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Recent Studies of the Urobilin Problem

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I. RECENT STUDIES OF THE UROBILIN PROBLEM*

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(I) Historical Introduction

It is not surprising that the urobilin problem has commanded the attention of so many investigators, as it bears directly upon basic and clinical aspects of hemoglobin metabolism and liver function. In the following no attempt will be made to review the literature in any comprehensive fashion. In this connection, however, special reference may be made to other papers and books which have dealt with the subject in detail[1,2,3,4,5]. The story of the urobilin group commences with Jaffé's discovery in 1868[6], of the presence in urine and bile of a substance exhibiting intense green fluorescence with zinc. Jaffé partially purified this compound, observed that it had a characteristic absorption band and described certain other characteristics. Because of the occurrence of the substance both in urine and bile, he gave it the name "urobilin". In 1871, VanLair and Masius[7] described what appeared to be an entirely similar compound regularly present in human feces. They were not certain that this was identical with Jaffé's urobilin and to be on the safe side they designated it "stercobilin". In the same year Maly first carried out the reduction of bilirubin, the principal pigment of the bile, with sodium amalgam[8]. He obtained a substance which appeared very similar to the compounds described by Jaffé, and VanLair and Masius. Since he had produced it by reduction of bilirubin, he gave it the name "hydrobilirubin". It soon became evident through the work of several investigators[9,10,11] that urobilin and stercobilin were excreted in considerable part as a colorless chromogen which LeNobel[9] was the first to name urobilinogen. For some time there was no ready means of detecting this chromogen in the excreta, and the knowledge of its transition to urobilin depended on the observation that when suitable extracts of fresh material were exposed to light and air, the development of the orange color of urobilin together with its green fluorescence with zinc and characteristic spectral absorption, were noted. In 1887 Ehrlich[12] had described the color reaction exhibited to a marked degree by certain urine samples, especially from cases of liver disease, when the urine was brought together with paradimethylaminobenzaldehyde and concentrated hydrochloric acid. This came to be known as the Ehrlich "aldehyde" reaction. Ehrlich was unable to define the natural substance responsible for the reaction. This remained for Neubauer, who pointed out, in 1901[11], that the Ehrlich reaction was due to urobilinogen.

Ten years later, a very great advance was made by Hans Fischer, who returned to the sodium amalgam reduction of bilirubin first described by Maly. Fischer, however, carried this out much more efficiently with the result that he obtained a colorless chromogen and was able to crystallize it[13]. This compound, first designated "hemibilirubin", later as mesobilirubinogen, was characterized by an intense Ehrlich aldehyde reaction with the same absorption as that shown by Ehrlich reacting urine samples. Exposure of mesobilirubinogen to light and air resulted in urobilin formation, that is to say, the development of an orange compound exhibiting intense green fluorescence with zinc together with urobilin absorption (maximum in the region of 495 mμ). Fischer then proceeded to isolate the same compound from urine samples rich in urobilinogen[14]. The crystals obtained by the reduction of bilirubin in vitro, or from the urine, were identical.

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Subsequent studies by Fischer and his co-workers clearly delineated the pathway of reduction of bilirubin to mesobilirubinogen or urobilinogen[15]. It was shown that the first stage in the reduction is dehydrobilirubin ($C_{33}H_{38}N_4O_6$), a compound having two hydrogens more than bilirubin. It has not been detected in nature and is very easily reduced further to mesobilirubin ($C_{33}H_{40}N_4O_6$). This substance is light yellow and still exhibits a Gmelin color play with nitric acid, but, also like bilirubin, it does not give an Ehrlich aldehyde reaction. In mesobilirubin the two vinyl groups characteristic of bilirubin have been reduced to ethyl groups. Further reduction produces a faintly yellow compound known as dihydromesobilirubin. This substance gives an Ehrlich aldehyde reaction and on further reduction is converted to the colorless chromogen, mesobilirubinogen, ($C_{33}H_{44}N_4O_6$).

In the twenty years following Fischer's Isolation and identification of mesobilirubinogen with the crystalline urobilinogen in the urine, a number of studies[3,16,17,18] had shown the basic importance and practical value of determining the urobilinogen excretion in the urine and feces, with special reference to variations in the rate of blood destruction, and to disturbances of liver function. It was clear, however, that altogether too little information was at hand as to the essential unity of the compounds characterized by the Ehrlich reaction or by green fluorescence with zinc, upon which the various quantitative methods were based. Although Fischer had clearly shown that mesobilirubinogen was identical with a crystalline urobilinogen excreted in the urine, the possibility certainly existed that the excreta might contain other compounds characterized by these reactions. It was of practical as well as fundamental importance to determine whether this were true, as if there were two or more urobilinogens, the possibility indeed existed that the intensity of their Ehrlich aldehyde reactions might be different, and consequently, that varying proportions of the substances in any given sample would lead to altogether different quantitative results, with ensuing confusion. With these considerations in mind, one of us(C.J.W.), in 1930, working in Hans Fischer's laboratory in Munich, began the attempt to isolate mesobilirubinogen, or any differing compound of this series, from human feces. This work was unusually arduous and disappointing. Because of the lability of mesobilirubinogen, it was necessary to use kilogram quantities of starting material and carry a long process of purification through in the same day in order to minimize the period of oxidation. The methods under investigation often required a twelve or fourteen hour period, at the end of which time, with good luck, a few ml. of an intensely Ehrlich reacting solution would be available. It was never possible, however, to obtain crystalline material in any of these attempts. Nevertheless, by a fortunate chance, crystals were first obtained in 1931, which had urobilin or stercobilin characteristics[19,20]. At first it was not clear whether this substance was a urobilin derived by simple dehydrogenation of mesobilirubinogen, but as a result of further work [20,21,22], it soon became evident that this was not the case. With improved techniques it became possible to isolate relatively large amounts of orange-yellow crystalline stercobilin from the feces. Reduction with sodium amalgam led very easily to a colorless chromogen exhibiting an intense Ehrlich aldehyde reaction. However, this could not be crystallized, and indeed, in the years that have intervened, despite many attempts, stercobilinogen has never been prepared in crystalline form. The possibility still existed, however, that the crystalline stercobilin was derived by simple oxidation of mesobilirubinogen, but that this was not reversible and that reduction led to a different chromogen. It was therefore essential to dehydrogenate mesobilirubinogen in vitro and crystallize the resulting urobilin in order to compare it with the crystalline stercobilin from feces. This was first accomplished in 1933[21,23,24], and it was at once evident that the material differed from crystalline stercobilin. The latter was more stable and readily yielded a beauti-

fully crystalline iron chloride molecular compound, also a crystalline hydrobromide. Fischer, Halbach and Stern[25] found that crystalline stercobilin from feces is strongly levorotatory, while the urobilin from mesobilirubinogen is optically inactive*. Lemberg and co-workers[26,27] noted significant spectroscopic differences which we have been able to confirm. Thus, stercobilin has an absorption maximum at 4925 A°. These substances are isolated primarily as the hydrochlorides, the melting points of which are not sharp. The free substances, however, have much more distinctive melting points, as will be noted in the following.

