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

Hemolytic Anemia

Volume XII Friday, April 4, 1941 Number 21

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Volume XII | Friday, April 4, 1941 | Number 21

INDEX

Published for the General Staff Meeting each week during the school year, October to May, inclusive.

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William A. O'Brien, M.D.

I. LAST WEEK

Date: March 14, 1941

Place: Recreation Room
Powell Hall

Time: 12:15 to 1:15 p.m.

Program: Movie: "Modern Nursing Technique"

Peritoneal Immunization
Charles Rea

Discussion
Owen H. Wangensteen
Wesley Spink
Milton Levine
Arild Hansen
K. W. Stenstrom

Present: 144

March 21 Holiday

March 28 Holiday

Gertrude Gunn
Record Librarian

- - -

II. MOVIE

Title: "The New York Hat"

Released by: Museum of Modern Art

- - -

III. ANNOUNCEMENTS

1. CURTIS B. NESSA

Formerly a member of our staff in radiology, and Gertrude Woldrick, formerly of our laboratory staff and now at Eitel Hospital, will be married April 19 at Medicine Lake.

- - -

2. CENTER FOR CONTINUATION STUDY PROGRAM

Obstetrics - April 3-5
Nutrition in the Public Welfare - May 26-28
Diseases of Infancy and Childhood - June 2-7
Diseases of Rectum and Colon - June 9-14
Obstetric and Newborn Nursing - June 12 - 14
Diseases of Heart - June 16-21
Dermatology and Syphilology - June 23-28
Health Problems in Industry - August 4-6
Impairment of Hearing - August or October (6 days)

- - -

3. NO MEETING

Next Week - Good Friday

- - -

4. CLINICAL RESEARCH CLUB

A meeting of the Clinical Research Club, University of Minnesota, will be held in Eustis Amphitheater at 8:00 p.m., Monday, April 7. The following papers will be presented:

1. A study of the influence of certain drugs and ions on the pore size of the cell membrane of the chick fibroblast.
..Peter Salzburg, M.D.,Physiology.
2. Studies relating to administration of bovine plasma and serum to man.
..Arnold Kremen, M.D., Surgery.
3. Stercobilin tolerance as a test of liver function.
..William Hollinshead, M.D., Med.
4. Fragility of erythrocytes as affected by anoxia, carbon dioxide inhalation and insulin hypoglycemia.
..Marguerite Booth, M.D.,
..Pediatrics.

* * * * *

All those interested are invited to attend

* *

IV. HEMOLYTIC ANEMIA

C. J. Watson
Wm. O. Clarke

In the earlier studies of hemolytic anemia, recognition was given to two types: namely, the familial or congenital variety (Minkowski), and the acquired form (Hayem-Widal). As one surveys the literature from the time of these earliest descriptions of hemolytic anemia, it becomes evident that the existence of an acquired form, as championed particularly by Widal,[1] became more and more discredited. During the ten years from 1925 to 1935, clinicians and pathologists were generally rather skeptical of the existence of acquired hemolytic anemia. Interest in this particular variety has been revived to a marked degree in the past five years, and there can be no doubt that hemolytic anemia is often acquired, at least in the sense that it is secondary to some other disease. The reasons for this revival of interest in the acquired form were as follows: (1) The recognition that there were hemolytic anemias in which the red blood cells were larger than normal and in which increased fragility was lacking, and (2) the realization that spheroidicity of the red blood cells and increased fragility, features which had hitherto been regarded as characteristic of an hereditary abnormality, could occur in vitro and in vivo as secondary phenomena. Naegeli[2] had thought that the spheroidal cells noted first by Minkowski[3] in cases of familial hemolytic jaundice (and later shown by Chauffard[4] to be associated in this disease with the fragility of the red cells to hypotonic saline), were formed in the bone marrow and that this formation was the essential hereditary fault of the disease. Much doubt has now been cast upon this belief. Haden[5] found that if red blood cells were subjected in vitro to hypotonic saline, they became spheroidal and that their fragility increased. These changes were most marked just prior to hemolysis. This, of course, does not explain the actual destruction of the spheroidal cells in vivo in cases of hemolytic anemia, since hypotonic conditions clearly do not exist in the body. Nevertheless, the fact that spheroidal cells and increased fragility may be produced not only by this method of Haden's, but by other experimental means in vivo as noted below, at once served to renew interest in the whole subject of acquired hemolytic anemia. There can be no doubt that in some cases of hemolytic anemia at least, the spheroidicity and increased fragility are acquired characteristics. Just what their exact relationship is to the familial form of the disease is not yet known. This is one of the main lines of present investigation in this field and further discussion of recent experimental data will be included in the following.

Classification of hemolytic anemia according to the material studied at the University of Minnesota Hospitals to the present date.

Certain forms such as acute hemolytic anemia due to sulfanilamide, lead poisoning, and paroxysmal hemoglobinuria, are not included in the following:

Table I

Summary of Types of Hemolytic Anemia and Jaundice
January 1, 1933 to March 31, 1941

Type	Cases	Female	Male
1. Microcytic Type	34	18	16
a. Familial or congenital microcytic type	31	16	15
b. Secondary or acquired microcytic type	3	2	1
(1) With hepatic or splenic disease	1		1
(2) With leukemia	1	1	
(3) With refractory anemia (Aplastic or hypo-regenerative)	1	1	
2. Macrocytic Type (secondary or acquired)	16	11	5
(1) With hepatic or splenic disease	5	3	2
(2) With leukemia	5	2	3
(3) With Hodgkin's disease	1	1	
(4) With hyperthyroidism	1	1	
(5) With chronic bleeding into ovarian cyst	1	1	
(6) With refractory anemia (aplastic or hypo-regenerative	1	1	
(7) With secondary infection (ovarian abscess)	1	1	
(8) Idiopathic acquired hemolytic anemia	1	1	
Total	50	29	21

