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

Laboratory Methods

Volume XII | Friday, May 23, 1941 | Number 27

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

Volume XII | Friday, May 23, 1941 | Number 27

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: May 16, 1941

Place: Recreation Room
Powell Hall

Time: 12:15 to 1:10 p.m.

Program: Movie: "Birthplace of Icebergs"

Physical Medicine
F. G. Rosendahl

Discussion
M. E. Knapp
K. W. Stenstrom
W. T. Peyton

Present: 138

Gertrude Gunn
Record Librarian

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II. MOVIE

Title: "Tramp"

Released by: M-M-A

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III. ANNOUNCEMENTS

1. MAY 30 - HOLIDAY

No staff meeting will be held on this date. There are two remaining meetings:
June 6 - Out-patient Medicine
June 13 - Anesthesia

2. ALUMNI ATTENTION!

The Annual Banquet of the Minnesota Medical Alumni will be held in connection with the State Meeting in St. Paul in May. It will be a buffet supper held in the Casino Room of the St. Paul Hotel on Monday evening, May 26th. The speaker will be Mr. Clifton M. Utley, Director of the Chicago Council on Foreign Relations and his subject will be "America in a World at War." Mr. Utley has appeared frequently on the University of Chicago Round Table Broadcasts and is internationally known as an authority on foreign affairs. We consider ourselves fortunate in obtaining him as guest speaker and are anticipating a large attendance at the banquet. The price of admission will be $1.50 per person. Tickets are on sale in St. Paul and Minneapolis, Rochester and Duluth and will also be on sale at the registration desk at the convention.

Gordon R. Kamman, M.D.

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3. GUESTS - UNIVERSITY OF MINNESOTA
May 22, 23, and 24, 1941.

Felix Fleischner, Radiologist, Greenfield, Massachusetts -- formerly Chief, Department of Roentgenology, Wilhelmina Hospital, Vienna;

LeRoy Sante, Professor of Radiology, St. Louis University School of Medicine.

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4. GUESTS - MINNESOTA STATE MEDICAL ASSOCIATION, St. Paul, May 26, 27, and 28, 1941.

Sumner L. Koch, Associate Professor of Surgery, Northwestern University Medical School;

Thomas M. Joyce, Professor and Head of Surgery, University of Oregon Medical School;

Edward D. Churchill, John Homans Professor of Surgery, Harvard Medical School;

Walter M. Simpson, Director of Kettering Institute for Medical Research and the Diagnostic Laboratories at Miami Valley Hospital, Dayton, Ohio;

LeRoy Sante, Professor of Radiology, St. Louis University School of Medicine;

Henry H. Kessler, attending orthopedic surgeon at Newark City Hospital, New Jersey;

Albert D. Kaiser, Associate Professor of Pediatrics, University of Rochester School of Medicine;

Henry C. Sweany, Medical Director of Research, Director of Laboratories of Municipal Tuberculosis Sanatorium, Chicago;

Colonel John R. Hall, M.C., Director of Hospital Division, Surgeon General's Staff of U.S.Army, Washington, D.C.

IV. LABORATORY METHODS RECENTLY INTRODUCED IN THE UNIVERSITY OF MINNESOTA HOSPITALS

Gerald T. Evans
Edward B. Flink
Olaf Mickelsen

During the past two years many technical changes have been introduced in the chemical laboratory of the University of Minnesota Hospitals. Some of these have involved improvements in the method of performing the routine analyses. At present we wish to present four new procedures that have been recently started or are under consideration as a new technique. These tests are:

1. The Exton-Rose one hour-two dose test of glucose tolerance.
2. The fractional phenolsulphonephthalein test of kidney function.
3. The various diagnostic tests using galactose.
4. The Sulkowitch test for calcium excretion in the urine.

The laboratory is now equipped to perform all of these tests and will be glad to take under advisement any case which seems to require such diagnostic procedure.

1. The One-Hour Two-Dose Glucose Tolerance Test

In 1913 Bang introduced the first reliable blood sugar determination. In the same year Jacobson suggested following the blood sugar after ingestion of a carbohydrate meal. Hammann and Hirschman introduced glucose in 1917 as the test substance. Various amounts of glucose have been used in the past, but as shown by Exton and Rose[2] and others the actual amount used when the amount varies from 50 to 100 grams of glucose makes very little difference in the shape of the tolerance curve.

In 1913 Allen[1] noted that normal individuals utilized as much glucose as can be administered orally and that the limits of tolerance in non-diabetic individuals are all apparent and not real. In contrast large doses of sugar in diabetics are not utilized and there is a real limit to tolerance. This principle has become known as Allen's paradoxic law of glucose utilization.

Hamman and Hirschman[5] and a number of other investigators found that by the administration of successive doses of glucose on the same day to normal men the peak of the sugar curve after the second dose is lower than the peak after the first dose, and the peak after the third dose is lower than that after the second dose. This phenomenon is called the Hamman-Hirschman effect in this country and the Staub-Traugott phenomenon in Germany. Staub and Traugott[9] proposed a two-dose test determining the blood sugars every hour for six hours and giving a dose of 1.75 grams glucose per kilogram of body weight after fasting and again at the three hour interval.

The one-dose glucose tolerance test has a number of disadvantages. There are a certain number of normal people who have a curve in the range of diabetics Gould, Altshuler, and Mellen[4] examined 59 non-diabetics and only 40% of tolerance curves could be called non-diabetic curves, whereas 60% gave curves which could be called diabetic (their criterion for normal was the return of the 3 hour blood sugar to the fasting level). Myers and McKean[8] found 19 of 57 diabetics had borderline normal curves. It has been demonstrated a number of times that repeated tests in normal individuals may vary widely--as much as 50 mg.% at the peak value.

It has been shown a number of times that patients who became nauseated showed a coincident dip in the blood sugar curves and a secondary rise when the nausea cleared. Nausea is more apt to occur with a large initial dose of concentrated glucose solution.

There are a number of diseases which may give a diabetic type of curve with the one-dose test: cholecystitis, eczema, hypertension, hyperthyroidism,

malignancy, melancholia and other mental states, and Parkinson's syndrome.

Sweeney has demonstrated that an exclusive protein diet, an exclusive fat diet, or starvation for 48 hours preceding the one-dose tolerance test in normal individuals produced an effect which made the glucose tolerance curve simulate the diabetic curve. The magnitude of this effect was associated with the procedure and occurred in the above order.

