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The NOVA SCOTIA MEDICAL BULLETIN

Editorial

Keeping An Open Mind

Having submitted to the Government of Nova Scotia a "Plan for Medical Services Insurance", it will be tempting to sit back and wait for "them" to pick up the ball and make the play. This, however, is not the role of leadership, and having seized the initiative we ought to be prepared to pursue the matter to the logical conclusion. This will be achieved only when it is possible for every Nova Scotian, rich or poor, to ensure that funds will be available to obtain the finest possible medical care. It is, therefore, our obligation to study payment methods and recommend suitable arrangements to Government. It is also our duty to see to the continuing provision of high quality medical care.

Taking the latter point first, we know that certain steps have been and are being taken. Our submission to the Royal Commission on Health listed as the highest priority item, the provision of an expanding program of medical education. This means money but it also means a continuing study of premedical, medical school and postgraduate education to achieve the best results. Is the curriculum up to date? Are the teaching methods sound? Are we making the best use of the study time available? When does "in service learning" become more service than learning? We expect our University to look closely to these matters. We ourselves need to look closely to the question of medical care. Already our Society's Special Research Committee is looking at medical manpower distribution and we await their report with interest. Is the Provincial Medical Board doing all it can to insure that high standards are being demanded and maintained by **all** those who practise in this Province? Are our reciprocal licensing arrangements and provincial board examinations really equivalent to those of the Medical Council of Canada? What about standards of practice 10, 20 or 30 years after graduation? We raise these questions only to suggest the need for open-minded self appraisal from time to time. We dare not become smug.

Going back to the first point, it is becoming increasingly clear that the last word has not been spoken on Medical Services Insurance. A year or two ago Canadian Medicine leaned heavily toward the principle of voluntary prepaid comprehensive medical service insurance. We ourselves in Nova Scotia cite Maritime Medical Care as the model. Yet our colleagues in New Brunswick

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NOVA SCOTIA DIVISION
OF
THE CANADIAN MEDICAL ASSOCIATION

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seem equally satisfied with the Blue Shield Plan, which is in many instances an "indemnity" scheme. The Canadian Medical Association has a special committee studying the Australian approach - a re-imbursement scheme. Our colleagues in British Columbia are concerned lest their creation for pre-paid care - Medical Services Association - grow so large that it becomes a monster which may slay its parent. Here too, it is obvious that we need to keep an open mind and continue to look for the best answer for the time and place.

Going on to the question of method of practice, there are questions to be asked and answered.

Is the day of the rugged individualist gone? Is group practice really the modern answer? By and large, we deplore salaried practice except in special circumstances where individual care is not purveyed. But we do not object to the senior doctor hiring a young graduate for what is sometimes a niggardly salary. We have heard sharp criticism of the recently announced Newfoundland Scheme for financing medical students on the grounds that the student must repay through indentured service. Yet when the same situation occurs in the Armed Services Training Plan, we patriotically applaud.

All in all, we have many problems to face. We believe, however, that no other profession is working so hard to try and find the best solutions. Hundreds of doctors are giving days and weeks each year to this study. Bit by bit, the answers are being found. Someone has said that Politics is the art of the possible. We have to work with the politicians. Therefore, advice we give them should be practical. This can be accomplished without compromising basic principles if we do not close our minds to new ideas.

S.C.R.

FROM THE BULLETIN OF 40 YEARS AGO

Simple Goitre

(Excerpts from publication by Department of Health, Ottawa).

A. - Nature. - It is a deficiency disease of the thyroid gland, due in largest measure to a lack of normal iodine supply to the gland. It occurs when the iodine content falls below 0.1 per cent. The deficiency effects manifest themselves in the main at three periods of life (1) the foetal period; (2) near puberty; (3) during pregnancy. They may then give rise to thyroid enlargement which later may be productive of adenomatous changes, passing over into malignancy. Cretinism and Myxoedema are due to the same fundamental cause - lack of available iodine for the glands' physiological requirements. Other theories in respect of the cause of endemic or simple goitre such as calcareous waters, sewage contaminated water, or specifically B. Coli, are no longer held to be adequate.

Message From The Medical Director Maritime Medical Care Incorporated

This article is being written at noon with a 5:00 p.m. deadline. Therefore, as my first communication with the Medical profession of Nova Scotia as Medical Director of Maritime Medical Care Incorporated, please forgive me if I ramble a bit.

I have now given up my private practice entirely to devote full time to being Medical Director. I hope that in the time I am here I can please most of you with my performance in your behalf. I say **most** because I do not believe anyone pleases everyone. For the past two months I have been filling in as part-time Director and at times feel like a schizophrenic for I have to be a Physician part-time and an Insurance Company executive part-time. Sometimes in this position I have to change hats quickly. However, my first duty is to you, the Medical profession, and I hope that with your co-operation, we can further improve the position of the Corporation both with the profession and the public. This is an important aspect at present, what with all the talk of socialized medicine in the wind. Since coming here, I have suddenly realized that public relations with our profession had deteriorated somewhat, although not seriously, and it is my sincere hope that I can be instrumental in returning it to its former high level.

In order to accomplish this, it is my intention during this first year of my tenure as Medical Director of Maritime Medical Care Incorporated to institute several new approaches. I hope they will meet with your approval and accomplish what I have said above.

First, I hope to be able to attend your Branch Society meetings as an Observer, if you will have me, in order that any question regarding Maritime Medical Care Incorporated that concerns the profession can be brought into open discussion on the spot. I think this will eliminate some of the griping in Doctor's Lounges and Operating Room, that we all seem prone to.

Second, I hope by personal interview, either at these meetings or elsewhere, to be able to eliminate personal problems any of you may have in your dealings with my Department. Along this line I would encourage you to come in and see me, or write me, or call me about a problem rather than letting it smoulder into a major issue.

Third, I hope to do a color slide review of the operation of Maritime Medical Care Incorporated to show you the operation of the Corporation. I suppose there are only a handful of doctors who have been in the Corporation offices to see how it functions. Few realize that we have 10,000 square feet of office space, eighty-six to ninety employees, and that last month we processed forty-one thousand account cards before you received your cheques. This color slide review might make an interesting showing for your Branch meetings at some future date.

Fourth, I hope by letters accompanying your cheques, through this Bulletin and the Newsletter, and maybe even by a small publication of our own, to acquaint you more rapidly with any changes in policy on fees that occur as time goes on. I think this is one area where we and the Nova Scotia Medical Society have fallen down. Regarding the 1963 Schedule of Fees, we are still in the discussion stage as there are major problems to be faced as far as the Corporation is concerned. To jump quickly into it could be fatal to its operation and we feel a responsibility to subscribers and participating physicians as well as our employees to do nothing that will interfere with its continued operation. Please be patient a while longer as this problem is being discussed currently between ourselves and the Executive of the Nova Scotia Medical Society. I am sure some decision will very soon be reached. You will be informed as soon as possible.

Fifth, in assessing your monthly accounts, I can only say that I will be as fair as possible in light of my seventeen years of General Practice. I will use the Taxing Committee when necessary and take to the Executive any matters of policy. Any setting of fees for new procedures or difficulties with any present ones will be referred to the Committee on Fees of the Nova Scotia Medical Society. This Committee at present is very active and has been very helpful and we now have a good liaison with them. Any changes will be communicated to you as above outlined.

Maybe this is all a pipe dream but it is the problem as I see it. I believe if we all pull together and back Maritime Medical Care Incorporated, we can eventually give Nova Scotians the best possible pre-paid Medical insurance available. Let's also face it, Maritime Medical Care Incorporated has been good to us as well. No forms to chase, no signatures to chase, no wayward patients to chase who have kept the payments. It may have cost us all a few dollars over the years, but after all, not many of us are suffering financially and the stronger we make our own Corporation now the better off we will all be if Medicare comes along.

Thanks for listening, and may I take this opportunity to wish all my colleagues and any who read this a most successful, happy and healthy New Year for 1964.

ART TITUS,
Medical Director

Bilirubin Metabolism

WILLIAM-PAUL WARREN, M.D.*

Introduction:

The earliest record of a description of jaundice was by Hippocrates about 400 B.C. Six hundred years later about 200 A.D., Galen associated jaundice with biliary stones. (1). About the same time, Aretaeus wrote the following.

"If the passages which convey the bile to the intestine be obstructed from inflammation or scirrhus, the bladder gets overdistended and the bile regurgitates; it therefore becomes mixed with the blood and the blood, passing over the whole system, carries the bile to every part of the body, which acquires the appearance of bile. But the hardened feces are white and clayey as not being tinged with bile, because the bowels are deprived of the secretion." (2).

This paper will discuss the metabolism of the pigment of jaundice — Bilirubin. It will outline current concepts of the sources, production, transportation, passage through the liver and breakdown as well as elimination of the bilirubin molecules. The current concepts of some of the hyperbilirubinemias will also be discussed.

