# Staff Meeting Bulletin Hospitals of the » » » University of Minnesota



# Hemoglobin Derivatives

Volume XVI | Friday, June 1, 1945 | Number 29

STAFF MEETING BULLETIN
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INDEX



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I.

# UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
## CALENDAR OF EVENTS
## June 4-9, 1945

No. 74

Monday, June 4

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler; C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 11:30 Allergy in Dermatology; Stephen Epstein; W-312, U. H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

4:00 - Public Health Seminar: Industrial Disease; Dr. Foker; 6th Floor Health Service, Women's Lounge.

Tuesday, June 5

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff; Main 515 U. H.

12:30 - 1:30 Pathology Conference; Autopsies; Pathology Staff; 104 I. A.

4:00 - 5:00 Physiological Pathology of Surgical Diseases: Physiology and Surgery Staffs; Todd Amphitheater, U. H.

4:00 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:30 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205, U. H.

4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

5:00 - 6:00 Roentgen Diagnosis Conference; A. T. Stenstrom, T. B. Merner; 515 U.H.

Wednesday, June 6

9:00 - 11:00 Neuropsychiatry Seminar; J. C. McKinley and Staff; Station 60; Lounge, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Acute Atrophy of Liver; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Physiological Chemistry Literature Review; Staff; 116 M. H.

4:30 - 5:30 Neurophysiology Seminar; Visual Agnosia; Jean Uehren; 214 M. H.

Thursday, June 7

9:00 - 10:00 Medicine Case Presentationl C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Physiological Chemistry; Intermediary Metabolism of Carbohydrates; M. F. Utter; 116 M. H.

4:00 - 5:00 Pediatric Journal Club; Review of Current Literature; Staff; W-205, U. H.

4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

4:30 - 5:30 Roentgenology Seminar; Normal Anatomy of the Lungs; E. A. Boyden, M-515 U. H.

Friday, June 8

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Stafv; E-214 U. H.

10:30 - 12:30 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department, U. H.

11:45 - 1:15 University of Minnesota Hospitals Staff Meeting. Discontinued for the Summer Quarter. Next meeting - October 5, 1945.

1:00 - 2:30 Dermatology and Syphilology; Presentation of Selected Cases of the Week; Henry Michelson and Staff; W-206 U. H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff; Todd Amphitheater, U. H.

Saturday, June 9

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:30 Surgery Roentgenology Conference; O. H. Wangensteen, L. G. Rigler and Staff; Todd Amphitheater, U. H.