From this work it was apparent that the feces, at least under ordinary circumstances, contain stercobilinogen and stercobilin in major proportion and that stercobilin differs significantly from the urobilin obtained by simple dehydrogenation of mesobilirubinogen. Evidence was obtained, however, that the feces also contained variable amounts of the latter substance as well. Even though this could not be crystallized in these earlier studies, it was possible to identify crystalline mesobilirubinogen after amalgam reduction of the mother liquor from which stercobilin had been crystallized[5]. This clearly revealed the presence in these mother liquors of a urobilin which could be hydrogenated to mesobilirubinogen. Subsequent work to be mentioned in the following, fully confirms this observation.

Upon the isolation of crystalline stercobilin from feces, the question at once arose as to whether it would also be found in urobilin or urobilinogen containing urine, using these terms in the broad sense, based solely on green fluorescence with zinc or the Ehrlich aldehyde reaction. As noted earlier, Fischer had already isolated crystalline mesobilirubinogen from the urine in two different instances. In a study in this laboratory in 1935, it was possible to isolate from the urine of a case of hemolytic jaundice a large amount of crystalline mesobilirubinogen together with a considerable amount of crystalline stercobilin[24]. Crystalline stercobilin was also isolated from the urine in a variety of other diseases such as cardiac failure with passive congestion of the liver, and cirrhosis of the liver[22,28]. In these instances no attempt was made to isolate the chromogen itself and it is quite possible that mesobilirubinogen was present in significant amount along with stercobilinogen.

Thus it has become clear that the term urobilin as used by Jaffé and many others after him applied to a variable mixture of at least two substances occurring in both urine and feces. Fischer quite naturally decided that urobilinogen was identical with mesobilirubinogen and the term has come to be used synonymously in this sense by many writers. From a strictly chemical standpoint it is best to employ it in this way and to separate it sharply from stercobilinogen on the one hand, and, as we shall see in the following, from d-urobilinogen on the other. From the clinical and physiological point of view, however, it is necessary to have a single term to cover the sum total of these substances determined quantitatively by means of the Ehrlich reaction, whether in feces or urine or in other material. On the basis of historical development, one can certainly justify use of the term urobilinogen for this purpose, and we together with many others have used it in this way. It is evident, however, that this has already resulted in a certain degree of confusion. Thus, Baumgärtel has drawn the incorrect conclusion[29] that we regard stercobilin as identical with the urobilin derived from mesobilirubinogen. This in spite of the fact that the difference between these substances, as already mentioned, was

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* (i) urobilin. This has often been designated as urobilin IX, α, but this applies equally to stercobilin and d-urobilin, all three being derivatives of the protoporphyrin IX of hemoglobin, the α methene bridge being split out in the transition to bile pigment.

first delineated in this laboratory. To avoid any further confusion from the standpoint of terminology, it is suggested that in the future the terms "urobilin or urobilinogen groups" be employed to designate any result based respectively on fluorescence with zinc or the Ehrlich aldehyde reaction, in discussing either qualitative or quantitative studies of natural material. This group includes the levorotatory stercobilin and its chromogen, stercobilinogen, the inactive urobilin and its chromogen mesobilirubinogen (urobilinogen) and as will be discussed below, the dextrorotatory urobilin and its chromogen, d-urobilinogen.

The fact that there was a third and dextrorotatory compound in the group, was first discovered in this laboratory in 1942[30]. A study of fistula bile revealed that in the presence of infection and especially upon incubation of infected samples in vitro, considerable amounts of a dextrorotatory urobilin could be obtained. This substance was isolated in crystalline form. Its absorption spectrum was shown to be the same as that of the inactive urobilin, thus differing from the levorotatory stercobilin. A further method of distinction was found to be a blue-violet color reaction when the substance was heated in dioxane containing a small amount of hydrochloric acid. This will be referred to again in the following. It was impossible at that time to obtain anything more than minute amounts of the material and for various reasons, chiefly related to the war, this study had to be given up temporarily. With the advent of aureomycin, it became evident that this substance has a profound influence on the bacterial flora of the colon, amongst other things, temporarily eliminating, or greatly reducing the ability of the flora to reduce bilirubin to the urobilinogen group [31]. After a variable period of time, whether the aureomycin is discontinued or not, the flora resume their reduction of bilirubin, but instead of producing stercobilinogen they produce mainly or entirely a chromogen which on simple oxidation gives rise to the dextrorotatory urobilin. This observation has of course given new impetus to the study of d-urobilin, and the results of our recent work in this direction will be considered in the following.

The history of the various concepts of origin of the urobilin group is of considerable interest in its own right. This has been reviewed in some detail elsewhere[1,5], and it will suffice now to mention only those milestones which are clearly pertinent to the present studies. Although urobilin had variously been regarded as enterogenous, hepatogenous, histogenous, hematogenous, and even renal in derivation, the classic studies of Friedrich v. Müller strongly supported the enterogenous theory as opposed to all the others. v. Müller based his main study on the well known fact that in complete biliary obstruction, as typified by carcinoma of the head of the pancreas, the feces and urine are lacking in members of the urobilin group. He fed urobilin free pig bile to such an individual and observed the transitory appearance of urobilin in the feces and urine. After the turn of the century, however, the hepatogenous theory was renewed, especially by Fischler, who claimed that dogs, with a complete external biliary fistula, excreted significant amounts of urobilin in the bile[32]. Meyer Betz[1] pointed out that the likelihood of the dogs licking up some of their own bile in these experiments, was not excluded. As a result of the reports of Fischler and others, McMaster and his co-workers at the Rockefeller Institute were induced to restudy the whole question of the origin of urobilin in a series of well planned experiments in dogs[33-40]. In brief, they found: 1) In the presence of a complete external biliary fistula where there was no opportunity for the dogs to obtain any of their own bile, urobilin promptly disappeared from the feces and urine. 2) Injury of the liver in such animals, whether with carbon tetrachloride or other chemicals, failed to result in the appearance of urobilin in urine or feces. 3) Artificial infection of the bile fistula by means of small bits of feces, was promptly followed by the appearance of urobilin in the bile and urine. The Rockefeller group concluded that urobilin

was enterogenous, but that it could be formed by the activity of the bacterial flora in the infected biliary tract. Until rather recently, this view has gone unchallenged, and the enterogenous concept has been generally held. Since World War II, Baumgärtel in Munich has published rather extensively about a concept which combines the hepatogenous and enterogenous theories of formation of members of the urobilin group[29]. Several other investigators, including Lemberg[41], Stich[42], and Rudolf[43], have accepted Baumgärtel's ideas either wholly or in part. In brief, these may be summarized as follows:

Bilirubin is said to be converted to mesobilirubinogen in the liver but not in the intestinal tract. The bacterial flora of the colon convert bilirubin only to stercobilinogen, not to mesobilirubinogen. The hepatic conversion is believed to be due to a specific liver cell dehydrogenase system which is activated by hepatic injury and "blocked" by biliary obstruction. Baumgärtel claims to have carried out the conversion of bilirubin to mesobilirubinogen by means of sterile "liver brei" in vitro, but the description of these experiments has never been given in any detail. It would be of particular interest to know what type of liver was employed and to what extent the presence of bacteria was carefully excluded. As is well known, animal liver usually contains resident bacteria and human liver gains bacteria rapidly after death. Baumgärtel states categorically that the liver cell dehydrogenase is unable to reduce bilirubin to stercobilinogen, conversely that bacterial dehydrogenases in the intestine are unable to convert mesobilirubinogen to stercobilinogen. In more recent papers, he has indicated that the conversion in the liver takes place in the bile rather than in the liver cell itself. So far as can be determined, he requires some degree of liver injury for the activation of the necessary enzyme. As noted above, we have observed that aureomycin temporarily abolishes or greatly reduces bilirubin reduction in the colon, and for a short time after its administration has been commenced, the urobilinogen group disappears from the feces and urine. When it returns, it is represented by the dextro-variety. Baumgärtel, however, has recently stated that[44] the reason for the disappearance of urobilinogen is not so much the effect of aureomycin on the intestinal flora, as it is a blocking effect on the liver cell dehydrogenase. This implies a type of liver cell injury. Thus, Baumgärtel's concept is in the curious position of requiring that biliary obstruction and aureomycin, on the one hand, depress the liver cell dehydrogenase, while liver injury of other types, such as cirrhosis and hepatitis, activate or heighten its effect. Baumgärtel states that if dihydrostreptomycin is given by mouth, the urobilinogen group disappears completely from the feces, but that in cases exhibiting urobilinogenuria, there is a persistence of mesobilirubinogen (urobilinogen) excretion in the urine. This he construes as being hepatic in origin. Our recent studies bear in considerable extent on Baumgärtel's concept. The results of these will be discussed in the following. Reference may first be made, however, to certain earlier studies in this laboratory which evidently were not taken into consideration by Baumgärtel, in the development of his present concept. We reported that mesobilirubinogen added to feces and incubated, was converted in part to stercobilin[5,45]. Baumgärtel, without mentioning these experiments, states that he was unable to effect such a conversion in a similar experiment and that in fact, such a result is out of the question. Baumgärtel has also failed to consider the significance of d-urobilin, especially that first observed in infected fistula bile, and never encountered in sterile bile. This is directly in line with the above mentioned observations of McMaster and his associates.

(II) Recent Studies

A. Methods of isolation and crystallization

A very much simpler and generally more satisfactory method of isolation of

the members of the urobilin group has been worked out and is reported in detail elsewhere[46,47]. These studies have included the direct conversion, in vitro, of bilirubin to urobilin. The method depends upon petroleum ether extraction of the chromogen, conversion to the respective urobilin by iodine in the petroleum ether, extraction of the pigment with water, conversion to the hydrochloride, extraction by chloroform, precipitation from a large volume of petroleum ether followed by primary crystallization from chloroform-acetone. This method is of equal value whether applied to solutions of mesobilirubinogen as obtained by reduction of bilirubin, or to the urobilinogen group in any given sample of feces or urine[47]. Recrystallization is effected to best advantage by solution in a small amount of methyl alcohol, concentration under reduced pressure to a syrup, addition of hot ethyl acetate, and further concentration under reduced pressure. On cooling, the pigment which is preponderant, whether stercobilin, i-urobilin, or d-urobilin, crystallizes in beautiful fashion. This method has the advantage of avoiding chloroform. As reported previously chloroform is incorporated in the molecule as chloroform of crystallization, which as will be noted subsequently, prevents an x-ray crystal pattern. This method of recrystallization has also paved the way for the crystallization of free d-urobilin, for the first time[47]. This has hitherto been impossible from chloroform or acetone or other solvents that have been attempted. To prepare the free d-urobilin, the hydrochloride is dissolved in a small amount of dilute sodium carbonate solution. It is then acidified in a separatory funnel with 5% tartaric acid and at once extracted with chloroform. A minimum amount is used, as a number of extractions are necessary. The chloroform is filtered through chloroform moistened paper and poured into a large volume of petroleum ether. The precipitated free d-urobilin is collected on a filter paper and dissolved in a very small amount of methyl alcohol. This is concentrated to a minute volume under reduced pressure. It is warmed and several ml. of hot acetone are added, small portions at a time, stopping at the point of any turbidity. On cooling, the free substance crystallized in long needles. This method is also much more satisfactory for the preparation of free stercobilin and the inactive urobilin.

2. d-urobilinogen and mesobilirubinogen.

d-urobilinogen has now been crystallized on many occasions from the feces of patients who have received terramycin[48] and it undoubtedly could also be obtained after the administration of aureomycin. The method is as follows: The feces are repeatedly extracted with 95% alcohol. The alcoholic extracts are then run through an aluminum oxide* column which retains the d-urobilinogen. The latter is subsequently eluted with water and after acidification with glacial acetic acid, is extracted into petroleum ether. The combined petroleum ethers are washed several times with water, filtered and then concentrated to a small volume under reduced pressure. On standing, the light yellow crystals of d-urobilinogen appear in this solution. Recrystallization is accomplished from a small amount of warm ethyl acetate.

Mesobilirubinogen has also been isolated from human feces, in one instance from a patient with hemolytic anemia who had not been treated with anti-biotics, and more recently from a woman who had been given terramycin and who first excreted d-urobilinogen. After approximately on month, the d-urobilinogen was replaced by mesobilirubinogen which has now persisted for four months. The method for isolation is identical with that for d-urobilinogen except that the petroleum ether must be taken to dryness after which the white residue is dissolved in a few m.l. of warm ethyl acetate. The characteristic crystals of mesobilirubinogen form in this solution on standing. Their appearance, plus the melting point and ease of oxidation to the inactive urobilin, serve to identify

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* Baker and Adamson.

it easily.