Sources:

About 70% of bilirubin comes from the degradation of hemoglobin, the other 30% having other sources. The studies of London *et al* (3) and Gray *et al* (4) using N^{15} labelled glycine shows this division well. This amino acid was fed to normal subjects for several days and then the stercobilinogen of the feces as well as the hemoglobin content of the blood was studied for N^{15} labelling. Figure 1 illustrates their findings. N^{15} labelled stercobilinogen was found in the feces at a time earlier than would be expected if all the bilirubin were derived from hemoglobin degradation. As may be seen from the graph there was an immediate peak in N^{15} labelled stercobilinogen corresponding to the phase when the N^{15} labelled erythrocytes were just beginning to enter the circulation. This is fraction No. 1 comprising 15 - 20% of the bilirubin and from the graphs it may easily be seen that it could not be derived from degraded hemogoblin. The current feeling is that one or a combination of the following must enter the picture — (a) the degradation of heme formed in excess of globin in the production of hemoglobin; (b) intracorpuscular degradation of hemoglobin during maturation of the early erythrocyte in the bone marrow; (c) destruction of newly formed and ill-formed erythrocytes in the bone marrow before they reach the circulation.

The second fraction of the isolated stercobilinogen, labelled with N^{15}, occurred between days 20 - 80 and comprised 10 - 15% of the bilirubin. As the curves on the graph illustrate, the concentration of N^{15} labelled hemin in the blood was stable as was the production of N^{15} stercobilinogen. Since the heme was not being degraded, therefore, the bilirubin could not have come from this source. It is felt that this portion came from other non-hemoglobin

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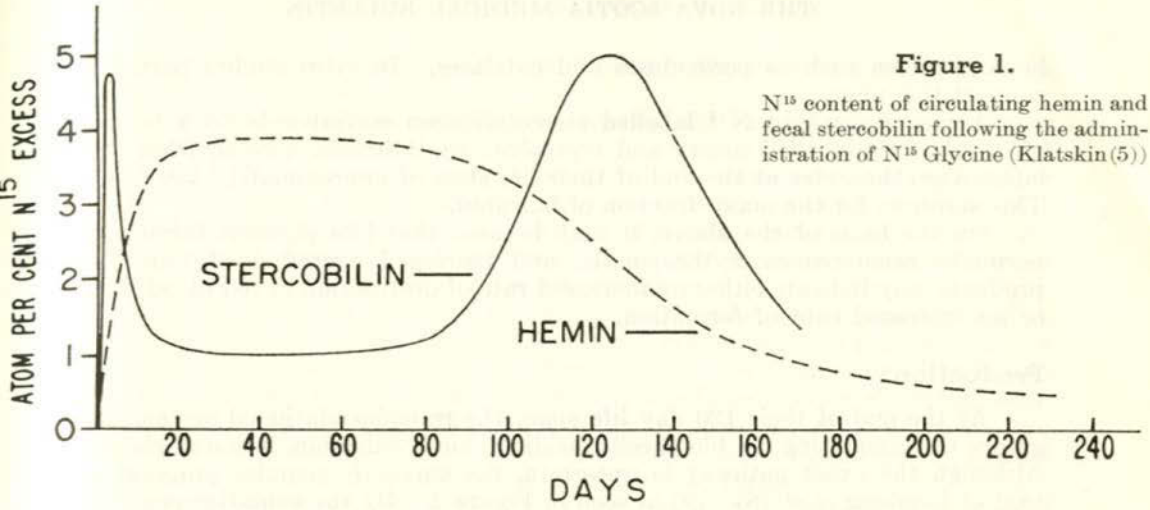

Figure 1.

N^{15} content of circulating hemin and fecal stercobilin following the administration of N^{15} Glycine (Klatskin (5))

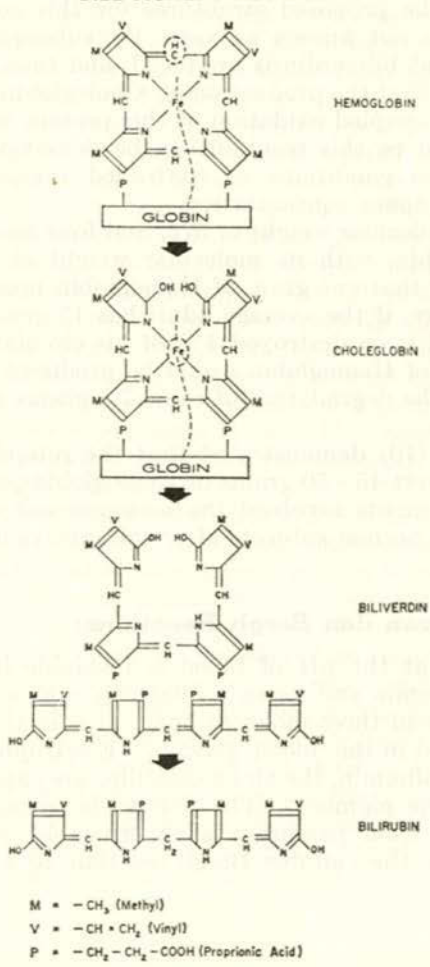

FIG. 2. Degradation of hemoglobin to bilirubin via the choleglobin pathway.

(Klatskin (5))

heme proteins such as peroxidases and catalases. In vitro studies partially support this view.

A second peak in N^{15} labelled stercobilinogen corresponds to a falling off of the N^{15} labelled hemin and represents the bilirubin derived from the labelled erythrocytes at the end of their life span of approximately 120 days. This accounts for the major fraction of bilirubin.

On the basis of the above, it may be seen that bile pigment formation normally accompanies erythropoiesis, and increased excretion of bilirubin products may indicate either an increased rate of destruction of red blood cells or an increased rate of formation.

Production:

At the end of their 120 day life span, the reticuloendothelial system degrades the circulating red blood cells yielding chiefly bilirubin, iron and globin. Although the exact pathway is uncertain, the currently popular proposal is that of Lemberg *et al* (8) (9) as seen in Figure 2. By the oxidative removal of the carbon atom of the alpha methene bridge, the porphyrin ring is opened producing the green, iron-containing, pigment-protein Choleglobin. The figure shows one of the proposed structures for this compound. However, the current pattern is not known as yet. By subsequent removal of iron and globin, the pigment biliverdin is produced, and then it in turn is reduced to bilirubin. It is felt that the production of Choleglobin from the hemoglobin probably involves the coupled oxidation of this protein with the ascorbic acid glutathione system, since this reaction can be demonstrated in vitro under simulated physiological conditions of controlled temperature, pH, oxygen tension and hydrogen donor concentration.

Bilirubin has a molecular weight of 572, and four moles of it are produced per mole of Hemoglobin, with its molecular weight of 68,000. From these figures it may be seen that one gram of Hemoglobin produces about 34 mgm. of bilirubin. Therefore, if the average adult has 15 grams of hemoglobin per 100 ccs. of blood, and if he destroyed 1% of his circulating erythrocytes per day, about 7.5 grams of Hemoglobin would be produced from the total blood volume of 5 liters. The degradation of these 7.5 grams should produce about 250 mgm. of bilirubin.

In 1958, Crosby (10) demonstrated that the reticulo-endothelial system has the ability to convert 45 - 50 grams of Hemoglobin per day to 1.5 grams of Bilirubin. His experiments involved the measurement of serum hemoglobin and bilirubin levels of normal subjects after the intravenous administration of hemoglobin.

Transport and the van den Bergh Reactions:

Bilirubin, which at the pH of blood is insoluble in water, has a great affinity for serum albumin and forms a relatively stable complex with it, in a ratio of between two and three moles to one. It is in this form that bilirubin is normally transported in the blood stream. Electrophoretic patterns have shown that as well as albumin, the alpha globulins are capable of binding a very small proportion of the pigment. The linkage is normally stable enough to prevent the complex from passing a semipermeable membrane. However, lowering the pH (as in the van den Bergh reaction, or with therapeutic levels

of salicylates and sulfasoxozole) can uncouple the complex and render the bilirubin ultrafiltrable. (11).

The balance between the bilirubin entering and that leaving the circulation determines the blood level with the normal concentration being between 0.5 mgm. and 1.0 mgm. per 100 mls. Zieve *et al* (12) found that the exact upper limit of normal is almost indefinite, since the distribution curve of supposedly normal subjects was assymmetrical with a skew to the right, suggesting an abnormal metabolism. In a large series, they have calculated that the upper limit of normal could be set at 1.5 mgm. per 100 mls.

In 1883, Erlich found that a mixture of sulfanilic acid, hydrochloric acid, and sodium nitrate, when added to a solution containing bilirubin, would give a red-violet coloured azobilirubin pigment. In 1913, van den Bergh and Snapper adapted this to serum, and later it was found that with certain sera, alcohol was not necessary for the reaction to proceed. On this basis, two pigments were postulated — Direct Bilirubin not requiring the alcohol and Indirect Bilirubin, requiring it to form the azo-pigment.

Much controversy was generated by the original papers — centering around whether or not there were actually two pigments; if so what were the basic differences, and the character of the binding proteins. That there were at least two distinct pigments was conclusively demonstrated by Najjer and Childs (13) in 1953, when they obtained two different forms of crystals, one from obstructive jaundice sera and the other from hemolytic jaundice sera. The ability to give the direct and indirect van den Bergh reactions, respectively was contained in these crystals. The indirect reacting crystals were in the form of flat plates while the direct reacting crystals were blunt ended rods.