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

# III. SOME NEWER CONCEPTS OF THE NATURAL DERIVATIVES OF HEMOGLOBIN AND RELATED COMPOUNDS.

Cecil James Watson

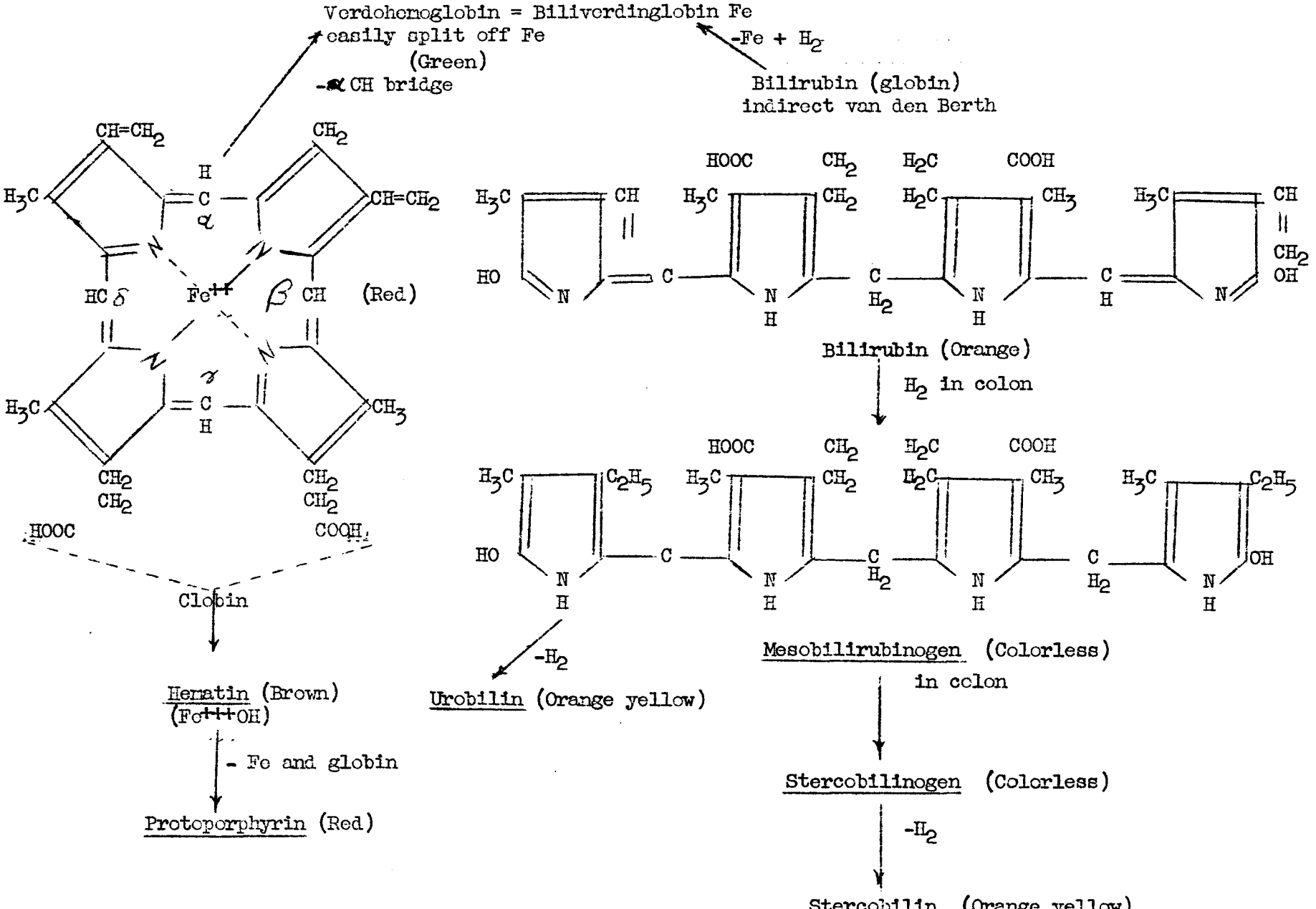
## 1. GENERAL CONSIDERATIONS

The name protoporphyrin was given by Hans Fischer[1] to the underlying porphyrin of the hemoglobin molecule. The name simply indicates that protoporphyrin is a representative or prototype of the various naturally occurring porphyrins insofar as its widespread occurrence and physiological significance is concerned. Protoporphyrin is the substance which binds the iron of the hemoglobin molecule. This was first established by the studies of Kämmerer[2], and of Fischer and Zeile[3], the earlier work of Hoppe-Seyler[4], Nencki and Sieber[5] having indicated that the underlying porphyrin of the hemoglobin molecule was hematoporphyrin. The latter substance is formed when hemoglobin is treated with concentrated sulfuric acid, but, as Fischer and his associates have clearly shown, it is an artificial compound without known biochemical significance. It is really unfortunate that the term hematoporphyrin is still used both in textbooks of biochemistry and clinical chemistry in referring to one or another of the naturally occurring porphyrins.

In Figure 1, the structural formula of the ferrous complex of protoporphyrin is shown. In accordance with the terminology of Anson and Mirsky[6] this is perhaps best designated as "heme". It is seen that the porphyrin ring is characterized by four pyrrol nuclei, each having a nitrogen at the apex of a ring of four carbon atoms. Each of the pyrrol nuclei is connected to one of its fellows by a methene (CH) bridge. The protoporphyrin molecule is distinguished from other porphyrins by the presence of two vinyl ($CH = CH_2$) groups, which are retained when the prophyrin ring opens as it does in the formation of bile pigment, as seen on the right in Figure 1. The protoporphyrin molecule is a di-carboxylic acid, two carboxyl groups being present in the form of propionic acid rests as seen in the lower part of the formula. It is probable that the globin or protein fraction of the hemoglobin molecule is attached to these carboxyl groups. Globin constitutes 96 per cent of the hemoglobin molecule. Since the molecular weight of the heme is slightly more than 600, and that of globin 60,000 to 70,000, it is evident that if there were one molecule of heme for one of globin, the heme would constitute but 1 per cent of the hemoglobin molecule rather than 4 per cent as noted. This, together with additional evidence, indicates an attachment of four heme molecules to one of globin.

It has been an important question in the past as to whether protoporphyrin is intermediate in the pathway between hemoglobin and bilirubin, or bile pigment. It was formerly believed, probably because of the ease with which hematin is formed in vitro by the treatment of hemoglobin with either acid or alkali, that hematin, a ferric complex of protoporphyrin, was the first step in the transition to bile pigment. Anson and Mirsky[6] showed that hematin as formed naturally is still attached to protein. In recent years, Hamilton Fairley[7] has shown that hematin is bound to the albumin fraction of the plasma protein when present in the circulating plasma in pathological states such as, for example, blackwater fever, severe liver disease, gas bacillus sepsis and others. It is important to note that globin has approximately the same molecular weight and the same electrophoretic behavior as albumin so that a hematin formed under natural conditions and still attached to globin would be expected to be associated with the albumin fraction. Fairley has employed the term methemalbumin to designate this association. There is no reason to believe, however, that hematin or methemalbumin is a normal intermediary substance in the transition of hemoglobin to bilirubin. Bingold[8] and Duesberg[9] in fact, have described evidence purporting to show that hematin, once formed in vivo, is not concerted to bile pigment. An extensive study of this question by Pass, Schwartz, and Watson[10] has nevertheless revealed quite clearly that hematin injected into human subjects is converted quantitatively into bile pigment, as judged by a

Figure I - HEMOGLOBIN AND DERIVATIVES



corresponding augmentation of the feces urobilinogen. It appears that free protoporphyrin, in contrast to hematin, is not capable of conversion to bile pigment in vivo, at least in dogs. Watson, Pass, and Schwartz[11] administered protoporphyrin to bile renal fistula dogs, but were unable to observe any increase in bilirubin output.

The studies of H. Fischer[12], Warburg[13], Barkan[14], Lemberg[15], and Engel[16] have all indicated that the transition of hemoglobin to bilirubin is over an entirely different pathway than the hematin-protoporphyrin chain as indicated in the lower left corner of Figure 1. The studies of Barkan and Lemberg in particular provided evidence that the first step in the transition to bilirubin, rather than the splitting-out of iron or the removal of protein as formerly thought, is the opening of the porphyrin ring by removal of the alpha-methene bridge. This results in the formation of what is perhaps best termed a verdohemoglobin (Lemberg), or green hemoglobin. As Barkan has shown, the iron in this type of hemoglobin is easily split off in contrast to that of the original hemoglobin molecule in which it is tightly bound[14,17]. Barkan and his associates[17,18] have provided considerable evidence that up to 5 per cent of the circulating hemoglobin is in this form, at least as judged by the relative amount of easily split-off iron in the circulating red blood cells. van Havemann[19] has described a method for the direct measurement of verdohemoglobin in the red cells, and reports values up to 3 per cent of the total hemoglobin in various individuals. One of the most interesting observations in this connection is that of Barkan[14] that upon the sterile incubation of red blood cells for as little as six hours, a distinct increase of iron and bilirubin in the supernatant plasma is observed without any diminution in the number of red blood cells.

It appears probable that verdohemoglobin is a biliverdin-globin-iron. It is certain that in the further transition to bilirubin, the iron is split off, and interestingly enough it (the "serum iron") travels thenceforth with the globulin fraction of the plasma[20] while the bilirubin remains with the serum albumin. The fact that bilirubin is found in the serum albumin fraction does not mean, however, that it has become detached from its original globin. As already mentioned, the ultra-centrifugal and electrophoretic behavior of globin is entirely similar to that of albumin, so that if the bilirubin were still attached to globin, one would expect to find it with the albumin fraction. The amount, of course, would be relatively so small that it would be most difficult to detect in the very much larger amount of albumin. It is logical to suppose that bilirubin attached to its original globin, indicated in parentheses in Figure 1, is responsible for the delayed or indirect van den Bergh reaction. Duesberg's postulation of a "bilirubinoglobin"[9] is quite in accord with the careful studies of Coolidge[21] who provided evidence that the indirect reacting bilirubin was attached to the albumin fraction by an actual valence bond while the prompt reacting type is only loosely adsorbed on the serum albumin fraction. Thus it is entirely within the realm of reason that bilirubin formed from hemoglobin is first divested of its globin by the liver cell, so that the bilirubin in the bile, free of protein, now exhibits a prompt direct van den Berth reaction. When this type of bilirubin returns to the blood because of regurgitation of bile due either to increased intrabiliary pressure or bile capillary injury, it becomes loosely adsorbed on the serum albumin, in which state it is still capable of exhibiting a prompt van den Bergh reaction. One may well ask why it does not become as tightly bound under these circumstances as it was before going through the liver cells into the bile. This cannot be answered with certainty, but it may be due to the fact that bile is weakly alkaline, and it is not unlikely that the bilirubin in the bile is the sodium salt. Since the sodium would replace the hydrogen of the two carboxyl groups, this would effectively prevent any recombination with protein, but it would not, of course, prevent a loose adsorption. It is, in fact, necessary to assume that the latter occurs, since the prompt direct reacting bilirubin, as well as the indirect type, is found with the serum albumin, as noted in the ultracentrifuge[22]. Another point