It will be noted that in the above classification but two instances are recognized as having had acquired spheroidicity and increased fragility to hypotonic saline. Increased fragility was present in three additional cases, all of which, because of increased mean corpuscular volume and increased mean cell diameter, are classified in the above with macrocytic hemolytic anemia. In two of these cases no evidence of spheroidicity was observed; in the third case, deeply staining microcytes were seen in the smear, although interspersed with frequent macrocytes. This was a case of acute (probably acquired) hemolytic anemia in association with a severe inflammatory process. The findings in this case are of considerable interest to the whole problem of hemolytic anemia, and they are therefore given in brief as follows:

Case #34. Hemolytic Anemia Following Operation for Tubo-Ovarian Abscess

♀ 47. Admitted to hospitals with diagnosis of ovarian carcinoma. Examination negative except for this mass. Hemoglobin 70%, White blood cells 12,300, 66% neutrophiles.

2-2-40. Laparotomy: Left tubo-ovarian abscess removed. Postoperative wound infection with fever and diarrhea. Rapid development of anemia.

2-27-40. Hemoglobin 18%, White blood cells 24,000, 70% neutrophiles, frequent normoblasts and myelocytes. MCV 126; MCD 8.0; Reticulocytes 9 - 28%. Fragility: H_1 .02; H_2 .02; (% above control). Stained smear exhibits some definite microcytes of deeply staining type (spheroidal). Macrocytes numerous. Feces urobilinogen 421 - 750 mg. per day. Icterus index 26. Van den Bergh - delayed reaction. Spleen easily palpable. Liver slightly enlarged. Repeated blood transfusions.

3-19-40. Gradual improvement. Hemoglobin 42%. White blood cells 9,800, Reticulocytes 4%.

3-28-40. Icterus index 9.

4-17-40. Much better. Hemoglobin 67%, White blood cells 7,600, 77% neutrophiles, Reticulocytes 3.4%. Spleen much smaller.

3-25-41. Letter from patient: Feels very well, good appetite, gain in weight.

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The findings in the above case raised many questions relating to the fundamental problem of hemolytic anemia. The first question is whether this patient had an underlying constitutional disturbance of her erythrocytes characterized by a latent mild spheroidicity and increased fragility to hypotonic saline which was affected in such a way by the tubo-ovarian abscess and the operation, that an acute hemolytic anemia developed. It is well known that members of hemolytic jaundice families in which the trait is definitely hereditary, may exhibit spheroidicity and increased fragility of the red blood cells to hypotonic saline and that they may go for many years without developing anemia. In fact, some of them undoubtedly go through life without any difficulty whatever. Was it possible, on the other hand, that all of the features of the above case were acquired, related in some way to the infection or the operation, or both? (It is noteworthy that the patient had had the infection for some time but that the acute anemia developed only after the operation was carried out.) It will be seen in the following that infection and hyperglobulinemia have been thought by some to be the cause of increased blood destruction. The acute hemolytic anemia of Lederer[6] is unquestionably related in some way to infection since these patients all have outspoken evidence of infection, usually including hyperpyrexia, and since they respond well as a rule to repeated blood transfusions and do not require splenectomy. In these respects the above described case is very similar to the Lederer type, but it is questionable whether Lederer's anemia is really a disease entity. This question has been discussed at length by Dameshek and Schwartz[7], who point out that a number of previous authors had described acute febrile hemolytic anemia.

A third question arises with respect to the above case. The mean cell diameter and the mean corpuscular volume indicated that on the average the red blood cells were larger than normal This is quite in contrast to the usual case of familial hemolytic anemia in which the mean cell diameter is very distinctly reduced, usually below or not more than slightly above 7.0 μ and the mean corpuscular volume is usually within the normal range, occasionally increased to a mild degree. (See Table II, below.)

Thus it appeared to be evident that

in this patient's blood, two fairly distinct varieties of erythrocytes were present, one of these colonies, that exhibiting increased fragility and spheroidicity, probably representing the minority; while the other, namely, the macrocytic colony, was in the majority. This statement can be made because of the presence of numerous macrocytes in the smear, the relatively high M.C.D. and M.C.V., and the slight increase in fragility. One other case in the series illustrates a similarly atypical anemia, partly microcytic and partly macrocytic. The findings in this case are also of so much interest that they are given briefly in the following:

Case #35. Refractory Anemia with Increased Blood Destruction

61.

7-19-40. Severe epistaxis, pallor, progressive weakness. Spleen not palpable. Hemoglobin 31; Red blood cells 1.47; White blood cells 2,400; 42% lymphocytes; Reticulocytes 2.5 to 3.5%. Bone marrow: Normoblastic hyperplasia. MCV 75.8; MCD 7.5; MCH 24.6; MCC 30%.

1-19-41. Spleen palpable. Reticulocytes 0.5 - 1.5%. Fragility H_1 0.03; H_2 .04 (% above control). Price-Jones curve revealed an average cell diameter of 7.6 - 7.7μ, corresponding well with the value of 7.5μ as obtained with the Pijper-Zeiss halometer. The curve, however, also revealed the presence of two colonies of cells, the larger one with a peak at 7.0μ, and the smaller colony with a peak at 8.5 (See Fig. 1).