Further evidence was added by the use of reverse phase partition chromatography as reported by Cole and Lathe (14) in 1953, and by them in conjunction with Billing in 1954. (15). These authors found three pigments were present in icteric sera. Two of these pigments I and II, were in the direct reacting portion of the bilirubin and pigment III is in the indirect portion. Analysis of the urine, and bile of necropsy gall bladders from patients with obstructive jaundice all yielded similar findings, with pigments I and II being the only pigments. Both these pigments, a monoglucuronide and diglucuronide of bilirubin respectively are water soluble and polar. Pigment I seems to be an intermediate between pigments III and II. Analysis of sera from patients with obstructive jaundice gives all three pigments (I - 45% of total; II - 26% of total and III 25% of total.)

Schmid (16) in 1956 treated the serum, urine, and bile of jaundiced and normal patients with an excess of diazotized sulfanilic acid dissolved in dilute hydrochloric acid. The stable diazonium pigments were purified, and the two pigments obtained by Chromatography were termed A and B. Sera from patients with hemolytic jaundice formed pigment B (the pigment III referred to above) and sera from obstructive jaundice formed pigment A (pigment I and II above). After acid hydrolysis or incubation with beta glucuronidases, B was converted to A with the release of glucuronic acid. This phenomenon suggested that the direct reacting bilirubin of obstructive jaundice was a conjugated form (with glucuronic acid) of the indirect reacting, free bilirubin, as found in hemolytic jaundice. At the same time, independently, the same conclusions were reached by groups in England and Czechoslovakia. The direct reacting being water soluble was readily excreted by the kidneys, but the indirect being insoluble in water is not excreted.

The Liver Cells:

A review of the present concepts of the structure and function of the liver cells (17) will aid the discussion of the passage of the bilirubin through the liver cell. The use of histochemistry, cytochemistry and the electron microscope have done much to outline the cell and its functions. Fig. 3. (Pg. 18).

By electron microscopy it has been shown that although the membrane is straight where two cells meet, there are numerous fingerlike projections — microvilli — where the cells line spaces, e.g. sinusoids and canaliculi. These microvilli are similar to those of other absorbing or secreting surfaces. Narrow projections of spaces between neighboring cells further increase the cell surface directed towards the sinusoids. This surface is considerably greater than that directed toward the biliary passages, reflecting the greater amount of hepatic cell function oriented towards the blood stream. The microvilli directed towards the blood stream are less regular and are longer than those directed towards the canaliculi. By histochemical techniques, enzymes may be visualized near the cell border suggesting functions located there. However, visualization does not necessarily imply selective localization.

The organelles are surrounded by membranes which originally seem to have been invaginations of the phospholipid containing cell membrane. The mitochondria, which are under the control of hormones, have the cellular energy providing elements. Histochemically — dehydrogenases, diaphorases, cytochromes, Krebs cycle enzymes, fatty acid and amino acid oxidases are here.

The area of the most specific liver functions is in the microsomes. Their cytoplasm contains double contours of irregular often parallel filaments called profiles. These are frequently widened into vesicles and are usually surrounded by fine granular material, the Palade granules, of ribonucleoprotein macromolecules. Profiles are also called Endoplasmic reticulum. They are the site of protein and cholesterol synthesis, detoxification by oxidation of drugs and conjugation, including bilirubin, by glucuronyl transferase. Glucose - 6 - phosphatase is also found here. Thus these organelles play a role in protein and enzyme synthesis, detoxification, blood sugar production and degradation. Speculation has these substances being released into the channels or cisternae of the endoplasmic reticulum.

Lysosomes are dark bodies located near the bile canaliculi. They have a single membrane and have been shown to contain the following enzymes — acid phosphatase, desoxyribonuclease, ribonuclease, cathepsin and glucuronidase. Ferritin and pigments (especially lipofuscin) are deposited in these organelles. The nucleus is closely associated with the endoplasmic reticulum and is the site of the chromosomes. Desoxyribonucleic acid is found histo — and cytochemically. Ribonucleic acid is found in the nucleoli, which is probably the source of cytoplasmic ribonucleoprotein.

The interorganelle substance includes glycogen and a supernatant, the cell sap of the cytochemists. Hezokinases, phosphorylases and ribonucleoproteins of small size are found in this substance. Most of the other areas of the liver cell have not been so thoroughly delineated as yet.

There are no portal vein branches accompanying the small connections between the liver cells and intrahepatic bile ducts. These epithelial cells differ from liver cells by lacking endoplasmic reticulum, having fewer and smaller mitochondria. These cells rest upon a basement membrane and have

no microvilli on their basal surface. However, on the side facing the bile canaliculi they do have microvilli.

The Hepatic Phase:

Most of the available evidence points to active transportation of bilirubin to the bile from the blood (18). This involves the uptake from plasma into the liver cell, the intracellular conjugation, primarily to glucuronides, and then the subsequent excretion into the bile canaliculus.

Indirect Bilirubin in the blood	➤➤	Conjugation in liver cell with glucuronic acid by glucuronyl transferase	➤➤	Direct Bilirubin in Bile

Unlike other substances, conjugation must proceed before bilirubin may be excreted into the bile, since no unconjugated bilirubin is found in fresh bile. The process of uptake by the liver cell of either unconjugated or conjugated bilirubin is almost an unknown process. Since bilirubin in the indirect form is almost insoluble at physiological pH, it has been suggested that it is either transferred from plasma proteins to the lipid containing sinusoid membrane or that plasma proteins transport the bilirubin as they enter the liver cells.

Hanson (19) after working with uranin, a flourescent dye which behaves as bilirubin, proposed the following concept of the pigment passage. Passive diffusion through the sinusoidal epithelial cell is followed by active concentration close to the endothelial surface. The pigment then passively diffuses across the cell, due to the concentration gradient, only to again be actively concentrated close to the canalicular surface, ultimately to be excreted in the bile. This unidirectional character is stressed by him and in liver cell injury it has been demonstrated that the two concentrating mechanisms are upset as well as the polarity of the cell thus allowing the reversal of bilirubin flow in a regurgitant fashion.

Weech *et al* (20) showed that, within certain limits, an amount of bilirubin proportional to the square of the concentration in the blood can be excreted by a normal liver. Thus, when the rate of bilirubin entering the circulation is increased, the plasma concentration rises and there is ultimately a rise in the excretion rate equal to the rate of entry to the plasma. It is in this way that a new equilibrium is established.

Bilirubin, as well as a wide variety of other alcoholic and phenolic compounds, is conjugated with glucuronic acid involving the enzyme system centering about glucurconyl transferase. In this process of conjugation, glucuronic acid derived from uridine diphosphate glucuronic acid (UDPGA), a heat stable nucleotide, is transferred to the carboxyl groups of bilirubin by the action of glucuronyl transferase, as found in the microsomes. The glucuronic acid of this system is formed from glucose.

Many authors feel that alternate pathways are present, for example —

conjugation with active sulfate, but under physiological conditions these do not contribute a significant amount to the overall picture. Extrahepatic conjugation, by alternate pathways, must play a role in some pathological states.

Fate of Bilirubin;

By virtue of bacterial action in the colonic region of the gastro-intestinal tract, bilirubin is reduced in stepwise fashion to two groups of urobilinogen compounds. These include (a) the colorless urobilinogens which react with with Erlich's aldehyde reagent to yield red colored compounds and (b) urobilins their colored oxidation products which on mixing with Schlessinger's solution, (Zinc acetate in alchohol), yield intense green flourescent compounds. Successive reduction of bilirubin leads to mesobilirubin, dihydromesobilirubin and finally to the two colorless compounds — mesobilirubinogen and stercobilinogen. The conversion of bilirubin to and the interconversions between the various members of the urobinogen groups have been demonstrated *in vitro* by using broth cultures of fecal flora. (21).

It has been known for some years that only 10% of bilirubin fed orally to a patient could be recovered as urobilinogen. However, when conjugated bilirubin is fed, a much higher percentage is recovered. The *in vitro* studies mentioned above have confirmed that the bacterial flora are more effective in dealing with the conjugated bilirubin. Suppression of this flora by antibiotics may lead to elimination of the urobilinogens from the feces with the appearance of free bilirubin thus lending further support to the concept of urobilinogen formation in the bowel by the bacterial flora.

Work done by Gilbertson *et al* (22), using crystalline bilirubin labelled with N^{15} has conclusively proven that a proportion of the bilirubin is reabsorbed from the intestine to recirculate through the liver and back again to the gut. These authors felt that intestinal absorption might be part of the explanation for previous failures to account for tube fed crystalline bilirubin as such or as known derivatives in the feces of subjects with bile duct obstruction. Whether conjugated bilirubin is also absorbed as such is not established. However, it seems unlikely that any large degree is absorbed as shown by other studies from their laboratories.

Mann and Koler (23) found that following I.M. injection of urobilinogen into rats, there was no increase in the excretion of bilirubin, but most of the urobilinogen was recoverable in the bile, suggesting that urobilinogen is not converted back to bilirubin and since the urobilinogen recovery from the bile was incomplete, it is possible that some may be degraded before it is excreted.

