, but gives no records of any case in which carotinaemia has occurred in ordinary persons. It seems possible that persons on a diabetic diet might have some degree of this condition present, but that point will be discussed later.

The only vegetable which may cause it in the quantities usually eaten is the carrot, so the avoidance of these on the day the blood is taken would be a safeguard against this fallacy.

Several modifications of Bernheim's technique have been described in the last few years by different writers.

A.L. Brown<sup>11</sup> devised a method which consists primarily in the comparison of the colour of the blood serum/

serum with a series of permanent arbitrary standards consisting of fifteen tubes containing multiples of the unit colour, the strength of the colour being etched on each tube. A solution of 0.15 Gm. of potassium bichromate in 100 cc. of water plus 2 drops of concentrated sulphuric acid is prepared, and by a series of dilutions with water fourteen lower standards are made from this. These standards are kept in air-tight containers of uniform bore and thickness. An identical tube graduated with six 0.5 cc. marks is used for the unknown serum.

0.5 cc. of the serum is placed in this tube, and the degree of colour of the sample is determined by matching it with standard tubes, the examination being carried out through a small eye-piece against a background of ground glass. The number of the tube which approximates to that of the sample is taken as the Icterus Index. If the original serum requires dilution before comparison can be made, this figure is multiplied by the number of dilutions.

A similar technique has been evolved by Murphy<sup>12</sup>. He used as arbitrary standards dilutions of potassium bichromate, which corresponded to the Icterus Index as follows:

Dilution/

<u>Dilution</u>	<u>Icterus Index</u>	<u>Dilution</u>	<u>Icterus Index.</u>
1 - 10,000 =	1.0	1 - 500 =	20.0
1 - 5,000 =	2.0	1 - 400 =	25.0
1 - 2,000 =	5.0	1 - 200 =	50.0
1 - 1,000 =	10.0	1 - 133 =	75.0
1 - 666 =	15.0	1 - 100 =	100.0

These standards are kept in tubes of uniform bore and thickness, and the serum contained in an identical tube is compared as before.

A third technique has been devised by Davis<sup>13</sup> in which a few drops of capillary blood are drawn up into a 2 mm. tube and centrifuged, the resulting serum being compared as usual with arbitrary standards. By this method venipuncture is obviated, which is an advantage in the case of children or in cases where repeated examinations are necessary, and the results obtained are said to be satisfactory.

Before discussing the results and values of the Icterus Index in different diseases, the findings in normal persons must be considered.

Bernheim<sup>14</sup> considers any case showing figures between 4 and 6 as being within normal limits. She found that, as well as in healthy persons, a normal figure, as was to be expected, was found in many diseases, /

diseases, e.g., Rheumatic Fever, Chorea, Renal Conditions, Tuberculosis, Venereal Disease, Gynaecological Conditions, Gastric Ulcer, and Myelogenous Leukaemia.

Barrow<sup>15</sup> quotes a group of cases which showed an Icterus Index of 6 or below before operation, in which no hepatic disease was suspected, and in which operation revealed no hepatic disease.

The writer has examined 55 cases of healthy persons, and has obtained in every case figures between 3 and 6. These differ slightly from Bernheim's figures of 4 to 6, but as the lower limit is of little importance and as the upper limits are identical, it may be said that any case showing an index of over 6 has a hyperbilirubinaemia.

The following is the writer's list of normal cases:

Icterus Index in Normal Persons.

<u>Name.</u>	<u>Icterus Index.</u>	<u>Name.</u>	<u>Icterus Index.</u>
1. Ly.	3.4	8. Miss Pr.	6.0
2. Miss Ft.	3.7	9. Miss Tr.	4.2
3. Miss Mg.	4.6	10. Fr.	4.1
4. Miss An.	6.0	11. Bt.	4.2
5. Fk.	5.0	12. By.	5.1
6. Tn.	5.2	13. My.	4.1
7. Miss O'Dl.	3.3	14. Sm.	4.5

	<u>Name.</u>	<u>Icterus Index.</u>		<u>Name.</u>	<u>Icterus Index.</u>
15.	Ly.	6.0	36.	Sn.	4.6
16.	Bn.	5.0	37.	Cn.	3.7
17.	An.	4.7	38.	An.	3.6
18.	Pr.	3.7	39.	Miss An.	4.0
19.	Kr.	5.7	40.	Bn.	3.7
20.	Hn.	6.0	41.	Hm.	5.2
21.	Mrs Fr.	3.7	42.	Bt.	4.1
22.	Hr.	5.3	43.	Pn.	6.0
23.	Hs.	4.7	44.	In.	3.0
24.	Me.	5.7	45.	Bd.	4.1
25.	Miss We.	3.0	46.	Sy.	4.0
26.	Fh.	4.6	47.	Gn.	4.4
27.	Br.	5.0	48.	Tr.	4.0
28.	Cm.	4.4	49.	Ht.	3.6
29.	Hm.	5.7	50.	Miss Mw.	3.5
30.	Be.	4.2	51.	Kl.	5.
31.	Mrs Br.	3.2	52.	Ey.	3.
32.	Br.	3.3	53.	Pn.	3.3
33.	Be.	2.5	54.	Lm.	4.
34.	Va.	3.0	55.	Tr.	3
35.	G1.	4.5			

In/

In addition to the above, the following cases of various diseases were investigated by the writer, and found to show figures which fell within normal limits:

Kidney Conditions.

<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1. Gr.	3.6	Chronic Parenchymatous Nephritis.
2. By.	2.5	Chronic Parenchymatous Nephritis.
3. Ge.	4.0	Renal Calculi.
4. Miss Ss.	3.9	Hydronephrosis.
5. Cn.	6.0	Chronic Parenchymatous Nephritis.
6. Mf.	4.8	Chronic Interstitial Nephritis.
7. Hl.	3.8	Renal Calculi.
8. 2092.	4.3	Chronic Parenchymatous Nephritis.
9. Hd.	3.2	Chronic Interstitial Nephritis.
10. Gy.	2.5	Uraemic Coma.
11. In.	3.5	Uraemic Coma.
12. Mrs Cn.	3.3	Renal Calculus.
13. Gy.	3.5	Chronic Interstitial Nephritis.
14. Bh.	3.3	Chronic Parenchymatous Nephritis.
15. Me.	3.8	Chronic Parenchymatous Nephritis.
16. An.	3.5	Pyelitis.
17. St.	3.0	Renal Calculus.

Venereal Diseases.

	<u>Number.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	1489, Female.	Syphilis.	4.0
2.	1061, Male.	"	4.7
3.	1242, "	"	5.7
4.	1625, "	"	4.4
5.	1762, "	"	3.7
6.	1895, "	"	4.1
7.	1925, "	"	5.7
8.	1931, "	"	6.0
9.	2014, "	"	4.2
10.	2017, "	"	5.2
11.	2056, "	Gonorrhoea.	3.6
12.	2070, "	"	4.2
13.	2074, "	Syphilis.	5.0
14.	2092, "	Gonorrhoea.	4.3
15.	2119, "	Syphilis,	5.0
16.	2129, "	"	4.1
17.	2134, "	Gonorrhoea.	4.6
18.	2146, "	Syphilis.	3.0
19.	2147, "	Soft Sore.	4.1
20.	2047, "	Syphilis.	4.0
21.	1775, "	Gonorrhoea.	5.2
22.	1531, "	Syphilis	4.5
23.	1856, "	Gonorrhoea	3.2
24.	1935, "	Syphilis.	5
25.	2156, "	"	3.3
26.	2158, "	"	3.3
27.	2184, "	"	5
28.	2187, "	"	3
29.	2190, "	"	5.7

Carcinoma of Stomach.

	<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	En.	Carcinoma of Stomach	2.9
2.	Fn.	" " "	2.4
3.	Tr.	" " "	3.0
4.	Em.	Carcinoma of Pylorus	3.0
5.	Gy.	Carcinoma of Pylorus	2.8

Gastric Ulcer.

	<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	Mrs Tr.	Gastric Ulcer.	4.2
2.	Wy.	" "	3.5
3.	Ww.	" "	5.1
4.	Mrs Fs.	" "	4.0
5.	Cy.	" "	3.4
6.	Miss Tn.	" "	3.7
7.	Mrs He.	" "	3.0
8.	Hs.	" "	4.0
9.	Cn.	" "	3.3
10.	Ms.	" "	3.0

Gynaecological Conditions.

	<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	Miss Ry.	Ovarian Cyst.	5.0
2.	Miss Hd.	Carcinoma of Ovary.	2.0
3.	Mrs Sn.	Ovarian Tumour.	5.0
4.	Mrs Hn.	Chronic Endometritis	3.8
5.	Mrs Gy.	" "	3.3
6.	Miss Hg.	Ovarian Cyst.	3.5
7.	Mrs He.	Salpingitis	4.0
8.	Mrs Ht.	" "	4.0
9.	Miss Bm.	Pyosalpynx	3.5
10.	Miss En.	Ovarian Cyst.	3.8
11.	Miss Tn.	Uterine Fibroids	3.7

Miscellaneous Conditions.

	<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	By.	Psoriasis.	5.1
2.	Miss Ft.	Bazin's Disease.	3.7
3.	Hs.	Carcinoma of Mediastinum	3.1
4.	On.	Carcinoma of Rectum.	3.6
5.	Pn,	Cerebral Tumour.	3.9
6.	Ay.	Subacute Pancreatitis.	5.0
7.	Aw.	Pleurisy with Effusion	3.0
8.	Rd.	Rheumatic Fever.	3.5
9.	Ck.	Miliary Tuberculosis	2.5
10.	McMn.	Meningitis	5.0
11.	Hn.	Epithelioma of Lip	3.5
12.	Sn.	Pulmonary Tuberculosis	3.0

Of the above cases it is of importance, as will be shown later, to note that normal figures were obtained in all cases of Renal Disease, Gastric Ulcer, and Carcinoma of the Stomach.

In addition to the above, normal figures were obtained in some cases of Diabetes, and in some cases of Cardiac Disease, but as these have a special bearing on the uses of the Icterus Index, they will be discussed later under their respective headings.

Having thus established the limits of the normal bilirubinaemia, we may now progress to discuss the hyperbilirubinaemia which occurs in various diseases, and to show how, by means of estimating the Icterus Index, this hyperbilirubinaemia may be used both in diagnosis, treatment and prognosis.

The findings obtained by means of the Icterus Index will be discussed under the headings of the various diseases in which it is of use.

It was shown by Friedman in an article on Latent Jaundice that there was a demonstrable hyperbilirubinaemia in cases of Cholecystitis without Jaundice. To demonstrate this, however, he used the Fouchet test, which does not seem to be either accurate or so reliable as the Icterus Index.

This statement has been made by other writers also, using the Icterus Index, and they/

GALL-BLADDER AND LIVER DYSFUNCTION,  
WITH AND WITHOUT JAUNDICE.

CHOLECYSTITIS AND CHOLELITHIASIS.

The Icterus Index is perhaps of greatest value in cases of disease of the right upper quadrant of the abdomen.

It is an unfortunate fact that the history given and the symptoms complained of by the patient, may still leave one in doubt as to whether the trouble is situate in the gall-bladder, the kidney, the stomach, or the appendix.

Given a straightforward case of typical biliary colic, combined with jaundice, the diagnosis is simple; but it is in cases where there is a vague history given, and in which the physical examination reveals little, that it is claimed the Icterus Index is of value.

It was shown by Friedman<sup>16</sup> in an article on Latent Jaundice that there was a demonstrable hyperbilirubinaemia in cases of Cholecystitis without Jaundice. To demonstrate this, however, he used the Fouchet test, which does not seem to be either so accurate or so reliable as the Icterus Index.

This statement has been borne out by Bernheim<sup>17</sup> and other writers who, using the Icterus Index, found that/

that in the presence of active gall-bladder dysfunction there is an associated hyperbilirubinaemia, which can be demonstrated by means of the Icterus Index, although it may not be sufficient to cause clinical Jaundice.

As has been shown previously, the normal person does not have an Icterus Index above 6.0; and again, clinical Jaundice does not appear until the index has reached 15 or over. We therefore have a period between the figures 6.0 and 15.0 in which the bilirubin content of the serum is raised, but in which there are no clinical manifestations of the rise. This period has been termed the "period of latent Jaundice", and any case showing an index which comes within its limits may be considered definitely pathological.

In proof of this, Bernheim quotes 31 cases of proved Cholelithiasis or Cholecystitis with no clinical Jaundice, in which the presence of latent Jaundice was shown by the Icterus Indices, which ranged from 7.1 to 15.0. In all of these cases the index returned to normal after operation.

Further cases are quoted by De Witt Stetten<sup>18</sup> in an article in which he states that cases of suspected stomach disorders which showed a high Icterus Index of 9.0 or 10.0 were found at operation to be biliary disorders. He suggests also that the test holds/

holds forth great possibilities as a means of differentiating between Renal and Biliary Colic, and also of making a differential diagnosis between such diseases as Acute Appendicitis, Perforated Duodenal Ulcer, and Gall-Bladder trouble.

But whilst the Icterus Index is undoubtedly of great value in the differential diagnosis of these conditions, it is not diagnostic "per se". By which is meant that one cannot say "Because the Icterus Index is "X", therefore the patient is suffering from "Y"; but it will be shown that if the Icterus Index findings are used carefully in correlation with the clinical findings, it can be of great assistance in diagnosis.

The difficulties that arise in connection with the above diseases are as follows.

Pathological renal conditions do not raise the Icterus Index, as has been shown, and, as will be seen later, a stone in the common bile duct invariably does, from which facts we may make a differential diagnosis between renal and biliary colic as De Witt Stetten suggests.

It is in connection with acute appendicitis and duodenal ulcer, however, that difficulty arises. In both these conditions, as in biliary dysfunction, the Icterus Index may be raised. This at first sight may seem to confuse the issue, but it was found that active/

active biliary dysfunction raised the Icterus Index to a definitely greater extent than did either duodenal ulcer or acute appendicitis. The lowest Index obtained in active biliary dysfunction was 10.0, whilst the highest Index due to duodenal ulcer was 8.6. Therefore one may reasonably conclude that an Index of over 9.0, points to gall-bladder trouble rather than duodenal ulcer or appendicitis.

The figures obtained with duodenal ulcer and acute appendicitis, however, are more confusing. The former<sup>x</sup> gave figures between 3.4 and 8.6, and the latter<sup>\*</sup> figures between 3.8 and 7.8. This does not enable one to differentiate between the two conditions from the Icterus Index alone, though the average figure of 6.2 for duodenal ulcer as against the average of 5.5 for acute appendicitis shows a tendency to a higher figure in the former disease.

The writer investigated the following cases of proved gall-bladder disease by means of the Icterus Index with the following results:

x Page 63 .

\* Page 71 .