Exton and Rose[2] in 1931 suggested a test which is based theoretically on the Hamman-Hirschman effect and Allen's paradoxic law. These investigators claimed certain distinct advantages over the one-dose method. Their original directions were as follows: 1. Have the patient fast over night; then collect fasting blood and urine samples: 2. Dissolve 100 grams of glucose in 650 cc. of water, flavor with lemon juice, cool, and divide the solution into two equal parts: 3. Collect fasting blood sugar and urine specimens and give one dose of the glucose solution after a 14 hour fast: 4. Collect blood and urine specimens and give second dose of the glucose solution at 30 minutes: 5. Collect blood and urine specimens at 60 minutes.

Exton and Rose[2,3] found fewer cases of equivocal results with this test than with the one-dose test, and the previous quite varied diets of 65 individuals, both normal and diabetic, had no appreciable effect on the curves. The test is much shorter than the one-dose test so that emotional factors in the patient are eliminated, particularly in nervous patients; there are fewer specimens to examine; there are fewer vena punctures necessary, thus contributing less discomfort to the patient. There is apt to be less nausea with the divided dose for two reasons, namely, the possibility of a more dilute solution and an actually smaller amount of glucose. Kelly[6] and his co-workers found that the test when compared with one-dose tests in the same patients gave fewer equivocal results. Gould, Altshuler, and Mellen[4] also found the two-dose test more specific in differentiating diabetic from normal individuals.

Of course the test is not infallible and does not give any particular aid in cases of hyperthyroidism and other metabolic disturbances which are often accompanied by hyperglycemia.

The following criteria were advanced by Exton and Rose for differentiating diabetics from normals. Normal tolerance curve: 1. A fasting blood sugar within the normal limits of the particular blood sugar method employed; 2. A rise in the blood sugar which does not exceed 75 mg. in the thirty minute sample; 3. The blood sugar in the sixty minute sample is less, the same, or does not exceed the thirty minute sample by more than 5 mg.; 4. All the urine specimens are negative to the Benedict test.

Diabetic tolerance curve: 1. A more or less steep curve of not less than 10 mg. of blood sugar following the second dose of glucose; 2. The relation of the blood and urine sugar values to the severity of the disease.

Matthews, Magath, and Berkson[7] in examining 117 normal individuals and 304 individuals with diabetes of varying severity found that it was possible to separate the two groups as follows: all individuals with values at the hour of less than 154 mg. were found to be normal and all individuals with values at the hour of 180 mg. or more were found to be diabetic. Only about 6% of the group had values in the intermediate zone. These observers concluded that the one-hour value is the only one which needs to be obtained.

We propose to use the test as outlined by Exton and Rose. The urine sugars can be determined by the qualitative Benedict's test. Since we have had a very limited experience with this test, it will be wise to obtain all three specimens originally suggested. There will undoubtedly be cases with equivocal results but in such cases further investigation and follow-up are

warranted. The test as proposed certainly has advantages in its brevity and sharper differentiation of borderline diabetes from normal. For children a dose of glucose according to the weight can be administered--1.75 grams glucose per kilogram body weight as the total dose to be divided into two portions. When one suspects spontaneous hypoglycemia, obtain specimens at three and four hours.

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Am. J. Clin. Path., 5: 299, 1935.

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2. The Fractional Phenolsulphonphthalein Test

Rowntree and Geraghty introduced the phenolsulphonphthalein test of renal function in 1910. They proved that the dye is not toxic when given intravenously or intramuscularly, and they found that 6 mg. of the dye is the most desirable amount to use. The original technique consisted in the collection of one and two hour urine specimens. During the past 30 years most clinicians have used this two-hour total excretion as an index of renal function. There are a number of reports in the literature to the effect that the test is quite insensitive to renal damage; consequently, the test has lost a great deal of popularity.

Before considering this test, it will be helpful to mention briefly some facts about the physiology of excretion of phenolsulphonphthalein. All investigators agree that the inulin clearance test is the only known true measure of glomerular filtration. Normal inulin clearance averages 120 cc. blood per minute. Homer Smith[10] and others have found the ratio of phenolsulphonphthalein clearance/inulin clearance to average 3.3 (for plasma concentrations of 1 mg. per cent or lower). This fact must be interpreted as indicating that the dye is excreted by the tubules as well as by the glomeruli; as a matter of fact, Smith has calculated that 94 per cent of the dye is excreted by the tubules. Further confirmation for the tubular excretion of the dye is the finding that the dye is excreted by the aglomerular kidney and by the mesonephros of the chick

embryo. Plasma proteins bind about 80 per cent of the phenolsulphonphthalein in a loose manner, so free and bound dye exists in equilibrium in the plasma.

In 1925 Shaw[8] demonstrated quite conclusively that a great deal more information could be obtained by collecting urine specimens every 15 minutes for two hours than by merely collecting one and two hour specimens. He collected the following data on a number of normal subjects by obtaining urine every 5 minutes; at 5 minutes 8 to 15 percent of the dye is excreted; the peak of elimination occurs at 10 minutes with a rapid falling off after the first 15 minutes. Shaw established a normal curve of values for 15-minute periods and these values agree essentially with Chapman and Halstead's[1] data which will be cited in more detail below.

It is surprising that Shaw's modification was not widely accepted clinically except in urologic surgery. Chapman and Halsted[1] in 1933 introduced a fractional phenolsulphonphthalein excretion test into the study of "medical" renal diseases. These investigators compared the efficacy of the fractional phenolsulphonphthalein test with the urea clearance test in 43 patients with renal diseases, including acute and chronic glomerulonephritis, renal amyloidosis, mercury poisoning, and arteriosclerotic renal disease (Addis classification). In these patients 14 (32.5 per cent) had a total output of 55 per cent or more but showed a delay in the elimination of the dye.

In a comparative study of the urea clearance test with the 2-hour output of phenolsulphonphthalein Peters and Van Slyke[6] have shown that when the urea clearance is between 40 and 60 per cent of the average normal value, about half the dye outputs are above and half below 55 per cent. An analysis of Chapman and Halsted's[1] shows that in 8 cases with phthalein outputs above 55 per cent and urea clearances between 40 and 60 per cent, all but 2 had delayed excretion of the dye. On the other hand there were 9 patients in whom the urea clearance was 76 per cent of normal or above; yet, the fractional phenolsulphonphthalein test showed an impaired renal function.