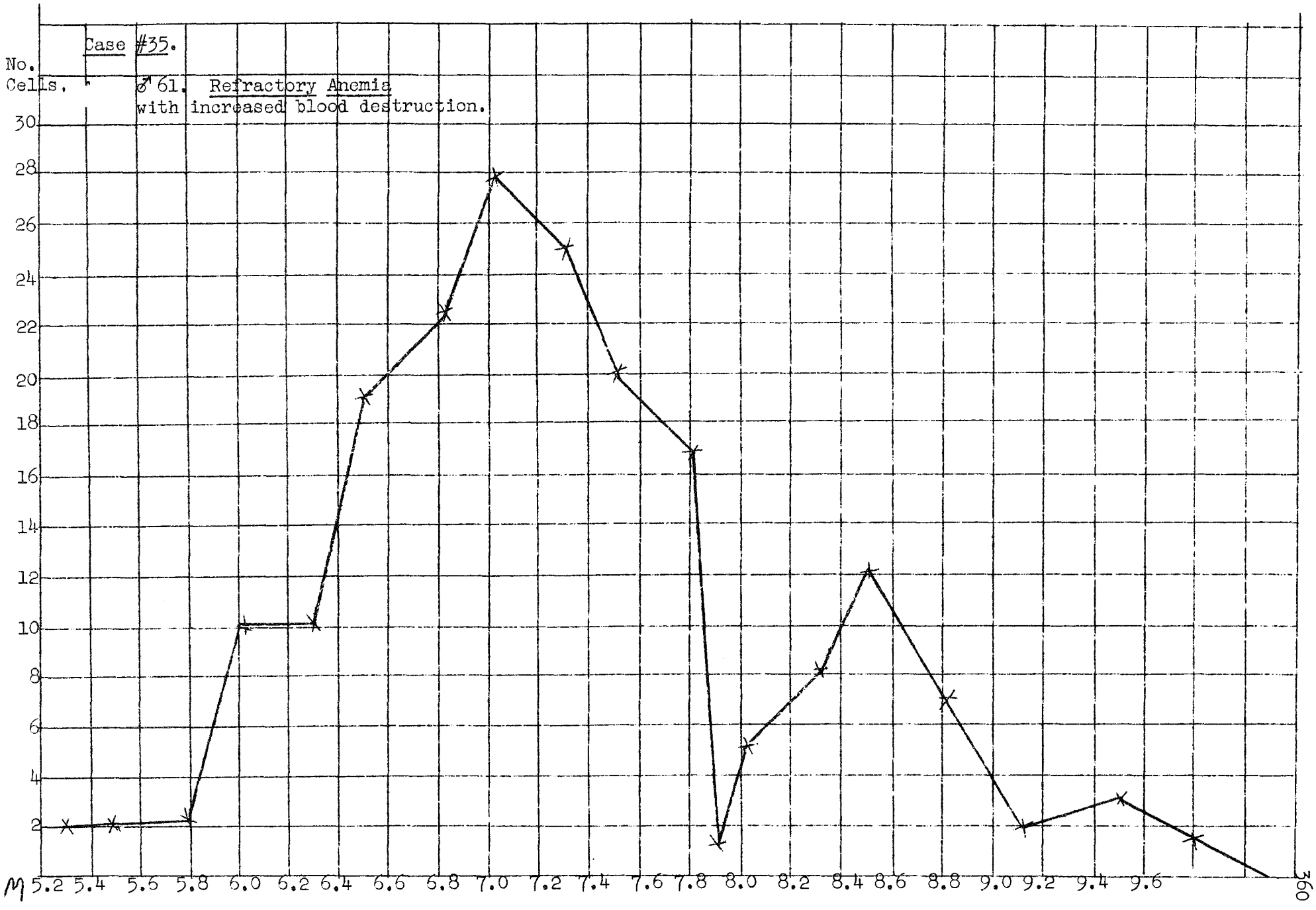
The mild spheroidicity and increased fragility as indicated by the above findings, are believed to be acquired or secondary. This case reveals how difficult it may be at times to classify a given anemia. In this instance some of the features of hyporegenerative or refractory anemia were combined with a hemolytic component.

Regeneration: Wastage ratio = $\frac{0.5}{3.5}$ (normal $\frac{1.0}{0.5}$)

Anemia progressive. Multiple transfusions required.

2-26-41. Splenectomy: Wt. 475 gms. No definite histologic changes.

3-31-41. Definite improvement since operation. Hemoglobin 55%; Red blood cells 3.79; White blood cells 7,050. Fragility H_1 .02; H_2 .02 (% above control).


Case #35.
No. Cells.
♂ 61. Refractory Anemia
with increased blood destruction.
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
M
5.2 5.4 5.6 5.8 6.0 6.2 6.4 6.6 6.8 7.0 7.2 7.4 7.6 7.8 8.0 8.2 8.4 8.6 8.8 9.0 9.2 9.4 9.6
360

By way of contrast with the above instances the typical cases of macrocytic hemolytic anemia exhibit mean cell diameters usually well above the normal average of 7.4 to 7.8 and likewise, considerably increased mean corpuscular volumes. Characteristic values are seen in Table III.

Table II

Cell Size and Fragility in Microcytic Hemolytic Anemia

Case No.	MCD	MCV	Fragility** H_1	H_2
5	7.2	94.6	.20	.10
6	7.2	91.	.08	.06
8	6.9	104	.18	.18
9	7.4	106	.04	.04
13	7.1	81	.24	
16	7.3	115	.26	.06
18	7.3	91	.20	.14
19	7	87	.22	.08
20	7.1	107	.20	.10
23	6.8	114	.10	.06
25	6.9	89	.26	
28	6.8	96	.14	.10
33*	6.5	69	.06	0
35*	7.5	75.8	.02	.04