<u>Name.</u>	<u>Pre-operative Icterus Index.</u>	<u>Remarks.</u>	<u>Post-operative Icterus Index.</u>	<u>Remarks.</u>
1. Mrs Ly.	12.8	No clinical Jaundice. Hepatitis. Thickened. Gall-Bladder and some Cholecystitis. No Cholelithiasis.	---	Laparotomy only performed.
2. Mrs Hn.	12.0	No clinical Jaundice. Cholecystitis and Cholelithiasis.	5.4	Cholecystostomy performed.
3. En.	15.0	Doubtful clinical Jaundice. Cholelithiasis, and stone in common bile duct.	---	Refused operation.
4. Miss Dn.	4.0	No clinical Jaundice. Cholelithiasis. No stones in the bile ducts. No Cholecystitis.	---	Cholecystectomy performed.
5. Mrs McHh.	6.6	No clinical Jaundice. Cholelithiasis. No stones in the bile ducts. No Cholecystitis. Acute Appendicitis.	4.4	Cholecystectomy and Appendectomy per- formed.
6. Ky.	50.0	Marked Clinical Jaundice. Cholelithiasis and stones in common bile duct.	---	Operation refused.
7. Mn.	25.7	Clinical Jaundice. Cholelithiasis and Cholecystitis. Gall-stones in the common bile duct.	6.0	Cholecystostomy performed.

<u>Name.</u>	<u>Pre-operative Icterus Index.</u>	<u>Remarks.</u>	<u>Post-Operative Icterus Index.</u>	<u>Remarks.</u>
8. Miss Ks.	20.4	Clinical Jaundice. Cholecystitis. One gall-stone impacted at entrance of cystic duct into common bile duct.	5.0	Cholecystostomy performed.
9. Mrs Tt.	10.0	No clinical Jaundice Cholecystitis and per- forated gall-bladder.	4.4	Cholecystostomy performed.
10. Miss O'Br.	23.6	Biliary colic of a few hours' duration. No Jaundice. Cholecystitis and Cholelithiasis. Gall-stones in the common duct.	3.5	Cholecystostomy performed.
11. Mrs An.	4.6	No clinical jaundice. Small fibrosed gall- bladder, containing two large stones, and two or three small stones. No stones in the ducts.	---	Cholecystostomy performed.
12. Mrs Sh.	4.1	No clinical jaundice. Small fibrosed gall- bladder, containing two large stones.	---	Cholecystectomy performed.

<u>No.</u>	<u>Name.</u>	<u>Pre-Operative Icterus Index.</u>	<u>Remarks.</u>	<u>Post-operative Icterus Index.</u>	<u>Remarks.</u>
13.	Miss Br.	35.5	Definite clinical jaundice. Stones in common bile duct.	---	Refused operation.
14.	Mrs Wd.	11.1	No clinical jaundice. One large and several small stones in gall-bladder. Sand in bile ducts and gall-bladder.	4.2	Cholecystectomy performed.
15.	Mrs Rr.	17.3	Biliary colic of a few hours' duration. No clinical jaundice. Cholecystitis and cholelithiasis.	3.7	Cholecystostomy performed.
16.	Mrs At.	16.6	Faint tinge of jaundice. Thickened gall-bladder. Stones in gall-bladder and common bile duct.	4.0	Cholecystectomy performed.

Of the above the following cases were of especial interest:

CASE 2. In this case the patient's history was as follows:

In January, 1927, she had an attack of 'pain in the stomach' associated with vomiting. This recurred in February, during which time she was in bed for six weeks, and stated that she was jaundiced. In April the pain recurred, but on this occasion was associated with 'shivering turns'. During the attack in which she came under observation in June, she again had attacks of shivering and some abdominal pain.

She had had Malaria while in India some years before.

In view of the rigors present, the possibility of a renal condition or a recurrence of Malaria had to be considered in addition to Cholecystitis. The Icterus Index of 20 removed the possibility of kidney trouble, and although, as will be shown, Malaria may cause a raised Icterus Index, no case has been recorded with an index as high as 12.0. Therefore Cholecystitis was diagnosed, and on operation this was found to be present.

CASE 3./

CASE 3. In this case the value of the Icterus Index in the diagnosis of Jaundice was shown.

On admission it was doubtful if Jaundice was present or not. The Icterus Index of 15.0 showed that the patient was just entering the stage of Jaundice, and operation was performed immediately before this developed further. The patient was tender over the appendix as well as over the gall-bladder, but the high Icterus Index pointed to gall-bladder trouble as against Appendicitis.

CASE 4. Here we have a case of Cholelithiasis, in which the Icterus Index was not raised.

The patient gave a history of repeated attacks of gall-stone Colic with Jaundice, the last of which was over a fortnight before. There was no clinical Jaundice. The explanation of the normal Icterus Index in this case seems to be that the patient from time to time passed a stone with resultant hyperbilirubinaemia and Jaundice, but owing to the fact that a fortnight had elapsed before she came under observation, the hyperbilirubinaemia had disappeared after the passage of the stone. That the mere presence of gall-stones, without associated Cholecystitis or any obstructive symptoms, will not raise the Icterus Index will be shown in other cases, and it is/

is a well known fact that many people carry gall-stones without suffering any symptoms from their presence.

CASE 5. This case is similar to the previous one in that the gall-stones were giving rise to no obstructive symptoms, and that there was no Cholecystitis. In view of the results found in cases of Appendicitis, which will be discussed later, it would seem that the raising of the Icterus Index to 6.6 was due to the acute Appendicitis present.

CASE 7. This case was seen at night in artificial light, and it was uncertain whether jaundice was present or not. He complained of pain and tenderness over the upper half of the abdomen with muscular rigidity. The possibility of a perforated duodenal ulcer was disposed of, and the presence of jaundice confirmed by the Icterus Index of 25.7.

At operation the stones were removed from the gall-bladder and ducts, and a cholecystostomy was performed. Two days later the Icterus Index was 15.0, the patient still having a tinge of jaundice. Later the Icterus Index fell to normal limits, the figure being 6.0.

CASE 8. In this case the value of the Icterus Index in prognosis is shown. There was a stone so tightly impacted at the entrance of the

the cystic into the common bile duct that it was impossible to remove it. Cholecystostomy was performed in the hope that the stone would either be discharged or passed on when the tension in the gall-bladder was released. The Icterus Index before operation was 20.4. Five days later jaundice had disappeared, and the Index was 11.5. Later the Index fell to 5.0. From the fact that the Index fell to normal after operation we may deduct that the stone left behind at operation had either been passed on or discharged. The prognosis, therefore, was better than it was immediately after the operation when the stone was still lodged in the duct.

CASE 10. In this case we find an Icterus Index of 23.6 without clinical jaundice. This is unusual, but is explained by the fact that the patient had been suffering from biliary colic for only a few hours, with the result that although the bilirubinaemia had passed the 'saturation point' of 15.0, there had not been time for the tissues to become stained with the pigment. Later in the day the patient became jaundiced.

CASES 11 & 12. Both of these cases again illustrate the fact that the mere presence of gall-stones without obstructive symptoms or associated cholecystitis will not cause a hyperbilirubinaemia.

CASE 15. This patient gave a history of an acute attack of pain across the upper half of the abdomen some hours previous to admission.

On admission the pain had passed off, leaving behind some tenderness in the region of the gall-bladder, but no clinical jaundice. The Icterus Index was found to be 17.3. Operation was not performed immediately, and by the next morning the patient had developed definite jaundice. This bears out, as has already been shown in Case 10, that it is possible to have an Icterus Index over 15.0 without clinical jaundice, but that this is only a temporary state of affairs, the jaundice appearing within a few hours.

From the above cases we may conclude that in active biliary dysfunction the Icterus Index will give definite and early indication of disease. The converse also holds good, for in no case investigated by the writer was there active biliary dysfunction found at operation in the face of an Icterus Index within normal limits previous to operation.

However, in cases where there is merely an indolent cholelithiasis with no associated inflammatory or obstructive changes, there will be no hyperbilirubinaemia, and in consequence the Icterus Index will not be raised.

This/

This is in agreement with the findings of Friedman and Straus<sup>19</sup> who found that in cases of cholecystitis without jaundice more than 90% showed a hyperbilirubinaemia if examined during an acute attack, but that if examined in the latent periods when complaining merely of flatulence and dyspepsia, these cases did not show a hyperbilirubinaemia.

At the same time, no other liver function test will reveal the mere presence of gall-stones in such cases. Post-mortem examinations have shown time and again that there are many people with gall-bladders containing stones which have not manifested themselves during life. In these cases it could not be expected that the Icterus Index would reveal their presence.

In addition to the above cases the following cases are of interest from the point of view of gall-bladder disease.

CASE A. Mrs Br. The history was that 4 years ago she had had supposed gall-bladder trouble, but that at a laparotomy nothing pathological had been found. Since that time she had been troubled by gastric symptoms of vague type, and by vague pains located over the gall-bladder. She was worried by the thought that it might be "gall-stones". Her Icterus Index was 3.2, in view of which fact, and the/

the previous operative findings, it was decided that the trouble was probably due to adhesions from the operation. The dyspepsia was treated on the usual lines, the patient reassured as to the condition of her gall-bladder, and the symptoms disappeared within a few weeks.

CASE B. Mrs Ah. Eight years previously this patient had had a cholecystostomy for cholelithiasis. Some time after the operation she began to suffer from slight pains in the upper right quadrant of the abdomen. These gradually became more severe, though there was no suggestion of biliary colic, nor was there a history of jaundice. A diagnosis of recurrence of the gall stones was made and a second operation performed. Her preoperative Icterus Index was 6.6. At the operation a practically normal gall-bladder was found, there being neither gallstones nor cholecystitis. There were, however, numerous adhesions in the region of the gall-bladder, involving the bile ducts, and evidently due to the previous operation. These adhesions were separated at the operation. Following the removal of these the Icterus Index dropped to 3.7. This case is of particular interest owing to the fact that it is to adhesions such as these that the raised Index obtained in some/

some cases of duodenal ulcer is due, and it proves that such adhesions are definitely capable of producing a hyperbilirubinaemia.

The uses of the Icterus Index do not end here, for it would seem reasonable to suppose, in view of the fact that in all 31 of Bernheim's cases the Index fell to normal after operation, that if in any case the Index did not show this post-operative fall, the operation had not been entirely successful from the prognostic point of view. It might be that there was still some interference with the bile ducts, such as adhesions, which had been overlooked, or possibly in an old standing case it might point to an associated hepatitis, which in itself will cause a hyperbilirubinaemia, while the possibility of a stone having been left in the ducts must be considered. The removal of stones from the ducts is sometimes a matter of great difficulty, and it seems that in cases where stones are to be left behind, the Icterus Index will enable one to determine whether the stone remains impacted or whether it is passed after the gall-bladder has been drained.

A case in point is Case 8 of the writer's series of gall-bladder cases, which has been discussed on Page 36 . Here the fact that the post-operative Index/

Index fell eventually to normal may be taken as evidence that the stone had either been passed on or discharged through the drainage tube, and under the circumstances the prognosis from being rather doubtful, in the presence of the stone left in the duct, becomes good.

The Icterus Index is also of great value in cases of frank or suspected clinical Jaundice. The need of a simple and practical method of accurately estimating the actual degree of icterus present at a given time has long been felt.

Doubt often arises in cases of suspected biliary or hepatic disease as to whether the patient is actually jaundiced or not. Confusion especially arises in people with sallow complexions.

At that stage tests for bile in the urine are inconclusive, but in the event of the serum showing an index of over 15.0, we may take it that Jaundice is present.

Bernheim<sup>20</sup> states that while it is possible to have clinical icterus with an Index below 15.0, it is not possible to have an Index over 15.0 without the patient becoming jaundiced.

The writer found that both were possible, for example Ky. (Jaundice cases No. 2.) was still jaundiced with an Index of 14.2, and Miss O'Bn. and Miss Rr. (Gall-stone cases Nos. 10 & 15) had Indices of 23.6 and/

and 17.3 respectively with no clinical Jaundice. The explanation of this is that although a certain degree of hyperbilirubinaemia results in clinical Jaundice, if the hyperbilirubinaemia is rising rapidly, the "saturation point" may be passed before the clinical Jaundice has had time to appear, with the result that if the serum is withdrawn at the psychological moment, there may be a marked hyperbilirubinaemia which has not yet had time to cause Jaundice, though this would occur in a few hours. In the case of Miss O'Bn. and Miss Rr. the biliary colic was only of a few hours duration when the serum was examined, and the Jaundice had not had time to appear.

The converse also holds good, and it may be that the bilirubinaemia has dropped below the saturation point when the blood is taken, but the Jaundice has not had time to fade.

However, in the average case, all writers are agreed that 15.0 is the figure at which Jaundice appears clinically.

De Witt Stetten<sup>21</sup> quotes cases of suspected post-operative Jaundice and of toxic Jaundice after the intravenous administration of acriflavine. In these cases the Icterus Index was estimated, and in all was found to be normal, and in no case did any clinical manifestation appear.

It would seem also that the Icterus Index would be/

be of great value in the detection of jaundice in the coloured races.

In cases where there is marked clinical jaundice, it is often difficult if not impossible to tell by clinical observation alone whether the jaundice is fluctuating. The very illumination by which the patient is examined alters the appearance of the jaundice, and even if one does form a definite opinion as to increase or decrease, there is no method of recording it. Estimations of bile in the urine give no help in this, as the concentration of the urine varies.

H.P. Maude<sup>22</sup> has carried out experiments to discover if the Icterus Index would serve as a definite indicator of jaundice and as a guide to the increase or decrease of jaundice in disease. The conclusions he came to were that "the Icterus Index is of value in determining the presence of jaundice, and offers a more delicate and accurate means of ascertaining the increase or decrease of Jaundice than does any clinical or laboratory test at present in use." From this it will be seen that in doubtful cases the estimation of the Icterus Index from time to time will show whether or not the jaundice is fluctuating.

In this connection the question of the differential diagnosis between malignant disease of the head of the pancreas with jaundice, and the cases of impacted/

impacted stone in the common bile duct arises. Here again it may be very difficult to make out if there is any variation in the depth of the jaundice clinically, but the estimation of the Icterus Index will at once show if the jaundice is fluctuating or steadily increasing, the latter of course pointing to malignant disease.

In this connection, however, it must not be forgotten that, while a steadily increasing jaundice points as a rule to malignant disease in these cases, it is possible that a tightly impacted stone totally occluding the common bile duct might also have the same effect.

This again emphasises the necessity of using the Icterus Index in correlation with the clinical observations made on the case.

The writer investigated the following cases which showed clinical jaundice.

#### Cases of Jaundice.

No.	<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1.	En.	15.0	Doubtful clinical jaundice. Gall-stone in common bile duct.
2.	Ky.	50.0	Marked clinical jaundice. Bile in urine, faeces pale. Gall-stone in common bile duct.
3.	Mn.	25.7	Definite clinical jaundice. Gall-stone in common bile duct.

<u>No.</u>	<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
4.	Miss Ks.	20.4	Definite clinical jaundice. Gall-stone impacted in common bile duct at entrance of cystic duct.
5.	Hl.	23.1	Clinical jaundice: post-operative after acute appendicitis.
6.	Miss McLd.	27.3	Arsenical intolerance.
7.	Pt.	18.0	Faint tinge of jaundice. Cardiac failure.
8.	Mn.	20.0	Definite clinical jaundice. Pernicious anaemia.
9.	2135.	243.2	Intense clinical jaundice. Acute hepatitis following arsenical intolerance.
10.	Miss Br.	35.3	Definite clinical jaundice. Gall-stone in the common bile duct.
11.	Tr.	63.2	Deep jaundice of three weeks' duration. Carcinoma of head of pancreas.
12.	Mrs At.	16.6	Faint tinge of jaundice. Gall-stone in the common bile duct.
13.	Mrs Dn.	36.3	Definite clinical jaundice. Infective cholangitis. Died.