Chapman and Halsted[1] demonstrated that forcing fluids in 4 patients with chronic renal disease and in 8 normal subjects caused no appreciable change in the dye output. This agrees with Shaw's[8] findings in normal individuals on the effect of forcing and limiting fluids. Anemia per se does not affect the excretion of the dye.

McGee and Martin[5] in a series of 290 patients found that abnormalities in the fractional phenolsulphonphthalein test occurred more often than abnormalities of either the concentration test or the urea clearance test. (But these investigators used specific gravity and 50 per cent of C_m as normal values for the last two tests so these tests automatically are rendered less sensitive than those judged by the usual criteria.)

Freyberg[3] in a study of 254 patients with various types of renal disease (including, however, normal pregnancy) used the fractional phthalein test, the Lashmet and Newburgh concentration test, and the urea clearance test; they concluded that the fractional phthalein test was too sensitive indicating impairment when it actually did not exist. Two reasons for this, however, are his use of 28 per cent as the minimum normal excretion in the 15-minute specimen whereas the originators of the test used 25 per cent as the minimum and his inclusion of patients with normal last-trimester pregnancy. Freyberg[4] and his co-workers later showed that there was definite diminution of the 15-minute specimen with a delay in the dye excretion curve in normal last trimester pregnancies. Explanations for this unreliability in late pregnancy are an increased circulation due to the fetus and a physiological dilatation of the upper urinary tract; however, the above factors do not obviate the estimation of the total output of the dye. Freyberg[4] also concluded that a 15-minute phenolsulphonphthalein excretion of 28 per cent or more of the injected dye quite definitely excludes serious renal damage.

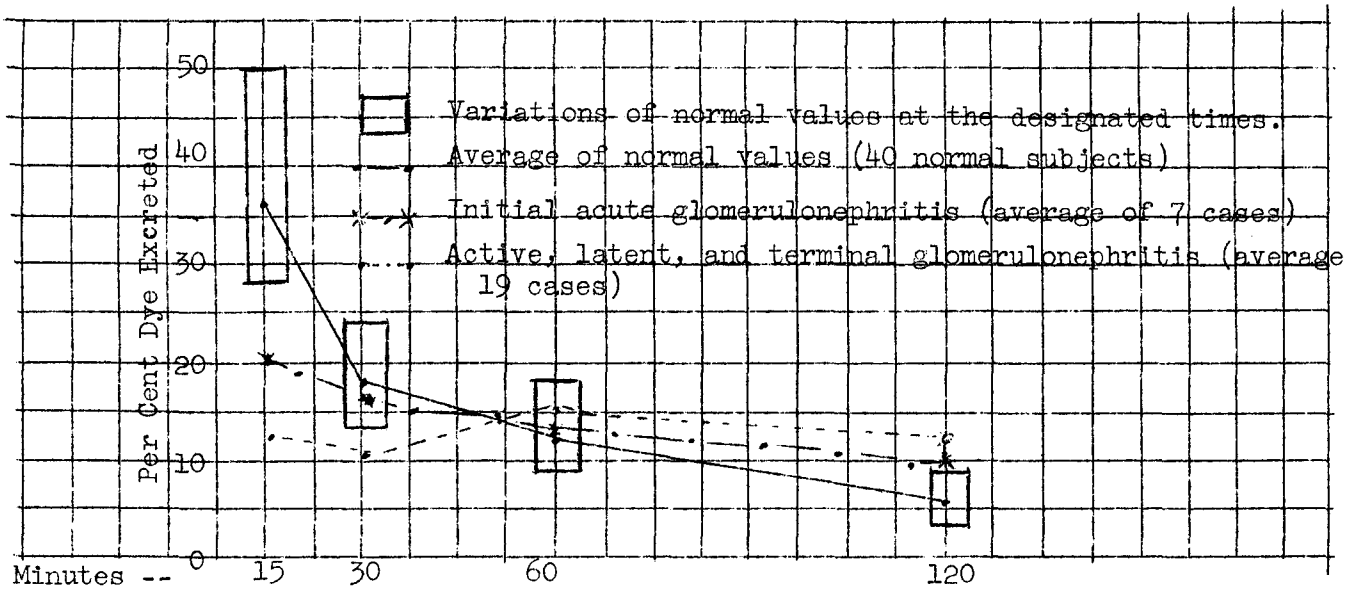
Chapman[2] found the fractional test unreliable as an index of renal function in: 1. congestive heart failure because of a decreased excretion of the dye and a consequent delay in the excretion peak; 2. in the nephrotic type of glomerulonephritis and true nephrosis (chemical) because of relative insensitivity of the test to renal damage; and 3. in hepatic cirrhosis because the liver does not excrete the usual 15 to 20 per cent of the dye, thus giving abnormally high urine values.

Shaw and McKenzie[9] obtained urine from each kidney in cases of unilateral kidney disease and demonstrated that the dye excretion curve of the normal kidney corresponded to a curve represented by half the values of the normal curve.

Chapman and Halsted's[1] directions for the fractional phenolsulphonphthalein test are as follows: 1. The subject drinks 600 cc. H_2O.; 2. 30 minutes later voids and discards that sample of urine; 3. 6 mg. of phenolsulphonphthalein (1 cc.) are injected at that time; 4. Voided specimens of urine are then collected at 15, 30, 60 and 120 minutes; 5. Patients with bladder-neck obstruction should have indwelling catheters during collection of specimens; 6. The percentage excretion is determined in each specimen by the usual technique using Duboxc or special colorimeter. (More recently Chapman[2] has collected only the first two specimens, namely, the 15 and 30-minute specimens, but we are not prepared to cut the test to this extent as yet.)

The following graph and table indicate normal pathological variations. Chapman and Halsted[1] state, "that an abnormal elimination of dye was reflected chiefly in the first 15-minute specimen, and so this is the most important specimen." They used 25 per cent of dye injected as the lowest limit of normal for the 15-minute specimen.

Graph



The variations of normal values and the average curves of values obtained in normals in initial acute glomerulonephritis and active, latent, and terminal glomerulonephritis. (Adapted from Fig. I, Chapman and Halsted's paper.)