* Microcytic Acquired Hemolytic Type
** Percentage Above Control

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Table III

Cell Size and Fragility in Macrocytic Acquired Hemolytic Anemia

Case No.	MCD	MCV	Fragility* H_1	H_2
34	8.0	126	.02	.02
36	8.1	135	.04	.02
39	7.9	101	.04	.04
41	8.3	111	0	0
43	8.2	125	0	0
46	9	155	0	0
47	8.3	118	.02	.04
50	8.2	119	0	0

* Percentage Above Control

Macrocytic hemolytic anemia has been described both in an idiopathic or primary, as well as a secondary variety. This type was considered in some detail by one of us (C.J.W.) in 1939.[8] More recently Dameshek[7] has repeatedly objected to the term macrocytic hemolytic anemia and obviously doubts that such a condition exists, although he does not deny that it may be noted in association with certain diseases (cirrhosis of the liver, reticuloendotheliosis. Dameshek believes that at least a majority of cases which have been described as macrocytic hemolytic anemia are, in reality, "pseudo-macrocytic." Dameshek thinks that the "pseudo-macrocytosis" is due simply to the increased number of reticulocytes which admittedly are considerably larger than the normal red blood cells. However, it must be emphasized that the mean erythrocyte diameter (M.C.D.) is not closely correlated with the reticulocyte percentage, as is revealed by the following data:

Table IV*

		M.C.D.	M.C.V.	Retic. per cent
Case 1.	Familial hemolytic jaundice	7.0	87.0	15.2
Case 2.	Familial hemolytic jaundice	6.9	104.0	27.6-
Case 3.	Familial hemolytic jaundice	7.0	77.0	14.0
Case 4.	Reticuloendotheliosis; macrocytic hemolytic anemia.	8.25	111.0	4.6-7.0
Case 5.	Splenic anemia; probable diffuse splenic fibrosis; macrocytic hemolytic anemia.	8.2	119.5	4.5
Case 6.	Cirrhosis of the liver; mild macrocytic hemolytic anemia.	8.4	100.0	3.6-
Case 7.	Hemorrhagic ovarian cyst; severe macrocytic hemolytic anemia	8.8	--	15.0

*From paper by Watson, Annals of Internal Medicine, Vol. 12, No. 11, May, 1939, p. 1787

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Following are case records which serve as examples of idiopathic and secondary macrocytic hemolytic anemia:

Case #36. Idiopathic or Acquired Macrocytic Hemolytic Anemia

, 55.

12-15-39. Weakness, anemia, mild intermittent jaundice 4 years. Spleen palpable 2 cm. below costal margin. Hemoglobin 44%, Red blood cells 1.74 mill., MCV 135, MCH 49, MCC 35, MCD 8.1, Reticulocytes 25%. I.I. 19. VdB indirect.

Smear: Predominantly macrocytic. Some Microcytes. Price-Jones mean = 7.5, 73% above normal of 7.25.

Fragility: H_1 .42; H_2 .34. Control H_1 .42; H_2 .30. F.U. 828 mg. per day. U.U. 4.3 - 10.6 mg.

1-17-40. Splenectomy. Spleen wt. 420 gm. Moderate diffuse reticular hyperplasia. Postoperative hemolytic crisis.
2-2-40. Hemoglobin 15%, Red blood cells, 0.9 mill., White blood cells 38,000.
2-13-40. Hemoglobin 21%, Red blood cells 0.9 mill., Reticulocytes 42%.
3-7-40. " 53%, " 2.27 " " 25%, F.U.337.
3-29-40. " 62%, " 2.80 " " 2.9%
10-24-40. " 80%, " 3.25 " " 0.6%, I.I. 7.
1-17-41. " 75%, " 3.64 " Feeling very well.

Case #41. Macrocytic Hemolytic Anemia with Leukemia

♂ 55.

11-16-38. Weakness, pallor, splenic enlargement 1 month. Hemoglobin 35; Red blood cells 1.63; White blood cells 14,300; 77% lymphocytes, occasionally immature.

M.C.V. 111; M.C.D. 8.25; M.C.H. 33; M.C.C. 30%.
Reticulocytes 4.6 - 7.0%.
Average F.U. 11-18 to 12-14: 1315 mg. per day.
Multiple transfusions. Reactions. No benefit.

4-19-39. Hemoglobin 46; Red blood cells 2.6. Splenectomy. 2200 gm. Definite histologic evidence of lymphatic leukemia. Marked improvement in blood and general symptoms. No transfusions.

Date	Hemoglobin	Red blood cells	Reticulocytes	F.U.	
5-24	59	3.3	2.6	180	
8-14	49	2.1	4.1	156	
9-30	38	1.2		1290	
10-20	39	1.8		653	
11-20	42	1.3		128	
11-24				217	White blood cells 52,000 89% lymphocytes
12-9	44	1.9	2.2		White blood cells 55,000
			1.8		86% lymphocytes

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Case #41 clearly illustrates the importance of secondary hemolytic anemia in certain cases of leukemia; also the fact that splenectomy may bring temporary improvement where other methods were unavailing.

The Mechanism of Hemolysis and its relation to anemia.

As already mentioned, it was Naegeli's belief that the more fragile sphercidal cells of familial hemolytic jaundice are formed in the bone marrow and are then more readily destroyed by the Spleen. In spite of the fact that spheroidicity and increased fragility can be produced experimentally, there is no evidence as yet which indicates whether these are primary or secondary features in familial hemolytic jaundice. There can be little doubt that they are secondary in those cases of acute or acquired hemolytic anemia, both clinical and experimental, in which they are seen (Dameshek). Dameshek and Schwartz[7] believe that at least in the cases of the acquired hemolytic anemias with increased fragility of the red blood cells and perhaps also in the familial group, the increased hemolysis is on the basis of over-production of iso-hemolysin. In support of this belief, he has reported an increased hemolysin titer in both experimental and clinical acute hemolytic anemia. This has not been confirmed. In Case 34 described in the foregoing in which there appeared to be definite evidence of an acquired spheroidicity and increased fragility, repeated attempts to demonstrate iso-hemolysin in the patient's serum were fruitless.