Of the above cases the following are of especial interest.

**CASE 2.** In this case we have an instance of the Icterus Index as an aid to diagnosis, and as a means of following the course of a case of jaundice.

The /

The patient, a man of 66 years, was jaundiced when he came under observation, and stated that he had been so for 7 weeks. He was not sure if there had been any changes in the degree of jaundice. He gave no history of biliary colic. Under the circumstances the possibility of a malignant involvement of the bile ducts became evident.

On 25.7.27 the Van der Bergh test gave a direct positive result, and the Icterus Index was 50.0

On 2.8.27 the Icterus Index was 31.8. The patient seemed a little less jaundiced, but the marked drop in the Icterus Index at once removed the possibility of malignant disease.

On 9.8.27 the jaundice seemed much the same in intensity, and the Icterus Index was 30.0.

On 16.8.27 the jaundice was definitely less, and the Icterus Index was 21.4.

On 30.8.27 the jaundice had almost entirely disappeared, and the Icterus Index was 14.2.

On 6.9.27 the jaundice disappeared, and the Icterus Index was within normal limits, i.e., 5.3.

It will be seen from the above successive figures that the Icterus Index fell in direct ratio with the clinical jaundice.

**CASE 5.** A few days after operation for acute Appendicitis this patient became suddenly ill. He had abdominal pain, and vomited on/

on several occasions. Doubt arose as to whether he was jaundiced.

The Icterus Index was found to be 23.1. From this one was able to state definitely that the patient was jaundiced, and the case was subsequently diagnosed as a mild case of delayed chloroform poisoning.

The patient improved rapidly. The jaundice disappeared, and a week later the Icterus Index was 6.6. This later fell to within normal limits, being 5.1 when the patient was eventually discharged.

**CASE 6.** This is a case which illustrates the value of the combined use of the Van der Bergh reaction with the Icterus Index.

The patient had been under arsenical treatment for Syphilis for some time when she developed pain in the right upper quadrant of the abdomen, with associated jaundice. In view of the fairly severe pain, biliary colic was diagnosed, but owing to the prolonged arsenical treatment doubt was thrown on this diagnosis.

A biphasic Van den Bergh reaction showed the jaundice to be due to the toxic effect of the arsenic.

To trace the progress of the case the Icterus Index was taken and found to be 27.3. The jaundice gradually disappeared, and at the end of a week the Icterus Index was 15.6, there being then merely a slight/

slight tinge of conjunctival jaundice. A week later the jaundice had disappeared, the index being 4.7.

**CASE 9.** This case is similar to Case 6, and again shows the value of the combined use of the Van den Bergh and the Icterus Index.

The patient had received only five injections of novarsenobillon before he became suddenly ill. He became jaundiced, and vomited frequently. There was slight pain in the right upper quadrant of the abdomen. The liver dullness was not diminished.

A biphasic Van den Bergh reaction showed the jaundice to be due to the toxic effect of novarsenobillon.

The Icterus Index on admission on 26.8.27 was 216.6.

The patient remained much the same clinically, with no appreciable change in the depth of jaundice, but the Icterus Index on the following dates varied as shown:

29.8.27 Icterus Index = 243.2.

31.8.27 Icterus Index = 228.5.

By 6.9.27 the jaundice was definitely less clinically, and the Icterus Index was 140.0.

On 13.9.27 Patient was still jaundiced, the Icterus Index being 30.0.

During the next week Patient did not improve at a corresponding rate, the jaundice remained stationary as /

as far as one could judge, and the Icterus Index was 29.2. Later the Index fell as follows.

27.9.27. Icterus Index = 27.2.

3.10.27. Icterus Index = 21.4.

On this date the Patient was discharged for home treatment; there was still slight jaundice clinically. A fortnight later he reported again. There was now no jaundice clinically, and the Icterus Index was 5.0.

Both this case and the previous one show how well the course of a case of jaundice can be followed by the Icterus Index. The figures obtained are far more reliable than clinical observations, and also enable an accurate record of progress to be kept.

**CASE 11.** This case is an instance of the value of the Icterus Index in the differential diagnosis between simple and malignant obstruction of the common bile duct.

The patient, a man of 63, had been jaundiced for three weeks. He had pain in the right upper quadrant of the abdomen, which was at times quite severe.

His Icterus Index on admission was 63.2. Three days later it was 76.1. In view of the rapid rise malignancy became the more probable, especially when the age of the patient was considered.

Further estimations were impossible, owing to the fact that the patient died two days later.

Autopsy showed a carcinoma of the head of the pancreas.

From the above cases it will be seen that in every case the Icterus Index rose and fell in relation to the increase or decrease of the clinical jaundice. That it forms a measure of the extent of the jaundice and enables one to follow the progress of the same by comparing the figures obtained is evident, and is a great advance on the old 'plus' or 'plus, plus', method of estimating increase or decrease, which was inexact and permitted such a gross personal error.

That the test is a delicate one is shown by the following case of Bernheim's:

"A case of gall-bladder disease which showed a preoperative high Icterus Index underwent the operation of cholecystostomy. Following this the index dropped to normal. Some days later the drainage of bile became obstructed, and the index rose to 7.5. The drainage was reestablished, and the index again fell to within normal limits.

The mere raising of the Icterus Index does not of itself indicate gall-bladder dysfunction. It is merely an indication of a hyperbilirubinaemia, and must be interpreted in accordance with the clinical manifestations of the case.

Take, for example, the jaundice which occurs in cases of catarrhal jaundice. Here as would be expected the Icterus Index is raised, but this gives no /



no indication of the nature of the disease. Nor does the height to which the Index is raised offer any aid to diagnosis, for it has long been established that the intensity of jaundice by itself is not a guide to the character, severity or permanency of the disease.

De Witt Stetten,<sup>23</sup> however, states that he found that in catarrhal jaundice the Index fell very suddenly, although there was no corresponding immediate clinical improvement, and suggests that this might be of use in diagnosis.

Apart from its diagnostic and prognostic value the Icterus Index is also of use in the placing of operative indications. For example, suppose we have a case of definite biliary obstruction by a stone, with obstructive jaundice, the question arises as to whether the Surgeon should operate in the face of the jaundice, or whether he should wait till it subsides. If the Icterus Index is observed from day to day, and it is found that in a few days it has dropped say 30 points, this probably means that the stone has been passed, and allows the Surgeon to wait till the jaundice has subsided entirely.

It is possible in view of De Witt Stetten's statement given above that if in a case of doubtful diagnosis we find a sudden and large drop in the Index, /

Index, we may infer that the case is one of catarrhal jaundice, and avoid operation altogether.

As a contrast to the first supposition, let us suppose that in the same case of definite obstructive jaundice the Icterus Index rises steadily, we should be able to advise operation at once, before the jaundice is too far advanced and the condition is critical.

In cases of doubtful diagnosis with clinical jaundice, if the Icterus Index is found to remain steady though raised, operation should according to De Witt Stetten be advised with caution, as he has found by following up cases of cirrhosis of the liver or malignant metastases in that organ, that the Index keeps steady in these chronic non-operable cases, and the possibility of one of these being present should not be overlooked in the presence of a steady but raised Icterus Index.

Shattuck and Browne<sup>24</sup> have carried out a series of observations as to the relative values of the Icterus Index, and some of the better known and more commonly used liver function tests.

The other tests used in their series were the Rowntree-Rosenthal dye test, the Van den Bergh, and the Fouchet test.

In their series they found in the type of case at present under discussion that all cases with clinical/

clinical jaundice showed an Icterus Index of 15.0 or over, the figures being higher in the more marked cases of jaundice.

They also found that all cases of proved gall-bladder disease without clinical jaundice showed figures which came within the period of latent jaundice, i.e., between 6.0 and 15.0.

In contrast with the above results obtained by means of the Icterus Index, they found that in cases of proved gall-bladder disease without clinical jaundice the Rowntree-Rosenthal dye test often showed normal figures.

In their cases with clinical jaundice the dye test showed by means of an increased dye retention the amount of damage to the liver parenchyma, and was therefore of value in estimating the surgical risk, but that the Icterus Index is also of value in the placing of operative indications has already been shown.

Again, while the dye test is an indication of the damage to the liver parenchyma, it is not a measure of the extent of clinical jaundice as is shown by a special case quoted by Shattuck and Browne, in which the diagnosis rested between catarrhal jaundice and malignant involvement of the bile ducts.

In this case the dye retention figures remained high but steady, while the Icterus Index fell gradually, though/

though clinically the jaundice remained stationary.

The case was eventually shown to be one of catarrhal jaundice, which proves that though the dye test shows high figures in jaundice, it does not indicate the degree of jaundice as does the Icterus Index.

This is borne out by Piersol and Dockus<sup>25</sup> who also found that though dye retention was high in intense jaundice it did not vary in proportion to the jaundice.

Using the Van den Bergh test in these cases of proved gall-bladder disease, both with and without clinical jaundice, Shattuck and Browne obtained positive results, but these results did not in any way indicate the severity of the disease.

This reaction will show, however, whether the jaundice is obstructive or not, and in suitable cases, used in conjunction with the Icterus Index, it is, as has already been shown, of great value, the former indicating the type of jaundice, and the latter the extent of it.

The Fouchet test was shown to be unreliable, proved cases of biliary disease often giving negative results.

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CIRRHOSIS OF THE LIVER.

Shattuch and Browne<sup>26</sup> report that in all cases of cirrhosis of the liver the Icterus Index was found to be raised, with the exception of one case of splenic anaemia with associated cirrhosis of the liver, from between 9.3 to 23.0.

The writer's cases of cirrhosis of the liver showed the following figures:

	<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	Ln.	Splenic Anaemia.	6.8
2.	Hn.	Cirrhosis of Liver, (Syphilitic).	7.4

CASE 1. This showed the following blood picture:

Red blood corpuscles 3,900,000

White blood corpuscles 4,600

Haemoglobin, 75%

Colour Index 0.9

Differential count:

Polymorphs 74%

Large Lymphocytes 2%

Small Lymphocytes 24%

The spleen was markedly enlarged, and the liver was one finger's breadth below the costal margin.

There was also marked ascites present, which necessitated/

necessitated repeated paracentesis.

In view of the fact that the liver was sufficiently damaged to give rise to ascites, the Icterus Index was lower than was expected. This, however, may be explained by the presence of the anaemia, which, as will be shown later, causes a low Icterus Index.

It is possible therefore that had there been no associated anaemia present, the Index would have been higher.

Shattuch and Browne suggest that in cases of splenic anaemia with cirrhosis of the liver and ascites the Icterus Index is of value in determining the risk of splenectomy. This would appear to be doubtful, as it has been shown that a raised Index due to the cirrhosis may be masked by the anaemia present, and it would seem that in the presence of ascites one is justified in assuming greater damage to the liver than the Icterus Index indicates. As, however, so few cases of this disease have been investigated by this method, it is difficult to draw any conclusions of real value.

Using other liver function tests in cases of cirrhosis of the liver, the above writers found that the Rowntree-Rosenthal dye test showed increased dye retention of from 7.0 to 15.0%, except in their case of splenic anaemia.

The Van den Bergh and Fouchet reactions were positive in all cases, but as usual gave no indication/

indication as to the severity of the disease.

These writers quote a special case which died within four months. During that time the Icterus Index rose steadily from 10.0 to 45.0, but though the dye test showed definite retention, this did not rise as the case went downhill.

It would seem therefore that with the exception of splenic anaemia, in which all tests seem useless, the Icterus Index is the most valuable with which to follow the progress of cases of cirrhosis of the liver.

That the Icterus Index may also be of value in differential diagnosis with regard to cirrhosis of the liver is shown by the fact that a case with enlargement of the liver, ascites and distension of the superficial abdominal veins, which was at first taken for a cirrhosis of the liver but was later shown to be portal thrombosis, gave an Icterus Index of 2.6.

#### CARCINOMATOUS METASTASES IN THE LIVER.

Shattuch and Browne<sup>27</sup>, investigating secondary involvement of the liver by carcinoma, report cases in which the Icterus Index was raised to between 8.2 and 15.7. These results were confirmed by operation, but were apparently taken from cases with extensive involvement of the liver.

The /

The above writers state that they found no liver function test to be of any value in disclosing slight or early involvement of the liver.

The writer investigated the following cases of secondary growths in the liver with the following results. The presence of the nodules in the liver was confirmed in every case at operation or by post mortem examination.

<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1. Miss Rn.	Carcinoma of Stomach	2.1	Liver two fingers below costal margin. Marked secondary anaemia. No Jaundice.
2. Hm.	Carcinoma of Colon.	2.3	Liver palpable. Secondary anaemia. No Jaundice.
3. On.	Carcinoma of Rectum.	3.6	No Jaundice.
4. Hs.	Carcinoma of Oesophagus.	3.1	Liver palpable. No Jaundice.
5. Mrs Hd.	Carcinoma of Ovary.	2.0	Palpable nodules on liver. No Jaundice.

None of the above cases showed clinical jaundice, and the involvement of the liver was not very extensive, but in each there were definite nodules palpable at operation.

In every case the Icterus Index was low, giving no indication of liver dysfunction. It is probable that/

that any rise in the Icterus Index in these cases is masked by the secondary anaemia so constant in malignant disease.

The fact remains that the Icterus Index is of no value in the early diagnosis of secondary metastases in the liver.

Comparing the Icterus Index with other liver function tests, Shattuch and Browne found that the Van den Bergh and the Fouchet reactions gave positive results in some cases, and that the Rowntree-Rosenthal dye test showed a retention of from 15% to 22%, but all these results were obtained only in advanced cases, and there seems to be no liver function test which will reveal early liver involvement in malignant disease.

Doubtless in advanced cases the Icterus Index would be raised just as the other liver function tests give positive results under similar conditions. It is not in the advanced cases that diagnosis is desired, however, but in those cases of malignant disease which are diagnosed early, and in which it would be of value to be able to detect liver involvement when considering the advisability of operation.

One is forced to admit, therefore, that, with the other liver function tests, the Icterus Index has failed in this particular.

HYPEREMESIS GRAVIDARUM.

In hyperemesis gravidarum we have, if we accept the usual metabolic auto-intoxication theory as to its causation, yet another example of a toxic effect on the liver.

The liver in these cases shows areas of necrosis in the centre of the lobules similar to that found in acute yellow atrophy, though not to such a marked extent.

Under the circumstances it is to be expected that there will be derangement of the liver function, which may betray itself by causing a hyperbilirubinaemia.

The writer investigated two cases of hyperemesis, and found the Icterus Index to be 8.1 and 10.7, the last case having a fatal termination.

Cases of this and other toxaemias of pregnancy are rare in a general hospital, and the writer was unable to investigate any but the above cases. Nor could any literature be found on this subject.

It would seem probable, however, that if the Icterus Index behaves in these cases as in other diseases, it might be of value in prognosis if repeated on successive occasions, and also in determining whether the termination of pregnancy is advisable in hyperemesis, a steadily rising Index being, of course, in favour of this step.