Table

A. Total Output: (40 normal subjects)

Highest total - 84%
Lowest total - 63%

B. Maximum, minimum, and average normal values in % of injected dye:

	15-Min.	30-Min.	60 Min.	120-Min.
Maximum	50%	24%	17%	10%
Minimum	28%	13%	9%	3%
Average	36%	18%	12%	7%

(Adapted from Fig. I, Chapman and Halsted's paper.)

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Conclusions

We propose to adopt the test as described by Chapman and Halsted and hope that it will be put into immediate use in place of the 2-hour total test. There can be no question of the superiority of the fractional phenolsulphonphthalein test over the old method of performing the test. Its sensitivity and reliability correspond quite closely to the urea clearance test, and as is perfectly obvious, it is a great deal simpler to perform than the latter test. The test is ideal for out-patient and office practice, for it requires no elaborate chemical laboratory equipment to perform. It is of equal value in following hospital patients.

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South.Med.Jour., 30:61-69, 1937.

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3. Galactose Test

The following report on the use of galactose in laboratory tests has been divided into three sections, depending upon the technique used in performing the tests.

(1) Oral galactose test with urinary sugar determinations

Probably one of the first to use galactose as a laboratory diagnostic test was Bauer. In 1906 he found that normal individuals could take about 30 gms. of galactose without the appearance of any sugar in their urine whereas patients with liver injury showed sugar in their urine under this circumstance. On this basis he developed a liver function test which attempted to measure the capacity of this organ to remove galactose from the portal blood. This test required the patient to empty his bladder in the morning before breakfast and then take 20 gms. of galactose. Urine specimens were collected at hourly intervals and were tested for sugar by means of the polarimeter. In order to determine whether all of the sugar so measured was really galactose, it was necessary to oxidize the sugar to mucic acid and then weigh that. On the second day, this test was repeated but at this time 40 gms. of galactose were given. If more than 4 gms. were excreted, there was good indication of liver damage. The results that Bauer secured with this test led him to suggest it as a means of differentiating the jaundice cases due to hepatic injury from those due to obstruction. His tables show, however, that one individual who was diagnosed as a case of catarrhal jaundice excreted only 2 gms. of sugar when 40 gms. of galactose were given. This was well within the normal range and indicated that the test was not infallible.

Many clinicians, especially in Germany, used the single galactose tolerance test in which only the 40 gms. of galactose were given and reported an excessive excretion of galactose in about 80 per cent of the cases of catarrhal jaundice and in about 7% of the cases of obstructive jaundice. The early reports on this test have been carefully summarized by Tumen and Piersol. These investigators found as some of the earlier reports showed that there was no correlation between the degree of jaundice and the galactosuria. They recommended that the upper limit of galactose excretion in normals be placed at 3 gms. Their own work which illustrates the type of response to this test secured by most workers can be summarized as:

Disease	No. of Cases	Galactosuria in gms. 0-2	2-3	3+
Toxic hepatitis	13	23%	23%	54%
Catarrhal jaundice	23	17.4%	4.3%	78.3%
Obstructive jaundice	18	83.4%	11.1%	5.5%

A number of reports have appeared in this country on the evaluation of this test (Shay, et al, Banks, et al), but they all emphasize the fact that the test is valuable mainly in differentiating jaundice of hepatic origin from that of extrahepatic origin. In the differentiation of other types of liver disease, other tests of liver function have to be used. Various efforts have been made to improve the accuracy of the oral galactose tolerance test. Shay suggested that all pooled urine samples showing a sugar excretion of over 3 gms. be submitted to the rapid fermentation test of Somogyi. Most workers had determined only the total urine sugar and considered it to be all galactose. One of the more recent of these modifications is that of Pollak which requires the ingestion within a period of 10 minutes of 1 liter of water or dilute tea containing 40 gms. of galactose. The urine samples are collected before the start of the test and then at half hour intervals for 2 hours. Two additional samples are collected at hourly intervals. The amount and specific gravity of each sample of urine is determined as well as the amount of galactose in each portion. The length of time during which galactose is excreted is also noted. The urinary galactose excretion is plotted against

time and on this basis an improvement in the detection of catarrhal jaundice is secured. Normal individuals and patients without any signs of liver disturbance never excrete more than 3 gms. of galactose and no sugar appears in the urine after the second hour. In 13 cases of cirrhosis of the liver 3 showed an excretion over 3 gms., 5 showed a concentration of galactose in the first samples of more than 0.6% (the upper limit of normal), and the remaining 5 showed a protracted excretion. The results of the test are divided into 4 groups depending upon the rate of galactose excretion, its concentration in the urine, and the length of the excretory phase. Meier has used this test in various diseases of the liver and reports that he has not been able to find various excretion curves for different diseases as Pollak reported and so considered primarily the amount and the length of the excretion period. He found an increased excretion time (more than 2 hours) in 13 out of 14 cases of cirrhosis of the liver while the total amount of galactose in the urine exceeded 3 gms. in only 4 of the 14 cases. Here it must be emphasized that the length of time was $2\frac{1}{2}$ hours in some cases and $3\text{-}3\frac{1}{2}$ in most cases. In obstructive jaundice and in other diseases, the values were within normal in practically all cases. Meier places great stress on the length of time during which the galactose is excreted in the urine. Even if a total of only 1 gm. is excreted over a 4-hour period, there is good evidence of cirrhosis. Kronicke reported the results of this test on a large number of normal, healthy people as well as patients showing no liver injury and in all cases, he found that the amount of galactose excreted never exceeded 3 gms. and was always absent from the urine 2 hours after the test was started. So far this fractional galactose tolerance test has been used only in Europe. All the workers there have used the polarimeter in the determination of urinary galactose. The ingestion of such a large amount of water with the galactose might overcome the argument that the excretion of galactose is related to the urine volume. Maclagan found that when the oral galactose test was repeated on two successive days on a person who had Graves disease, 4 gms. of galactose were excreted in 2 hours when the urinary volume was 250 cc. but when the volume was only 28 cc., 0.9 gms. of galactose were excreted.