B. Conversions

1. Mesobilirubinogen to stercobilin.

As indicated in the foregoing, evidence had previously been gained in this laboratory that mesobilirubinogen could be converted to stercobilinogen by the activity of fecal bacteria. This has been denied by Baumgärtel. Since this was a point of much basic significance, experiments were undertaken to confirm or deny our previous results. In these earlier studies, reliance had been placed solely upon the isolation of larger amounts of crystalline stercobilin from samples to which mesobilirubinogen had been added, than from control samples. While the differences seemed to be too great to be otherwise explained than by a transition of mesobilirubinogen to stercobilinogen, it was determined now to carry out the study by means of cultures of fecal bacteria using N^{15} tagged mesobilirubinogen. Sborov, commencing his work in this laboratory and continuing it at the Army Medical Service Graduate School in Washington, had devised a simple cultural method permitting reduction, in vitro, of bilirubin to stercobilinogen by means of fecal bacteria. This was based on the work of Kämmerer and Miller[49] of a quarter of a century ago, who were the first to reduce bilirubin to an Ehrlich reacting chromogen by means of fecal bacteria in vitro. The chromogen was not isolated or identified. Sborov and his co-workers found that with suitable modifications of the cultural method, they were able to reduce bilirubin consistently to stercobilinogen (this of course does not exclude mesobilirubinogen as an intermediary). In order to obtain a supply of N^{15} bilirubin, it was necessary first to devise a method of crystallizing bilirubin from human feces. A few techniques that had been reported in the literature previously were found to be quite unsatisfactory. A new method was eventually worked out and has proven very useful[50]. It permits isolation of crystalline bilirubin in gram quantities from the feces of hemolytic jaundice patients who have recently received aureo-or terramycin. By employing the new technique of isolation in such an individual and at the same time giving him N^{15} glycine, it was possible to obtain a considerable supply of N^{15} labeled bilirubin. This was reduced with sodium amalgam in the usual way[13] and the crystalline mesobilirubinogen was isolated. It was then added in varying amounts to fresh cultures of human fecal bacteria. The data for a typical experiment are given in the following: Media which had been inoculated with 1 gm. of normal feces containing 1.47 mg. of stercobilin, was incubated for 12 hours at 37° C. During this period a heavy growth of bacteria took place. 82.4 mg. of mesobilirubinogen labeled with .594 atom per cent excess of N^{15} was then added. After 48 hours of further incubation, the culture was discontinued and extracted with petroleum ether. The stercobilinogen in this extract was oxidized with iodine and converted to stercobilin, 9.8 mg. of crystals being obtained. Identification of the pigment as stercobilin was readily accomplished through optical activity measurement, absorption maximum and lack of reaction in the dioxane-HCl and Lemberg tests. Analysis revealed that it contained .555 atom per cent excess of N^{15}, the only conceivable source of which was the labeled mesobilirubinogen. From this and other experiments with entirely similar results, it was quite clear that fecal bacteria readily converted mesobilirubinogen to stercobilinogen. The whole significance of this observation will be discussed in the following.

2. d-urobilin to mesobilirubinogen.

This conversion is easily carried out by means of reduction with sodium amalgam or ferrous hydroxide. Crystalline mesobilirubinogen has been isolated repeatedly following such conversion and has in turn been converted by iodine dehydrogenation[46] to the optically inactive urobilin. This reduction is of importance in the standard urobilinogen procedure. The Ehrlich reaction of

d-urobilinogen is more intense than that of either mesobilirubinogen or stercobilinogen. Discrepancies on this account do not occur, however, as with the ferrous hydroxide reduction employed in the procedure, both d-urobilinogen and d-urobilin are converted to mesobilirubinogen before they are quantitated. The ease of this reduction is entirely similar to that observed in the case of dihydromesobilirubin[15], the substance which is intermediary between mesobilirubin and mesobilirubinogen. This as a matter of fact, at once suggested an identity between d-urobilinogen and dihydromesobilirubin. The latter, however, has a different melting point, and gives a Gmelin reaction, in this respect being clearly distinct from crystalline d-urobilinogen as isolated by the methods described in the foregoing. It should be mentioned that d-urobilinogen can also be obtained by reduction of d-urobilin, if the reduction is sufficiently brief. Further transition to mesobilirubinogen by addition of two more hydrogens occurs rather quickly. In one of the first papers on d-urobilin, it was reported that the addition of mesobilirubinogen to infected bile resulted in an increased formation of d-urobilin. This requires confirmation with tagged material, an experiment which has not yet been carried out. In view of the present very clear evidence that d-urobilinogen has two less hydrogens than mesobilirubinogen, this earlier result is rather difficult to understand, nevertheless it is possible that the direction may be reversed in a biological system with the proper conditions.

3. d-urobilin to stercobilin.

Since it has now been shown that d-urobilin is readily reduced to mesobilirubinogen and that mesobilirubinogen is converted by means of fecal bacteria, to stercobilin, it seems highly likely that fecal bacteria are capable of converting d-urobilin to stercobilin. Preliminary studies have indicated that this is correct.

4. d-urobilin to mesobiliviolin and glaucobilin.

At the time d-urobilin was first described, Dr. Schwartz discovered that it behaved differently than stercobilin or urobilin when heated in a solution of dioxane containing a small amount of hydrochloric acid. In the case of d-urobilin, a violet and then dark blue color was promptly observed on heating the solution in a boiling water bath. With stercobilin there was little or no change, while with the inactive urobilin, a violet and then dark blue color was promptly observed on heating the solution in a boiling water bath. With stercobilin there was little or no change, while with the inactive urobilin, the color became pink or pinkish violet and often faded rapidly. The d-urobilin employed at that time was crystallized from chloroform or chloroform acetone. It was somewhat more red than the pure material obtained with the present methods as described above, and it was of interest, therefore, to test the dioxane-HCl reaction with the purest material. To our surprise it was found that the blue reaction is not as intense as with the less pure material such as first obtained from chloroform-acetone. On heating for two minutes, the solution becomes a dark violet rather than the deep blue which characterizes the red crystals from chloroform. If the colored mixture is esterified with methyl alcohol-HCl, or methyl alcohol-H_2SO_4, and the mixture of esters taken into chloroform, this in turn on to a column of aluminum oxide and eluted with chloroform-ether, according to Fischer's method[15], a blue and a violet zone are readily separated, the former being more intense with the esters obtained from the less pure d-urobilin. As far as can be determined, the blue compound is identical with glaucobilin, and the violet, with mesobiliviolin. (Lemberg[41] uses the term mesobiliverdin for the blue glaucobilin, the formula of which is $C_{33}H_{38}N_4O_6$). The reason for the lesser intensity of the blue reaction with the purest material, is not clear. The possibility is considered that an oxidative catalytic impurity is responsible for the greater conversion which obviously occurs. Despite this difference, the dioxane-HCl test remains a very valuable one for purposes of detecting

d-urobilin in concentrates of urobilin group solutions from natural sources, as from feces, urine, or bile. Preliminary studies of this method combined with optical activity measurements have yielded very encouraging results, but are too preliminary for discussion at this time.