of importance is the chloroform-insolubility of the prompt reacting bilirubin and the relative chloroform-solubility of the indirect or delayed reacting bilirubin[23,24,25,26]. At first glance it would seem that this ought to be just the opposite, since the latter is tightly bound to protein. On closer inspection, however, it is readily appreciated that while the sodium salt is chloroform insoluble, it would nevertheless exhibit a prompt reaction with the van den Bergh (diazo) reagent, the sodium acting to hasten this type of reaction. Conversely, the chloroform might very well be expected to disrupt the bond between globin and bilirubin in the delayed or indirect reacting type, or to combine with the globin, with the result in either case that the bilirubin would be extracted by the chloroform.

The attachment of protein probably affects the type of van den Berth reaction only in an indirect way, since it is reasonably certain that the diazonium compound does not attach at the carboxyl groups. The exact mode of formation of the azobilirubin is unknown. It has been suggested that a "furan" ring forms by junction of the vinyl and hydroxyl groups of pyrrol nucleus IV (See Figure 1), thus providing a CH group for reaction with the diazonium salt[27]. It may be noted, however, that mesobilirubin which is obtained by reduction of the vinyl groups of bilirubin to ethyl groups, also exhibits a delayed van den Berth reaction which is made prompt by conversion to the sodium salt. This suggests that the middle standing methylene ($CH_2$) group in the bilirubin molecule is the point of attachment of the diazonium compound. Many analogous conjugated systems are known which form azo dyes in this way. Coupling at this point would be expected to be hastened if the bilirubin were a sodium salt, delayed if the carboxyl groups were bound to globin. The effect of alcohol in the indirect reaction would then be explained, most probably, as a loosening of the bond with protein thus removing its deterring action on the coupling of the methylene group with the diazonium salt.

Snider and Reinhold[28] have questioned the existence of any essential difference between the prompt direct types and the delayed or indirect reacting types of bilirubin, at the same time advancing the view that the difference is one of amount only. However, if one plots the reaction curve of an icteric serum with the diazo reagent, one sees a sharp rise in the curve during the first minute, then a shoulder, followed by a slow steady increase (Figure 2). This type of reaction curve clearly indicates the presence of two substances having different reaction times. If there were but one substance reacting with the diazo compound, a typical parabolic reaction curve would be expected. The contrast between the composite curve of reaction of the prompt and delayed components with the diazo compound, as compared with the hypothetical curve of but two substances is shown in Figure 2. Similar data have been provided by others[29,30,31]. On the basis of the reaction curve seen in Figure 2, it is quite evident that a measurement at one minute is synonymous with the prompt-reacting bilirubin, and that for practical purposes one need only measure the one minute and the total[26], the latter employing alcohol in accordance with Malloy and Evelyn's procedure[32].

No information was available in the literature as to the relative proportions of the one minute or prompt direct reacting and the fifteen minute delayed direct reacting fractions of the total serum bilirubin in normal individuals. Data for 27 normal medical students is given in Table I. From this it is evident that the upper limit of normal for the 1' bilirubin is unlikely to exceed 0.2 mg. per 100 cc. It is believed that this value ought to be studied more intensively with relation to the earlier stages of liver injury, particularly of the intrahepatic bile duct system, leading to regurgitation jaundice. Similarly, it is thought that T - 1', or the difference between the 1' and the total bilirubins, expresses the retention of bilirubin (globin) by the hepatic cells. This value, in other words, is regarded as a measure of retention jaundice. The data shown below in Table II reveal quite clearly the characteristic differences which are encountered in cases of relatively pure retention jaundice as con-

Figure 2

REACTION CURVE OF PROMPT AND DELAYED DIRECT REACTING SERUM BILIRUBIN COMPARED WITH HYPOTHETICAL (PARABOLIC) CURVE OF A SINGLE BILIRUBIN WITH THE DIAZO REAGENT