Bergenheim and Fåhreus' studies[9] of sedimentation have been responsible for a new line of investigation with respect to the mechanism of hemolysis. These investigators showed that if red blood cells were allowed to sediment and were then simply resuspended in the same plasma, that they had now become on the average more spheroidal and more fragile to hypotonic saline. In other words,

simple packing of the erythrocytes and lack of motion with the proper amount of plasma between adjacent cells, causes them to become abnormal in the same sense that they are abnormal in many cases of hemolytic anemia. This problem has been investigated in more detail by Ham and Castle[10] who have shown that it is possible to produce typical hemolytic anemia experimentally by various agglutinating substances. Principally by means of a globulin-like material known as Concanavallin which causes marked in vivo agglutination of red blood cells, Ham and Castle were able to produce marked hemolytic anemia with spheroidicity of the red blood cells and increased fragility to hypotonic saline. They regarded it as conceivable that infection may produce hemolysis by virtue of a hyperglobulinemia; in other words, they would regard acute hemolytic anemia of the infectious or Lederer variety as possibly due to the increased rouleaux formation which is in turn secondary to hyperglobulinemia. In this connection, however, it should be pointed out that marked hyperglobulinemia is often seen without any evidence of hemolytic anemia. For example, the most marked increases of globulin are observed in cases of multiple myeloma, and so far as we are aware, hemolytic anemia is not a feature of this disease. Multiple myeloma is, in fact, an excellent example because it is the only disease in which in vivo agglutination due to excessive rouleaux formation has actually been observed. In this disease, erythrocyte clumping has been seen with the ophthalmoscope in the retinal vessels, following pressure on the eyeball to produce stasis.[11]

Excessive rouleaux formation of this type is to be distinguished from autohemagglutination due to increased titre of "cold" agglutinins.[8] The latter does not occur until the temperature is considerably below 37°C, and is then reversible when the blood is warmed, while the former is irreversible. Autohemagglutination of the "cold" type, although common in acquired hemolytic anemia, probably has no relation to the in vivo hemolysis.

Ham and Castle logically suggest that the role of the spleen in hemolytic anemia is in the production of erythrocyte stasis. It is well known that the blood leaving the spleen through the splenic vein is relatively concentrated, the hematocrit percentage being considerably higher than in the splenic artery blood. Furthermore, it has been shown even in the case of a normal spleen that the red blood cells in the splenic vein are more spheroidal on the average and are distinctly more fragile toward hypotonic saline than are the cells in the splenic artery.[12,10] Examples of such observations are recorded in Table V. These observations were made in collaboration with Dr. John R. Paine of the Department of Surgery.

Table V

Splenic Artery and Vein Blood as Obtained at Splenectomy (relative concentration)

Type of Case	Source of Blood	Hemoglobin in gm. per 100 cc.	Hematocrit %	Fragility H_1	Fragility H_2
1. Familial hemolytic anemia	Splenic vein	12	36.4	.68	.50
	Splenic artery	12.2	37.9	.66	.48
	Splenic vein after adrenalin	14	53.1	.70	.62
	Splenic artery after adrenalin	12.9	36.1	.68	.52
2. Macrocytic hemolytic anemia	Splenic vein	12.8	43.2	.52	.40
	Splenic artery	13.0	40.2	.50	.40
	Splenic vein after adrenalin	15.0	69.3	.54	.44
	Splenic artery after adrenalin	13.8	45.4	.52	.40
3. Banti's disease	Splenic vein	11.1	33.1	.46	.38
	Splenic artery	11.0	33.3	.46	.36
	Splenic vein after adrenalin	13.2	59.8	.50	.40
	Splenic artery after adrenalin	11.5	38.6	.46	.38

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Ham and Castle's theory with respect to erythrostasis in the spleen agrees well with the belief of Bergenheim and Fåhreus as to the mechanism by which spheroidicity and increased fragility are produced when erythrostasis occurs, such as following the above mentioned sedimentation. Bergenheim and Fåhreus have identified a substance which they name lyso-lecithin. They have shown that normal serum contains a lecithinase (an enzyme) capable of splitting the hemolytic substance, called lyso-lecithin, from the serum lipoids. The adsorption of lyso-lecithin by stagnant red blood cells, as in the sedimentation experiments, or whenever there is erythrostasis in vivo, as in the normal spleen, is believed by Bergenheim and Fåhreus to result in hemolysis. They have shown that lyso-lecithin is formed in the spleen, and believe that it constitutes a normal mechanism of erythrocyte destruction. At this point it may be mentioned that Singer[13] has recently reported studies of lyso-lecithin concentration in cases of hemolytic anemia. In brief, he has not found any increase of this substance, and he therefore concludes that it is probably not related, at least insofar as increased production of lyso-lecithin is concerned, to the mechanism of hemolysis in familial hemolytic anemia. He has found, however, that the spheroidal cells of familial hemolytic anemia are more sensitive to lyso-lecithin than is true either of normal cells or of the spheroidal cells of acute hemolytic anemia of the acquired form.[14]

Certain it is that the spleen is not the primary seat of disease in familial hemolytic anemia in spite of the fact that clinical results of splenectomy are uniformly good as illustrated by the following data. The spheroidicity and increased fragility persist after splenectomy, although it is quite true that they are usually not so marked,