C. Analyses

1. Melting points

It was previously noted that the melting points of the members of the urobilin group crystallized as the hydrochlorides from chloroform or acetone were not sufficiently sharp to permit identification. The melting points of free stercobilin and the optically inactive urobilin from acetone, are fairly distinctive. As pointed out, however, it was impossible to obtain satisfactory crystalline material with d-urobilin, using acetone as a solvent. The new methods of crystallization of the hydrochlorides from methyl alcohol-ethyl acetate and of the free substance from methyl alcohol-acetone have been very helpful in providing sharper melting points as seen in table I.

2. Elementary analyses

New analyses have been made of the free (i) urobilin and d-urobilinogen, with the results shown in table II. Preliminary analyses of the free d-urobilin, now being repeated, are in best agreement with the formula $C_{33}H_{40}N_4O_6$.

Table I

Melting Points of Urobilins

	Free	Hydrochloride
Stercobilin	234°-236°	157°-161°
(i) urobilin	176°-177°	159°-163°
d-urobilin	170°-171°	162°-165°

Table II

Elementary Analyses

			C	H	N
1.	(i) urobilin $C_{33}H_{42}N_4O_6$	Calculated	67.12	7.12	9.49
		Found	67.00	7.23	9.43
2.	d-urobilinogen $C_{33}H_{42}N_4O_6$	Calculated	67.12	7.12	9.49
		Found	67.06	7.07	9.15

3. Absorption Spectra

The absorption maxima of d-urobilin and the optically inactive urobilin are identical (4945 Å), while that of stercobilin is at 4925 Å. The dis-

tinctive infra red spectra* of the three compounds will be reported in detail elsewhere.

4. X-ray crystallography

The x-ray crystal patterns* of the hydrochlorides from chloroform clearly indicated the presence of some other substance in the crystal. Evidence had already been presented in an earlier paper[22] for the presence of chloroform in the crystals of stercobilin hydrochloride crystallized from chloroform. Recrystallization of the hydrochloride from methyl alcohol-ethyl acetate, confirmed this explanation, as the crystals of the three members of the group now gave excellent and distinctive patterns. These will also be described in detail separately.

5. Many attempts have been made to measure the hydrogen uptake of d-urobilin in being reduced to d-urobilinogen, or the hydrogen loss when the transition is in the opposite direction, as effected by iodine. Measurement of hydrogenation has been unsatisfactory because of the variable fraction which goes on to mesobilirubinogen. Hydrogen loss has also been difficult to measure because variable fractions are oxidized farther than to d-urobilin.

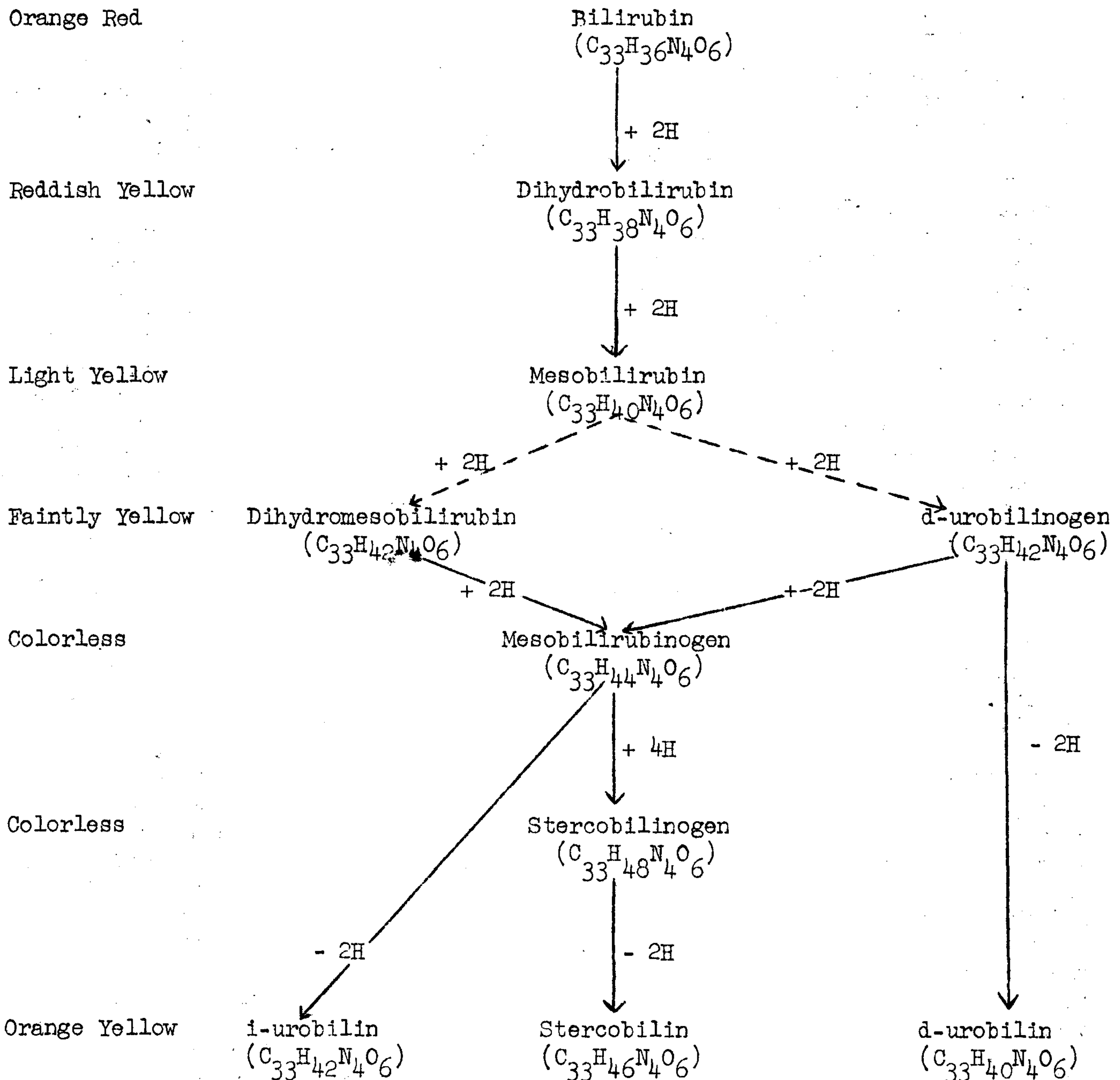
6. The optical activity of the d-urobilin is as great or greater than that of any known compound. The specific activity of the purest material dissolved in $CHCl_3$ (the hydrochloride repeatedly recrystallized from methyl alcohol-ethyl acetate), is approximately: $\alpha^{d}_{20^{\circ}C.} = +5000$. That of stercobilin hydrochloride similarly determined is ca. -4000.