DUODENAL AND GASTRIC ULCER.

It has been stated previously that there is a possibility of confusion arising in the diagnosis of gall-bladder dysfunction by means of the Icterus Index, owing to the fact that a raised figure may also be shown by duodenal ulcers. The explanation of this rise is that in these latter cases, and particularly in those of old standing, adhesions are formed in the region of the common bile duct, at its entrance into the duodenum. These adhesions may in some cases constrict the common bile duct, and by so doing cause obstruction to the outflow of bile, with a consequent hyperbilirubinaemia.

In the case of gastric ulcers these adhesions around the common bile duct are not present, and in consequence these cases show a normal Icterus Index.

Bernheim<sup>28</sup> quotes sixteen cases of duodenal ulcer which had an Icterus Index varying between 7.5 and 13.6. Two cases which had had haematemesis showed an Icterus Index of 5.0. All her twelve cases of gastric ulcer showed normal figures.

Shattuch and Browne<sup>29</sup> in a series of ten cases of duodenal ulcer found a raised Index in nine of these.

In a series of 19 cases of duodenal ulcer proved by operation the following figures were obtained.

Cases of Duodenal Ulcer.

No.	Name.	<u>Icterus</u> <u>Index.</u>	<u>Remarks.</u>
1.	Mn.	5.1	Duodenal ulcer of 3 years standing. Pyloric stenosis.
2.	Qn.	6.6	-----
3.	Wr.	8.3	Duodenal ulcer of 3 years standing.
4.	St.	7.5	-----
5.	Wd.	3.5	Old standing ulcer. Some pyloric stenosis.
6.	Pe.	6.9	Recent ulcer of 7 months standing.
7.	Miss Bs.	7.5	-----
8.	Hn.	8.3	-----
9.	Tr.	4.0	-----
10.	Gr.	5.0	Perforated duodenal ulcer.
11.	Mrs De.	6.4	Pyloric stenosis.
12.	Bs.	7.5	-----
13.	Cy.	3.4	-----
14.	Me.	8.6	-----
15.	Mrs Wr.	5.2	-----
16.	Gn.	6.4	-----
17.	Cn.	2.1	Double haematemesis within 10 days.
18.	Sn.	2.6	Haematemesis.
19.	Cn.	3.4	Haematemesis.

From the above list of cases it will be seen that although in a large proportion of cases of duodenal ulcer there is a raised Icterus Index, this does not necessarily occur.

Two explanations of this are evident:

Firstly, there are a certain number of patients suffering from duodenal ulcer who, although they have never suffered a definite haematemesis, are being gradually rendered more anaemic by the 'leaking' of the ulcer with consequent 'melaena'. The anaemia thus caused will undoubtedly mask any rise in the Icterus Index due to the presence of the ulcer. Cases in point are Nos. 5 and 13 of the writer's series. Both of these patients were anaemic, though neither had had any severe haemorrhage such as a haematemesis.

Secondly, it must be remembered that while, as stated by the American writers, there are in some of these cases adhesions which may involve the bile ducts, these adhesions are not present in every case, and that when they are absent there is no reason to expect a hyperbilirubinaemia. This is borne out by the fact that several of the writer's cases of proved duodenal ulcer showed normal figures.

All the writer's cases which had had recent haematemesis showed a low or even sub-normal figure, which is in marked contrast to Bernheim's average figure of 5.0 quoted above. The low figure in these cases is due to the secondary anaemia, as will be shown later.\*

With regard to the possibility of confusion arising between duodenal ulcer and gall-bladder dysfunction when using the Icterus Index, it will be seen by comparing the figures obtained that this is a more theoretical than a practical objection, as the highest figure obtained with duodenal ulcer was lower than the lowest figure obtained in gall-bladder dysfunction.

With regard to gastric ulcer, Bernheim quotes twelve cases, all of which showed a normal Icterus Index. The writer's figures were in complete agreement with this, all his proved cases, as shown below, giving normal figures.

#### Cases /

Cases of Gastric Ulcer.

<u>No.</u>	<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1.	Mrs Tr.	4.2	Hourglass stomach.
2.	Wy.	3.5	Perforated gastric ulcer. Died.
3.	Ww.	5.1	Hourglass stomach.
4.	Mrs Fs.	4.0	Hourglass stomach.
5.	Cy.	3.4	----
6.	Miss Tn.	3.7	----
7.	Mrs He.	3.0	Hourglass stomach & recent ulcer.
8.	Hs.	4.0	Perforated gastric ulcer.
9.	Cn.	3.3	----
10.	Ms.	3.0	Recent Gastric ulcer - perforated.

Of the above cases of gastric ulcer the following are of especial interest.

**CASE 1.** This patient gave a history of long standing dyspepsia, which took the form of abdominal discomfort, but did not seem to be specially related to meals in any way. She had been treated for some time for gall-stones with associated dyspepsia. No clinical evidence pointing to gall-stones could be found. The Icterus Index of 4.2 did not suggest the presence of stones, though as has been shown in the writer's series of these cases it did not altogether preclude it. However, in view of the low/

low Icterus Index an X-Ray examination was made, and an hour-glass stomach was found to be present, due to an old standing gastric ulcer.

**CASE 4.** This case was almost identical with Case 1. Here the patient gave such a misleading history that operation for gall-stones was actually performed, but the gall-bladder was found to be healthy, while the stomach showed a constriction due to an old gastric ulcer.

It has been suggested by Barrow and Armstrong<sup>30</sup> that the Icterus Index might be of use in the differential diagnosis between duodenal and gastric ulcer. A raised Index would certainly exclude gastric ulcer, but as has been shown above it is possible to have a normal Index in both gastric and duodenal ulcer, so that a normal Index in a doubtful case would be of no assistance in the differential diagnosis.

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TYPHOID FEVER  
AND OTHER ALIMENTARY DISORDERS.

Bernheim<sup>31</sup> reports four cases of typhoid fever, which all showed a raised Icterus Index lying between 9.0 and 11.5. The probable explanation of this rise is obstruction of the smaller bile passages, due either to the typhoid bacilli in the bile, or to the focal necrosis of the liver, which is a constant accompaniment of typhoid.

Barrow and Franklin<sup>32</sup> have pointed out the diagnostic and prognostic value of the Widal haemoclastic crisis test in typhoid fever, and Barrow and Armstrong<sup>33</sup> working on the Icterus Index have shown that the results of the latter run parallel to the former in this disease. They record twenty-four cases in their series. In none of these was jaundice present. The average Icterus Index was 12.0, and the Widal haemoclastic crisis was positive in 80% of the cases, i.e. nineteen. The diazo reaction of the urine could not of course be averaged.

That the Icterus Index is of more use than the commonly used diazo reaction in the urine seems obvious. The fact that there is a variable degree of excretion or filtration, as the case may be, of bilirubin through the kidneys, together with a variable concentration of bilirubin in the blood serum explains the variations in the diazo reaction.

It/

It is an accepted fact that certain cases may have a very high concentration of bilirubin in the blood before the tissues take on the icteric tinge. It seems probable also that the kidneys do not begin to excrete bile until this stage of saturation has been reached.

Now, the Icterus Index will show a rise in bilirubinaemia long before the saturation point is reached and clinical icterus appears, or before bile is present in the urine and a positive diazo reaction is obtained.

From this it will be seen that the Icterus Index is of more value than the diazo reaction, as it is raised earlier in the disease, and it is possible that in some cases, if the hyperbilirubinaemia never reaches the kidney threshold, there will be a raised Icterus Index, but the diazo reaction will still be negative, and will remain so during the course of the disease.

Bernheim<sup>34</sup> has also used the Icterus Index in the differential diagnosis between typhoid fever and trichiniasis. Four cases of trichiniasis are quoted, all of which showed normal figures, and in three of these cases a positive Widal reaction was obtained. As all the above writer's cases of typhoid showed a raised Icterus Index, this test may be said to have a definite value in distinguishing these two conditions, which/

which may easily be confused, especially in the presence of a positive Widal reaction.

Barrow<sup>35</sup> found that in addition to typhoid fever, other alimentary disturbances may cause a raised Icterus Index. He quotes such disturbances as colitis, amoebae and other intestinal protozoa; in some cases he found the Index to be as high as 10.0.

In all his cases there was a leucocyte count of 6,500 on an average. He therefore suggests that the leucocyte count may have some relation to liver function, and that it may be an indication of the state of the detoxicating powers of that organ at a certain time.

Whether this is so or not, it seems probable that in these alimentary disorders there is toxic absorption from the alimentary tract by way of the portal system. The toxins thus absorbed will be carried to the liver, and by their effects on that organ will give rise to the hyperbilirubinaemia found in those cases.

The writer has examined the following cases of alimentary disorders, with a view to discovering the effects on the liver by means of estimating the hyperbilirubinaemia.

<u>No.</u>	<u>Name.</u>	<u>Disease.</u>	<u>Icterus Index.</u>
1.	Wt.	Perforated appendix. General peritonitis. Died.	6.2
2.	Bt.	Appendicular abscess of three days' standing.	7.9
3.	Wn.	Acute appendicitis. Adhesions round appendix.	5.9
4.	Hs.	Acute appendicitis. Concretion at tip. Appendix inflamed.	6.0
5.	Wg.	Acute appendicitis. Base of appendix gangrenous.	6.9
6.	Mrs McHn.	Acute appendicitis.	6.6
7.	Ah.	Chronic appendicitis. Numerous adhesions.	5.8
8.	Mrs Oy.	Acute appendicitis.	4.0
9.	Miss Nn.	Acute appendicitis.	5.4
10.	Miss An	Chronic appendicitis. Adhesions.	4
11.	Mrs Pe	Chronic appendicitis	3.5
12.	Dd.	Chronic appendicitis "Kinked"	3.5
13.	Miss Aa.	Chronic appendicitis. Adhesions.	5.1
14.	Miss Ld.	Appendicular abscess. Died.	4.0
15.	Miss Mr.	Chronic Appendicitis. Adhesions	3.5
16.	In.	Acute Appendicitis	6.1
17.	Miss Tt.	Acute Appendicular Colic.	3.8
18.	Miss Wy.	Acute Appendicitis.	4.0
19.	Miss An.	Chronic Appendicitis. Very Numerous Adhesions.	4.5
20.	Le.	Acute enteritis. Food poisoning	4.1
21.	Sn.	Tapeworms.	4

It will be seen from the above figures that the Icterus Index in acute appendicitis is not raised to a marked degree, and that a large percentage of cases show normal figures.

The fact that there is hyperbilirubinaemia present in some cases of appendicitis has previously been remarked on by Bang,<sup>36</sup> who found that cases of acute appendicitis showed a hyperbilirubinaemia, and suggested that the fact might be of value in the differential diagnosis between this condition and salpingitis. He found no hyperbilirubinaemia in cases of chronic appendicitis.

The writer's findings in acute appendicitis show such an inconstant and slight hyperbilirubinaemia that one can hope for little help in the differential diagnosis from salpingitis.

With regard to the remaining types of alimentary disorders, the writer's figures were not as high as those reported by Barrow. Chronic appendicitis and the cases of enteritis examined all show normal figures. No cases of protozoal infection were encountered.

It would seem, therefore, that the toxic effects on the liver in the chronic intestinal disorders are small if any; and that while in the case of acute appendicitis, and particularly of appendicular abscess, there/

there seems to be some toxic absorption, this is not present in any marked degree.

From the above findings it will be seen that the raised Icterus Index obtained in certain cases of appendicitis is uncertain and cannot be held to be an aid to diagnosis in this condition.

Being unable to find any other cases of raised Icterus Index in the literature, I have therefore examined 10 cases of acute appendicitis, and in 7 of these the Icterus Index was raised, and in the other 3 it was normal.

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The Icterus Index was raised in 7 out of 10 cases of acute appendicitis, and in 3 out of 10 cases of chronic appendicitis.

It is therefore seen that the Icterus Index is raised in this disease, but, being so uncertain, it cannot be held to be an aid to diagnosis. It is therefore suggested that the Icterus Index should not be used as a guide to diagnosis in this disease.

It is also noted that the Icterus Index was raised in 7 out of 10 cases of acute appendicitis, and in 3 out of 10 cases of chronic appendicitis, despite the fact that the Icterus Index was normal in 3 out of 10 cases of acute appendicitis, and in 7 out of 10 cases of chronic appendicitis.

The writer is aware of no other cases of raised Icterus Index in the literature, and therefore it is suggested that the Icterus Index should not be used as a guide to diagnosis in this disease.

PERNICIOUS ANAEMIA.

The so-called 'biscuit' colour of the patient suffering from pernicious anaemia is a common phenomenon. That this is due to a hyperbilirubinaemia has been shown by Blankenhorn,<sup>37</sup> although bile is seldom present in the urine of these patients.

Using Gmelin's test Blankenhorn obtained positive results in 16 out of 20 cases, and states that "Bilirubin is frequently present in the blood in pernicious anaemia, and is the cause of the jaundice".

Bernheim<sup>38</sup> in her series quotes ten cases of pernicious anaemia in which the Icterus Index was constantly raised, varying from 6.5 (taken during a remission) to 12.5.

Shattuck and Browne<sup>39</sup> also found a raised Icterus Index in this disease, but, using the Rowntree-Rosenthal dye test in the same cases, obtained normal figures.

Maude,<sup>40</sup> on the other hand, states that all his cases with one exception gave an Icterus Index within normal limits, despite an icteric hue clinically.

The writer's cases shown below correspond with those of Bernheim, the Icterus Index in every case being above normal.

Cases/

Cases of Pernicious Anaemia.

<u>No.</u>	<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1.	Ky.	9.4	-
2.	Hs.	8.2	-
3.	Mrs Mn.	9.0	-
4.	Rn.	8.6	-
5.	Mn.	20.0	Clinical jaundice present.
6.	Ah.	8.0	-
7.	Tn.	8.6	-
8.	Wn.	7.8	-

The details of the above cases are as follows:-

<b>CASE 1.</b>	Red blood corpuscles,	3,000,000
	Haemoglobin,	60%
	Colour Index,	1.0

Blood picture:

Anisocytosis and poikilocytosis.

Nucleated red corpuscles present.

Punctate basiphilia and polychromasia.

Icterus Index: 9.4

<b>CASE 2.</b>	Red blood corpuscles,	1,340,000
	Haemoglobin,	34%
	Colour Index,	1.3
	White blood corpuscles,	12,000

Blood/

Blood Picture:

Megalocytes + + Megaloblasts +

Punctate basiphilia.

Macropolyocytes type 1.

Icterus Index: 3.2.

Van den Bergh: Indirect Positive.

The case was treated by liver by the mouth,  $\frac{3}{4}$  lb. being given daily for five weeks. At the end of that time the blood showed the following changes:

Red blood corpuscles, 3,184,000

Haemoglobin, 63%

Colour Index, 1.1

White blood corpuscles, 6,300

Blood picture:

No abnormal white corpuscles.

No nucleated red corpuscles.

Anisocytosis very much less marked.

Icterus Index: 4.4.

Van den Bergh: Faint indirect positive.