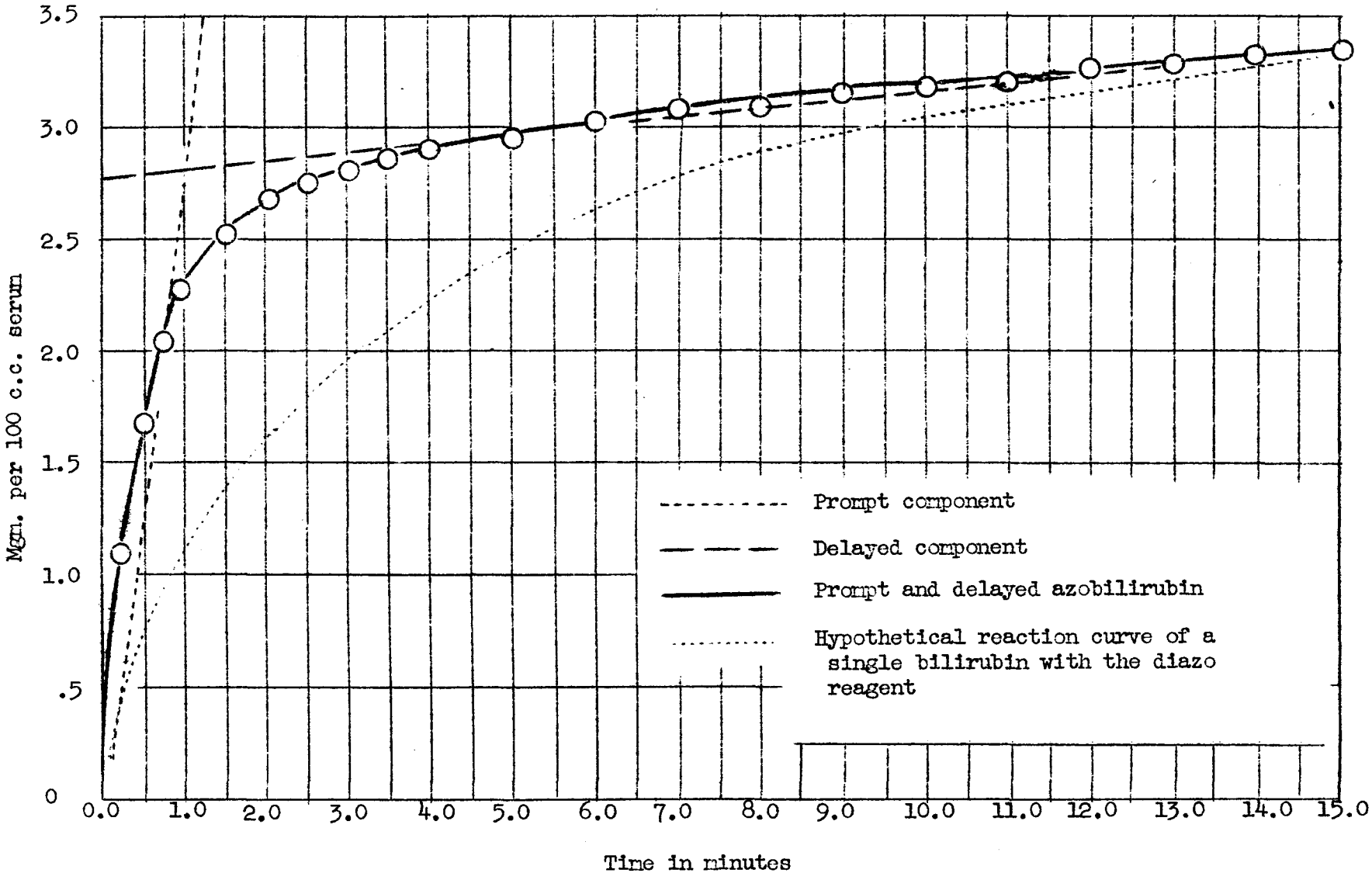


Table I

THE SERUM BILIRUBIN FRACTIONS IN 27 NORMAL MEDICAL STUDENTS

| Number | 1 minute | 15 minutes | Total (Evelyn-Malloy) |
|---|---|---|---|
| 1. | .078 | .101 | .768 |
| 2. | .094 | .285 | .506 |
| 3. | .125 | .252 | .638 |
| 4. | .141 | .637 | .900 |
| 5. | .047 | .188 | 1.034 |
| 6. | .047 | .252 | .638 |
| 7. | .063 | .125 | .474 |
| 8. | .110 | .252 | .703 |
| 9. | .094 | .252 | .537 |
| 10. | .063 | .157 | .443 |
| 11. | .094 | .188 | .537 |
| 12. | .078 | .157 | .671 |
| 13. | .125 | .252 | .571 |
| 14. | .063 | .157 | .571 |
| 15. | .125 | .252 | .637 |
| 16. | .063 | .188 | .506 |
| 17. | .125 | .206 | .314 |
| 18. | .110 | .379 | .474 |
| 19. | .063 | .173 | .251 |
| 20. | .000 | .125 | .506 |
| 21. | .031 | .188 | .637 |
| 22. | .063 | .237 | .637 |
| 23. | .047 | .157 | .606 |
| 24. | .163 | .141 | .377 |
| 25. | .125 | .237 | .443 |
| 26. | .063 | .252 | .314 |
| 27. | .157 | .303 | .671 |
| | range .000 - .157 | | range .251 - 1.034 |

trasted with regurgitation jaundice of various cause. Slight elevations of the 1' bilirubin are noted in each of the former group. Whether these represent a beginning conversion of the delayed to the prompt reacting type, in other words, a slight overlapping, or whether an actual regurgitation due to mild liver injury, cannot be determined. In any event, the striking difference between the two groups, and the correlation of the 1' bilirubin with bilirubinuria, is obvious.

To return briefly to the interesting question of the opening of the porphyrin ring in the transition of hemoglobin to bilirubin, it is evident that if the ring were to open at one of the other of the four methene bridges, a differing bilirubin or bilirubinoid substance would result. Since this possibility had never been excluded, Watson and Schwartz[33] carried out amalgam reduction of a number of different samples of human fistula bile from various individuals. As noted in Figure 1, the reduction of bilirubin results in the formation of a colorless chromogen known as mesobilirubinogen (one of the two urobilinogens). The oxidation of mesobilirubinogen results in the formation of urobilin, an orange-yellow ;igment. This compound is easily crystallized and identified by means of melting point determination. In every instance of the fistula bile study, the urobilin isolated was the same (urobilin IX,a). This indicates beyond doubt that it is always the alpha-methene

Table II

THE 1' AND TOTAL SERUM BILIRUBIN IN CASES OF RETENTION AS CONTRASTED WITH REGURGITATION JAUNDICE

| Case No. | Diagnosis | Serum bilirubin 1' | Serum bilirubin Total | Urine bilirubin |
|---|---|---|---|---|
| | **Retention** | | | |
| 1. | Infantile cirrhosis | 0.59 | 14.8 | 0 |
| 2. | Constitutional hepatic dysfunction | 0.96 | 8.8 | 0 |
| 3. | Familial hemolytic jaundice | 0.3 | 3.5 | 0 |
| 4. | Familial hemolytic jaundice | 0.24 | 3.2 | 0 |
| 5. | Familial hemolytic jaundice | 0.71 | 9.8 | 0 |
| 6. | Familial hemolytic jaundice | 0.38 | 5.2 | 0 |
| | **Regurtigation** | | | |
| 1. | Cirrhosis | 1.9 | 4.0 | + |
| 2. | Subsiding hepatitis | 1.2 | 2.6 | + |
| 3. | Common duct stone | 6.4 | 8.4 | + |
| 4. | Cirrhosis | 5.9 | 11.4 | + |
| 5. | Carcinoma of pancreas | 6.1 | 8.7 | + |
| 6. | Carcinoma of pancreas | 27.0 | 44.5 | + |
| 7. | Carcinoma of pancreas | 17.8 | 31.8 | + |
| 8. | Acute atrophy | 31.9 | 51.2 | + |
| 9. | Familial hemolytic jaundice and common duct stone | 5.2 | 11.0 | + |
| 10. | Common duct stone | 20.0 | 29.4 | + |

bridge which is split out, rather than any of the other three in the protoporphyrin molecule.