D. Relationships based on the above information. Although information is by no means complete as to the exact character of the members of the urobilin group, the newer data, which has been described in the foregoing, permit a much more confident approach to a consideration of relationships between these individuals. As a better means of supporting this discussion, a plan of probable relationships is seen in table III. While the structure of d-urobilinogen has not yet been established, it seems clear that it is an isomer of dihydromesobilirubin. The elementary analysis, appearance and general behavior of the compound, strongly support this conclusion. It has now become clear that in terms of hydrogen content, d-urobilin, far from being a stereoisomer of stercobilin, has six less hydrogens, actually less than the optically inactive urobilin. These two compounds stand in much closer relationship to one another, both from the standpoint of general behavior and the number of hydrogens. It is believed that d-urobilin is also an isomer of mesobiliviolin. The initial conversion to mesobiliviolin in the dioxane-HCl reaction is quite probably a matter of molecular rearrangement. Mesobiliviolin is optically inactive in contra-distinction to the enormous activity of the d-urobilin. It appears quite unlikely that this optical activity is not due to asymmetric carbon atoms, but rather to an asymmetry of the molecule itself. This is also in much better accord with the finding that on reduction to d-urobilinogen, the optical activity disappears or at least becomes so small that it is no longer measurable with the concentrations that can be examined. Fischer and Siedel have suggested a formula for stercobilin, including four asymmetric carbon atoms, to explain its remarkable levorotatory activity. The fact that this activity is so great and that it also disappears on simple reduction to stercobilinogen, together with the observations just mentioned in relation to the dextrorotatory urobilin, may well bring into question the formula that has been suggested for stercobilin, and this whole matter would appear to require renewed study. Although the relationship shown in table III indicates that d-urobilinogen represents an aberrant pathway, the possibility exists that it is one of two isomeric dihydromesobilirubins formed and rapidly converted to mesobilirubinogen, but that

* Determined through the courtesy of Profs. Bryce Crawford and Wm. Lipscomb, Division of Physical Chemistry, University of Minnesota..

Table III

Bilirubin and Related Compounds



under the effect of aureo- or terramycin, the bacterial flora are able to form only one of the two isomers and not to carry it farther. In our earlier studies some emphasis was placed on the need of an unknown fecal factor to permit the transition to go onward to stercobilinogen, while in the infected bile d-urobilinogen appeared to be the end product. It is possible that the action of aureo- or terramycin is to remove or prevent formation of some fecal metabolite needed for the normal activity of the bacterial flora, or to prevent them from utilizing it. The fact remains that d-urobilinogen is very commonly encountered in infected bile samples in patients who have not received anti-biotics. The available information would also be in accord with a concept in which d-uro-

bilinogen is the normal intermediary between mesobilirubin and mesobilirubinogen. This is discussed again in the following.

(III) Discussion

The urobilin of Jaffé has clearly become expanded into a group of three very similar compounds, the levorotatory stercobilin, the optically inactive urobilin, and a dextrorotatory urobilin. It is clear that Vanlair and Masius were thoroughly justified in their use of the term stercobilin. Nevertheless, it is also clear that Jaffé's urobilin was probably stercobilin, at least in the main. This is the preponderant member of the group normally, either in feces or urine. A great deal of additional study is necessary to learn more about the proportion of the members of the group that may be present under different conditions. It is interesting that MacMunn, (also the discoverer of cytochrome under the name of "histohematin") noted that the urobilin of the bile under certain circumstances differed slightly from that of the feces and urine[51]. It is possible that MacMunn actually encountered d-urobilin[30].

The direct conversion of bilirubin to crystalline (i)* urobilin, in a certain sense completes the chapter which Maly began in 1871. There is little reason to doubt that Maly's hydrobilirubin was a mixture of (i) urobilin with other substances derived by the dehydrogenation of mesobilirubin or mesobilirubinogen, such as mesobiliviolin and mesobilifuscin. The method for preparation of crystalline urobilin[46] as referred to in the foregoing, provides a rapid means of obtaining a pure material for whatever purpose. The new methods for isolation and crystallization of stercobilin, (i)-urobilin and d-urobilin from natural sources[47] also make these compounds much more easily available. The methods are believed to be of special value in relation to isotope studies in accordance with the fundamental observations of Shemin, Rittenberg, and London. The application of the method makes it relatively easy to obtain stercobilin or d-urobilin (in patients who have been given aureo- or terramycin) in experiments where N^{15} glycine has been given to tag the protoporphyrin of the hemoglobin molecule and the various bile pigments. We have employed this method in obtaining relatively large amounts of N^{15} d-urobilin from cases of hemolytic jaundice to whom aureo- or terramycin has been administered**. In one such instance it was possible to crystallize 6.2 gms. of bilirubin in the early period after administration of aureomycin and 1.65 gms. of N^{15} d-urobilin during a subsequent period. The atom percent excess of N^{15} varies of course, from sample to sample, but the amount just given referred to materials with a sufficiently high content to be of value in other experiments. This will be described in detail elsewhere.

The recent studies which have been referred to in the foregoing, clearly reveal that mesobilirubinogen is intermediary between d-urobilinogen and stercobilinogen, but whether d-urobilinogen is normally in the pathway or not remains to be determined. It is believed to be one of the dihydromesobilirubin isomers and as mentioned above, the possibility exists that both isomers are normally formed and rapidly converted to mesobilirubinogen. If this is true, one would have to assume that the effect of aureo- or terramycin is to emphasize the formation of the one isomer (d-urobilinogen) and to block its further transition to mesobilirubinogen. It is also possible however, that d-urobilinogen formation represents either the normal or an abnormal sequence. Further work is necessary to determine this point. Our earlier conclusion that mesobilirubinogen is readily converted

* Optically inactive.

** G. W. James[52] has also obtained relatively large amounts of d-urobilin from cases of hemolytic jaundice and was kind enough to submit some of material to us for comparative purposes.

to stercobilinogen by fecal bacteria has been fully confirmed in the present studies. The use of N^{15} mesobilirubinogen in cultures of fecal bacteria has provided the clearest evidence on this point.