Table VI

Results of Splenectomy
January 1, 1933 to March 31, 1941

Type	Number	Death		Relief of Anemia and Jaundice	
		Post-Op.	Later	Partial	Complete
1. Microcytic Type	26				
a. Familial or congenital type . . .	23	1			21
b. Secondary or acquired type	3	1		2	
(1) With hepatic or splenic disease	1	1			
(2) With leukemia	1			1	
(3) With refractory anemia (Aplastic or hyporegenerative . . .	1			1	
2. Macrocytic Type (secondary or acquired)	5	2		1	2
(1) With hepatic or splenic disease	2	2			
(2) With leukemia	1		1	1	
(3) With chronic bleeding into ovarian cyst	1				1
(4) Idiopathic acquired hemolytic anemia	1				1
Total	31	4	1	3	23

Table VII

Fragility Before and After Splenectomy
(Percentage Above Control)

Case No.	Before Splenectomy		After Splenectomy		Time After Splenectomy
	H_1	H_2	H_1	H_2	
5	.20	.10	.10	.04	14 mos.
7	.08	.06	0	.02	1 wk.
8	.10	.18	.04	.06	9 days
10	.26	.06	.10	.08	17 days
			.06	.02	3 yrs.
11	.08	0	.08	.08	3 yrs.
13	.24		.18	.06	7 days
14	.22	.10	.20	.14	9 days
16	.26	.06	.14	0	15 days
22	.26	.10	.20	.02	5 wks.
28	.14	.10	.22	.04	1 yr.
*33	.06	.06	0	0	5 days
*35	.02	.04	.02	.02	20 days
**36	.04	.02	.02	0	2 mos.
			.02	.02	9 mos.

*Microcytic Acquired Type
**Macrocytic Acquired Type

Blood Destruction and Jaundice

The rate of blood destruction and the presence and degree of jaundice are dependent respectively on the spleen and liver. If the spleen is enlarged because of engorgement with red blood cells as is regularly the case in any patient with an active hemolytic anemia, then there is certain to be an increased rate of blood destruction. Many have spoken of this as "hypersplenism." It should be emphasized again that the spheroidal cells which are more fragile to hypotonic saline may be present without any splenic enlargement or any increase in the rate of blood destruction. This type constitutes the latent cases. It is of no little interest that the normal goat possesses red blood cells of exactly the same type as that encountered in patients with hemolytic anemia, namely, small spheroidal cells that are very fragile to hypotonic saline, yet the goat does not exhibit anemia or jaundice. The presence of jaundice in patients with hemolytic anemia is unquestionably related to liver function. Thus there are cases in which there is no jaundice whatever, and again, cases exhibiting a very marked degree of jaundice. Except for the actual "crises" of the disease, the degree of anemia and of jaundice exhibit an inverse relationship. In our entire series, the patients who exhibited the most jaundice had the least anemia, and vice versa. These cases illustrating the extremes in the series are as follows:

Familial Hemolytic Jaundice

Case 1.

Male, 18.

Splenomegaly, jaundice since infancy, microcytes, increased fragility of erythrocytes; mother has large spleen, frequent jaundice.

Hemoglobin 81

Icterus index 94

Van den Bergh indirect

Urobilinogen (Urine 19.7
(Feces 705.0

- - -

Familial Hemolytic Jaundice

Case 2.

Male 16.

Severe anemia, no jaundice. Microcytes, increased fragility, splenomegaly.

Reticulocytes 17%

Icterus index 8

	Date	Hemoglobin	Urobilinogen Urine	Urobilinogen Feces
	8-8	24	trace	792.9
Splenectomy	8-21			
	9-10	74	trace	91.7

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The patients with the most marked degree of jaundice also exhibit the most marked urobilinogenuria indicating at least a relatively sluggish liver function. Most textbooks of medicine state that all cases of hemolytic anemia or jaundice exhibit an increased urobilinogen in the urine. This certainly is not correct. Cases are not infrequently observed with considerable anemia and little or no jaundice, also no increase of urobilinogen in the urine. This is simply another evidence of good liver function. It seems evident that in this disease a sluggish liver function is somewhat of an asset since the patients who have the least jaundice have the most anemia, and vice versa. As Chauffard once said[4], these patients are "more jaundiced than really sick." This of course applies to the cases with the most sluggish liver function. They are the ones who are not willing to consider splenectomy because in spite of considerable jaundice they are not anemic and they are able to get along very well.

During the crises of the disease which are quite variable from case to case, sometimes being entirely omitted, it is true that anemia and jaundice increase together for a brief period of time, and when the crisis is over, they usually decrease together for a similarly brief period. Except for this, however, the inverse relationship already pointed out usually obtains.

With respect to the hemolytic crises it may be stated that these have never been observed in the familial variety after splenectomy, whereas two of our cases of the acquired, macrocytic type have exhibited very severe increases in blood destruction during the postoperative period. In spite of this, both went on to recovery. One of these has been followed for six years and has remained entirely well. The other has been well for fifteen months. The findings in the latter case have been given in the foregoing (Case #36).

The jaundice in these cases is of retention type, indicating that simply bilirubin is retained. There is no regurgitation of bile as in mechanical jaundice or jaundice due to diffuse liver damage. In accordance with this the Van den Bergh reaction except in complicated cases is either delayed or indirect in type and bilirubin is not present in the urine. Recent studies indicate that the delayed or indirect Van den Bergh reaction and the failure of bilirubin to appear in the urine are due to the fact that the bilirubin which has not gone through the liver cells is in actual chemical combination with the serum albumin. With the exception of six cases, the Van den Bergh reaction in our entire series was either delayed or indirect in type, in accordance with what has already been said. Of these six cases, five had complicating disease. In one, ulcerative colitis, chills and fever, also pregnancy; in another, cardiac enlargement and profound anemia in a patient who later developed active tuberculous constrictive pericarditis with ascites, and two cholelithiasis was the complicating factor. Two of the cases had leukemia which may well have accounted for sufficient liver damage to bring about some degree of regurgitation jaundice, and thus cause a prompt Van den Bergh reaction. In the sixth case, on one occasion, the Van den Bergh reaction was reported as direct in type. In two other occasions it was delayed and indirect. No explanation for this one direct reaction was recorded. The record, however, was not clear as to whether this was prompt direct or delayed direct in type.