The reduction of bilirubin to mesobilirubinogen undoubtedly takes place at least mainly in the colon, and is believed to be related to the reducing activity of the bacterial flora. It was long believed that mesobilirubinogen was the only urobilinogen, but the isolation of crystalline stercobilin from the feces and urine [34,35,36,37] and its reduction to a chromogen differing from mesobilirubinogen, together with the obvious physical differences between crystalline stercobilin and the urobilin obtained by oxidation of mesobilirubinogen[27,38,39,40], proved beyond question that there are really two urobilinogens in the feces and pathological urines, which are perhaps best designated as mesobilirubinogen and stercobilinogen. It was possible to show, both by feeding of mesobilirubinogen to human subjects, and by incubating crystalline mesobilirubinogen with feces, that this substance is converted to stercobilinogen through some as yet unknown agency of the bacterial flora of the intestine[41]. From a clinical standpoint, it is best to use the term urobilinogen to indicate the composite or the sum of these two chromogens. No different physiological significance can be ascribed to the one and not to the other. Their relative proportions in various samples of feces have been shown to vary, but this, as well, probably relates to varying bacterial activity.

It is readily seen from the diagram

in Figure 1 that urobilinogen (as represented by mesobilirubinogen plus stercobilinogen) will be increased in the feces in the presence of an increased rate of hemoglobin catabolism, and decreased under converse circumstances, or when there is an interference to the outflow of bile, so that less bilirubin is permitted to enter the intestine. Thus in the hemolytic anemias, the amount of urobilinogen in the feces is markedly increased, while in hypochromic anemias, which are often associated with a throttling of the rate of blood destruction, the amount is commonly decreased. In biliary obstruction, especially that due to cancer, little or no urobilinogen may be present in the feces. Under normal circumstances, both of the urobilinogens are reabsorbed from the colon into the portal circulation and returned to the liver[39]. In the presence of liver injury or lowered function of the liver cells, varying fractions of the urobilinogen returning in the portal blood are refused and go over into the general circulation to appear in the urine, so that urobilinogenuria is an evidence of diminished hepatic function. If bilirubin is prevented from entering the intestines because of interference with the outflow of bile, urobilinogen will not be formed and hence will not be found in more than traces in either feces or urine. This is highly characteristic of jaundice due to cancer of the extrahepatic biliary tract. For further details relating to the clinical aspects of urobilinogen excretion, a number of publications which have appeared within the last ten years may be referred to[42-49].

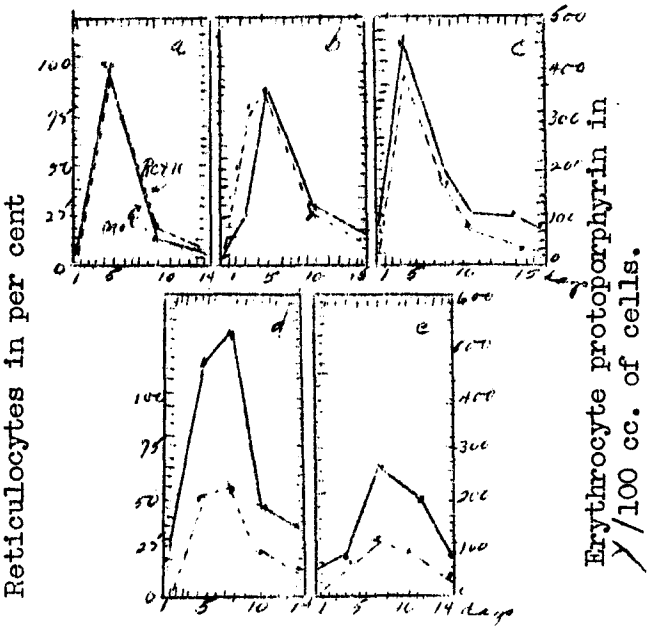
## 2. THE ERYTHROCYTE PROTOPORPHYRIN

The presence of free protoporphyrin in the erythrocytes was first reported by van den Bergh and Hyman in 1928[50]. This observation was soon confirmed[51-53]. Subsequent studies have indicated that at least three factors are concerned with respect to the amount which will be found in the erythrocytes of a given individual. These are as follows: (1) Percentage of reticulocytes, (2) the presence and degree of iron deficiency or of factors interfering with the utilization of iron in the synthesis of hemoglobin, as for example, lead, (3) formation of protoporphyrin from hemoglobin in the erythrocytes.

It has been amply demonstrated that the reticulocytes are rich in protoporphyrin[54,55] but that the protoporphyrin concentration of the red cells is not necessarily correlated with the reticulocyte percentage[56]. In induced hemolytic anemia, as for example in acute phenylhydrazine anemia of the rabbit, the reticulocyte curves closely follow those of protoporphyrin concentration.

Figure 3

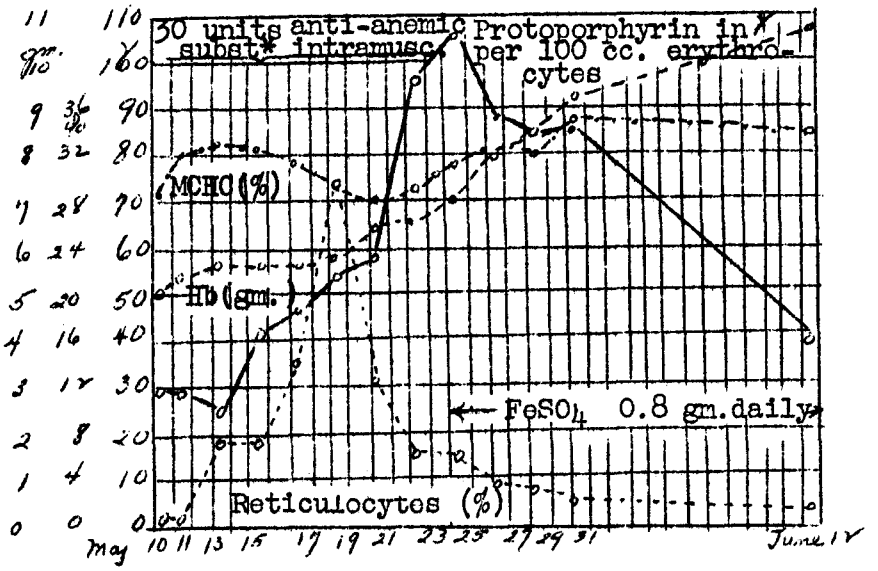
Erythrocyte protoporphyrin concentration and reticulocyte percentage in 5 rabbits (a to e) with acute phenylhydrazine anemia. From paper by Watson, Grinstein, and Hawkinson, J. Clin. Investig., 23:69, 1944[56].