**CASE 3.** Red blood corpuscles, 800,000

Haemoglobin, 17%

Colour Index, 1.0

White blood corpuscles, 4,500

Blood picture:

Megaloblasts + ,

Macropolyocytes, types, 1 &amp; 2, + + ,

Punctate basiphilia.

Icterus /

Icterus Index: 9.0.

Van den Bergh: Indirect positive.

The case was treated by the same liver treatment as Case 2, also for five weeks. At the end of that time the blood showed the following changes:-

Red blood corpuscles,	3,670,000
Haemoglobin,	56%
Colour Index,	0.76
White blood corpuscles,	6,500

Blood picture:

No abnormal white cells.

No megaloblasts or normoblasts.

Very few megalocytes.

Icterus Index: 3.8

Van den Bergh: Negative.

<b>CASE 4.</b> Red blood corpuscles,	800,000
Haemoglobin,	20%
Colour Index,	1.2
White blood corpuscles,	3,400

Blood picture:

Marked anisocytosis.

Megalocytes + , Megaloblasts + + ,

Polychromasia.

Howell-Jolly bodies frequent.

Macropolyocytes, types 1 and 2.

Icterus Index: 8.6

Van den Bergh: Indirect positive.

The case was treated by the usual liver treatment for five weeks. At the end of that time the blood showed the following changes:-

Red blood corpuscles,	2,560,000
Haemoglobin,	54%
Colour Index,	1.0
White blood corpuscles,	6,800

Blood picture:

Anisocytosis not marked.

No nucleated red cells.

No Macropolyocytes.

No Megalocytes.

Icterus Index: 3.7

Van den Bergh: Negative.

**CASE 5.**

Red blood corpuscles,	1,400,000
Haemoglobin,	30%
Colour Index,	1.07
White blood corpuscles,	4,600

Blood picture:

Megalocytes ++, Megaloblasts +,

Punctate basiphilia,

Icterus Index: 20.0

Van den Bergh: Indirect positive.

This case was also treated by liver for five weeks. At the end of that time the blood showed the following changes:

Red/

Red blood corpuscles,	3,300,000
Haemoglobin,	75%
Colour Index,	0.86
White blood corpuscles	5,300

Blood picture:

No nucleated red cells.

No hypersegmented polymorphs.

Icterus Index: 5.5

Van den Bergh: Faint indirect positive.

**CASE 6.**

Red blood corpuscles,	1,360,000
Haemoglobin,	28%
Colour Index,	1.1
White blood corpuscles,	4,900

Blood picture:

Megaloblasts + + + , Megalocytes + + + ,

Macropolyocytes, types 1 and 2.

Icterus Index: 8.0

Van den Bergh: Indirect positive.

This case was also treated by liver for five weeks. At the end of that time the blood changes were as follows:

Red blood corpuscles,	3,062,400
Haemoglobin,	57%
Colour Index,	0.9
White blood corpuscles,	8,100

Blood picture:

No nucleated red blood cells seen.

Icterus Index: 4.1

Van den Bergh: Negative.

<b>CASE 7.</b> Red blood corpuscles,	1,680,000
Haemoglobin,	40%
Colour Index;	1.2
White blood corpuscles:	3,700

Blood picture:

Megaloblasts and megalocytes present.

Anisocytosis and poikilocytosis + + + .

Icterus Index: 8.6

Van den Bergh: Indirect positive.

This patient was also suffering from weakness of the left arm, which he was unable to raise to the level of his shoulder on admission. This weakness was evidently due to amyotrophic lateral sclerosis.

He did not react to treatment so rapidly as usual, but after ten weeks of treatment by liver on the usual lines, coupled with massage and artificial sunlight to the shoulder, a marked improvement resulted. The patient could raise his arm well above the shoulder, and was much improved in general health. The blood changes after ten weeks were as follows:

Red blood corpuscles,	4,744,000
Haemoglobin,	84%
Colour Index,	0.8
White blood corpuscles,	7,800

Blood picture:

No megaloblasts or normoblasts.

Average size of red blood corpuscles normal.

Icterus/

Icterus Index. 3.3

Van den Bergh: Negative.

**CASE 8.**

Red blood corpuscles	1,312,000
Haemoglobin,	38%
Colour Index,	1.5
White blood corpuscles,	3,200

Blood picture:

Red blood corpuscles increased in size.

Occasional megaloblasts.

Poikilocytosis. Anisocytosis marked.

Icterus Index: 7.8

Van den Bergh: Indirect Positive.

The patient was treated by the usual liver diet for five weeks, at the end of which period the blood changes were as follows:

Red blood corpuscles,	3,560,000
Haemoglobin,	78%
Colour Index,	1.1
White blood corpuscles,	7,000

Blood picture:

No nucleated red cells.

Average size of red corpuscles large.

No abnormal white corpuscles.

Icterus Index: 4.5

Van den Bergh: Faint Indirect positive.

Of the above cases, numbers 2, 3, 4, 5, 6, 7, & 8 are of special interest, in that they show the results of the liver treatment first recommended by Minot and Murphy in 1926<sup>41 & 42</sup>, and again reported on by the same writers in 1927<sup>43 & 44</sup>, and the value of the Icterus Index in the prognosis of pernicious anaemia.

The improvement in these cases under liver treatment is all the more remarkable when it is remembered that cases 3, 4, and 6 showed the second or megakaryocyte type of macropolyocyte described by Cooke<sup>45</sup>. This writer states that the presence of these cells is of "grave prognostic import, few cases having lived beyond a few days of its appearance", which makes the improvement of these cases of great interest.

With regard to the value of the Icterus Index in the prognosis of these cases, it will be seen above that as the blood picture improved, so did the Index fall, from which we may deduce that, although of course the repeated examination of the blood in these cases is essential, we have in the Icterus Index an additional indication of the progress of the disease.

Murphy and Monroe<sup>46</sup> report that on a liver diet there was a definite drop in the Icterus Index as early as the eighth day of treatment, and that the Index fell to normal in three weeks.

In/

In 1923, Friedman<sup>47</sup>, using the Van den Bergh reaction, attempted to show that the estimation of bilirubinaemia was of value in the prognosis of pernicious anaemia. His results showed that these estimations were of value, but the writer has also used Van den Bergh reactions in his cases for comparison, and as will be seen these do not give the same definite and delicate indication of progress as the Icterus Index.

It has been suggested by George and Brown<sup>48</sup> that the Icterus Index should be used as a means to differentiate between pernicious anaemia and the anaemia due to malignant disease and particularly that due to carcinoma of the stomach. These writers found a raised Index in all cases of pernicious anaemia, and a subnormal Index in all cases of malignant disease, and secondary anaemias from any cause. It would seem, therefore, that in cases in which the diagnosis lies between carcinoma of the stomach and pernicious anaemia, the Icterus Index provides us with an additional means of establishing a definite diagnosis. It must not be forgotten, however, that in cases of malignant disease advanced secondary involvement of the liver may also raise the Icterus Index.

As a matter of interest, it would seem that the fact that an acknowledged haemolytic anaemia, such as pernicious anaemia, gives a raised Icterus Index, while/

while the anaemia in cases of carcinoma causes a low Icterus Index, goes to prove that the anaemia in the latter cases is secondary, and not haemolytic as has been suggested.

It is generally recognized that the anaemia of carcinoma is secondary, and not haemolytic as has been suggested. The anaemia is secondary, and not haemolytic as has been suggested. The anaemia is secondary, and not haemolytic as has been suggested.



In the present case, the anaemia is secondary, and not haemolytic as has been suggested. The anaemia is secondary, and not haemolytic as has been suggested. The anaemia is secondary, and not haemolytic as has been suggested.

of which the Icterus Index is raised to 1.0 and 2.0 as a result of the anaemia.

For cases of carcinoma, the anaemia is secondary, and not haemolytic as has been suggested.

MALARIA.

While discussing the effects of the haemolysis present in pernicious anaemia on the bilirubinaemia, it is opportune to consider the condition of malaria.

Here we have a disease in which the parasites actually present in the blood are responsible for the destruction of large numbers of red blood corpuscles. As a result of this destruction there is an increase in the amount of haemoglobin at the disposal of the liver, with the result that there is an excessive formation of bile pigments by the liver with consequent hyperbilirubinaemia.

Bernheim<sup>49</sup> reports four cases of malaria, in all of which the Icterus Index was raised to between 7.5 and 8.0 as a result of the above hyperbilirubinaemia.

No cases of malaria have come under the observation of the writer.

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SECONDARY ANAEMIA.

Conversely to the cases of pernicious anaemia quoted above, all cases of secondary anaemia showed a low Icterus Index. Bernheim<sup>50</sup> quotes a series of thirty-three cases which gave figures between 2.3 and 3.9. In no other diseases were such low figures obtained.

The explanation of these low figures lies in the fact that in these cases with a low red blood count and deficient haemoglobin there is a reduced amount of the latter at the disposal of the liver, with a resultant hypobilirubinaemia.

The figures obtained by the writer were as follows:

Cases of Secondary Anaemia.

<u>Name.</u>	<u>Red Blood Corpuscles.</u>	<u>Haemo-globin.</u>	<u>Colour Index.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1. Sn.	2,000,000	25%	0.6	2.6	Haematemesis.
2. Cn.	1,500,000	20%	0.6	2.1	Double haematemesis in one week.
3. Miss Ow.	2,480,000	20%	0.4	2.8	Abortion.
4. By.	1,840,000	20%	0.5	2.5	Chronic Nephritis.
5. Cn.	3,970,000	45%	0.6	3.4	Haematemesis.
6. Hs.	3,540,000	35%	0.5	3.1	Carcinoma of mediastinum.
7. On.	3,940,000	45%	0.6	3.6	Carcinoma of rectum.
8. Hm.	1,950,000	20%	0.5	2.3	Carcinoma of pelvic colon.
9. Miss Rn.	2,100,000	20%	0.5	2.1	Carcinoma of stomach.

It seems probable in view of the low figures obtained in these cases that the writer's lowest normal Index of 3.0, in contrast to Bernheim's figure of 4.0, was due to secondary anaemia, so common among hospital patients.

The low figures caused by secondary anaemias also open up the possibility of a fallacy in the Icterus Index readings. It is reasonable to suppose that a patient suffering from a disease which usually raises the Icterus Index, but who also has a secondary anaemia, might show an Index within normal limits instead of the raised one expected from the principle condition.

Instances of this in the writer's cases are Case 15 of the Heart series<sup>x</sup> and Case 2 of the Pneumonia series\*. In both of these there was a lower figure obtained than was expected, and in both cases there was a secondary anaemia present. In the case of heart disease the figure fell to subnormal after treatment with digitalis on the usual lines.

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<sup>x</sup> Page 90 .  
<sup>\*</sup> Page 105 .

CARDIAC DISEASE, WITH AND WITHOUT DECOMPENSATION.

In cases of cardiac failure the so-called sub-icteric tinge of the skin, which sometimes appears in cases with decompensation, is probably due to a hyperbilirubinaemia caused by the congestion of the liver, which is undoubtedly present in these cases. Following this line of argument, Bernheim<sup>51</sup> found that cases of cardiac disease with decompensation showed a raised Icterus Index. This was also found to vary in accordance with the clinical condition, the greater the heart failure, the higher being the Index. In Bernheim's series of forty-one cases, those with cardiac lesion but no cardiac failure clinically all showed an Icterus Index within normal limits. Cases with slight decompensation showed figures between 6.0 and 9.0, while those cases which showed figures between 12.5 and 15.0 all died in a few weeks with one exception.

Shattuck and Browne<sup>52</sup> bore out Bernheim's results, and also compared the Icterus Index findings with those of other liver tests in cardiac cases. They found that the Rowntree-Rosenthal dye test showed a dye retention in cases with decompensation, but this retention did not vary in accordance with the degree of decompensation clinically. The Van den Berg and Fouchet reactions gave positive results in cases with cardiac decompensation, but gave no indication as to the degree of decompensation.

The /

The writer carried out investigations on cases of heart disease, with and without decompensation, with the following results:

Cases of Heart Disease, with and without Decompensation.

<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1. Hn.	10.5	Aortic incompetence. Bronchitis. Heart markedly dilated. Fibrillation. Oedema of legs and feet. Very breathless, and a little cyanosed.
2. Pr.	6.9	Diffuse dilatation of descending aorta. Mitral systolic and accentuated 2nd sound. Deep seated pain, but no other evidence of cardiac failure.
3. Br.	8.5	Double aortic murmur. Heart dilated. Orthopnoea. Oedema of feet and legs.
4. On.	7.5	Aneurysm. Aortic diastolic and mitral systolic. Mild anginal attacks. Breathless on exertion. No oedema.
5. Wn.	7.3	Aneurysm. Mitral systolic (functional). Breathless on exertion. No oedema.
6. Pt.	12.0	Right Bundle branch block, and mitral systolic and presystolic murmurs. Aortic systolic murmur. Extreme orthopnoea, and cyanosis. Marked oedema. Heart dilated.
7. Ae.	8.0	Case alternated between coarse auricular fibrillation and auricular flutter. Uncontrollable by digitalis. Orthopnoea. Some oedema of legs. Occasional cyanosis.
8. Hh.	5.8	Mitral incompetence. Heart not dilated. No evidence of any decompensation. Patient plays football.

Name.	<u>Icterus</u> <u>Index.</u>	<u>Remarks.</u>
9. In.	8.0	Myocarditis and bronchitis. Orthopnoea and oedema of legs. No valvular disease. Dilated heart.
10. Miss Ls.	4.0	Double mitral murmur. Heart not dilated. Haemoptysis. No oedema. Some breathlessness on exertion. Active tuberculosis at apex of right lung.
11. Cn.	5.1	Mitral incompetence. Heart not dilated. No oedema. Bronchitis with slight asthma.
12. Gr.	3.6	Mitral incompetence. Heart not dilated. Slight breathlessness on exertion. Oedema of legs and feet. Albuminuria and granular casts.
13. Hl.	8.8	Mitral stenosis. No oedema. Palpitation and breathlessness on slight exertion.
14. Gy.	3.1	Mitral incompetence. Heart not dilated. Hemichorea. Anaemic. No decompensation.
15. Ds.	6.0	Mitral incompetence. Heart slightly dilated. Marked oedema of legs and scrotum. Slight orthopnoea.
16. Mrs Cn.	15.3	Auricular fibrillation. Oedema of lungs. Blood-stained frothy sputum. Oedema of legs and feet. Liver enlarged.
17. Wd.	9.5	Auricular fibrillation. Orthopnoea. Oedema of feet and legs. Chronic bronchitis.

Of the above cases the following merit special comment.

**CASE 6.** In this case of right Bundle branch block the patient was suffering from extreme orthopnoea with cyanosis on admission.

There was marked oedema of the extremities. The heart was dilated. His Icterus Index at that time was 12.0. A week later he had even more marked orthopnoea, and could not sleep. His Index was then 15.3. At the end of a fortnight the patient was "in extremis". His skin took on the so-called 'Subicteric tinge', and the Icterus Index rose to 18.0. Two days later he died.