Theoretically there should be a normal daily output of urobilinogen of 250 mgm. from hemoglobin plus 20 - 30 mgm. from other sources. This would be the case if it is assumed that the degradation of hemoglobin entails its quantitative conversion to bilirubin, and its ultimate excretion as urobilinogen. However, the usual amount found is 100 - 200 mgm. in feces and 0 - 3.5 mgm. in the urine (24). An alternative pathway bypassing bilirubin for hemoglobin breakdown is the most attractive hypothesis to explain this discrepancy. No direct evidence for this exists but the observation of Katz *et al* (25) and others that the use of adrenal corticosteroids in obstructive jaundice led to

significant decrease in serum bilirubin concentration and urine excretion without change in concentration of stool urobilinogen tends to lend indirect support to the above hypothesis. That the red blood cell destruction is slowed or the hemoglobin breakdown in the reticuloendothelial system is inhibited by the corticosteroids are possibilities but the findings are also consistent with the view that under some conditions hemoglobin may be degraded to colorless compounds that do not couple with the diazotized sulfanilic acid.

Normally, a small amount of the urobilinogen from the gut escapes into the general circulation and is excreted in the urine. The factors governing this renal excretion are poorly understood. Under physiological conditions, no bilirubinuria is found, but characteristically it is present when the plasma level of bilirubin is raised by biliary obstruction or hepatocellular disease, but not when raised by a hemolytic process. The difference has been attributed to the greater solubility in water of the conjugated than the unconjugated bilirubin and it has been shown that urinary bilirubin is in the conjugated form.

Under appropriate conditions, small amounts of both types of bilirubin may be found in lymph and C.S.F. especially when the levels are high. The C.S.F. bilirubin is independent of the C.S.F. protein level.

The Hyperbilirubinemias:

Hyperbilirubinemia depends upon the entry of bilirubin to the serum at a rate faster than its removal. Basically, one or more of the following mechanisms may be involved, (a) increased production, (b) impaired liver capability to handle the bilirubin and (c) regurgitation of bilirubin.

The yellow staining of the skin is due to this excess pigment being bound to elastin thus explaining the observation that in the jaundiced cadaver large amounts of yellow pigment are seen in the skin, conjunctivae mucus membranes of the intestines, the media of the blood vessels, the kidneys, and the liver but not in the cornea, cartilage or nerve tissue. Extracellular plasma albumin may be one of the binding mechanisms since bilirubin is normally bound to albumin while in the serum.

It has also been shown that the skin stains more readily with direct than with indirect reacting bilirubin. The clinical observation that, for any given blood level of bilirubin, the skin is more deeply pigmented in obstructive than in hemolytic jaundice is possibly because of the greater solubility of bilirubin glucuronide in the body fluids. In the infant brain, the reverse is true as shown by the development of kernicterus in hemolytic jaundice.

There are many ways in which jaundice may be classified. Here they will be discussed in the following pattern:—the clinically more common adult types of prehepatic, hepatic and post-hepatic jaundice; neonatal jaundice; the syndromes based on overproduction, and cholestasis; and lastly those based on enzyme deficiencies, the familial and hereditary non-hemolytic and non-obstructive types.

Hemolytic Jaundice:

Here the hyperbilirubinemia is due to accelerated bilirubin production for one or other reasons. It has been established that a normal adult may excrete 220 - 440 mgm. of bilirubin per day but is capable of excreting much

more. Since about 250 mgm. is normally produced daily, a two or even three fold increase in erythrocyte destruction, as is often found in hemolytic states, is needed to lead to bilirubin retention. At least 85% of the pigment in the elevated serum is unconjugated. The remainder is direct reacting pigment, possibly derived from extrahepatic conjugation.

Hepatocellular Jaundice:

Theoretically, this type should include the features of deranged uptake, transport and conjugation of bilirubin, giving unconjugated bilirubin. However, in practice, the pattern of pigments is identical to those of obstructive jaundice discussed below, suggesting that retention is accompanied by some regurgitation. The question as to why there is little or no rise in unconjugated bilirubin arises since there is disturbance of the glucuronyl transferase activity in the liver. An explanation is that, although this activity is reduced there is greater reduction in excretion, and so the conjugated bilirubin accumulates and diffuses back into the circulation. It has also been shown that there is increased glucuronyl transferase in the circulating blood suggesting extrahepatic conjugation of the bilirubin.

Obstructive Jaundice:

Any process which obstructs the excretion of conjugated bilirubin into the bile will lead to retention and later regurgitation into the circulation. One or the other of the following may account for this regurgitation — (1) rupture of distended bile canaliculi, (2) through tears or functional leaks in the canals of Hering, which link the canaliculi with the terminal ducts, (3) reversal of polarity of the cells as previously discussed. Conjugated bilirubin is the major pigment found in the serum. Early the diglucuronide predominates but later the monoglucoronide composes the major portion. The increased amounts of unconjugated bilirubin usually found, probably reflect the secondary hepatocellular aspect which arises in obstructive jaundice (26, 27). Unknown intra and extra hepatic factors probably determines the differential between the various pigments found. Since both the mono and diglucuronide pigments are water soluble, they appear in the urine, the diglucuronide usually predominating.

Neonatal Jaundice:

Unconjugated bilirubin is the major pigment involved here, but unlike hemolytic jaundice, excess production of bilirubin is not necessarily a factor. During intrauterine life, fetuses are spared from jaundice as the placenta excretes bilirubin. This of course ceases after birth. Infants only become jaundiced if their liver is unable to handle bilirubin. In small and premature babies with immature livers, there is accordingly a greater tendency for plasma bilirubin levels to rise due to a relative lack of function of the glucuronyl transferase system. As a result of this, many new born infants, and especially those suffering from hemolytic disease of the newborn, are exposed to considerably higher plasma concentrations of bilirubin than are ever obtained in the adult suffering from obstructive or hemolytic jaundice. Plasma concentrations of bilirubin may rise to 40 - 50 mgm. per 100 mls, while in the adult,

although similar pigment concentrations might be attained the bilirubin concentration would be less than 20 mgm. per 100 ml serum. Of interest is the Gunn rat which has a picture similar to neonatal jaundice due to an hereditary deficiency of glucuronyl transferase. A second enzymatic deficiency that of UDPG dehydrogenase, may further handicap the newborn. (28). It has been estimated that the combined effects of these two deficiencies may lower the liver capacity to excrete bilirubin to as little as 1 - 2% of that of a normal adult. (29).

Occasionally large amounts of conjugated bilirubin accumulate in the plasma, due to obstruction resulting from hemolytic disease, the inspissated bile syndrome. These infants appear to have the ability to conjugate bilirubin so that dangerously high levels of unconjugated bilirubin are not observed and exchange transfusions are not indicated. Maldeveloped or absent bile ducts will give a similar picture.

Other causes of neonatal jaundice are related to drug administration. Large doses of vitamin K analogues and sulfasoxizole given to premature infants raises the serum bilirubin levels in these infants and increases their susceptibility to kernicterus.

Lathe and Walker (30) found that the serum of pregnant women and some newborn infants inhibits the conjugation of bilirubin by rat liver. Arias *et al* (31) after studying breast-fed infants with prolonged neonatal jaundice found that the breast milk strongly inhibited glucuronide formation of bilirubin *in vitro*. The offending substance isolated was one of the progestational hormones of the pregnanediol group. Each of the mothers had high levels in their milk and had had previous babies with prolonged jaundice during the neonatal period. Taking the babies off breast feeding led to rapid clearing of the jaundice.

Jaundice Due to Bilirubin Overproduction:

Raised levels of indirect reacting bilirubin are commonly found in Pernicious Anaemia. It is generally accepted that hemolysis plays a role here; it is also believed that overproduction of bilirubin unrelated to hemolysis may contribute to the development of the jaundice since a large proportion of the bile pigment excreted by these people is derived from sources other than the destruction of circulating erythrocytes. Whereas normally only a small percentage of red cells are destroyed in the marrow, in pernicious anaemia a very large percentage is destroyed there before ever reaching the circulation. This may be part of the reason for this jaundice. Israels *et al* (32) have termed a similar situation "shunt hyperbilirubinemia" in their discussion of an unusual form of indirect reacting hyperbilirubinemia, where they emphasized the concept that the overproduction of bilirubin in these cases occurred over some pathway not involving breakdown of hemoglobin from circulating erythrocytes, but may have been derived from cells destroyed by the bone marrow prior to release.

Glydil in a series of papers (33, 34, 35, 36, 37) reported his investigations using nicotinic acid in the induction of hyperbilirubinemias and hypersideremias. Much of the work suggests that the response is probably due to increased breakdown of Hemoglobin in the reticuloendothelial system.

Cholestatic Jaundice:

Although in these syndromes biochemically it would seem as though the patient has obstructive jaundice, anatomically no obstruction is found. Most commonly it occurs in drug reactions e.g. with chloropromazine, methyltestosterone, and norethandrolone. Occasionally, similar pictures are found in (a) viral hepatitis, (b) as a rare complication of pregnancy, (c) in the Rotor syndrome, (d) in the Dubin-Johnson syndrome (38). This is occasionally familial in nature. Its principal features are an obstructive type jaundice and the presence of a dark pigment in the hepatic parenchymal cells. The Rotor syndrome (39) resembles the Dubin-Johnson except for the lack of pigment in the liver cells.