On the other hand, in cases of pernicious anemia followed before, during, and after liver therapy, it was shown that the peak protoporphyrin concentrations were usually reached sometime after the peak reticulocyte response. A typical example is shown in Figure 4. This finding was in accord with the previous observations of Seggel and coworkers[57,58] on the percentage of fluorescytes as affected by liver therapy

Figure 4

Erythrocyte Protoporphyrin Concentration, Reticulocyte Percentage, Hemoglobin in Grams per 100 cc. of Blood, and Hemoglobin Concentration of the Erytorocytes, Before and After Liver Extract Therapy in a Case of Pernicious Anemia. C.S.,M,53. From paper by Watson, Grinstein and Hawkinson[56].




*Liver concentrate, 10 units per cc., intramuscularly, on May 10th; this dose was repeated on May 27.

in pernicious anemia. According to Seggel and others[59], the fluorescytes are red blood cells exhibiting a red fluorescence in ultraviolet light, presumably due to their content of protoporphyrin.

The normal range of concentration of the erythrocyte protoporphyrin is from 15 - 40 γ per 100 cc. of erythrocytes[56], usually below 30 γ. Values up to 40 γ are noted in apparently healthy females but are correlated with mild reductions in hemoglobin and hematocrit percentage probably on the basis of blood loss during menstruation[56]. Iron deficiency anemia is characterized by marked increases often of 10 to 20 fold. In the main, a rough inverse relationship exists in these cases between the hemoglobin concentration of the red cells and the amount of protoporphyrin (Table III). It is seen, however, that in certain instances (cases 51 and 52) the values are not as elevated, in spite of a more severe anemia and greater reduction of hemoglobin concentration, as they are in others (cases 37 and 44). The impression has been gained that a better correlation exists with the degree of chronicity as indicated by the history, and by the presence of the "epithelial" evidence of iron deficiency, i.e., dry hair and skin, changes in the finger nails, glossitis, dysphagia. Cases 37,44 and 47 were illustrative.

The protoporphyrin concentration of the red blood cells in pernicious anemia in relapse is uniformly within the normal range. This is shown by the data in Table IV. These values are in striking contrast to the findings in the vast majority of anemias of other types, notably the iron deficiency anemias and the refractory or hyporegenerative variety. Of the seven cases of refractory anemia listed in Table V, it is seen that five had considerably elevated erythrocyte protoporphyrin values. It is apparent that iron deficiency was not

Table III

Erythrocyte Protoporphyrin in Iron Deficiency Anemia

| Case No. | Hemoglobin in Gms. per 100 cc. | Hematocrit % | M.C.C. | Reticulocyte % | Protoporphyrin in γ per 100 cc. of erythrocytes |
|---|---|---|---|---|---|
| 34 | 9.8 | 36 | 30 | 0.9 | 221 |
| 35 | 9.45 | 29.4 | 32 | 1.2 | 103 |
| 36 | 7.45 | 24 | 31 | 0.7 | 50 |
| 37 | 5.75 | 23 | 25 | 6.2 | 613 |
| 38 | 7.00 | 28 | 25 | 2.2 | 143 |
| 39 | | 30 | | 0.6 | 117 |
| 40 | 9.75 | 35.5 | 27.4 | 0.9 | 165 |
| 41 | 5.25 | 18 | 29 | 1.2 | 77 |
| 42 | 9.45 | 32.5 | 29 | 4.0 | 70 |
| 43 | 8.3 | 28.5 | 29 | 2.8 | 137 |
| 44 | 10.95 | 40 | 27 | 2.0 | 320 |
| 45 | 9.5 | 33 | 29 | 1.8 | 208 |
| 46 | 7.3 | 31.8 | 23 | 2.1 | 142 |
| 47 | 6.18 | 29 | 21.4 | 5.9 | 504 |
| 48 | 8.95 | 31 | 29 | 0.9 | 309 |
| 49 | 6.87 | 24.6 | 28 | 1.5 | 105 |
| 50 | 7.8 | 34 | 23 | 1.8 | 221 |
| 51 | 4.13 | 19 | 21.7 | 1.9 | 253 |
| 52 | 4.55 | 18 | 25.3 | 5.1 | 172 |
| 53 | 8.3 | 31.5 | 26 | 8.3 | 128 |

Table IV

Erythrocyte protoporphyrin in pernicious anemia (relapse)

| | | | | | |
|---|---|---|---|---|---|
| 1 | 5.06 | 18.7 | 27.1 | 1.0 | 29 |
| 2 | 9.0 | 23 | 39.1 | 0.9 | 23 |
| 3 | 5.0 | 17 | 32. | 1.0 | 29 |
| 4 | 5.0 | 19 | 26.3 | 0.3 | 22 |
| 5 | | 37 | | 1.1 | 15.7 |
| 6 | 3.44 | 11 | 31.2 | 0.3 | 16 |
| 7 | 7.8 | 25 | 31.2 | 0.5 | 23.5 |
| 8 | 10.45 | 38 | 27.5 | 0.6 | 20. |
| 9 | 4.63 | 15 | 31. | 1.1 | 20 |
| 10 | 6.8 | 21.5 | 31.6 | 0.7 | 27 |
| 11 | 8.07 | 27 | 30 | 1.8 | 20 |
| 12 | 3.44 | 11 | 31.2 | 0.1 | 30.03 |
| 13 | 6.95 | 23 | 30.2 | 1.0 | 20 |
| 14 | 8.8 | 22 | 40 | 1.0 | 27 |
| 15 | 4.67 | 15 | 31 | 1.1 | 35 |