While our own studies do not exclude a formation of mesobilirubinogen in the liver, they show that this is not required to bring the available information about the urobilin group into harmony. Baumgärtel's thesis that mesobilirubinogen is formed only in the liver depends in considerable part on the belief that it cannot be converted to stercobilinogen by the activity of fecal bacteria. He has recently claimed that the disappearance of the urobilinogen group from the intestine when aureo- or terramycin is given, is due, not to an interference with bacterial reduction of bilirubin, but rather to a specific block of the necessary dehydrogenase system in the liver. Since he has also stated repeatedly that liver injury is necessary for the formation of mesobilirubinogen, it would appear that he requires a specific type of injury for this activity, while other types, such as biliary obstruction, block it. He has not indicated the category in which he places carbon tetrachloride and toluylene-diamine in this regard. This is important, since McMaster and his co-workers years ago showed that while these substances regularly caused urobilinuria in the intact dog, they did not produce it in the dog with a total external biliary fistula. This result seems of critical importance to us, but Baumgärtel refers only to McMaster's experiments with liver injury in the presence of complete biliary obstruction, stating that the "enzyme block" as already mentioned, is responsible for the lack of urobilinogenuria under these circumstances. Obviously, this could scarcely apply to the experiments in the bile fistula dogs.

Baumgärtel claims that when dihydrostreptomycin is given by mouth to human beings it produces a complete disappearance of the urobilinogen group from the feces, but at the same time, if the individual had mesobilirubinogen in the urine at the outset of the experiment, it does not disappear. Assuming that this were correct*, it would not however, require an hepatic, formation of the mesobilirubinogen nor exclude a bacterial one in the colon. Evidently he did not consider the possibility that the dihydrostreptomycin had simply lowered the reducing ability of the bacterial flora in the cecum to the point where the mesobilirubinogen-stercobilinogen transition no longer occurred. If at the same time the mesobilirubinogen formation was relatively small, it is not at all inconceivable that all of it was reabsorbed and excreted in the urine. We have under observation at the present time a case of hemolytic jaundice in which the findings bear to some extent on this question. In this instance the administration of terramycin at first resulted in almost complete disappearance of the urobilinogen group from the feces, with excretion of bilirubin. After a short time the amount of bilirubin rapidly declined and increasing amounts of d-urobilinogen were observed. Although the terramycin was stopped the d-urobilinogen persisted for some weeks, after which it became apparent that the patient was now excreting mesobilirubinogen, easily converted into vitro to (i) urobilin. At the present time, as a matter of fact 5 months after cessation of terramycin this patient is still excreting mesobilirubinogen as the preponderant substance, in fact it has been impossible to demonstrate either stercobilin or d-urobilin. This clearly indicates that the effect on the bacterial flora may be of relatively long duration. It seems quite unlikely to us that these findings could be explained on the basis of an hepatic origin of mesobilirubinogen. In another case d-

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* We have thus far repeated this experiment in two individuals, one with cirrhosis of the liver, one with familial hemolytic jaundice. In neither did the fecal urobilinogen disappear, and in fact in the case of hemolytic jaundice there was no significant reduction in amount even after a week on the drug.

urobilinogen is still preponderant in the feces nine months after discontinuance of the terramycin. If it were being formed in the liver, as a precursor of mesobilirubinogen, or vice versa, one would have to assume that a terramycin effect on the liver had actually persisted for this entire period after its discontinuance, which appears highly improbable.

There is much reason to believe that in hemolytic states, in which large amounts of bile pigment are entering the intestinal tract, the proportion of mesobilirubinogen appearing in the feces is greater (in comparison with stercobilinogen), than under normal circumstances. This is emphasized by Meyer[53] who did not believe in an extraintestinal origin. Our recent results indicate that this increase in the proportion of mesobilirubinogen is due to a relative inability of the bacterial flora to effect reduction to stercobilinogen.

In the foregoing, special emphasis has been placed on the evidence which is readily marshalled against Baumgärtel's concept, as it appears that certain others[41,42,43] have accepted without question his belief in the dual origin of the urobilinogen group and in the impossibility of conversion of mesobilirubinogen to stercobilinogen.

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II. MEDICAL SCHOOL NEWS

Coming Events

November 21 J. B. Johnston Lectureship in Neurology; "Hypophysectomy in Man," Prof. Herbert Olivecrona, Professor of Neurosurgery, Stockholm, Sweden, Museum of Natural History Auditorium; 8:00 p.m.
November 21-22 Continuation Course; Conference on Pemphigus and the Bullous Dermatoses for Dermatologists
December 4-6 Continuation Course in Endocrinology for General Physicians
December 5 Journal-Lancet Lecture; "Some Studies on Experimental Diabetes," Dr. Dwight J. Ingle, Senior Research Scientist, Research Division, The Upjohn Company, Kalamazoo, Michigan; Owre Amphitheater; 8:00 p.m.
December 15-17 Continuation Course in Gynecology for Specialists

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Continuation Course

On November 21 and 22, the University of Minnesota will present a "Conference on Pemphigus and the Bullous Dermatoses" for dermatologists. The one-and-a-half day session will be devoted to the consideration of the pathology, physiology, clinical characteristics, and treatment of the bullous dermatoses.

Several distinguished authorities in this field will participate: Dr. Herman Beerman, Chairman and Professor, Department of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, Philadelphia; Dr. Walter F. Lever, Instructor, Department of Dermatology, Harvard University Medical School, Boston; and Dr. Stephen Rothman, Professor and Head, Section of Dermatology and Syphilology, University of Chicago. The course will be presented under the direction of Dr. H. E. Michelson, Professor, Department of Medicine, and Director, Division of Dermatology; and the remainder of the faculty will include members of the clinical staff of the University of Minnesota Medical School and the Mayo Foundation.

Dr. George E. Moore To Leave

Dr. George E. Moore, Associate Professor, Department of Surgery, has been named Director and Chief of Surgery at the Roswell Park Memorial Institute in Buffalo, New York. Announcement of Dr. Moore's appointment was made recently by Dr. Herman Hilleboe, New York state Health commissioner. The Roswell Park Institute is a cancer hospital and research center which is affiliated with the University of Buffalo Medical School where Dr. John Paine, former member of the University of Minnesota Surgery Department, is chief of surgery. Dr. Moore's appointment comes as recognition of his outstanding work in the cancer field, and his friends and colleagues in Minnesota join in extending him best wishes for success in his new post.

* * *

Faculty News

On November 6, Dr. Irvine McQuarrie spoke at the meeting of the North Carolina Pediatric Society which was held at Duke University Medical School, Durham, North Carolina. His subject was "Clinical and Metabolic Studies on Spontaneous Hypoglycemia." He also presented a paper entitled "Cushing's Syndrome in Children" at the Annual meeting of the Interstate Postgraduate Medical Association in Cleveland, Ohio, on November 11.