Histologically, the liver cells are normal in all these except for the excessive pigment of the Dubin-Johnson type. The portal triads may show some mild inflammation but the bile ducts are always normal. However, canalicular bile thrombi are found in each of these types, except in the Dubin-Johnson and Rotor syndrome. An elevated serum conjugated bilirubin is characteristic of all members of this group. It is believed that the defect must lie within the cells themselves, since (a) the jaundice is chronic and often familial and (b) the only abnormal liver function tests are those measuring excretory capacity (BSP retention, direct bilirubin and radiography of the extrahepatic biliary system) and (c) *in vivo* and *in vitro* studies of glucuronide formation are normal.

Familial and Hereditary Non-Hemolytic, Non-Obstructive Jaundices:

Three major disorders are recognized in this group. They are all characterized by retention in the plasma of unconjugated bilirubin without increased hemolysis or overt liver disease.

1. **Crigler-Najjar Syndrome** (40) is also called familial non-hemolytic jaundice with kernicterus. Here levels of 12 - 45 mgm% of unconjugated bilirubinemia develop and persist. Often the only positive signs are those of icterus and kernicterus. The routine type of hemotologic and liver function tests are normal, as are the extrahepatic biliary system and the liver histology. Fecal urobilinogen excretion is decreased and only scanty amounts of bilirubin are found in the bile. Studies have shown decreased formation of salicylate, menthol and tetrahydrocortisone glucuronides. The non-jaundiced parents of these children appear to be heterozygous for this defect, as they have a decreased capacity for glucuronide formation when compared with other adults. There does not seem to be any compensatory increase in conjugation of bilirubin with sulfate or other substances, in an effort to bypass the defect in glucuronide formation due to defective glucuronyl transferase. Chronic, unremitting jaundice develops.

2. **Lucey-Driscoll Syndrome:** (41) also called transient familial hyperbilirubinemia, is a rare condition in which all infants born of seemingly normal mothers have severe nonhemolytic acholuric jaundice immediately after birth, with indirect reacting bilirubin values of 20 - 60 mgm.%. These children must have exchange transfusions if kernicterus is to be prevented. Those infants who survive usually become anicteric in about four weeks. They seem to have normally delayed development of the glucuronyl transferase system

but they and their mothers have high plasma titres of an inhibiting substance. This may be the pregnanediol recently described by Arias and discussed earlier.

3. **Gilbert's Disease** — also known as Constitutional Hepatic Dysfunction seems to have two main categories. (1) patients with chronic often familial unconjugated bilirubinemia of 1 - 4 mgm.%, often intermittent, may fluctuate with activity, intercurrent infections and ingestion of alcohol. Occasional hepatomegaly and the icterus, often first seen during adolescence or after hepatitis, are the only physical findings. Hepatic histology and function tests are normal. An heterogeneous population makes up this group. Some have compensated hemolytic anaemias, others seem to have histological and biochemical residuals of this, and occasionally other family members have jaundice related to glucuronyl transferase deficiency, so that this might be another presentation of this syndrome. (2) The second group are patients who have chronic non-hemolytic acholuric jaundice with bilirubinemia levels of over 5 mgm%. Their only complaints are vague fatigue and dyspepsia. The icterus is first noticed either shortly after birth or within the first decade and persists at the same level (between 5-20 mgm%). Red cell survival time, haematologic and hepatic studies are normal. Reduced fecal urobilinogen and no bilirubinuria are found. However, the gall bladder contains conjugated bilirubin. By paper chromatography studies, it has been shown that the plasma bilirubin is entirely unconjugated. These patients have decreased capacity to form menthol glucuronide, suggesting a defect in the glucuronyl transferase system. This has been substantiated by studies of liver hemogenates obtained from biopsy specimens. Thus this group seems to have the same deficiency as the Crigler-Najjar group.

Summary: In summary this paper has discussed the sources, production, transportation, van den Bergh reactions, the nature of the pigments, the passage through the liver and the fate of bilirubin. The pathophysiology of some of the bilirubinemias has also been briefly discussed.

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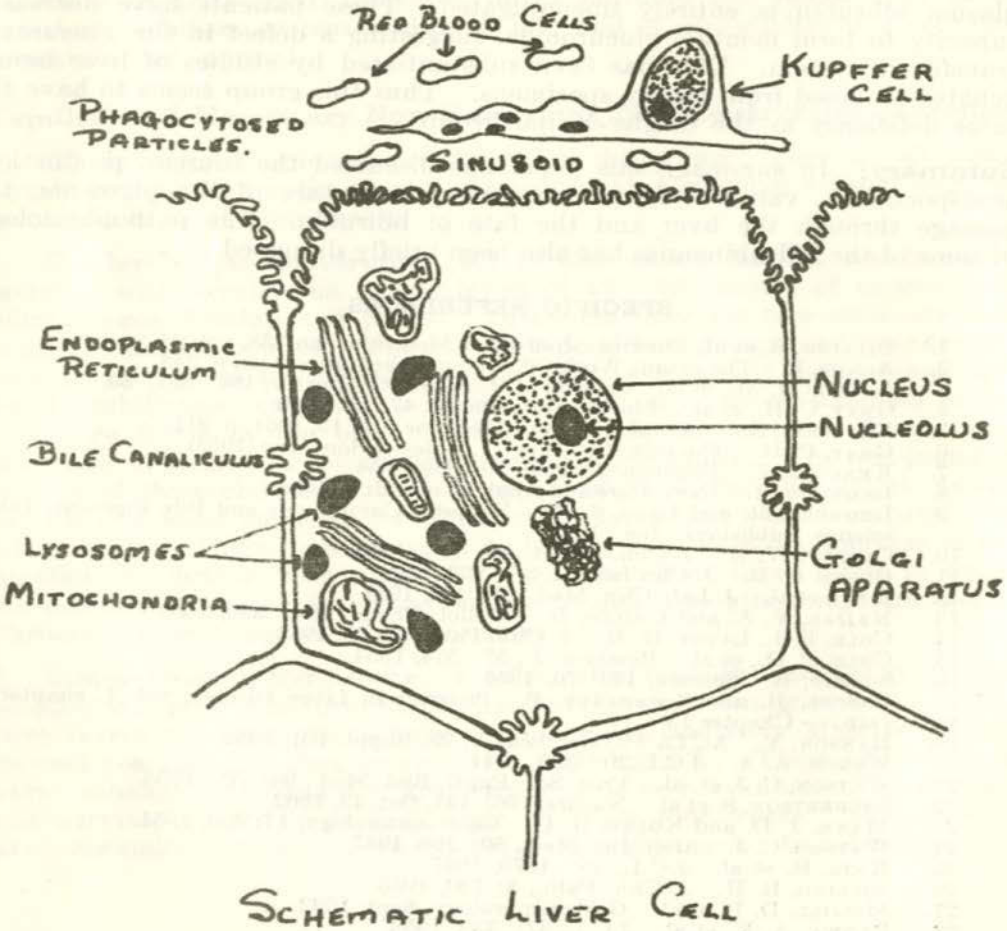

Figure 3

RELATIVES OF PATIENTS WITH LUPUS ERYTHEMATOSUS

The importance of hereditary factors in the development of systemic lupus erythematosus has long been suspected because of the frequent familiar incidence of the disease and the occasional occurrence of systemic lupus erythematosus in twins. Recently, the possible role of genetic factors in the development of systemic lupus erythematosus, rheumatoid arthritis and certain other diseases possibly involving disturbances in the immune response has received increasing attention on the basis of careful studies of several large families, and the systematic evaluation of asymptomatic relatives of patients with rheumatoid arthritis, systemic lupus erythematosus autoimmune thyroiditis, and agammaglobulinemia. Based on a thorough study of two large families with a high incidence of systemic lupus erythematosus, other collagen diseases and hypergammaglobulinemia, Leonhardt has postulated the existence of a "genetic predisposition to the overproduction of gamma globulins." Holman and Deicher and, subsequently, several other observers have studied the asymptomatic relatives of patients with systemic lupus erythematosus and have observed an unusually high incidence of hypergammaglobulinemia and rheumatoid factor in their sera

Similar studies on sera from asymptomatic relatives of patients with rheumatoid arthritis, autoimmune thyroid disease and agammaglobulinemia have also demonstrated a high incidence of rheumatoid factor, thyroid autoantibodies and abnormalities in the serum proteins respectively.

In spite of recent advances in the study of these diseases, little is known concerning the etiology and pathogenesis of the lesions of systemic lupus erythematosus and rheumatoid arthritis. In view of the above cited studies and the many clinical and serologic similarities between these two conditions, the possibility arose that careful evaluation of relatives of patients with systemic lupus erythematosus might provide a useful approach to the study of some of the etiologic mechanisms, and might also more clearly delineate the relationship between these two diseases.

A study presented by Morteo, Franklin, McEwen, Phythyon and Tanner (Arthritis and Rheumatism, 4: 356, 1961) gives data obtained from 44 relatives of 19 patients with systemic lupus erythematosus. The results offer additional evidence that systemic lupus erythematosus and rheumatoid arthritis are closely related diseases, and the findings are consistent with the hypothesis that they may, in some as yet unknown manner, reflect a genetically determined abnormality in the immune response and the synthesis of gamma globulins.