Table V

Erythrocyte protoporphyrin in Refractory (hypo-regenerative or apalstic) Anemia

| Case No. | Hemoglobin in Gms. per 100 cc. | Hematocrit % | M.C.C. | Reticulocyte % | Protoporphyrin in γ per 100 cc. of erythrocytes |
|---|---|---|---|---|---|
| 54 | 6.25 | 19.6 | 32 | 2.3 | 76 |
| 55 | 7.1 | 23 | 31 | 0.9 | 147 |
| 56 | 7.98 | 27.5 | 29 | 1.0 | 36 |
| 57 | 5.17 | 17 | 30.2 | 2.1 | 94 |
| 58 | | 8 | | | 20 |
| 59 | 4.17 | 12 | 35 | 0.8 | 74 |
| 60 | 8.3 | 24 | 34.6 | 3.2 | 132 |

the cause of these elevations, since the mean corpuscular hemoglobin concentrations are either approximately normal or within the normal range. The cause of the elevation in these cases is not at all clear. It is evident that thw increase cannot be ascribed to an increase in reticulocytes. In case 59, for example, the reticulocyte count was 0.8 per cent with an erythrocyte protoporphyrin of 74 γ . In this instance, the mean corpuscular concentration of hemoglobin was 35 per cent, so that there was no evidence of any iron deficiency whatever. In such instances as this, it is possible that the third of the three factors mentioned at the outset may be operative, viz., the formation of protoporphyrin from hemoglobin within the erythrocytes. The only evidence in favor of this possibility is the observed increase of protoporphyrin in the erythrocytes upon sterile incubation of blood in vitro[56]. It is possible that this might occur wherever red blood cells are sequestered, as for example, in the splenic pulp. Further study of this question is needed. In a previous report[56], a case of myeloid leukemia with severe myelophthisic anemia was recorded in whichno reticulocytes could be demonstrated in the peripheral blood on repeated occasions. The color index was 1.0. In this instance, it was evident that neither iron deficiency nor reticulocytes were contributing to the presence of the protoporphyrin in the red blood cells, the amount of which was 43 γ per 100 cc. Here again, it may be inferred that formation from hemoglobin had occurred, although proof of this derivation is lacking.

Of the group of cases in Table VI, case 68 is of particular interest, since this patient was thought at first to have pernicious anemia, the peripheral blood exhibiting macrocytosis and an almost normochromic state. The high erythrocyte protoporphyrin was the first clear indication that this assumption was incorrect, and the bone marrow aspiration subsequently revealed the typical appearance of multiple myeloma rather than pernicious anemia. It is of interest to note that of the five cases of polycythemia vera, the only distinctly abnormal value, that of 68 γ per 100 cc. in case 73, was associated with a significant lowering of the mean corpuscular hemoglobin concentration to 27 per cent. This patient had been bled repeatedly and undoubtedly suffered from iron deficiency.

In Table VII, the data from three cases is given in which elevations of the protoporphyrin in the red cells were associated with heavy metal poisoning. Case 80 was of particular interest because of the coexistence of peripheral neuritis. Occasional stippled cells were found in the peripheral blood after prolonged search. They were more numerous in the bone marrow which was normoblastic in type. The markedly increased erythrocyte protoporphyrin in the absence of iron deficiency suggested lead poisoning, and upon further questioning it was ascertained that this individual had had considerable contact with tetraethyl lead while working as a filling

## Table VI

### Erythrocyte Protoporphyrin in Leukemia, Hodgkin's disease, Polycythemia, Myeloma, Lymphosarcoma

| Case No. | Diagnosis | Hemoglobin in Gms. per 100 cc. | Hematocrit % | M.C.C. | Reticulocyte % | Protoporphyrin in γ per 100 cc. of erythrocytes |
|---|---|---|---|---|---|---|
| 61 | Myelogenous leukemia | 8.15 | 30 | 27.2 | 3 | 78 |
| 62 | Myelogenous leukemia | 8.65 | 30.8 | 28.1 | 0.3 | 56 |
| 63 | Myelogenous leukemia | 9.02 | 34 | 26.5 | | 40 |
| 64 | Myelogenous leukemia | 10.65 | 31 | 34.4 | | 48 |
| 65 | Lymphatic leukemia | 12 | 37 | 32.5 | | 23 |
| 66 | Lymphatic leukemia c acquired hemolytic anemia | 6.15 | 24 | 25.6 | 28 | 119 |
| 67 | Lymphatic leukemia | 3.23 | 10 | 32.3 | 3.5 | 40 |
| 68 | Myltiple myeloma | 7.52 | 24.5 | 31 | 3.4 | 126 |
| 69 | Multiple myeloma | 11.5 | 38 | 30.3 | | 31 |
| 70 | Lymphosarcoma | 6.94 | 24 | 28.6 | 1.5 | 171 |
| 71 | Hodgkin's | 8.6 | 32 | 27 | 4.0 | 44 |
| 72 | Hodgkin's | 10.95 | 35.5 | 31 | 1.0 | 70 |
| 73 | Polycythemia vera | 17.5 | 64 | 27 | 1.5 | 68 |
| 74 | Polycythemia vera | 19.6 | 65 | 30 | 0.8 | 40 |
| 75 | Polycythemia vera | | 68 | | 0.5 | 24 |
| 76 | Polycythemia vera | | 61.5 | | 0.6 | 39 |
| 77 | Polycythemia vera | 13.5 | 41.5 | 32.5 | 0.8 | 46 |

## Table VII

### Erythrocyte Protoporphyrin in Heavy Metal Poisoning

| | | | | | | |
|---|---|---|---|---|---|---|
| 79 | Pb poisoning | 10.0 | 34 | 29.4 | 14.6 | 240 |
| 80 | Pb poisoning | 6.6 | 18.5 | 35.7 | 1.9 | 470 |
| 81 | Arthritis, patient receiving gold therapy | 9.45 | 27 | 35 | 0.7 | 107 |

station attendant. Subsequent study of the urine revealed in the neighborhood of 1000γ of coproporphyrin per day, at least ten times the normal range. This increase was shown to be composed of the type 3 isomer which is entirely characteristic of lead poisoning.

The erythrocyte protoporphyrin is usually distinctly increased in the hemolytic anemias, as contrasted with pernicious anemia. Data from 7 cases are shown in Table VIII. This finding constitutes further evidence against the view that pernicious anemia is a hemolytic anemia in the strict sense.