Differential Diagnosis

This is usually not difficult, but on occasion one of the other forms of retention jaundice may be confused with hemolytic jaundice, and it may be emphasized again that hemolytic anemia may be associated with jaundice due to primary liver disease; also with other diseases which may or may not be associated with jaundice. Bleeding into a body cavity may be productive of jaundice, anemia, increased reticulocyte count, and increased urobilinogen excretion in the feces; in other words, clinical features which indicate the presence of hemolytic anemia. Under

such circumstances, the local signs due to the collection of blood are of greatest importance. The spleen is usually not enlarged but it should be pointed out that it may not be palpable in outspoken hemolytic anemia. In one case of the present series, the spleen was at no time palpable, although at the time of operation it weighed 420 grams. Most important of all is to separate familial hemolytic jaundice from a relatively rare condition originally described by Gilbert[15] under the name of simple familial cholemia, more recently discussed under the heading of constitutional hepatic dysfunction.[16] This is a pure retention jaundice without bilirubinuria. Important in distinguishing it from hemolytic jaundice is the absence of splenic enlargement, the absence of anemia, the absence of increased reticulocyte count, and the absence of any changes in the red blood cells, either microcytosis or macrocytosis; also the absence of any increased excretion of urobilinogen in the feces. The following case abstract is illustrative.

Constitutional Hepatic Dysfunction

Male, 20.
Persistent slight jaundice for many years. No pain. No nausea, vomiting, chills, or fever. No pruritis.
Exam.: Definite, mild icterus. Liver and spleen not palpable.
Hemoglobin 98%. Reticulocytes 1.7%. Av. diam. Red blood cells 7.6.
Fragility of erythrocytes normal.
Icterus index 36. Van den bergh +, delayed, and indirect type.
Feces urobilinogen: 168 mgm. per day (normally 40-280).
Urine urobilinogen: trace (normally 0 - 3).
Urobilin tolerance*: 7.2 mgm. (normally 1 - 4).

*This followed the injection of 50 milligrams of crystalline stercobilin intravenously. The distinct elevation in urinary excretion indicates definite hepatic dysfunction.

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Hemolytic anemia due to sulfanilamide

Sulfanilamide in full therapeutic dosage rather regularly increases the rate of blood destruction. This has been shown by means of careful studies of serum bilirubin levels, urobilinogen excretion, and reticulocyte count before, during, and after periods of sulfanilamide administration.[17] As a rule, however, this increase in the rate of hemoglobin metabolism is insufficient to produce anything more than a mild degree of anemia. This mild anemia is the usual accompaniment of sulfanilamide therapy if at all intensive or prolonged. Cell measurements have shown that it is of a slightly macrocytic hypochromic variety. The hypochromic tendency indicates a disturbance in the formation of hemoglobin. This, together with the reported excretion of coproporphyrin III in the urine[18], indicates that sulfanilamide affects the blood forming organs in a manner similar to lead which also produces increased blood destruction, and, similarly, with a hypochromic tendency. In occasional cases receiving sulfanilamide, an acute and rapidly progressive, even fatal, hemolytic anemia may develop. This is, at least in one sense of the word, an idiosyncrasy to the drug, and in this form it is necessary that the drug be stopped at once. In the more usual type, namely, the mild and slowly progressive anemia, it is unnecessary to discontinue the drug. Transfusions will suffice to keep the hemoglobin at a relatively normal level.

The exact mechanism by which sulfanilamide steps up the rate of blood destruction is unknown. There is reason to believe that sulfanilamide paralyzes

the activity of catalase. It has been suggested that this is the manner in which the drug is bacteriostatic since catalase destroys peroxide and in the absence of catalase peroxide accumulates and prevents bacterial growth.[19] Catalase is also known to reside in the red blood cells, and recent work[20] indicates that it is very important in preventing destruction of hemoglobin within the red blood cells by destroying peroxide which would otherwise enter and cause oxidation. Since it is clear that sulfanilamide easily gains access to the red blood cells it is not impossible that it prevents the normal protective action of catalase insofar as hemoglobin is concerned, thus permitting undue oxidation of hemoglobin within the erythrocytes.