(2) Oral galactose test with blood sugar determinations

In an attempt to still further improve the oral galactose tolerance test, the changes in the blood sugar were studied. The first work along this line showed that there was no appreciable difference in the blood sugar curves of normals and those with catarrhal jaundice. In fact the blood sugar values were not as reliable an index of liver function as the excretion of galactose. Before 1927 all investigators determined the total blood sugar since there wasn't any reliable method available for galactose. In that year Somogyi introduced a rapid method for the determination of galactose based on the differential fermentation of glucose by yeast. The determination of the blood galactose following the ingestion of 40 gms. of galactose was first made by Althausen and Wever. They took blood samples at 5, 15, and 30 minutes. The blood galactose curve was higher in a case of Graves' disease but no cases of liver disturbances were reported. Maclagan has adapted this procedure as a liver function test. He gives 40 gms. of galactose in 250 cc. of water to a patient after an overnight fast. Blood samples are collected at $\frac{1}{2}$, 1, $1\frac{1}{2}$, and 2 hour intervals. The glucose in the samples is removed by means of yeast fermentation and the remaining sugar determined as galactose. The yeast fermentation method as modified by Raymond and Blanco consists in washing the Fleischmann's bakery yeast with water and then centrifuging. This is repeated 6 or 7 times till the supernatant liquid is free of turbidity. The cells are finally removed and suspended in 3 times their weight of water. If this suspension is kept in the refrigerator it is good for 2 weeks. One cc. of this yeast suspension will ferment all the glucose in 0.2 cc. blood within 4-5 minutes; the blood is usually diluted with 1 cc. of water before the yeast is added. The

solution is then deproteinized and any-one of a number of blood sugar methods can be used. One should be careful to run standard solutions of galactose in order to compensate for the difference in the reducing power of glucose and galactose.

MacLagen finds that the maximum galactose concentration in the blood may occur either at the ½, 1 or 1½ hour sample (usually at 1 hour). In normals, the maximum value seldom exceeds 40-50 mg.% and all the galactose has practically disappeared from the blood within 2 hours. Patients with catarrhal or toxic jaundice and those with hyperthyroidism showed levels up to 125-150 mg. %. He has added the blood galactose values for the ½, 1 and 1½ hour samples together and called this the "galactose index." The upper normal value for this index is 160 and the average in this series is 68. This is not exceeded by his normals, his diabetics nor his cases of obstructive jaundice whereas all of his 10 cases of toxic jaundice are higher. He is inclined to the view that the high galactose index in hyperthyroidism is an indication of liver damage.

The oral galactose tolerance test has been suggested as a means of determining whether an increased basal metabolic rate is due to hyperthyroidism or to such factors as anxiety, apprehension or cardiac trouble. Althausen, Lockhart and Soley use an oral dose of 40 gms. of galactose in 400 cc. of water and then collect blood samples at 5, 15, 30, 60 and 120 minutes. The galactose is determined in these samples after removal of the glucose by means of yeast fermentation. They maintain that the maximal concentration of galactose in normal controls never exceeds 30 mg.% with a range between 13 and 31 mg.% and this peak may occur in the 30 or 60 minute sample. Their cases of hyperthyroidism showed a maximum average peak of 68 mg.% with a range from 25 to 152 mg.%. A large number of patients with disturbances of the thyroid gland were studied by these workers. They were unable to find any close correlation between the B.M.R. and the galactose tolerance test, although those patients who had a high B.M.R. also had high peaks in their galactose curves. Their curve showing these relations is given below. The independent influence of thyroxin on the B.M.R. and the rate of intestinal absorption is used to explain this difference. When they used alpha-dinitrophenol, they were able to increase the basal metabolism without changing the rate of absorption of glucose. However, they claim that among patients with definite clinical hyperthyroidism, doubtful results are secured less frequently with the galactose tolerance test than with the B.M.R. The value of the galactose test as an aid in diagnosis is especially stressed when the B.M.R. in true cases of hyperthyroidism is below 20%. By means of an intravenous administration of galactose they say that cases of hepatic insufficiency could be distinguished from hyperthyroidism. Under these conditions, patients with hyperthyroidism show a normal response whereas those with liver disturbance show an elevated blood galactose. Here, they maintain, is further proof of the fact that the response to the oral galactose test in cases of hyperthyroidism is due to an increased rate of absorptdn without any change in the ability of the liver to metabolize the sugar. Most of their patients with myxedema showed an abnormally low amount of galactose in the blood which was lower than that of the normal controls.

(3) Intravenous galactose with blood sugar determinations

In 1931 Pollak made a series of blood sugar determinations in normal controls who were given an oral dose of 40 gms. of galactose. He also made similar tests on these people when varying amounts of galactose were given intravenously and by this means found that the injection of 20 cc. of a 40% galactose solution produced the same increase in the blood sugar as the oral dose. His normal controls showed an increase in blood sugar[1] following the intravenous dose of galactose to 141 to 157 mg.% or 42-70% above the original level. The patients with diseases of the liver showed an increase of 10 to

36%. There was no correlation between this test and a subsequent oral test in which the amount of sugar excreted in the urine was determined. Budak, from the same clinic with which Pollak was associated, reported that he was unable to find any appreciable difference in the blood sugar rise in his control patients and those with liver diseases.

Pollak's conclusions are directly contrary to the results secured with the intravenous test when the yeast fermentation method has been used to distinguish the rise in galactose from the increase in the blood sugar. Now it is recognized that in cases of catarrhal jaundice, the blood galactose reaches a higher maximal value and is maintained over a longer period of time than in the normals. A possible explanation for the early discordant results might rest on the fact that when galactose is given, there is a rise in the blood glucose (Harrison). This extra glucose comes presumably from the liver and in cases of liver damage the glycogen stores may be depleted to such an extent that the blood sugar cannot rise very high.

King, Harrison and Delory reported their results of the intravenous galactose test in rabbits with livers damaged by carbon tetrachloride. They used a dose of 1 gm. per Kg. of body weight and took samples at 5, 60, 120 and 180 minute intervals. Most of the galactose disappeared from the blood of their normal animals within 3 hours, but there was still a considerable amount (25-90 mg.%) present in the rabbits poisoned with carbon tetrachloride. King and Aitkin used this test in humans but reduced their dose to 0.5 gm. per kg. body weight in their early work and then changed to a standard dose of 50 cc. of a 50% galactose solution since the results by the two methods were the same. Blood samples were taken just before the injection and again at $\frac{1}{2}$, 1, $1\frac{1}{2}$, and 2 hour intervals thereafter. In both their normals and patients with non-hepatic diseases, the blood galactose always dropped to less than 10 mg.% at the end of the second hour. In 12 out of 15 cases of toxic or non-obstructive jaundice there was an increased blood galactose ranging from 15 to 82 mg.% in the 2 hour sample. All of the cases of obstructive jaundice behaved like their normals.