A study of 44 relatives of 19 patients with systemic lupus erythematosus showed that: (1) 11 per cent had clinical evidence of a collagen disease: (2) the sera of one-third of the asymptomatic relatives contained rheumatoid factor, while the incidence of hypergammaglobulinemia biologic false positive tests for syphilis and antinuclear antibodies was greater than in the control population; (3) three-quarters of the patients had at least one relative with clinical and/or laboratory abnormalities. The possible significance of these findings in the pathogenesis and etiology of systemic lupus erythematosus is discussed.

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An Approach To The Problem Of Jaundice*

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Once the level of serum bilirubin rises above 2 mg/ 100 ml, skin and mucous membranes become sufficiently stained, and jaundice can be clinically detected.

The cause of jaundice may be hepatic or extrahepatic, extrahepatic causes being either pre- or posthepatic.

The Prehepatic group includes all the processes involving the formation and metabolism of bilirubin before it is taken up by the liver. The main feature of this group is the predominant rise of unconjugated (indirect reacting) bilirubin. Conjugated bilirubin is also found, but only in small amounts, not exceeding 15% of the total, unless a considerable hepatocellular damage has already occured, when this percentage rises.

In a normal person 80 - 85% of bilirubin is derived from "worn out" red blood cells. The remaining 15 - 20% most likely comes either from heme formed in excess of globin (1) or from immature cells destroyed before they have reached circulation. (2). In some blood disorders, such as pernicious anemia, congenital porphyria, and thalassemia, 40 - 80% of bilirubin is of such "hemopoetic" origin. (3, 4, 5,).

Whatever the source of bile pigment, in this group it is not the liver that is primarily at fault. The liver can conjugate and excrete far more bilirubin than normally required, and serum bilirubin does not rise above 5 mg/100 ml even when the rate of red blood cell destruction increases sixfold. (6).

When jaundice is due predominantly to indirect reacting bilirubin, with well coloured stools and a normal colour of urine, blood smear study becomes mandatory, reticulocyte count must be done repeatedly, and further investigation proceeds along hematolgical lines.

The Posthepatic group includes various types of extrahepatic obstructive jaundice. Classically, little or no bile passes the obstruction, stools are clay coloured, urobilinogen is absent from urine, but serum shows elevated values of conjugated bilirubin which passes the renal filter easily and discolours the urine.

Many of these patients are seen only when the picture becomes more complex due to the superimposed hepatocellular damage. Therefore the history of onset and the early course of jaundice become very important, and when suggestive of this type of jaundice there must be a very thorough search for benign or malignant causes of obstruction.

It is here useful to remember that even in the best hands, cholecystectomy carries the risk of postoperative stricture. A not uncommon cause is periductal hematoma, followed by fibrous organization. A recent Scandinavian study states that operative injuries are found in approximately 1 in every 300 - 400 cholecystectomies. The initial injuries go un-noticed in about 50% of cases. (7).

An undetected common duct stone, or trauma secondary to probing of the duct can lead to formation of a stricture. It is therefore most desirable, as

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a part of a complete history, to obtain from the surgeon a detailed report on his findings and extent of exploration, and on any possible mishaps during cholecystectomy.

The commonest cause of extrahepatic obstructive jaundice is an impacted stone, with or without a later developed stricture.

One must however seek a neoplasm, benign or malignant, either of the common bile duct or Pancreas.

The search for a pancreatic tumor must include careful radiography of the duodenal mucosa, lateral films with contrast medium may show anterior displacement of the stomach or the "inverted 3" sign of the duodenum. Courvoisier's sign is frequently absent and may be misleading.

In equivocal cases we must seriously consider exploratory laparotomy while liver damage is still minimal. If the operation has been delayed for any reason, X-ray studies repeated a few weeks later may shed additional light on the problem.

The percutaneous cholangiogram has recently been used in cases when all other methods had failed to show convincingly whether or not the jaundice was an obstructive one. (8). Under anesthetic a needle is inserted into the liver and then gradually withdrawn. If extrahepatic obstructive jaundice is present, the needle will enter one of the dilated intrahepatic biliary ducts and some bile will be withdrawn. An equal amount of radioopaque dye is then injected, and radiographs are made. Though quite safe in hands of an expert, the technique does carry risk of biliary peritonitis. The operation should be carried out within hours once the obstruction has been demonstrated.

It is generally in the **third group, when the disease originates primarily in the liver,** that most of the difficulties in diagnosis are encountered. Traditional classifications in such instances must often be amended. All combinations of types of bilirubin may be found in sera of this group, and various factors have to be taken in consideration.

A good approach is to try to answer the question whether one is dealing with a congenital or an acquired jaundice. If acquired, whether it is acute or chronic, also, whether it is infectious, non-infectious, or drug-induced (toxic or allergic).

Viral hepatitis is still the commonest illness in the **infectious group,** and is at present on the increase on this continent. (9) Isolation is practised but has one major weakness. It is almost impossible to isolate the patient during the most infectious period. Recent studies have shown that there is ample time for a patient to infect others before the illness is clinically recognized, as virus has been demonstrated in the stool on the 25th day of incubation, which is approximately 2 - 3 weeks before the onset of jaundice. Virus can be detected in blood over approximately the same period of time. (10).

History and clinical picture, together with local epidemiological data make the diagnosis fairly easy. Both types of serum bilirubin are elevated, and in an occasional patient there predominates conjugated bilirubin of so called cholangiolytic type of hepatitis. This picture is not unlike that seen in chlorpromazine jaundice. Again, it is essential to obtain history of exposure and that of prodromal symptoms. One must always look for an enlarged and tender liver and palpable spleen. Elevated S.G.O.T. reflects the extent of

necrosis of liver cells. Only occasionally will liver biopsy be required for precise diagnosis.

Though complete healing occurs in most instances, it is important to remember that liver failure and hepatic coma do occur, and that mortality increases with age. Occasionally one sees a transition to chronic hepatitis and postnecrotic cirrhosis. The patient should be followed at intervals for at least one year after an acute attack.

A careful history regarding parenteral medication and laboratory exposure must be taken to dismiss the possibility of homologons **serum hepatitis.**

Weil's disease is uncommon in this part of the country, but if this disease is suspected, one must search for possible renal involvement and for spirochetae.

In these days of fast air travel it is also possible to come across an occasional case of **yellow fever.** However, detailed discussion of this and other rare entities is beyond the scope of this article.

In the **noninfectious group,** drug induced jaundice is becoming increasingly common, and it is important to be familiar with drugs capable of affecting the liver. The list of these drugs is lengthening every day.

There are two major effects of the drugs on liver: toxic reaction and sensitivity reaction.

In **toxic** reactions the clinical picture is often very similar to that of acute viral hepatitis, but mortality is in the range of 20%. (11). The extent of liver damage is dose dependent, and the effect is immediate. Carbon tetrachloride, chloroform, D.D.T., Naphtalene, Benzene derivatives, metallic poisons, Cincophen, and drugs such as Iproniazide and Zoxazolamine, are all known to produce direct liver damage.

The **hypersensitivity** type of jaundice is classically produced by Chloropromazine. The effect on the liver is not immediate, and jaundice often appears during the second or third week of treatment. There is, also, no dose dependency. Many other drugs can produce a similar type of jaundice, especially those in the tranquilizer group. Stelazine, Promazine, Pacatal, Compazin, P.A.S., Thiouracil, Methyltestosterone, Norethandrolone have been reported to produce this type of jaundice, and many more are being added to the list.

A good review of effects of drugs on the liver has appeared in May 1963 issue of "Disease-a-Month". (12). Familiarity with this problem is mandatory at present.

So far we have dealt with the acute form of hepatic type of jaundice.

Possible Division:

Cirrhosis of the liver heads a large and frequently seen group of **chronic liver diseases with jaundice.**

The preoccupation with alcoholic cirrhosis of postwar years tends to distract one from other types of cirrhosis that must always be considered in this group of patients, as such:

Hepatolenticular degeneration (**Wilson's disease**) in which we must look for possible Parkinsonian type of tremor, facies and corneal Keiser Fleischer ring, and inquire about family history. Urinary copper and serum ceruloplasmin determination are essential for diagnosis.

Hemochromatosis, will seldom be missed if attention is paid to glucosuria and elevated blood sugar. Skin must be assessed for texture and pigmentation, and history and features of possible malabsorption noted. Determination of serum iron and iron binding capacity establishes the diagnosis

Primary biliary cirrhosis, which prefers females, mostly young and middle aged, though men are not immune. Marked features of a slowly progressing intrahepatic obstructive jaundice with an almost invariable history of pruritus will direct one's attention to this group of diseases. Here we frequently encounter hirsutism, Cushinoid appearance, striae, and menstrual irregularities.

Juvenile cirrhosis and other rarer types must be borne in mind, but cannot be discussed here.

The big group of **Laennec cirrhoses**, which is seldom missed, and is usually associated with alcoholism and deficient diet.

Finally, **postnecrotic cirrhosis**, thought to be one of the late sequelae of infectious hepatitis.

To make a diagnosis of cirrhosis of the liver without further elaboration is a poor approach to the problem. The type of cirrhosis must be specified, then one must assess the stage and activity of the disease and ascertain the presence or absence of complications. Only then can a rational prognosis be made and treatment planned.

The first step in approaching the patient with jaundice of any cause is to establish the presence or absence of liver failure.