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V. GOSSIP

Chief Surgeon Owen H. Wangensteen has again been honored by the people of Pennsylvania through the John Scott Award of the City of Philadelphia for the development of the suction siphonage method of treatment of acute intestinal obstruction. Following the winning of the Samuel Gross prize for 1935 this represents a unique honor for any member of our medical profession. In recognition of these and other distinctions, Dr. Wangensteen was entertained by his fellows and former fellows at a party at the Minneapolis Club Tuesday, April 2. Thirty-five were present, including Charlie Mead of Duluth; Jim Hibbard of Wichita, Kansas; Leslie Tasche of Sheboygan, Wisconsin, and Ray Buirge of New Hampton, Iowa. Telegrams were received from Bill Peyton, now on tour of neurological centers; Sam Randall, Watertown, South Dakota; Herb. Carlson, Minot, North Dakota; and Winifred Schweppe, Eitel Hospital. Dr. George Eitel was toastmaster. O. J. Campbell presented the scroll signed by all the fellows. Each fellow gave one outstanding experience while on the Service. Personal felicitations were received from "President Roosevelt" by way of radio. All were proud of their chief and the fact that they were now or at one time had been connected with the department. A good time was had by all.....During spring vacation I visited Rockford, Illinois -- Rockford Women's Club and Rockford College -- and Northfield, Carleton College. Rockford is not on one of the main lines to Chicago but can be reached by getting off at one of the station stops near there (Oregon or Rochelle). Our party drove up the Rock River Valley which was just beginning to show signs of spring. Mrs. Hanna Sims McCormick, owner of both Rockford papers, has a fine estate between Oregon and Rockford. She has given most of it to the Girl Scouts for a camp. There are several signs indicating that deer may pass over the road. Rockford is about 85,000 and is over half Swedish. To provide a contrast to the blondes, there are also many Italians there. As Rockford is located just below the border, it is 20 miles closer to Madison than to Chicago. There are 148 physicians in Rockford, including several graduates from the University of Minnesota (the Canfield twins and their father, Harry). Jacob Bendes, formerly of Glen Lake, practices there. Other Minnesota graduates are William Beyer - '26, Harry Warner - '26 (practice OALR together). Harold Palmer - Iowa '25 is the pathologist spark plug of the community. In the afternoon I addressed the good ladies on "How to Grow Old Gracefully." Afterward I learned that there was a good note-taker in the crowd who did a most realistic job of reporting what I said. In the evening I went to Rockford College for dinner. This is a girls' school of 300 students and 45 faculty members, now in its 94th year. It has many distinguished graduates including Jane Hull; Martha Wright, daughter of the late Frankie Wright, is one of their top graduates. Julia Diehl (Mrs. H.S.) is also listed as one of their outstanding students. The buildings are old and unpretentious except the library which was completed in 1940 at a cost of $130,000. The dedicatory address was made by Archibald MacLeish, Librarian of Congress, and son of a Rockford trustee and former president, Mrs. Andrew MacLeish of Glencoe, Illinois. The John Hall Sherratt Library, named in memory of a former president of the college board of trustees, has large windows overlooking Rock River. The four divisional reading rooms are devoted to the humanities, social sciences, arts, and science. The stacks are open to everyone -- students and faculty. The use of the library is adapted to the type of teaching which is carried on in an informal way. Students of history meet their teacher twice a week for a discussion but spend most of their time in the library. There are fireplaces in three of the reading rooms and the whole place has an informal air. After dinner the faculty group went to the porch for coffee where we were joined by a group of students who spent the evening with us. They were selected because it was assumed they might find something of interest in what I would say. They were sincere, interested, and much at ease. The whole picture, however, was one of bushy hair, toothy teeth, and much legs. We finally got around to the subject of marriage

courses which they seemed to think would be an interesting addition to their curriculum. At a late hour I was driven to the train. On the next day I took part in a vocational conference at Carleton College. Every year Carleton holds an opportunity session for its students. The Chapel Exercise this year was given by our own Ed. Williamson after which we divided into groups for panel discussions. This in turn was followed by group question and answer periods, and this by consultation with individual students (just like confession). It was thus possible for each student to have had three contacts with each advisor. In our group, Lucille Petry spoke on nursing; Elizabeth Jones on occupational and physical therapy, and David Raudenbush on law. Other panel discussions were concerned with art, applied science, business opportunities for men or women, education, professional writing, professional service, and social work. The medical questions largely centered around whether or not they should take the arts or science curriculum, enter the medical school at the end of the third or fourth year, which extra courses they should take in addition to the required ones (the only information we have on this point is that students who took extra courses in biology did not do as well or any better than students who took only the required courses which were prerequisite to certain biological applications in medicine), which was the best medical school, where they should take their internship, when they should start specialty training, what size town in which they should locate, and when they should get married. There were panel discussions on interior decoration, radio, photography, drama, chemistry, engineering, aviation, conservation, insurance, salesmanship, banking, office management, advertising, secondary school teaching, public school music, educational guidance, librarianship, secretarial, retail store management, home making, journalism, creative writing, public welfare, group recreation, and family welfare. Although a great deal of work is being done on vocational guidance only a few rules seem to apply. One is to beware of attempting to follow through on a vocation which desire dates back to a tender age. Second is to follow the vocation which has in it the kind of people you like. Third is that several changes seem to be permissible before a final choice is made. That evening we had a celebration over radio station WCCO which included a return to the air of many old time acts (Tim and Tina, City Hall Politicians, and others). In addition, Al Smeby, who has been giving markets for 15 years, Announcer Mildred Simons, who has been with WCCO since the station started, and yours truly who has been broadcasting over 13 years, put on a melodrama in which I took the part of the villain. There were plenty of sound effects and the script sounded not unlike Truth and Consequences. ...Three days later I went on another vocational conference (radio) with a group of pre-medic and medic students, and again the first question was "What are they going to do about medical students and the draft?"....Strange as it may seem, recent studies indicate that youngsters expect more, not less, help from adults in making their decisions and formulating their plans. In the junior high school group the only real gripe on parental interference came in the unwanted assistance in selecting the proper type of radio programs. It appears that most parents have looked with so much awe upon their children that they did not realize that they wanted help. Another study in regard to university students suggests that parents who take a "middle ground" interest in the courses of their children were the best kind....For some unknown reason, we became confused with the spring vacation dates for staff meeting and passed by the date that Out-Patient Department Admissions Director Macnider Wetherby had been assigned for his program. As he was going on his spring vacation, it was not possible to give him an early date. He will appear on the June 13 meeting which is the last of the series...A group of 40 physicians from Minnesota are taking a special course in Obstetrics at the Center for Continuation Study this week. Upon their return to their local medical societies they will report on what they have learned. James E. Fitzgerald, Northwestern University, Chicago, and Buford G. Hamilton, University of Kansas, Kansas City, are serving on the guest faculty.....