**CASE 7.** This patient was admitted suffering from a coarse type of auricular fibrillation. Once under observation it was observed that this alternated with periods of auricular flutter. There was orthopnoea with occasional cyanosis. Oedema of the legs was present. On admission the Icterus Index was 8.0. The patient's condition did not yield to treatment by the usual methods. A week later the Index was 8.3. At the end of a fortnight the orthopnoea was more marked, and there was some oedema of the face. The Icterus Index had risen to 9.1. Unfortunately the writer lost sight of the case at this stage.

**CASE 12.** On admission this patient was suffering from oedema of the feet and legs, and some orthopnoea. There was also a mitral systolic murmur present. The heart was not dilated. The Icterus Index however was 3.6. On further investigation it was found that there had been transient oedema of the face, while the urine contained some albumin and granular cases. It was eventually shown that the case was one of chronic nephritis, which was the cause of the oedema. The breathlessness was probably due to the associated anaemia. The mitral systolic murmur was apparently either functional or incidental.

**CASE 15.** On admission the patient was suffering from mitral incompetence. The heart was slightly dilated, and there was marked oedema of the legs and scrotum. There was also slight orthopnoea. The Icterus Index, however, was only 6.0. The explanation of a normal Index in a case with evident cardiac decompensation clinically is that the rise in the Index was masked by the fact that the patient was suffering from a secondary anaemia, which, as has already been shown, will cause a lowering of the Icterus Index. This contention is borne out by the fact that after treatment by digitalis the patient made an excellent recovery. The heart was reduced in size, and the oedema disappeared, as did the orthopnoea, /

orthopnoea, and when the patient was in this improved condition the Icterus Index dropped to 2.7, which low figure is indicative of the secondary anaemia present.

**CASE 16.** On admission the patient was suffering from marked cardiac decompensation due to auricular fibrillation. The heart was dilated, there was marked orthopnoea and oedema of the legs. There was also some oedema of the lungs, causing a copious frothy sputum. A few days later the patient showed a tinge of jaundice, and the Index rose to 25.0. Ten days after admission the patient died.

**CASE 17.** On admission the patient was suffering from auricular fibrillation. The heart was decompensated with resultant orthopnoea and oedema of the feet and legs. The patient also suffered from chronic bronchitis. The Icterus Index at this stage was 9.5. Treatment by digitalis on the usual lines resulted in a rapid and marked improvement. The orthopnoea was relieved, and the oedema disappeared. Six weeks later, when the signs of active decompensation had entirely disappeared, the Icterus Index had fallen to 3.3.

The above figures will be seen to agree with those of Bernheim. In all cases the Icterus Index was /

was higher or lower in accordance with more or less heart failure.

It will be seen that in Cases 6 and 16 the Index gradually rose as the patients went downhill.

It will also have been noticed that the Index was gradually but steadily rising in Case 7. This it is reasonable to suppose may be taken as a bad prognostic sign, the steady rise indicating a gradually increasing degree of decompensation.

It would seem that, if repeated readings of the Icterus Index were taken at intervals in cases of cardiac disease, they would be of value in prognosis, as there seems to be no doubt that the Icterus Index varies in accordance with the degree of cardiac decompensation.

An advantage of this method of estimating the degree of decompensation is that it gives one a definite figure corresponding to the degree of decompensation at a stated time. This can be charted, and the curve obtained by repeated readings will give definite and tangible evidence as to the progress or retrogression of the case.

CASES UNDER ARSENICAL TREATMENT.

Perhaps the most common cases in which arsenical preparations are administered over long periods are those of syphilis.

Owing to the well-known vulnerability of the liver to arsenic, which may result in arsenical poisoning, any test which could be employed as a routine measure, and which would give indications as to the manner in which the liver was tolerating the drug, would be of great value in these cases.

It must be remembered, however, that because a case of syphilis on a course of arsenical treatment develops jaundice, this is not necessarily due to the effects of the arsenic. This has been emphasised by O'Leary<sup>53</sup>, who, while pointing out the necessity for keeping in mind such possible causes as gall-stones and carcinoma of the head of the pancreas, gives the following list of possible causes of jaundice in syphilitic patients under arsenic.

1. Toxic or infectious hepatitis.
2. Arsenical hepatitis which may progress to liver atrophy.
3. Syphilitic disease of the liver, which may take the form of either:
  - (a) Herxheimer effects,
  - (b) Syphilitic hepatitis,
  - (c) The jaundice of acute syphilis.
  - (d)/

(d) Syphilitic cirrhosis.

(e) Too rapid fibrosis from too vigorous anti-syphilitic treatment.

That estimations of the bilirubin content of the blood serum might be of use as a guide to the tolerance of arsenical treatment was first suggested by Chargin and Orgel<sup>54</sup>. The method these writers employed, however, did not allow them to make comparative readings,

As an advance on the above writers' methods, Schamberg and Brown<sup>55</sup>, employing the quantitative Van den Bergh reaction, have followed up a series of cases under arsphenamin treatment. Their results showed that in those cases which were susceptible to arsenic, and gave clinical evidence of arsenical poisoning, there was a raised amount of bilirubin in the serum. They also found that this hyperbilirubinaemia could be detected by serum examinations before clinical manifestations were present.

Working on the lines suggested by Schamberg and Brown, the writer investigated the cases shown below. All these were cases of syphilis undergoing courses of intravenous arsenical injections. In place of the Van den Bergh test the writer used the Icterus Index. Observations were taken at regular intervals with a view to finding the reaction of the liver to prolonged treatment. The following cases were examined every three weeks during treatment.

No.	Name.	Remarks.	Icterus Index at intervals of 3 weeks.					
			First Seen.	3 wks.	6 wks.	9 wks.	12 wks.	15 wks.
1.	1531	Just starting course of SS.	4.5	4.5	4.8	5.0	4.3	4.5
2.	1625	On course of SS.	4.4	4.4	4.0	4.2	4.0	3.3
3.	1762	Just starting course of NAB.	3.7	3.0	3.0	2.9	3.0	-
4.	1925.	do. do.	5.7	5.0	4.7	5.0	5.3	-
5.	1931.	do. do.	6.0	6.0	5.9	6.0	6.2	-
6.	1935	Just starting course of SS.	5.0	5.0	5.0	4.8	4.0	-
7.	2012	NAB for 9 weeks previously.	7.3	8.3	4.2	-	-	-
8.	2017	Just starting course of NAB.	5.2	4.0	4.4	4.4	4.4	-
9.	2056	Provocative injection previously	3.6	3.0	3.3	3.0	3.0	-
10.	2074	4 Injections SS.1 previously.	5.0	4.5	4.5	4.0	4.0	-
11.	2111	2 " "	8.0	5.0	5.0	5.0	5.0	-
12.	2119	2 injections NAB previously.	5.0	4.9	4.7	4.8	4.7	-
13.	2122	3 " "	8.0	8.0	8.1	8.0	-	-
14.	1229	Just starting course of NAB.	4.1	3.7	3.3	3.3	3.3	-
15.	2146	do. do.	3.0	3.0	3.0	3.0	3.0	-
16.	2147	do. do.	4.1	4.0	4.6	4.2	4.3	-
17.	2156	do. do.	3.3	3.3	3.3	3.3	3.3	-

In addition to the above the following cases were investigated:

**CASE 2053.** This patient developed a dermatitis while under treatment with silver salvarsan.

When first seen the dermatitis was well marked, and the Icterus Index was 9.3. The arsenic was stopped, and in a week the Index dropped to 6.9. Following this the patient did not report for six weeks, at the end of which time the dermatitis had disappeared, and the Icterus Index was 5.0. Arsenical medication was recommenced, and after three weeks' treatment there was no sign of a recurrence of the dermatitis, and the Index was still 5.0.

**CASE 2072.** This patient also developed a dermatitis while on silver salvarsan. Doubt arose as to whether arsenic was the cause of the condition. An Acterus Index of 6.6 pointed to arsenical dermatitis, and the arsenic was stopped.

In three weeks the dermatitis had disappeared, and the Index dropped to 5.0. Arsenical medication was recommenced, and a fortnight later the Icterus Index had risen to 5.7. A week later the Index was 6.3, and there were signs of a recurrence of the dermatitis. The patient was therefore placed on medicinal treatment for a time, and the dermatitis disappeared.

**CASE 1489./**

**CASE 1489.** (Female). This patient had always shown a marked reaction to intravenous arsenic, which necessitated her detention in Hospital over night. Owing to the rapidity with which the reaction occurred, it was thought to be of 'nervous' origin. Her Icterus Index between injections was 4.0. Following an injection of Karsulphan the Icterus Index was taken after 2 hours and 5 hours. In both cases the Index was 4.0. It was therefore concluded that, as there was no rise in the Icterus Index during the reaction, there was no toxic element due to the arsenic present.

**MISS McLD.** This case has already been referred to in the section on Jaundice<sup>x</sup>, Case No.6. Mention is again made of the case to show the value of the Icterus Index in following the progress of these cases of arsenical hepatitis.

When first seen there was definite clinical jaundice, and the Icterus Index was 27.3. A week later the jaundice had diminished, the Index being 15.6. On the complete disappearance of the jaundice the Index fell to 4.7.

**CASE 2135./**

**CASE 2135.** This case has also been previously referred to in the section on Jaundice, Case No.7.\*

Here again when the case first came under observation there was deep clinical jaundice, and an Icterus Index of 216.6. This varied in relation to the jaundice as has been shown. The patient made a good recovery, the jaundice disappeared and the Index fell to 5.0.

Owing to the presence of a secondary sore on the lip, it was decided to recommence the arsenic after a month's rest. Accordingly two injections of Novarsenobillon, Gm. 0.15 were given at an interval of a week. After each injection the Index remained at 5.0. Following this an injection of 0.3 gm. was given on two successive weeks and the Index was still 5.0. The course was proceeded with on guarded lines until an injection of 0.6 gm. still left the Icterus Index at 5.0.

From the above figures it will be seen that in the vast majority of cases, even after prolonged courses of arsenic, the Icterus Index remains within normal limits. It will also be seen that in a large percentage of the cases there is a slight rise in the Icterus Index at the commencement of treatment, followed by a gradual fall as treatment is continued. In some cases the Index rose to above normal at this stage. The preliminary rise is apparently due to the toxic effect of the arsenic on persons not accustomed to it, but as tolerance is acquired under continued treatment, so does the Index return to its original level.

It will be observed that there is no relationship between number of injections of arsenic and the amount of bilirubin present.

A case of special interest is No.13 of the writer's series. This patient had an Index of 8.0, which remained stationary at that level for a period of nine weeks whilst under observation. In view of the fact that the Index showed no evidence of fluctuation despite continued treatment, it seems probable that the high figure was due, not to the arsenical medication, but to some extraneous cause, such as duodenal ulcer.

A raised Icterus Index was found in all cases of arsenical hepatitis and dermatitis, and was found to/

to vary in accordance with the progress of the disease. It would seem, therefore, that we have in the Icterus Index a method of following the toxic effect, if any, of the arsenic preparations on various patients.

The blood can be easily withdrawn at the time of giving the injections, and if examined at regular intervals will give definite evidence of the tolerance of the patient to arsenic. Patients with Indices within the period of latent jaundice should be watched carefully, and a steady rise in the Index through that period must be regarded as a danger signal.

Similarly, in patients who have a definite toxic hepatitis with jaundice, the Icterus Index will enable one to judge when the ill effects of the arsenic have disappeared; for though clinical jaundice may have disappeared, one may consider that further arsenical treatment is contraindicated until the Index has returned to normal.

In these cases also, if arsenical treatment is recommenced we have in the Icterus Index a valuable check on the treatment, and a means of preventing a recurrence of the hepatitis.

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CASES OF PNEUMONIA.

It is generally admitted that the appearance of clinical jaundice in pneumonia is a bad prognostic sign. Bernheim<sup>56</sup>, however, has shown in those cases without clinical jaundice that the so-called latent jaundice as disclosed by the Icterus Index is also of prognostic value. Her results are shown by the accompanying diagram, which is taken from her article in the Journal of the American Medical Association. From this it will be seen that in her series all cases with an Index of 7.5 or below recovered, and that while all cases above that figure did not die, a higher Index was definitely of more serious prognostic import. Bernheim therefore takes 7.5 as the limit for a favourable prognosis. However, of the two fatal cases which had an Index of 7.9, one had a severe secondary anaemia, and the other a valvular lesion of the heart which did not show signs of decompensation till almost the termination of the illness. Bernheim points out that these additional factors would account for a low Icterus Index in each case, and that being so it would seem that her suggested 'limit of safety' of 7.5 is perhaps rather low.

The figures obtained by the writer in cases of lobar pneumonia are shown below.

Cases /

Cases of Pneumonia.

<u>No.</u>	<u>Name.</u>	<u>Icterus Index.</u>	<u>Remarks.</u>
1.	Nn.	7.4	Double Pneumonia. Recovered.
2.	Mrs Tr.	5.2	Died. Secondary anaemia following abortion.
3.	Mrs Iy.	8.7	Recovered.
4.	Ee.	4.5	Recovered.
5.	An.	4.0	Recovered.
6.	Ty.	7.5	Recovered.
7.	Miss O'Dl.	8.3	Recovered.
8.	Tr.	10.0	Died.

From the above figures it will be seen that no case of the writer's with an Icterus Index of 7.5 or below was fatal with one exception. In this case, No.2, the patient contracted pneumonia while convalescent after an incomplete abortion a fortnight previously. She showed a marked secondary anaemia, which would account for a low Icterus Index despite the pneumonia.