According to Sh. Sherlock (13), the syndrome of hepatocellular failure comprises some or all of the following features:

1. General deterioration of health.
2. Jaundice.
3. Circulatory changes.
4. Fever.
5. Fetor hepaticus.
6. Neurological changes.
7. Ascites.
8. Terminal hyponatremia.
9. Changes in nitrogen metabolism.
10. Endocrine changes.

One may agree or disagree with this definition, but it is a sound policy to search for these features.

The activity of the liver disease can be evaluated by the clinical picture and a few *essential tests*, though most of these are only indirectly reflecting the presence of the liver disease.

Floculation and turbidity tests generally reflect the state of Serum globulin. They are positive in a vide variety of other diseases involving connective tissue and reticuloendothelial system. However, when considered

together with other clinical and laboratory evidence, they are useful, as their positivity generally parallels the activity of hepatocellular disease.

Elevation of **S.G.O.T.** and **S.G.P.T.** reflects the degree of necrosis of the cells and is always found in acute hepatocellular jaundice. In chronic liver disease, elevated values suggest the presence of an active process with continuous destruction of cells. Of course one must exclude conditions resulting in massive necrosis of cells elsewhere in the body, such as occurs in myocardial infarction, extensive trauma of skeletal muscles, acute pancreatitis and lobar pneumonia.

The liver is capable of very extensive regeneration, and newly formed cells are rich in **alkaline phosphatase.** Thus moderate elevation of alkaline phosphatase over a prolonged period speaks of an active process with constant regeneration of cells. However, high levels are often found in primary and secondary hepatic neoplasms, and there is a moderate elevation of this enzyme in obstructive jaundice of any type. It is hardly necessary to mention that we must rule out presence of a bone disease associated with increased activity of osteoblasts, such as Paget's Disease, if elevated alkaline phosphatase is to be attributed to hepatic causes.

Serum albumin is produced by the liver cell, and changes in its level serve as a useful guide suggesting improvement or deterioration of the liver function.

Prothrombin is also manufactured by the liver cell, and estimation of **prothrombin time** is a valuable index of its capacity to form this globulin, provided, however, that there is no significant impairment of absorption of Vitamin K necessary for formation of prothrombin. Obstructive jaundice will often result in hypo-prothrombinemia which can be corrected by parenteral K vitamin, if a reasonable integrity of liver cells has been preserved.

Once the diagnosis and activity of liver disease are established, and presence or absence of liver failure determined, one must consider **complications.**

It is of prime importance to establish the presence of **oesophageal varices.** They present a constant threat of hemorrhage, which often precipitates hepatic coma by further depressing the liver function. Even when bleeding is arrested, it tends to recur after relatively short periods of time, and prognosis is very poor. Up to 80% of patients who have bled significantly from the varices are dead within a year. (14). Therefore one must always consider possibility of operative intervention in patients with varices.

Incidence of **duodenal ulcer** is higher in patients with liver disease than in general population.

Anemia is common and can be due to chronic blood loss, hypersplenism and mild hemolysis.

Radiological examination of the upper G.I. tract is thus very important, and has to be supplemented by endoscopy when necessary.

Infections are frequent in chronic liver disease and often precipitate liver failure. One must not forget to look for urinary infections, though symptoms may be minimal.

Steatorrhea, disturbance in metabolism of calcium, hyperlipemia and hypercholesterolemia with xantomaton deposit are rather the features of the disease, notably of primary biliary cirrhosis, than the complications.

The last group one should consider includes various **inborn errors of metabolism of bilirubin.**

Jaundice is the only clinical manifestation of liver disease in this group. Mainly it is caused by a defective uptake and conjugation or defective excretion of bilirubin from liver cells.

The group with **predominant elevation of unconjugated bilirubin** includes several entities:

"Physiological" Jaundice of newborn and **jaundice of prematurity** is due to "immaturity" of enzymatic system concerned with bilirubin conjugation.

The same mechanism plays a contributory role in the **jaundice of Rhesus positive infants,** while hemolysis is the major factor.

Crigler - Najjar syndrome applies to the type of unconjugated bilirubinemia with lifelong jaundice. Few of these patients grow into adulthood.

While there is no evidence that conjugated bilirubin has a deleterious effect on cellular metabolism, unconjugated bilirubin has marked affinity for brain tissue, and possibility of Kernicterus is an ever present danger in the newborn with high level of this type of bilirubin. (15).

Gilbert's disease is a mild unconjugated bilirubinemia commonly seen in young males. Level of unconjugated bilirubin fluctuates usually between 1 - 4 mg/100ml, with elevation tending to occur during periods of stress, fatigue, emotional tension, etc.

The group with **predominant elevation of conjugated bilirubin** is considerably smaller.

Chronic Idiopathic Jaundice (Dubin Johnson Syndrome) (16) is a mild disorder with both free and conjugated bilirubin in plasma. Clinically it resembles Gilbert's Disease. Liver histology here is normal, but an as yet unidentified pigment is found in the cells. B.S.P. test is abnormal, and gallbladder cannot be seen on oral cholecystography.

Familial Nonhemolytic Jaundice with Conjugated Bilirubin (Rotor's Syndrome) (17) is another type of mild, fluctuating jaundice, aggravated by fatigue, infections, emotional upsets, etc., While B.S.P. retention is similar to that found in Dubin Johnson Syndrome, cholecystogram is normal, and no pigment is present in liver cells.

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BOOK REVIEW

An Appraisal of Present Concepts in Anaesthesiology. Edited by John Adriani. 267 pages. The C. V. Mosby Company. Price: $7.75.

The object of this review is to supply information to specialists in Anaesthesia who are practising outside of university centres and do not have access to scientific journals.

The book is a collection of monographs by residents in training dealing with a number of subjects which are not adequately covered in standard text books. These presentations are, of necessity, less than authoritative and often incomplete but, nevertheless, contain much useful information. It was disappointing to find that such an experienced writer as Adriani had applied a light hand in editing this book.

The style of the individual contributors is varied and is often obscure. Occasionally the obscurity leads to erroneous presentation of the facts. The section on intrapleural and intrapulmonary pressures on page 72 is contradictory as well as erroneous, and in the section on vagovagal reflexes the following sentences appear: "The experimental distention of the stomach, especially the cardia, results in a decrease in coronary flow in dogs. This response does not follow the administration of atropine or vagus section." A specialist well versed in physiology automatically corrects the second sentence to read: "This response does not occur with prior administration of atropine or vagus section." But the busy specialist, out of touch with basic sciences, would easily misinterpret these sentences. The misstatements in writing result from a looseness of expression which is common to residents in training and one would expect that careful editing would have removed them.

On the whole, the subjects are well chosen though I doubt the usefulness of including three sections on cardiopulmonary bypass in a book primarily directed at specialist Anaesthetists outside major centres. With these reservations, the book can be recommended as readable, compact and well presented.

D.E.P.

Para Medical Organizations (8)

Canadian Paraplegic Association

(Maritime Division)

This voluntary organization exists to assist the person paralyzed from disease or injury to the spinal cord back to the goal of independence in his home community. Often, especially in cases of high paralysis such as cervical injury with quadriplegia, all known rehabilitative resources may be needed to achieve this goal. The Canadian Paraplegic Association, through its executive and rehabilitation officers, attempts to assess the patient's needs at various stages of his long "road back", working closely with the many agencies and persons concerned. A resumé of some of the Association's activities at these various stages might be illustrative and explanatory to physicians and to families of the patients.

A. **During the first hospital treatment period -** The Association's representative commonly makes first contact with the patient about the time he becomes aware or is informed that his paralysis is permanent. Support is given through the period of reactive depression which is naturally a common sequel. Liaison is provided with the patient's family. Help is offered in regard to investigating liability in the case of accidents, and advice and occasionally, if necessary, financial support given in the pursuing of claims for damages. The matter of continuing education where it has been interrupted is investigated. Tutors have been provided. Arrangements for obtaining lessons from the Department of Education or from schools or universities have been made.

B. **During the period at the Rehabilitation Centre -** The Association's rehabilitation officer is a member of the total rehabilitation team and sits in on the conferences where his patient's goal is set, and plans made for its accomplishment. As the patient becomes physically stronger and more independent, and the time approaches for his return home, the rehabilitation officer, who, by this time, has frequently gained the patient's confidence as adviser and friend, may help in many ways - e.g.:

(a) Make contact with the patient's family doctor for a discussion of his case and an offer of the Association's assistance.

(b) Work with the family doctor to acquaint the patient's family with the problems of a paraplegic patient, the complications that might develop, and and the do's and don't's of paraplegic care.

(c) Help prepare the physical surroundings of the home - setting up of ramps, preparation of doors and bathrooms, etc. for wheelchairs, the provision of medical appliances and supplies for bowel and bladder care, etc.

(d) Provide or assist in obtaining a wheelchair.

(e) Assist in arranging for further education or for vocational training courses or apprenticeships.

(f) Contact previous employers or prospective new employers.

(g) Arrange for or assist in transportation.

(h) Assist in locating suitable living quarters if away from home on course, or if no home to go to.

(i) Contact municipal or provincial welfare agencies to aid in temporary support and/or disability pension.