Discussion

Our experience with these galactose tests has been too limited to warrant any critical statements. Shay, Schloss and Bell have considered the factors which make galactose the ideal substance for a liver function test on theoretical grounds. These reasons include such things as: Galactose in normal animals is absorbed at nearly the same rate as glucose (the ratio is: glucose: galactose = 100 : 110). There is no kidney threshold for galactose, and its excretion is not influenced by any endocrine disturbances. It is a substance which can be used by the normal liver but whose utilization imposes a slightly higher demand on the liver than glucose does. Most experimental work has indicated that the liver is the only organ which can utilize galactose.

One factor that may require further investigation as far as the galactose tests are concerned is the relation between body fat and the metabolism of this sugar. It has recently been shown that dietary fat is necessary for the normal metabolism of galactose. Schantz, Elvehjem and Hart showed that when normal rats were placed on a skim milk ration, galactose was excreted in the urine within 2-4 days. The concentration of sugar in the urine (all of it was galactose) amounted to 0.5 to 1.6%. The blood sugar curves of these rats showed an increase to 200 mg.% or more following the ingestion of the skim milk whereas the levels reached in the rats receiving whole milk were less than 140 mg.%. As high as 35% of the ingested galactose was excreted by the rats on skim milk. Similar results were secured in the calf and the pig. Butter fat was not the only substance which was able to prevent the loss of galactose in the urine. When lard, corn oil, cocoanut oil, linseed oil, palmitic or oleic acids were added to the skim milk at a level of 3-4%, the rats were again able to utilize all the galactose.

Schantz and Krewson have shown that any straight chain fatty acid containing an even number of carbon atoms greater than 12 will prevent the loss of galactose when added to the skim milk at a level of 3-4%. Acids containing less than 12 carbon atoms or an uneven number of carbon atoms were ineffective.

The above phenomenon may explain some of the invalidities secured with the galactose tests, both in the diagnosis of liver function and in hyperthyroidism. Whatever the cause, there are still some cases which fall in the doubtful region, and here one can only recommend the use of other tests.

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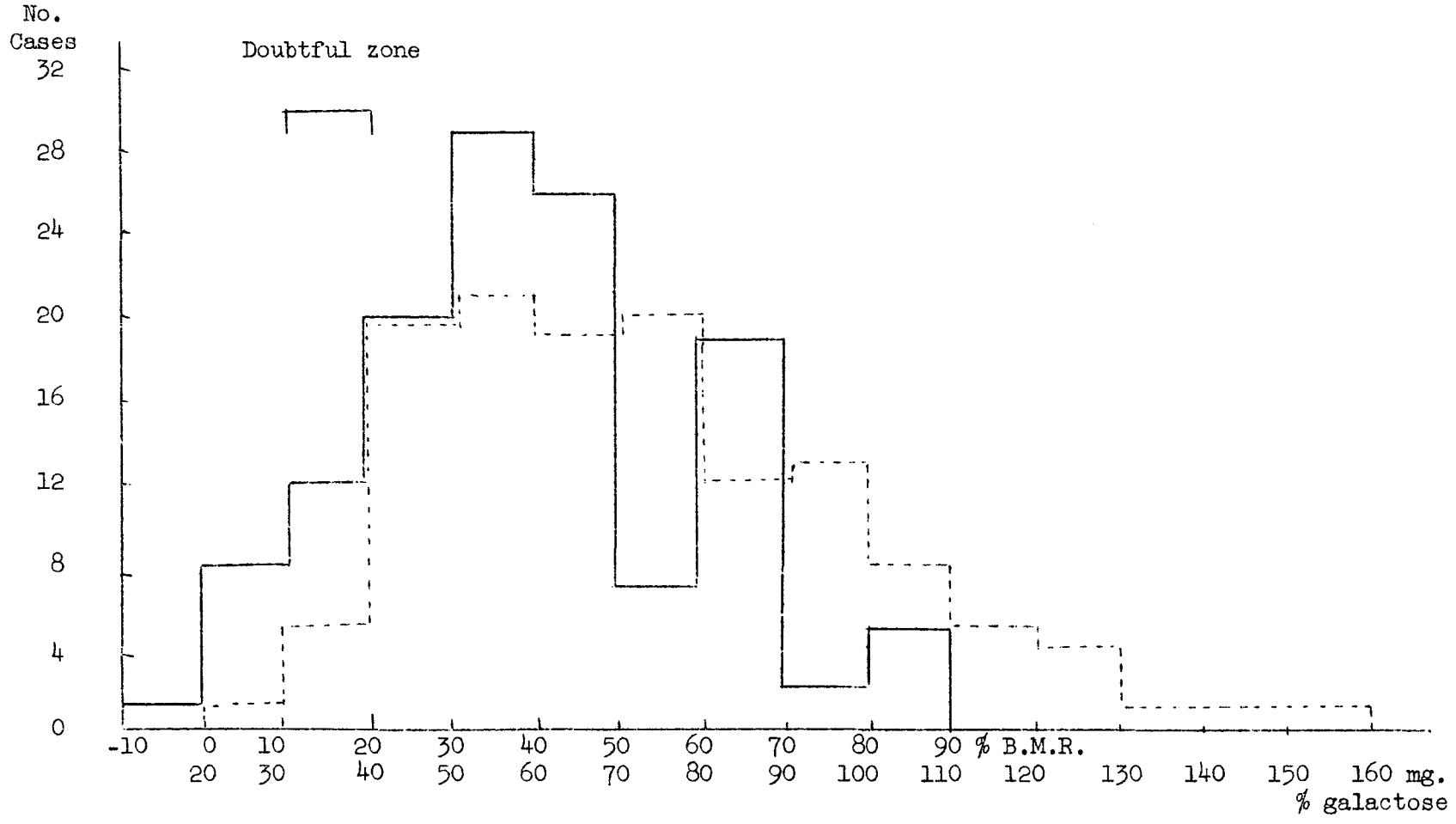
[1]He did not determine the galactose present because he was unaware that any such test was available and concluded his article with a hope for such a test.



Distribution of the B.M.R. (solid line) and the maximal galactose values in the blood of 130 patients with clinical hyperthyroidism (broken line).