Doctors Lewis Thomas, Lewis Wannamaker, and Floyd Denny visited Fort Warren Air Force Base, Cheyenne, Wyoming, on October 30 and 31 as consultants to the Surgeon General to advise on future activities of the Streptococcal Disease Laboratory there and to report on research now in progress at the University of Minnesota Heart Hospital.

Dr. Robert B. Howard, Director, Department of Continuation Medical Education, and Assistant Professor, Department of Medicine, was recently elected to membership in the Minnesota Society of Internal Medicine.

III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

November 17 - 22, 1952

Monday, November 17

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

11:30 - 12:30 Physical Medicine Seminar; Heart Hospital Auditorium.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:30 Physiology Seminar; The Anti Gonadotropic Effect of Lithosperm; Elizabeth Cranston; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - 5:30 Seminar on Fluid and Electrolyte Balance; Gerald T. Evans; Todd Amphitheater, U. H.

4:00 - 5:00 Pediatric Seminar; Subject to be announced; Dr. Colle; Sixth Floor West, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

4:30 - Public Health Seminar; 15 Owre Hall.

4:30 - 6:00 Physiology 114A and Cancer Biology 140 -- Research Conference on Cancer, Nutrition, and Endocrinology; Drs. Visscher, Bittner, and King; Hormonal Mechanisms in Mice in Relation to Breast Cancer; J. J. Bittner; 129 Millard Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Erling Platou; Station K.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Monday, November 17 (Cont.)

Ancker Hospital

8:30 - 10:00 Chest Disease Conference.

1:00 - 2:00 Medical Grand Rounds.

Veterans Administration Hospital

8:00 - 9:00 Neuroradiology Conference; J. Jorgens, R. C. Gray; 2nd Floor Annex.

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; J. Jorgens, Conference Room, Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; C. K. Aldrich; Bldg. I.

Tuesday, November 18

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Physiology 114D -- Current Literature Seminar; 129 Millard Hall.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 X-Ray Conference; Presentation of Cases from St. Cloud Hospital; Doctors Nessa and Anderson; Eustis Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Medical-Roentgenology Conference; Auditorium.

1:00 - 2:30 X-ray - Surgery Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

12:30 - Grand Rounds; Fractures; Sta. A; Willard White, et al.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Cal, and Lipschultz.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Tuesday, November 18 (Cont.)

Veterans Administration Hospital

7:30 -		Anesthesiology Conference; Conference Room, Bldg. I.
8:30 -		Infectious Disease Rounds; Dr. Hall.
8:45 -		Surgery Journal Club; Conference Room, Bldg. I.
9:00 -		Liver Rounds; Drs. Nesbitt and MacDonald.
9:30 -		Surgery-Pathology Conference; Conference Room, Bldg. I.
10:30 -		Surgery Tumor Conference; L. J. Hay; J. Jorgens; Conference Room, Bldg. I.
1:00 -		Chest Surgery Conference; Drs. Kinsella and Tucker; Conference Room, Bldg. I.
2:00 -	2:50	Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.
3:30 -	4:20	Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, November 19

Medical School and University Hospitals

8:00 -	9:00	Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.
11:00 -	12:00	Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.
12:30 -	1:20	Radioisotope seminar; Film: The Radioisotope: Part IV. Methodology PMF-5145-C; 12 Owre Hall.
1:30 -	3:00	Physiology 114B -- Circulatory and Renal System Problems Seminar; Dr. M. B. Visscher, et al; 214 Millard Hall.
4:00 -	5:30	Physiology 114C -- Permeability and Metabolism Seminar; Nathan Lifson; 214 Millard Hall.
4:30 -		ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.
5:00 -	5:50	Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.
8:00 -	10:00	Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 -	9:30	Clinico-Pathological Conference; Auditorium.
2:00 -	4:00	Medical Ward Rounds;
3:30 -	4:30	Journal Club; Surgery Office.

Minneapolis General Hospital

9:30 -		Pediatric Rounds; Max Seham; Stations I and J.

Wednesday, November 19 (Cont.)

Minneapolis General Hospital (Cont.)

10:30 - 12:00	Medicine Rounds; Thomas Lowry and Staff; Station D.
11:00 -	Pediatric Seminar; Arnold Anderson; Classroom, Station I.
11:00 -	Pediatric Rounds; Erling S. Platou; Station K.
12:00 -	Surgery-Physiology Conference; Drs. Zierold and E. B. Brown; Classroom.
12:30 -	Pediatric Conference; Closed Head Injuries; Lyle A. French, Station I Classroom.
1:30 -	Visiting Staff Case Presentation; Station I, Classroom.
2:00 - 4:00	Infectious Disease Rounds; Main Conference Room, Bldg. I.
4:00 - 5:00	Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

Veterans Administration Hospital

8:30 - 10:00	Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room, Bldg. I.
8:30 - 12:00	Neurology Rehabilitation and Case Conference; A. B. Baker.
4:00 -	Combined Medical-Surgical Conference; Conference Room, Bldg. I.
7:00 p.m.	Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, November 20

Medical School and University Hospitals

8:00 - 9:00	Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.
9:00 - 11:50	Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
11:00 - 12:00	Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.
12:30 -	Physiological Chemistry Seminar; Riboflavin Antimetabolites; W. Mizuno; 214 Millard Hall.
1:30 - 4:00	Cardiology X-ray Conference; Heart Hospital Theatre.
4:00 - 5:00	Physiology-Surgery Conference; Todd Amphitheater, U. H.
4:30 - 5:20	Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.
4:30 -	ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.
5:00 - 6:00	X-ray Seminar; Thoracic Surgery Conference; Dr. Varco, et al; Eustis Amphitheater, U. H.
7:30 - 9:30	Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Thursday, November 20 (Cont.)

Ancker Hospital

4:00 - Medical Pathological Conference; Auditorium.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

Friday, November 21

Medical School and University Hospitals

8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; The Syndrome of Thrombosis of the Internal Carotid Artery; Sidney K. Shapiro and William T. Peyton; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Physiology 124 -- Seminar in Neurophysiology; Ernst Gelhorn; 113 Owre Hall.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Friday, November 21 (Cont.)

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I., Classroom.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - X-ray Conference; Oscar Lipschultz; Classroom, Main Building.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

Saturday, November 22

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; Thrombocytopenic Purpura; F. E. Schaar; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

11:00 - Pediatric Clinic; C. D. May and Floyd Denny; Classroom, 4th Floor.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Hagen, Goldish, and Aufderheide
11:15 - 12:00 Morphology . . . . . . Dr. Aufderheide