C. **Upon return to home community and afterwards** - This is the most important phase in the opinion of the Association and most attention is focused upon the services offered through its field rehabilitation officers. Many rehabilitation programs, otherwise successful, have failed dismally because of lack of follow-up into the home community. For example, in Nova Scotia over ten years ago and before any field services were available, a survey of 25 Workmen's Compensation Board paraplegic patients was made, all of whom had had the benefit of modern treatment in a rehabilitation centre in Ontario or Quebec. After an interval of two years it was found that only two were gainfully occupied. Every effort is made during the first crucial period at home to help the patient to accept his handicap, adapt himself to his new situation and become established in some useful and gainful occupation before too long. Funds may occasionally be provided to aid in establishing a small business - for example, a shoe repair, radio or watch repair shop, canteen, or small grocery store, etc. Before direct financial assistance is made, the resources of the home community are investigated. Contact may be made with prospective employers or the town council, service clubs, the clergy, the bank manager, and interested friends of the patient. The assistance of other voluntary agencies such as the Polio Foundation or the Red Cross is sometimes sought where a combined effort is required. Frequent visits by the field officer at this stage are well repaid by the successful establishment of the patient, whether at home or elsewhere, in a worthwhile occupation. Needless to say, the gain in self respect and happiness to the patient and his family is immeasurable and the saving to the community in welfare payments substantial. Later visits need not be as frequent, and are directed towards the prevention and/or early treatment of complications, and contact with the family physician towards this end.

Other activities of the Association include an active campaign to eliminate steps in public buildings, co-operation in a national conference to establish construction and building codes for handicapped persons, frequent contact with suppliers of equipment for the para or quadriplegic to obtain the latest in motorized wheelchairs, patient lifters, hand controls for automobiles, and other mechanical and electrical aids, participation in national and international conferences on rehabilitation, co-operation with other agencies in promotion of safety and accident prevention, and an active program to expand the work of the Association more effectively into all of the Atlantic provinces.

The doctors of the Atlantic provinces are requested to advise the Association of any paraplegic patients they may have who have not received treatment in the Rehabilitation Centres in Halifax or Fredericton or are not registered with the Association, that they might be called upon by a field rehabilitation officer. The doctors may be assured of the Association's desire to cooperate with them, and are urged to avail themselves of any of the services of the Association on their patients' behalf by writing or calling the Executive Director, Mr. D. E. Curren, at the Canadian Paraplegic Association office, Building No. 7, 5775 University Avenue, Anderson Square, Halifax.

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*Information re the history of the Association, its present officers and directors, current budget, principal financial supporters, and fund raising activities is available on request. Attention is directed to a recent scientific exhibit in Post Graduate Medicine, Vol. 34, No. 2, Aug. 1963, p. 157-164 on the Role of the Family Physician in Managing Paraplegia by the C. F. Strong Rehabilitation Centre in Vancouver, B. C.

Personal Interest Notes

Greetings for 1964 to all readers. The Editor appeals again to everyone to send in any items of interest and to thank those who in the past year were cooperative in this respect.

Appointed Medical Director of Maritime Medical Care, Inc.

Dr. Arthur W. Titus, well-known Halifax physician for the last sixteen years, has been appointed Medical Director of Maritime Medical Care, Inc., it was announced recently by the Medical Plan's Board of Directors. Dr. Titus, a native of Yarmouth, N. S., is married to the former Lorraine Fuller, also of Yarmouth, and they have two children. He was graduated in Commerce from Mount Allison University in 1939 and earned his Bachelor of Science degree from Dalhousie University in 1942. Five years later he was awarded his M.D., C.M. degree from the same University. He is a licentiate in the Medical Council of Canada; a member of the College of General Practice of Canada, as well as a Director of that body. He is also a Director of the Speech and Hearing Clinic in Halifax. Dr. Titus also served as Treasurer of the Medical Society of Nova Scotia for many years, as well as on many committees of the Society.

Dosco Doc to Retire

Dosco employees on Dec. 18, including many old friends in the corporation service called around at the steel company's emergency hospital to bid their official farewell to a man who has been associated with Dosco for 53 years.

Dr. John George Brooks Lynch, the corporation's chief medical officer is 78 years of age. He is a native of Almonte, Ont., and came to Sydney in 1910. He holds a record of service with many community organizations and is a former president of the N. S. Medical Society. He was in charge of medical operations during two Springhill mine disasters and other industrial mishaps.

Dr. Lynch graduated from McGill Medical School in 1908. He holds honorary fellowships in the American Industrial Medical Association and the similar society in Quebec province.

Congratulations

To Dr. Clarence L. Gosse, President of the N. S. Medical Society on his appointment to the Board of Governors of the American College of Surgeons.

To Dr. Robert O. Jones, Head of the Dept. of Psychology, who, at the Dalhousie Medical Society Ball in December was chosen **Professor of the Year** by the students.

Births

To Dr. and Mrs. Donald C. Brown (née Eleanore Buck, R.N.) a son, Mark Andrew, at Highland View Hospital, Amherst, on December 17, 1963.

To Dr. and Mrs. Alan S. Kaplan (née Nancy Arons), of Levittown, N. Y., a son, Scott Seth, at North Shore Hospital, Great Neck, N. Y. on November 27, 1963. (Dr. Kaplan graduated in 1963 from Dalhousie)

To Dr. and Mrs. J. Douglas McLean (née Dorothy Keating), a daughter, Elizabeth Ainslie, at the Halifax Infirmary on December 3, 1963.

Marriages

Our best wishes go to Dr. Caroline Mary Davies, daughter of Dr. and Mrs. D. R. Davies, of Oxford, N. S., who was married in the Cathedral Church of All Saints, Halifax recently to Dr. Edward Carl Abbott, son of the Hon B. J. Abbott, St. John's, Newfoundland. Both the bride and groom are recent graduates from Dalhousie Medical School. They will reside in Toronto where the groom is pursuing postgraduate studies.

Amalgamation

The N. S. Chapter, Canadian Foundation for Poliomyelitis and Rehabilitation and the N. S. Society for Care of Crippled Children, have agreed in principle to amalgamation and it is hoped that the new organization will be functioning early in the spring of 1964.

Post-Graduate Division, Faculty of Medicine

Continuing medical education opportunities during the Spring of 1964.

Short Course in Psychiatry - February 3rd to 5th inclusive.

Announcements detailing this course for practitioners have been mailed throughout the Atlantic area with copies to hospital bulletin boards. It will be held in the Victoria General Hospital Pavilion commencing at 8.30 a.m. Monday, February 3rd as part of the continuing medical education programme of the Department of Psychiatry.

Short Course in Surgery - March 2nd to 5th inclusive 1964.

This course is designed primarily for doctors who have an active surgical practice. The course will be given if a minimum number of fifteen candidates apply and a maximum number of twenty-five will be accommodated. The course will consist of:

1. Special topics in the Basic Sciences as applied to Surgery.
2. Surgical problems and their management.
3. Problems in the Surgical Specialties.

All topics will be presented on the basis of recent advances.

The guest teacher for the course will be Dr. Angus D. MacLaughlin, Professor of Surgery, The University of Western Ontario.

March 23rd, 24th, 25th, 1963, a short course in the theory and practice of Auscultation of the Heart will be presented by the Department of Medicine. This is open to all doctors with a special interest in Cardiovascular Diseases and registration will be limited.

Day in Cancer 1964 - Saturday, April 18th, 1964, at the Victoria General Hospital by the Nova Scotia Tumor Clinic and the Post-Graduate Division of the Faculty of Medicine, with the assistance of a grant from the Nova Scotia Division of The Canadian Cancer Society.

The course will deal with advances in the treatment of Cancer and an outstanding authority in the field of Cancer and Chemotherapy, Dr. Robert B. Golbey, Memorial Hospital for Cancer and Allied Diseases, New York will be the guest teacher.

It is hoped that all doctors interested in the treatment of Cancer will plan to attend this meeting. Detailed announcements will go forward to all practitioners and hospitals in early March.

Regional Refresher Courses have been arranged to start in early January, in the Digby General Hospital and the Soldiers Memorial Hospital, Middleton. Others will commence sponsored by the Lunenburg-Queens Medical Society and by the Pictou County Medical Society in March and conclude in April.

A Colchester-East Hants Regional Course commenced in the Fall and will extend through the Spring period with monthly meetings.

A series of six weekly meetings were held in Yarmouth and Shelburne during the Fall period.

Regional Courses can be provided for two other areas in Nova Scotia before the Summer. Early inquiries from any branch society or hospital staff interested are desirable.

The Medical Society of Nova Scotia is in receipt of a Federal Provincial Health Grant to support a programme of education and service designed to reduce disability arising out of Haemolytic Diseases of the newborn. The educational component of this programme designed to facilitate the most effective use of the service programme to follow will be presented in sixteen centers throughout the Province, during the Spring of 1964 by teams of teachers from the Departments of Paediatrics and Obstetrics at Dalhousie University. This programme was approved at the annual meeting of the Medical Society and the active participation of every doctor dealing with a newborn is solicited.

NOTICE TO MEMBERS

Post-Graduate Division Levy

Please note that the levy per member of The Medical Society of Nova Scotia for the Post-Graduate Division of the Faculty of Medicine is now $10.00. The increase from $5.00 to $10.00 was authorized at the Annual Meeting of the Society (1963) to be effective 1964. It will appear in the 1964 billing for membership dues.