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4. The Sulkowitch Test

This is a useful test for the detection of hyperparathyroidism. The laboratory indications of hyperparathyroidism include an elevated serum calcium, a low plasma phosphorus and an excessive urinary excretion of calcium. Previously, the latter has not been used very extensively as a diagnostic aid because there was not any very simple method for the determination of calcium in the urine. Such a method is now available and has been used to a limited extent in this hospital. The basis of the test was first described by Barney and Sulkowitch who studied qualitatively the amount of calcium in the urine of patients with urinary calculi.

This procedure was utilized by Albright and his coworkers in the study of patients with hyperparathyroidism. At most, the procedure as originally outlined gives a very rough indication of the calcium concentration in the urine. The method, which depends upon the precipitation of calcium oxalate at a controlled pH, has been modified in our laboratory so that it gives a reliable value for the quantitative calcium excretion in the urine. The patients are placed on a low calcium, neutral ash diet for a period of four days during which time 24 hour urine collections are made. Calcium determinations are made on these samples by the method described below.

The following diet devised by Miss Marion Winter of the Dietetics Staff supplies 1562 calories per day and 0.3822 grams of calcium per day.

NEUTRAL ASH - LOW CALCIUM DIET (WINTER)

Food	Weight in Gms.	Calories	Calcium	Phos-phorus	Excess Acid	Excess Base
		Breakfast				
Orange juice	162	123.18	.047	.0235		7.29
One egg	50	74.00	.0335	.0140	5.5	
20% Cream	30	62.00	.0280	.1720		.20
Sugar (2 tbsp.)	10	40.00				
White toast (1 slice)	30	77.00	.0081	.0560	2.1	
Butter (1 square)	10	76.90	.0015	.0020		
Coffee						
Total		453.08	.1181	.2675	7.6	7.49
		Dinner				
Rice (dry)	30	105.20	.0027	.0288	2.79	
Lean beef	100	151.00	.0110	.2120	10.60	
Asparagus	100	20.40	.0213	.0390		.8
Sliced tomato	100	20.00	.0110	.0260		5.6
Lettuce	20	3.20	.0086	.0084		1.48
Mayonnaise	10	68.70	.0012	.0037	.14	
Butter	10	76.90	.0015	.0020		
Apple	100	60.00	.0070	.0120		3.70
Total		505.40	.0643	.3319	13.53	11.58
		Supper				
Baked potato	50	63.00	.0105	.0290		5.00
Veal chop	100	177.00	.0120	.2150	9.80	
Lettuce	50	8.00	.0215	.0210		3.70
Mayonnaise	10	68.70	.0012	.0037	.14	
Bread	30	77.00	.0081	.0560	2.10	
Butter	10	76.90	.0015	.0020		
Pear	100	64.00	.0150	.0260		3.60
Milk	100	69.00	.1300	.0930		1.80
Total		603.60	.1998	.4457	12.04	14.10
Total for Day		1,562.08	.3822	1,0451	33.17	33.17

Reagents for the determination of calcium in urine

1. 0.2 N solution of sodium acetate - 27.22 gm. per liter.

2. 0.2 N acetic acid - made by diluting 11.3 cc. glacial acetic acid to 1 liter.

3. Sodium acetate buffer of pH 4.2 made by mixing 265 cc. 0.2 N sodium acetate + 735 cc. 0.2 N acetic acid.

4. Sulkowitch reagent which contains 8.34 gm. oxalic acid + 8.34 gms. ammonium oxalate made up to 500 cc. with the acetate buffer.

5. Standard calcium solution. Prepared by dissolving 2.5 grams of C.P. calcium carbonate in about 25 cc. of N hydrochloric acid. This solution should be adjusted to a pH of 4 with dilute sodium hydroxide. This solution contains 1 mg. of calcium per cc. and should be diluted further so that each cc. contains 0.1 mg.

Procedure

1. If any precipitate is present in the urine, it should be acidified with concentrated hydrochloric acid to a pH of 4 in order to make sure that all the calcium is in solution. This can be done with the aid of Fisher's alkacid paper. The volume of hydrochloric acid required to adjust the urine to this pH should be noted and subtracted from the final total volume.

2. Mix the sample thoroughly and then measure the volume of the 24 hour specimen.

3. Transfer 1/300 of the total urine volume to each of two colorimeter tubes and add sufficient distilled water to make a volume of 10 cc. in each tube.

4. Add 5 cc. of the acetate buffer to the first tube and with a filter transmitting light at 600 mu adjust the galvanometer to 100 while this control tube is in the colorimeter. We have used an Evelyn photoelectric colorimeter (Rubicon Company, Philadelphia) for this work. The center setting for the control tube is carefully determined.

5. Add 5 cc. of the Sulkowitch reagent to the second tube and exactly five minutes later with the center setting found for the control tube, determine the turbidity by means of the colorimeter. Be sure to shake the tube just before making the reading.

6. A similar procedure is carried out using standard solutions of calcium instead of urine. These standards are used in securing a curve for the colorimeter which is made by plotting the galvanometer readings on semilogarithmic paper against the concentrations. The amount of calcium in the sample is determined from the standard curve, and this value is then multiplied by 300 to give the amount excreted in 24 hours.

The urinary calcium concentration has been determined on some of these samples by another method (Sobel & Sobel) and found to check very well with our modification of the Sulkowitch test.

Interpretation

Normal individuals on this diet excrete about 100 mg. or less of calcium in the urine and 280 mg. in the feces (Steggarda and Mitchell). In cases of hyperparathyroidism, the urinary excretion of calcium is increased to as much as 400-500 mg. per day whereas the fecal excretion shows no change or is decreased (Bauer, Albright and Aub, 1930). Albright, who has studied this disease very extensively, uses a diet containing 100 mg. of calcium per day. We have preferred the higher level of calcium since it more nearly approaches the daily requirement and so accentuates any abnormality in utilization which may be present.

Our experience has been too limited with this condition to state the lower limits of calcium excretion which are indicative of a hyperactivity of the

parathyroids. Most of the cases of hyperparathyroidism so far studied have shown a daily urinary excretion of 200 mg. or more per day on the low calcium diet. The more significant figures are those for the excretion on the last two days of the low calcium regimen.

The differential diagnosis of hyperparathyroidism has been concisely stated by Albright, Aub and Bauer whose chart is reproduced on the following page.