With regard to cases showing an Icterus Index above 7.5, the writer, after comparing the clinical findings with the Icterus Index in each case, came to the conclusion that in the severer cases of pneumonia the Index is raised higher than in the milder/

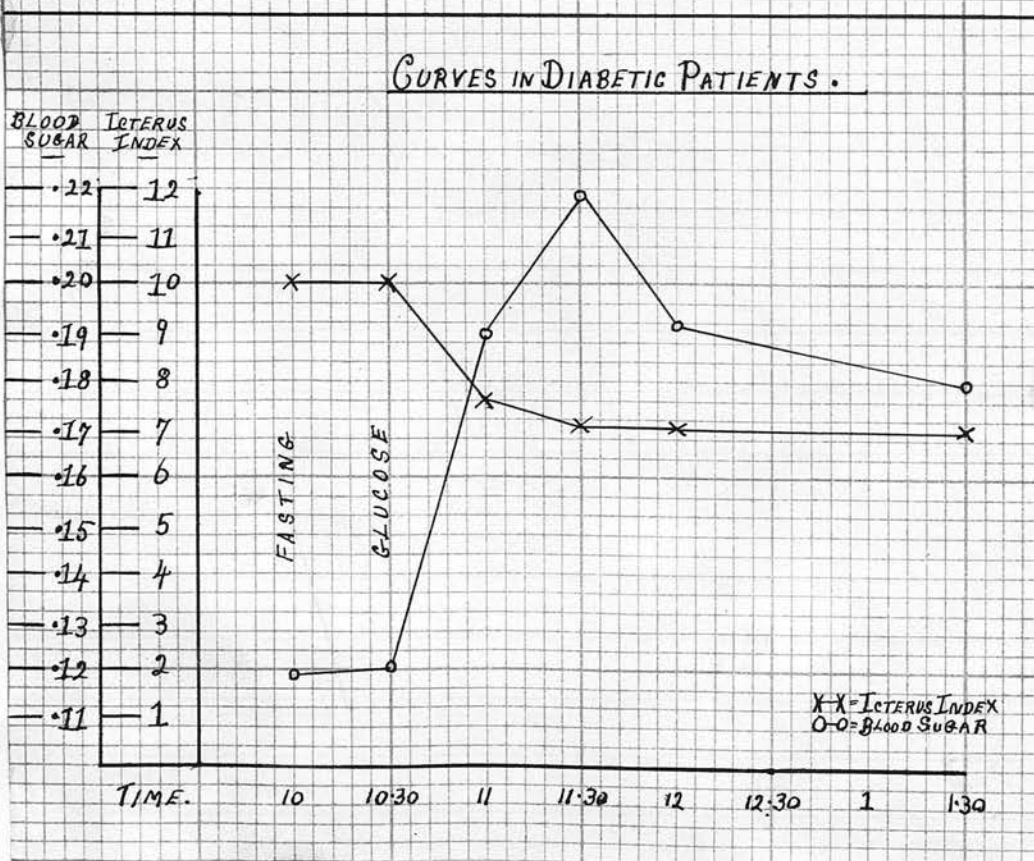
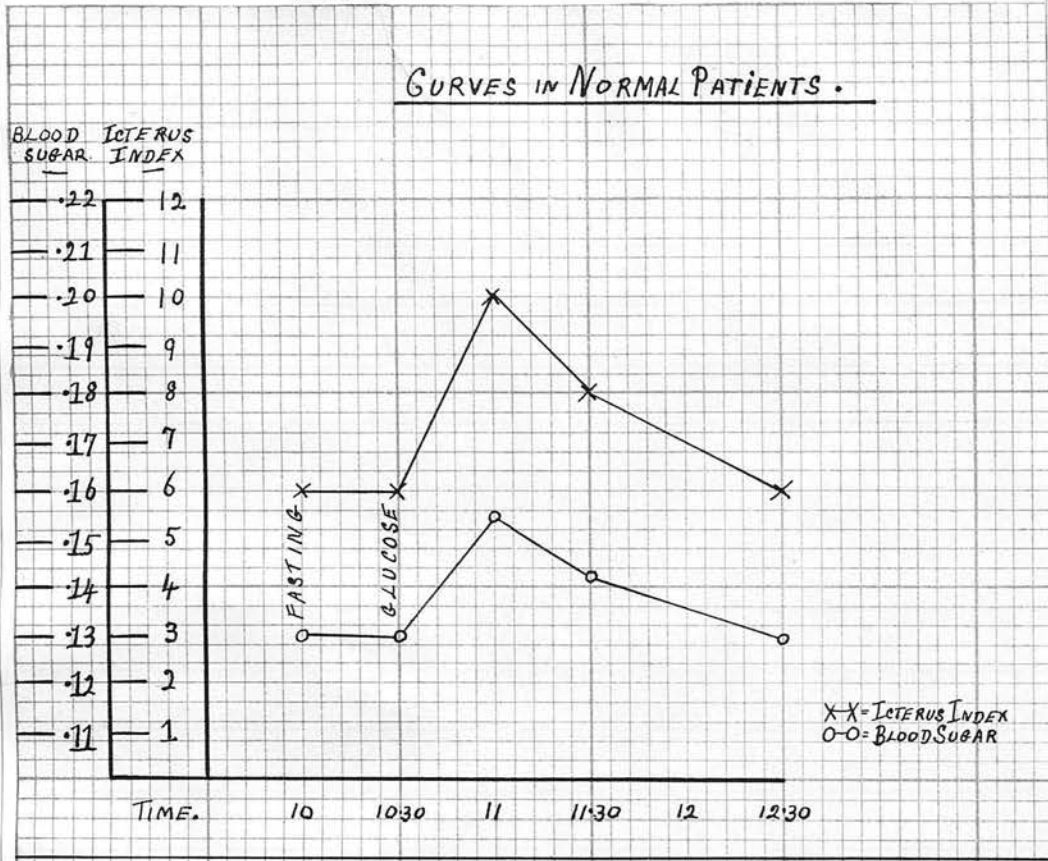
milder ones. Evidence of this is given by the fact that cases 3, 7, and 10 of the writer's series were all seriously ill as compared with other cases under observation, and that the Indices of these cases were the highest in the series.

It may be said, therefore, that the higher the Icterus Index, the worse is the prognosis. It is not possible to be dogmatic in one's prognosis however, as it will be seen from Bernheim's table that cases with an Index even as high as 15.0 may recover.

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THE BLOOD SUGAR AND ICTERUS INDEX FINDINGS IN NORMAL AND DIABETIC PATIENTS.

(Reproduced from Bernheim.)



DIABETES MELLITUS.

Bernheim<sup>57</sup> in her series of cases quotes thirty-two cases of diabetes mellitus in all of which the Icterus Index was raised to between 7.5 and 15.0. No definite explanation of this is offered by Bernheim, but she endeavours to draw a parallel between the Icterus Index and blood sugar. Comparisons were made between normal and diabetic subjects, estimations of both the blood sugar and the Icterus Index being taken before and at intervals after the injection of 1.5 gms. of glucose per kilo of body weight. The results of these experiments as reported by Bernheim showed that in diabetes the Icterus Index was high in the fasting state, and became lower as the blood sugar rose; while in normal individuals a normal Index in the fasting state rose as the blood sugar rose after ingestion of the glucose. Bernheim's charts are reproduced on the opposite page.

Bernheim suggests, therefore, that there is some relation between the blood sugar and the pigment metabolism, but offers no explanation on the point.

The writer examined a series of 13 cases of diabetes mellitus, and obtained the following figures:

Cases of Diabetes Mellitus.

<u>No.</u>	<u>Name.</u>	<u>Icterus Index.</u>
1.	Cm.	6.2
2.	Dn.	3.8
3. /		

<u>No.</u>	<u>Name.</u>	<u>Icterus Index.</u>
3.	Tr.	7.5
4.	Miss O'Dl.	3.3
5.	Miss Mg.	8.9
6.	Mrs Ty.	5.2
7.	Tr.	7.5
8.	Hs.	4.9
9.	An.	3.2
10.	Mrs Gt.	3.7
11.	Mrs Wn.	5.0
12.	Miss Il.	4.4
13.	Mrs At.	4.0

From the above figures it will be seen that the writer's results are by no means in agreement with those of Bernheim.

There seems to be no reason why a disease caused by a lesion in the pancreas should cause a hyperbilirubinaemia, and under the circumstances it seems more probable that the high Icterus Index obtained in these cases is due, not to a hyperbilirubinaemia, but to carotinaemia.

The possibility of carotinaemia causing a raised Icterus Index has already been discussed,\* and a patient on/

on a diabetic diet is extremely likely to develop this condition, owing to the large amounts of green foods consumed over a long period.

From his observations the writer concluded that there is no reason to believe that the Icterus Index will be of any clinical value in cases of diabetes, and that a raised figure obtained in these cases is probably fallacious.

Before entering on a final discussion on the Icterus Index, it is of interest to reproduce two charts, the one taken from Bernheim's article in the Journal of the American Medical Association<sup>58</sup>, the other from Barrow's article in the American Journal of Medical Science<sup>59</sup>.

These charts, reproduced on the following pages, show at a glance the figures obtained with the Icterus Index by these authors in the various diseases.

It has been suggested that by comparing the Icterus Index obtained in any given case with these tables it would be possible to make a diagnosis.

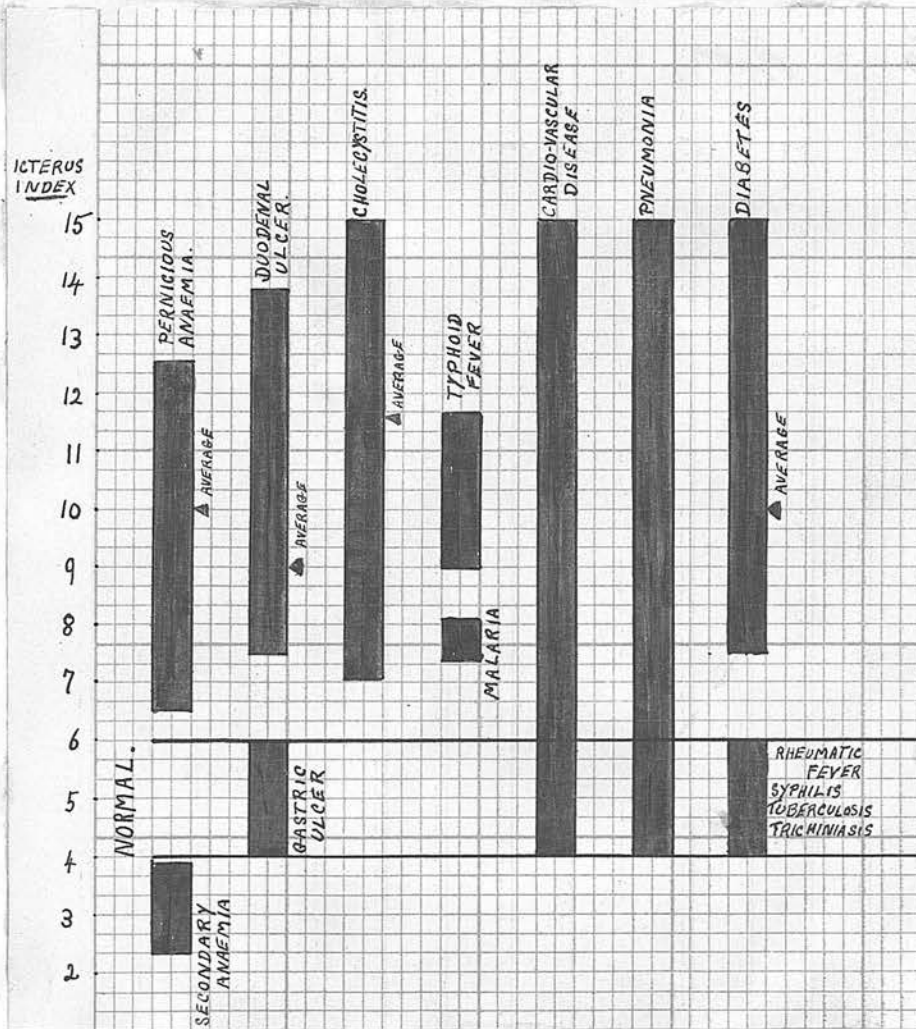
It will have been seen, however, that there is overlapping in the Icterus Index findings in various diseases, and one must also deprecate any tendency to use the Icterus Index as a specific test, while emphasising the necessity of bearing in mind the clinical findings in every case; the Icterus Index to be used as an additional factor in diagnosis.

A third chart has been added which has been drawn up on the lines of the two previous ones from the figures obtained by the writer.

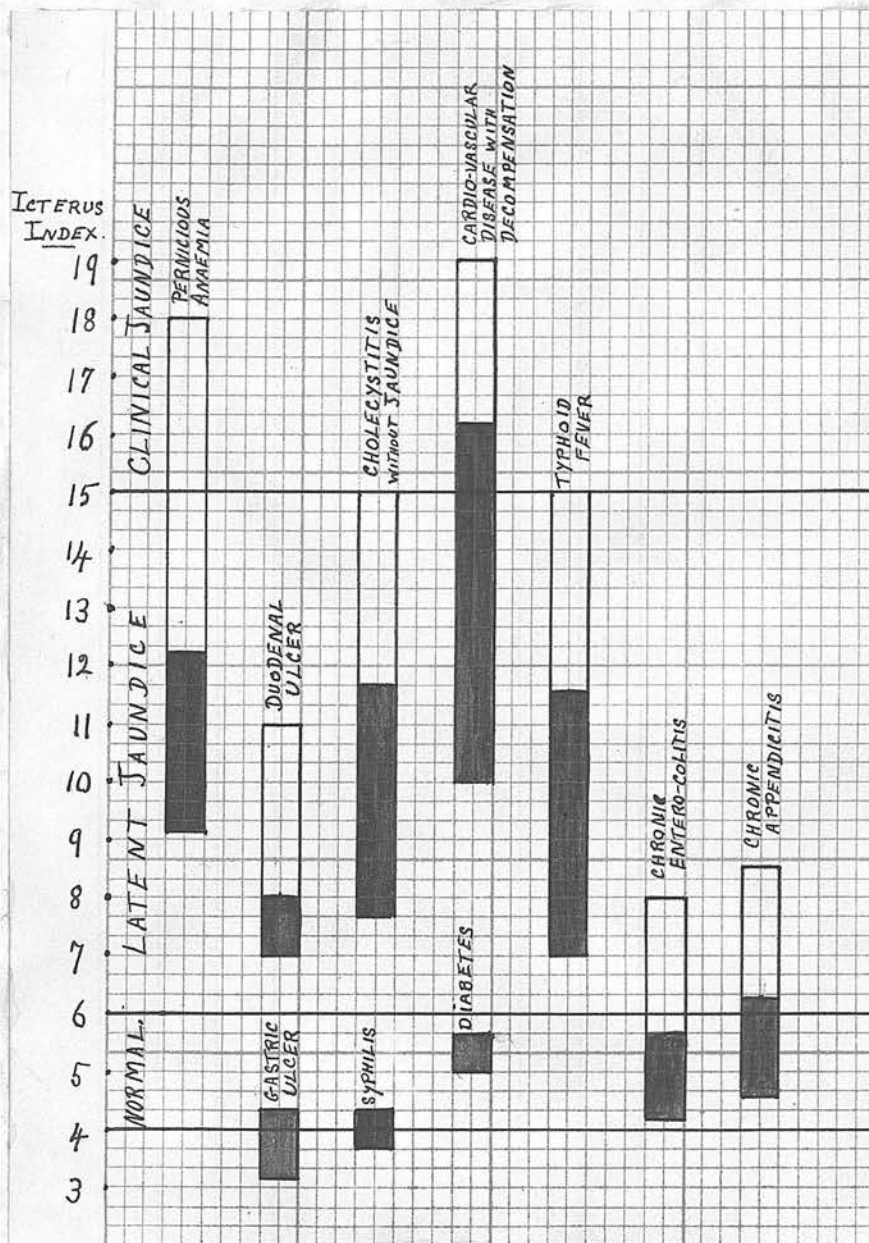
REPRODUCTION OF CHART OF ICTERUS INDICES.

BY BERNHEIM.

The Icterus Index in Various Diseases.