Table VIII

Erythrocyte protoporphyrin in hemolytic jaundice

| Case No. | Hemoglobin in Gms. per 100 cc. | Hematocrit % | M.C.C. | Reticulocyte % | Protoporphyrin in γ per 100 cc. of erythrocytes |
|---|---|---|---|---|---|
| 16 | 12.1 | 37 | 32.7 | 7.1 | 48 |
| 17 | 5.35 | 21.5 | 25 | 49.7 | 144 |
| 18 | 9.00 | 33 | 27.2 | 7.1 | 60 |
| 19 | 6.75 | 24 | 29 | 31 | 86 |
| 20 | 11.7 | 32 | 33 | 5.9 | 37 |
| 21 | 2.73 | 8 | 34.2 | 5.3 | 42 |
| 22 | 8.15 | 31.5 | 26 | 8.2 | 122 |

Summary.

1. The transition of hemoglobin to bile pigment, at least under normal conditions, is believed to be via hematin and protoporphyrin, but rather over an intermediate verdohemoglobin, a substance in which the porphyrin ring has opened, the globin and iron still being attached, in other words, a biliverdin-globin-iron. It is probable that the next step is a reduction to bilirubin with splitting off of iron. There is much reason to believe that the globin remains attached until the bilirubin passes through the liver cell, bilirubinglobin exhibiting a delayed or indirect van den Bergh reaction and not being excreted in the urine; the sodium bilirubinate of the bile exhibiting a prompt (1') van den Bergh reaction and being readily excreted in the urine. The former type is characteristic of retention, the latter of regurgitation jaundice.

The bilirubin of the bile is reduced in the colon to a colorless chromogen, mesobilirubinogen, a considerable fraction of which is further changed by the activity of the bacterial flora of the feces, to stercobilinogen. Both of these chromogens exhibit an intense Ehrlich aldehyde reaction, and together they represent the urobilinogen of the feces and urine. A considerable fraction of the urobilinogen formed in the colon is reabsorbed into the portal blood and goes to the liver. The normal liver adequately disposes of this fraction, albeit in an unknown way. In the presence of liver functional derangement, varying fractions of urobilinogen are refused by the liver and pass into the general circulation to appear in the urine.

2. The above experience with the erythrocyte protoporphyrin in the anemias has revealed that this determination, quite apart from its fundamental interest, is at times of diagnostic value. Thus in several instances a significant elevation of the erythrocyte protoporphyrin has indicated that the initial impression of pernicious anemia was incorrect, and has led to the search for other information. Conversely, a normal value in the presence of anemia, has often correctly indicated or confirmed the diagnosis of pernicious anemia. Marked elevations have aided in confirming the presence of iron deficiency and have given some insight into

the degree of its severity. In certain cases, high values for the erythrocyte protoporphyrin have suggested the possibility of heavy metal toxicity, the existence of which has then been borne out by subsequent study. In general, the following ranges of concentrations are suggestive of one of the anemias in the group indicated.

| | Erythrocyte Protoporphyrin Concentration |
|---|---|
| Pernicious anemia | 15 - 30 γ % |
| Hemolytic anemia<br>Refractory or hyporegenerative anemia<br>Leukemia, Hodgkin's disease, myeloma | 30 -150 γ % |
| Iron deficiency anemia<br>Anemia due to heavy metal toxicity | 50 -600 γ %<br>usually greater than 150γ%. |

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III. GOSSIP

Forrest Ray Moulton, permanent secretary of the American Association for the Advancement of Science, and Justus J. Schifferes, former Medical Editor of Minneapolis, have just published a most interesting volume entitled the "Autobiography of Science". Subjects include original contributions in the fields of Medicine,Biology, Chemistry, Physics, Astronomy, Optics, Botany, Genetics, Anthropology, Geology, Aeronautics, Psychology, and related fields. In each instance the story is told in the words of the person responsible for the contribution. This makes the book ideal for laymen and scientists alike. The authors hope to prove to the general reader that he can understand, and that he can enjoy the literature of science. In this they have succeeded for it is good reading for those interested in special subjects, or for those who pick it up and read it at random. Physicians will find the original reports of many of their favorites. Some of the great names in science are purposely omitted not because their contributions are unworthy, but rather because the authors have tried to make the book a tour in which highlights along the way are brought to our attention. In each instance, stories of the beginnings rather than the end results have been selected. It is interesting to note that fewer than half, only 45, were originally written in English. Spelling and punctuation and re-paragraphing have been done in order to make the subject matter more readable. According to the authors the book can be read in any one of six ways, that is, as a story book, a history book, a textbook, a source book, or a chronicle. The history of science is one of man's most brilliant chapters in this great book of time. The authors extend a grateful appreciation to another Minnesotan, Richard E. Scammon, Professor at the University of Minnesota, for encouragement and assistance. The book, published May 17, 1945, sells for $4.00 by Doubleday Doran & Company, Incorporated. We predict that it will be one of the best sellers for people who are looking for something to give to their doctor as a present. The many friends of Justus J. Schifferes will be pleased to know of his most recent literary success.....The accomplishments of physicians who practice in small places is a source of pleasure to me. The other evening I visited at the home of Dr. A. I. Arneson, of Morris, Minnesota. He lives in a mansion of bygone days, which was erected 54 years ago, but has been modernized without destroying its original charm. His hobby is collecting fluorescent stones. He took us in a dark room, and after our eyes had become accustomed to the darkness, he turned on a ultraviolet lamp over his stone collection. Stones which had been black or gray, now shone with the brilliance of the rainbow, or like the jewels of the emperor's crown. These stones are found in certain sections of the world, and are located by using a similar lamp after dark. And as if this were not enough, he took us to the second floor, to his gun repair and rebuilding shop. The superintendent of schools who was along, said the equipment in this room exceeded that of the high school shop. Dr. Arneson is looking forward to another hobby, postwar. He has just purchased a lakeside farm on which he intends to build a house involving the principal of solar orientation. The house will be faced to the south, and one side will be made of plate glass windows. Below the house the ground falls in a series of terraces to the lake some distance away. You may remember the story about Mr. Keck, the architect, who appeared on one of our courses at the Center for Continuation Study. He told us when the sun is shining in the wintertime the interior of one of these homes gives you the feel of a spring day. Many of our physicians throughout the state lead similar broad lives, and practice good medicine, too. The strength of Minnesota's medical profession is built about these men who come at regular intervals for further instruction at the University for developments in medicine....This is the last staff meeting of the year. Col. Leonard T. Peterson, who was to have appeared on the program June 15, will come at an earlier date that week. The June 8th meeting has been postponed 'til fall due to a conflict in schedule of surgical department. An index for this year's volume and for last year's volume will be available in the Record Room. This will be sent to mail subscribers....Good-bye, Good luck! And our deepest appreciation for your help.....