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Points in Differential Diagnosis Between Hyperparathyroidism and Other Bone Diseases

Disease	Differential Points as Regards			Serum		Plasma Phosphatase	Miscellaneous
	Symptoms	Roentgen Studies	Biopsy	Calcium	Phosphorus		
Hyperparathyroidism with bone involvement	Bone; pain, deformity, fracture, tumor; polyuria; those related to stones	Increased radiability generalized; deformity; cysts; tumors; fractures; stones	Rarefied bone; fibrosis of marrow; osteoclasis+++; osteoid tissue only slightly increased; osteoblasts +++	High	Low	High	All age groups
"Senile" osteoporosis	No bone tumor, polyuria or stones	No cysts, tumors or stones	No fibrosis of marrow; osteoclasts normal; osteoid tissue normal or decreased; osteoblasts decreased	Normal	Normal or low	Normal	
Paget's disease	Bones enlarged; no polyuria; stones infrequent	Polyostotic but not generalized; bones hypertrophied, e.g., thickened skull	May occasionally be difficult or impossible to differentiate	Normal or slightly high	Normal or slightly high	Very high	Runs in families; predilection for weight-bearing bones; seldom seen under 40; arteriosclerosis +++
Osteomalacia	No bone tumor, polyuria or stones	No tumors or stones; bending deformities +++	Osteoid tissue +++; osteoblasts ++; osteoclasts decreased	Normal or low	Low	High	Practically absent in this country except with fatty diarrhea
"Solitary" cysts	Confined to cysts	No generalized changes; cysts may be multiple	Cannot differentiate if taken from lesion	Normal	Normal	Normal	
Solitary benign giant-cell tumor	Confined to tumor	No generalized changes	Cannot differentiate if taken from lesion	Normal	Normal	Normal	

Points in Differential Diagnosis Between Hyperparathyroidism and Other Bone Diseases (Cont.)

Disease	Differential Points as Regards			Serum		Plasma Phosphatase	Miscellaneous
	Symptoms	Roentgen Studies	Biopsy	Calcium	Phosphorus		
Osteogenesis imperfecta	Fractures +++; no bone tumor, polyuria or stones	Cysts rare; no tumors or stones	No fibrosis of marrow; osteoclasts normal	Normal	Normal	Normal or very slightly elevated	Hereditary, often coupled with blue sclerae and deafness; improves after cessation of growth
Multiple myeloma	Can cause same bone symptoms & renal sympt.	Can be almost indistinguishable	Tumor tissue	Normal or high	Normal or high	Normal	Bence-Jones proteinuria
Metastatic malignancy	.....	Bones not involved, normal; seldom affects bones of forearms and lower legs	Tumor tissue	Normal or high	Normal or high	?	? Primary focus
Basophilic aenoma of pituitary (Cushing's disease)	Obesity, hirsutism and amenorrhea	Usually only osteoporosis	.....	Normal	? Low	?	Abdominal striae; hypertension

V. GOSSIP

A practical joker is now a hospital patient in St. Paul. One of his friends, also a practical joker, solemnly assured their mutual friends that the sick one was very fond of licorice. One visitor after another has brought this particular variety of candy when they made their sick visits. The one who is ill has now collected over 12 pounds....Hospital visitors at State Institutions for the Insane when they are members of the family group usually show something in common with the patient. In one hospital where many patients have the freedom of the grounds, hospital visitors are frequently spied leaving the institution and are reported by the townspeople as run-aways. Hospital physicians may learn a great deal about their institutions by sitting in with the crowd as they wait to be served at the main desk. Director Dermatologist Henry E. Michelson once overheard a discussion by two negroes concerning the relative merits of the services of the Vanderbilt Clinic and other New York Institutions. The climax came when one negro told the other that the "spinal fluid was the juice of the human body." A physician waiting with our group the other day overheard one visitor say to the other, "The reason it takes them so long for them to come down to talk to you is that they don't know what to say." Another one said, that you could be certain that an operation was indicated if they advised it as it is so hard to get into the surgical department as a patient. In our Out-patient Department we have had many amusing mistakes occur when visitors with patients have been called in for physical examinations and have gone part way through the procedure before making any complaint. One in particular did not mind having his temperature taken, his respiration and pulse recorded, and his blood pressure measured, but he did object to a blood test just to drive his friend home from the hospital.....A certain railroad restaurant over town is a favorite spot for several faculty members and the President of a Minnesota college. Eating in a railroad restaurant seems different..... Assistant proctologist William C. Bernstein is just back from a two-week clinical trip to Dallas, Texas, where he spent most of his time in the clinic of Curtice Rosser. Dr. Rosser will be remembered by many as a guest faculty representative on one of the Proctology courses. While in Dallas, Bill visited a physician who has made miniature railroading a hobby. He is an admirer of the B and O system, and builds all his equipment like theirs. His engines average about 18 feet in length and are exact copies. His track now is more than two and one-half miles in length, but his neighbors may give him rights of way so that it may be extended to 12 or 15 miles. In addition to being an expert at his hobby, he is an excellent surgeon. He has built a swimming pool on his grounds which he made available to physicians' families..... More and more the importance of a hobby is becoming evident. Obstetrician A. L. Dippel makes children's furniture and toys, and has a complete wood-working shop in his basement. One of his specialties is a teeter-totter which can be operated by one child. It does not tip, and the O'Brien's testify that it is an attractive play device for the neighborhood. Several other staff members also find their outlets in this way. Hobby shows at medical societies attract an interesting array of articles. One of the meetings of the Minnesota State Medical Association brought in guns, paintings, etchings, book binding, music, wood carving and nursing bottles. The latter is a hobby of pediatricians and Dr. Robert Rosenthal has one of the best local collections. The Mead and Johnson collection was sent here a few months ago but arrived too late for one of the courses at the Center, so it was shipped on without being unpacked. Few men with hobbies speak of them as most of us make weak excuses when asked what our hobbies are. The psychiatrists tell us that occupational therapy is one of the best outlets for the mind worker. Women teachers from one of our local colleges go to the country each summer so that they may garden... When our prospective enrollees were examined this spring, these men were found to have approximately the same number of defects as those who did not go to college. Their defects, however, were of a different variety, being marked in the special senses -- vision and hearing, which undoubtedly guided them in a college career.....