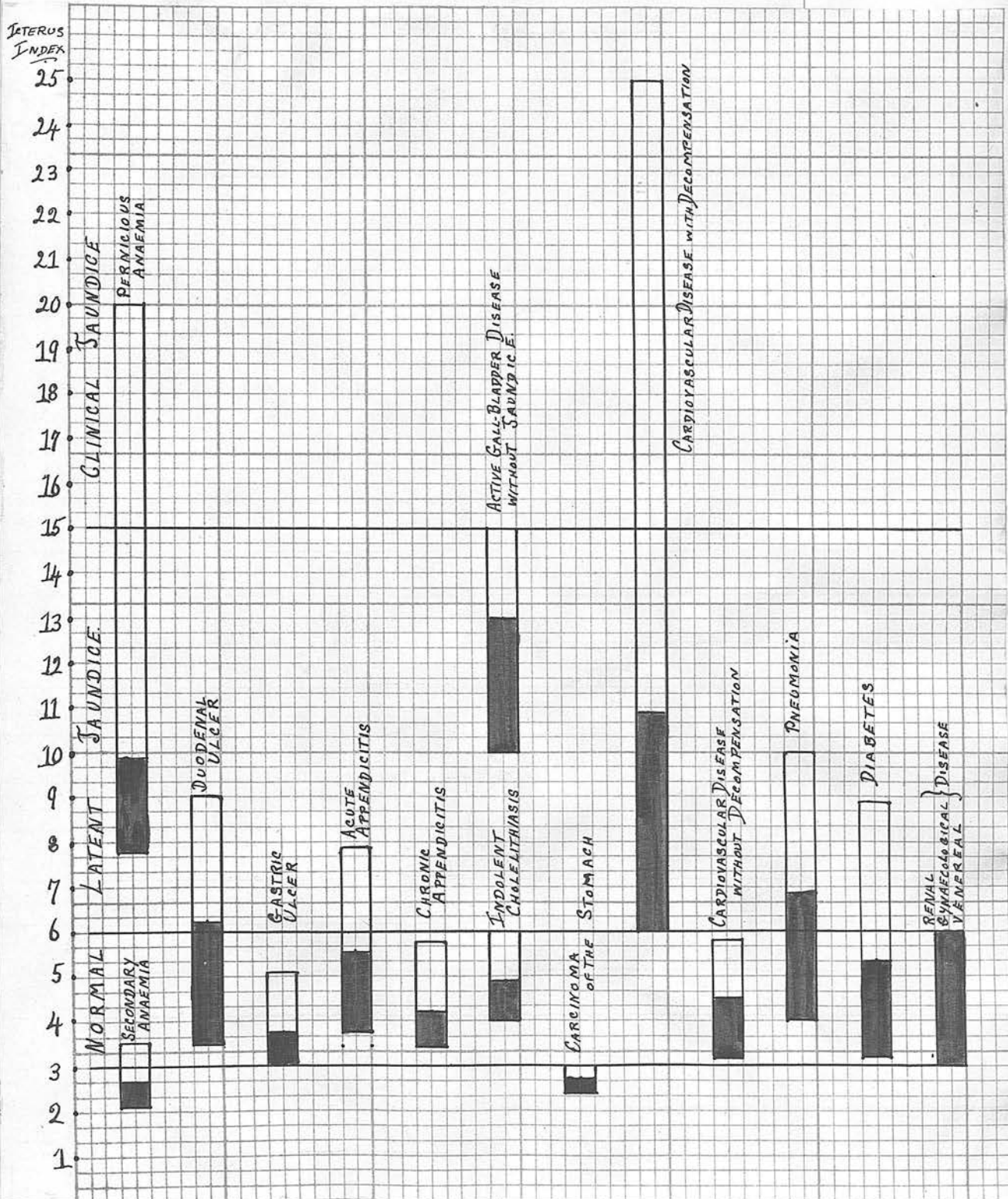


REPRODUCTION OF CHART OF ICTERUS INDICES  
BY BARROW.



Solid black represents the minimum to the average Index.  
White represents the average to the maximum Index.

CHART OF THE ICTERUS INDICES FOUND IN  
VARIOUS DISEASES by THE WRITER.



Solid black represents the minimum to the average Index.  
White represents the average to the maximum Index.

DISCUSSION.

Before one can claim any definite place for the Icterus Index as a useful test of liver function, some comparison is necessary between it and those tests already in every day use. The merits and demerits of these other liver function tests have already been discussed under the various diseases in which they were employed, but to sum up it may be said that:

**Firstly:** the Fouchet reaction is not a delicate enough test to be of any real value when compared with the advantages offered by other tests.

**Secondly:** the Rowntree Rosenthal dye test has several disadvantages as regards its technique in the first place. It necessitates the introduction into the blood stream of the dye. This is in most cases harmless, but the fact that Maurier and Gatewood<sup>60</sup> reported three cases of death within three to seven days of the performance of this test proves that it is not entirely without risk.

Further evidence of the toxicity of the phenoltetrachlorophthalein used is given by Bloom and Rosenau<sup>61</sup>, who found that the use of this drug produced a positive Van den Bergh reaction in a normal subject within sixty/

sixty minutes.

Other disadvantages in the technique of this test are that it necessitates the withdrawal of blood from the patient four times, and that a special colorimeter is required to obtain the readings.

With regard to the findings of the test in the face of disease, this test is undoubtedly a measure of the extent of the liver damage, but it is not so delicate as the Icterus Index in the lesser forms of liver dysfunction, when the patient is at the stage of latent jaundice. Moreover, the dye test has not the wide application of the Icterus Index, being merely indicative of the damage to the liver parenchyma, and not to hyperbilirubinaemia from any cause as is the latter test. Nor is the dye test so delicate in showing the progress or retrogression of individual cases.

**Thirdly:** the Van den Bergh reaction has its greatest use in the differentiation of obstructive from haemolytic jaundice, and when used to show this in conjunction with the Icterus Index, which shows the extent of liver dysfunction, it is undoubtedly of great value. When this is done the same sample of blood/

blood may be used for both tests, the Icterus Index being read first, and the serum then used for the Van den Bergh reaction.

That the quantitative Van den Bergh reaction is of value cannot be denied, but it has no advantages over the Icterus Index, and has a decidedly more complicated technique.

No comparative experiments with the laevulose tolerance have been recorded, but here again one meets with the technical disadvantages of the repeated withdrawal of blood, the complicated blood sugar estimation, and the limited range of application of the test. In these respects this test is very similar to the Rowntree Rosenthal dye test.

With regard to the value of the Icterus Index in gall-bladder dysfunction as compared with other tests of gall-bladder function, the most modern method of determining gall-bladder disease is that of cholecystography. That this method in capable hands can be of great value is shown by the results obtained by Wilkie and Illingworth<sup>62</sup>; but that the investigation is by no means so reliable in less practised hands is shown by the varied and contradictory results obtained by the average investigator.

Again, there are technical disadvantages. If the intravenous method is used, a foreign dye - phenoltetraiodophthalein/

phenoltetraiodophthalein - is introduced into the circulation, and that this is not without danger of toxic effects is shown by Graham<sup>63</sup>, who found a systemic reaction to the drug in 37% of patients thus injected. That the oral method is at least as much if not more open to the same criticism is shown by the same writer, who found a reaction in 50% of cases investigated on these lines. In addition to this there is the necessity for an X-ray examination, or even, as recommended by Illingworth<sup>64</sup>, a series of X-ray photographs in certain cases.

From the above comparisons it will be seen that the Icterus Index has the advantage of being a clinical test with a simple technique, which requires only the withdrawal of blood, the centrifuging of the serum, and the comparison of the latter with a standard colour in a type of colorimeter which is in every day use. It is a process which requires no specialised laboratory methods, and may be carried out quickly even without previous experience, though it must be admitted that some experience of colorimeters is helpful in reducing the 'personal error' factor to a minimum. However, if haemolysis is carefully avoided, and cloudy serum discarded, little difficulty will be experienced in matching the serum and the standard.

A further advantage of the Icterus Index is its wide application, the test being of value in a number of

of different diseases.

While discussing the advantages of the simple technique of the Icterus Index, mention may be made of the possibility of haemolysis. In this we have the greatest source of error in the test. The slightest trace of moisture in the needles or test tube used will cause haemolysis: mere drying with towels is not sufficient to avoid this with certainty, and for all practical purposes dry sterilisation is essential. To emphasise further the importance of this, it may be repeated that while the slightest haemolysis will give high faulty readings, any greater degree will render the serum entirely valueless.

While the Icterus Index undoubtedly has advantages over other liver function tests, it must not be supposed to be of value 'per se' in diagnosis. It must be regarded essentially as an "Index" of bilirubinaemia, and not as a specific test for any disease in particular. The clinical interpretation must depend on the factors present that will cause the hyperbilirubinaemia shown, and any deductions made from the Icterus Index findings must be made in correlation with clinical observations.

Similarly, when used in prognosis one estimation of the Icterus Index is not, in the majority of cases, of much value, but the variation of the Index from time to time is of great value in estimating the progress/

progress of the disease in suitable cases.

Certain fallacies also must be borne in mind when one is interpreting the Icterus Index readings. In the first place it will be remembered that the three conditions, cholecystitis, perforated duodenal ulcer, and acute appendicitis, which may be confused clinically, may all give raised Icterus Indices. This undoubtedly detracts from the diagnostic value of the Icterus Index in these conditions, as it prevents one from making a definite diagnosis from the Index alone. However, when it is remembered that in the majority of cases cholecystitis raises the Index to a greater degree than does duodenal ulcer, which in turn gives higher figures than acute appendicitis, in which condition the Index often remains normal, it will be seen that we have an additional factor in our differential diagnosis which may turn the scale in favour of one or other of these conditions. Again, the mere presence of gall stones causing no obstruction, and not associated with cholecystitis will not raise the Icterus Index, and it is in these cases that cholecystography is of value. Also it must be remembered that, in cases showing clinical jaundice, while a steadily rising Index points to malignant obstruction of the common bile duct, it is possible that a tightly impacted stone occluding the duct may produce the same effect.

Another /

Another fallacy which as far as can be ascertained has not previously been remarked upon is the effect of an incidental secondary anaemia on an Icterus Index raised from any cause. Under these circumstances it is possible, as the writer has shown, that though the Index is raised by the pathological process present, it may have been so lowered in the first place by the secondary anaemia that the subsequent rise still leaves the patient with an Index within normal limits, or at least with an Index not raised to the extent expected.

The writer has obtained unexpectedly low figures in cases of heart disease and pneumonia, which were complicated by secondary anaemia, and there seems to be no doubt that this is definitely a previously overlooked factor of error which must be taken into consideration when making deductions from Icterus Index readings in these anaemic cases.

CONCLUSIONS.

1. That we have in the Icterus Index a delicate clinical test for hyperbilirubinaemia, which, if used in correlation with the clinical findings, will in certain diseases be of value in diagnosis, treatment, and prognosis.
2. That the technique is a simple one, requiring no specialized laboratory experience. Some of the more recent modifications of the technique are especially simple, and while not so accurate as Bernheim's method, are perhaps sufficiently so for general purposes.
3. That normal persons show an Icterus Index which lies between 3.0 and 6.0.
4. That an Icterus Index of over 6.0 may be considered as denoting a pathological hyperbilirubinaemia.
5. That with an Icterus Index of 15.0 or over there is almost invariably clinical jaundice present.
6. That the Icterus Index varies directly in proportion to the degree of jaundice. In this connection it has been found that the Icterus Index follows very closely any variations in the jaundice, and may be taken as a means of recording/  
ing/

recording increase or decrease of the latter.

It is as a means of following up cases of jaundice that the Index has been found especially useful.

7. That in cases of cholecystitis and cholelithiasis, by means of variations in the Icterus Index, taken in conjunction with the clinical findings, the former are of value in the placing of operative indications.
8. That the Icterus Index is of value in the post operative prognosis in cases of gall-bladder disease.
9. That the mere presence of gall-stones, without obstructive symptoms or associated cholecystitis, will not cause a hyperbilirubinaemia with a resultant raised Icterus Index.
10. That the mere height to which the Icterus Index is raised in a case of jaundice is not evidence for or against malignancy, but a steadily rising Index points to malignant obstruction of the common bile duct. In this connection the possibility of a simple tightly impacted stone, completely occluding the duct, must not be forgotten.
11. That the Icterus Index may be used to differentiate between renal and biliary conditions, the former giving normal figures.
12. /

12. That while a raised Index may be caused either by effects on the liver or by haemolytic processes, the figures obtained are usually higher in the former.
13. That the Icterus Index is of no value in the diagnosis of early secondary malignant deposits in the liver.
14. That as duodenal ulcer commonly causes a raised Index, while gastric ulcer gives normal figures, the Icterus Index may be of use in the differential diagnosis of these conditions.
15. That confusion may arise owing to the fact that both biliary dysfunction and duodenal ulcer cause a raised Icterus Index. It is sometimes difficult to make a positive diagnosis between these two conditions, but the clinical findings and the fact that biliary disorders almost invariably give higher figures than duodenal ulcer should enable one to decide the diagnosis in the majority of cases.
16. That though a raised Icterus Index is sometimes obtained in cases of acute appendicitis, this is uncertain, and cannot be considered as of value in diagnosis.
17. That cases of chronic appendicitis do not raise the Icterus Index.

18. That the Icterus Index is raised in pernicious anaemia, and that variations in the Index are of prognostic value in that disease.
19. That the Icterus Index is of value in the differential diagnosis between pernicious anaemia and carcinoma of the stomach, the latter giving a normal Index.
20. That cases of secondary anaemia show a subnormal Icterus Index, and that therefore this test may be used to differentiate primary and secondary anaemias.
21. That there seems to be small ground for supposing that the Icterus Index may be used as a means of deciding for or against splenectomy in Banti's disease.
22. That the low Icterus Index caused by secondary anaemia may mask a raised Index due to disease. This fallacy must be kept in mind when interpreting results of Icterus Index readings in anaemic patients.
23. That the Icterus Index is raised in cases showing cardiac decompensation, and that this rise is directly proportional to the degree of decompensation.
24. /

24. That repeated Icterus Index readings in cardiac cases are of value in following the progress of the case, and in forming one's prognosis.
25. That mere valvular disease or any other cardiac disease without decompensation will not raise the Icterus Index.
26. That cases of arsenical hepatitis and dermatitis cause a raised Icterus Index.
27. That venereal disease in general, and syphilis in particular, does not raise the Icterus Index, but the intravenous administration of arsenic for syphilis often causes a preliminary rise in the Index at the start of treatment. This rise disappears as treatment is continued and does not contraindicate further arsenical medication.
28. That in a case receiving arsenical treatment an Icterus Index rising steadily through the period of latent jaundice is a danger signal of oncoming intolerance.
29. That until the Icterus Index has returned to normal in a case of arsenical hepatitis, further arsenical treatment is contraindicated.
30. That we have in the Icterus Index a convenient 'tolerance' test for patients receiving intravenous arsenic, which, if performed at regular intervals/

intervals, should prove of great value in the anticipation and prevention of such complications as hepatitis and dermatitis.

31. That any rise in the Icterus Index in cases receiving arsenic is not in any way proportional to the amount of arsenic given.
32. That a high Icterus Index in pneumonia is a bad prognostic sign.
33. That in the majority of cases of diabetes, the Icterus Index is not raised, and that the high figures obtained in some cases is probably due to carotinaemia.
34. That the Icterus Index is raised in cases of hyperemesis gravidarum. Opportunities for investigating the possible prognostic value of this rise have not, however, presented themselves, and no definite statement can at present be made.

In conclusion the writer wishes to express his gratitude to Professor Murray-Lyon for permission to work in the Biochemical Laboratory on those cases collected at the Royal Infirmary, Edinburgh, and also to Dr W.E. Cooke for permission to work in his Laboratory on those cases collected at the Royal Albert Edward Infirmary, Wigan.

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